Pathological Correlates of Electrodiagnostic Studies: The Special Use of the Nerve Biopsy

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Disclosure

- Relevant financial relationships or off label usage: None

Learning Objective

- To evaluate the correlation between electrophysiological findings and nerve pathology.
- To introduce the concept of targeted fascicular nerve biopsy.

Should Nerve Biopsies be Done?

- Historically, nerve biopsies have been important in evaluation of neuropathies.
- Many experts advise that nerve biopsies should now be done infrequently and used mostly for research.
- What is the place (if any) for nerve biopsies in the modern clinical practice?

Role of Nerve Biopsy

- Drawbacks to nerve biopsy
  - invasive
  - may produce new symptoms and deficits
  - may be avoided by other tests
  - only views a small portion of the nervous system
  - does not evaluate motor problems well since it usually is a sensory nerve (sural)

Order of Evaluation

- When evaluating a peripheral neuropathy, the nerve biopsy comes last.
  1. History and neurological examination
  2. Nerve conduction and EMG
     - demyelinating vs. axonal
     - level of involvement: root, plexus, peripheral nerve
  3. Laboratory tests (including CSF)
  4. Quantitative sensory and autonomic tests
  5. Only after the above tests, nerve biopsy is considered (invasive and side effects)

Information Gained by Nerve Biopsy

- Neuropathic information (axonal degeneration, segmental demyelination)
- Interstitial information (inflammation, amyloid, vessel changes, etc.)
- Most of the neuropathic data can be inferred from NCS and EMG.
- The most important information gained from a nerve biopsy is about the interstitium (little way of inferring this data from electrophysiology).

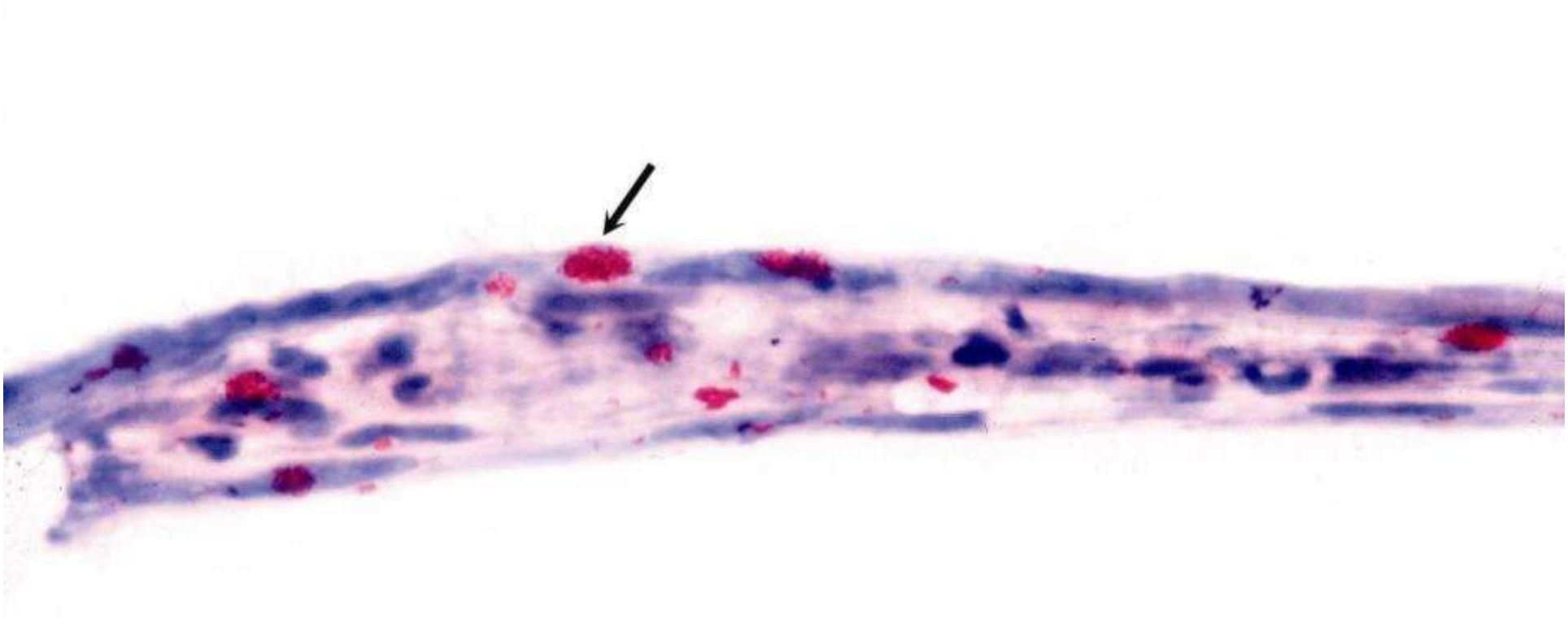
Information Gained by Nerve Biopsy

- Neuropathic
  - axonal degeneration vs. segmental demyelination vs. other
  - density of nerve fibers
  - size of fibers involved: large myelinated, small myelinated or unmyelinated
  - spatial pattern: diffuse, focal or multifocal

Information Gained by Nerve Biopsy

- Interstitial Pathology
  - inflammatory demyelinating (AIDP, CIDP)
  - large vessel necrotizing vasculitis
  - small vessel vasculitis (microvasculitis)
  - granuloma
  - ischemic injury (perineurial thickening, neovascularization, injury neuroma)
  - infiltrative pathology (amyloidosis, lymphoma, tumor, etc.)
  - infectious (leprosy, etc.)

Leprosy
(acid fast bacilli, Fite stain)



From: Dyck et al, Greenfield's Neuropathology 7th ed., 2002

Site of Nerve Biopsy

- Selecting the appropriate site is the most important first step.
- If an unaffected nerve is biopsied, a diagnosis probably cannot be made.
- For symmetric sensorimotor polyneuropathy, a sural may be most appropriate.

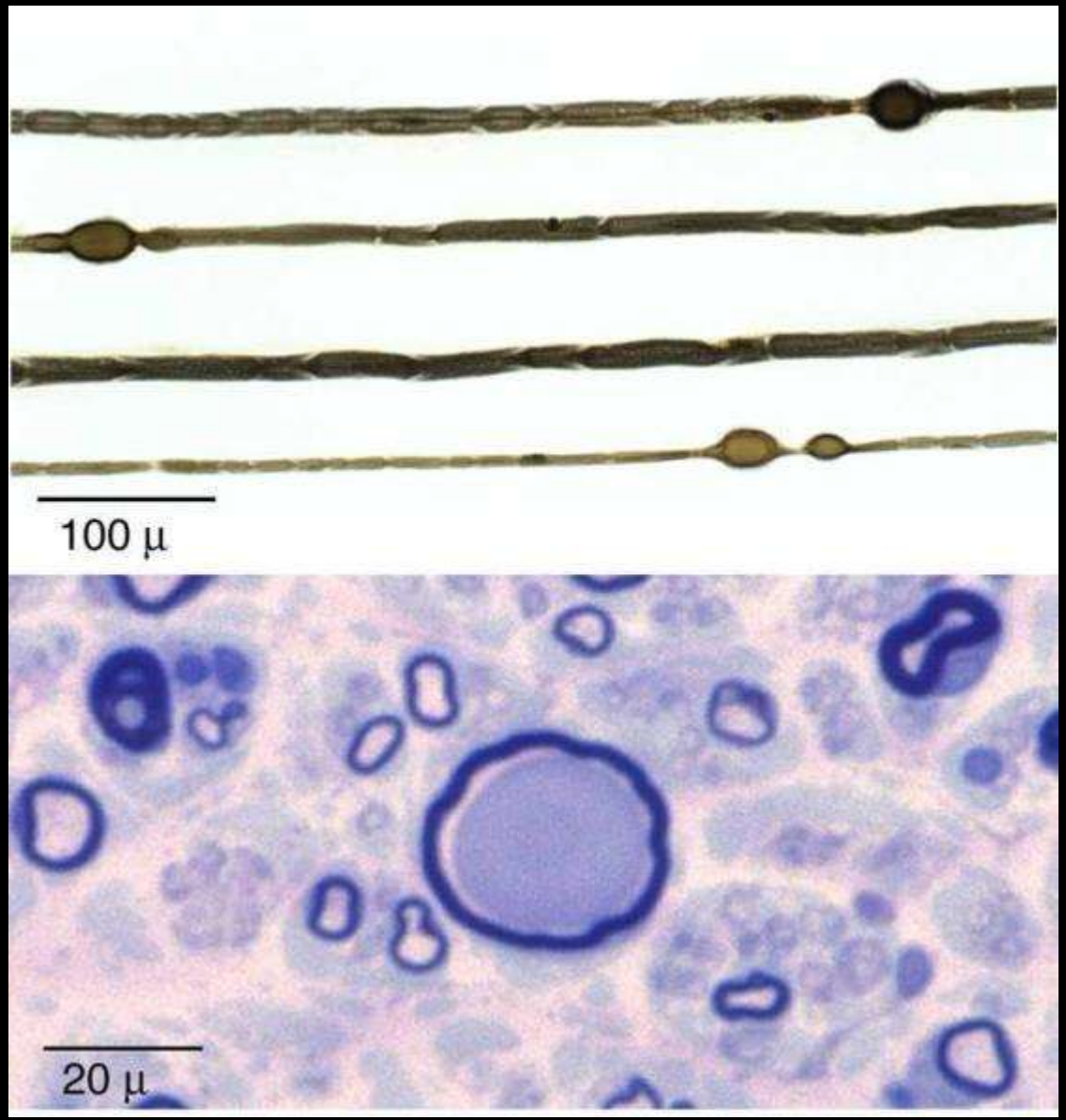
Site of Nerve Biopsy

- Whole vs. fascicular nerve
- Cutaneous (sensory) vs. mixed (motor and sensory)
- Most biopsies are taken from a whole distal cutaneous nerve since most neuropathies are length-dependent.
- With improved imaging (MRI), fascicular nerve biopsies from focal nerve lesions are now possible.

Specific Pathological Findings

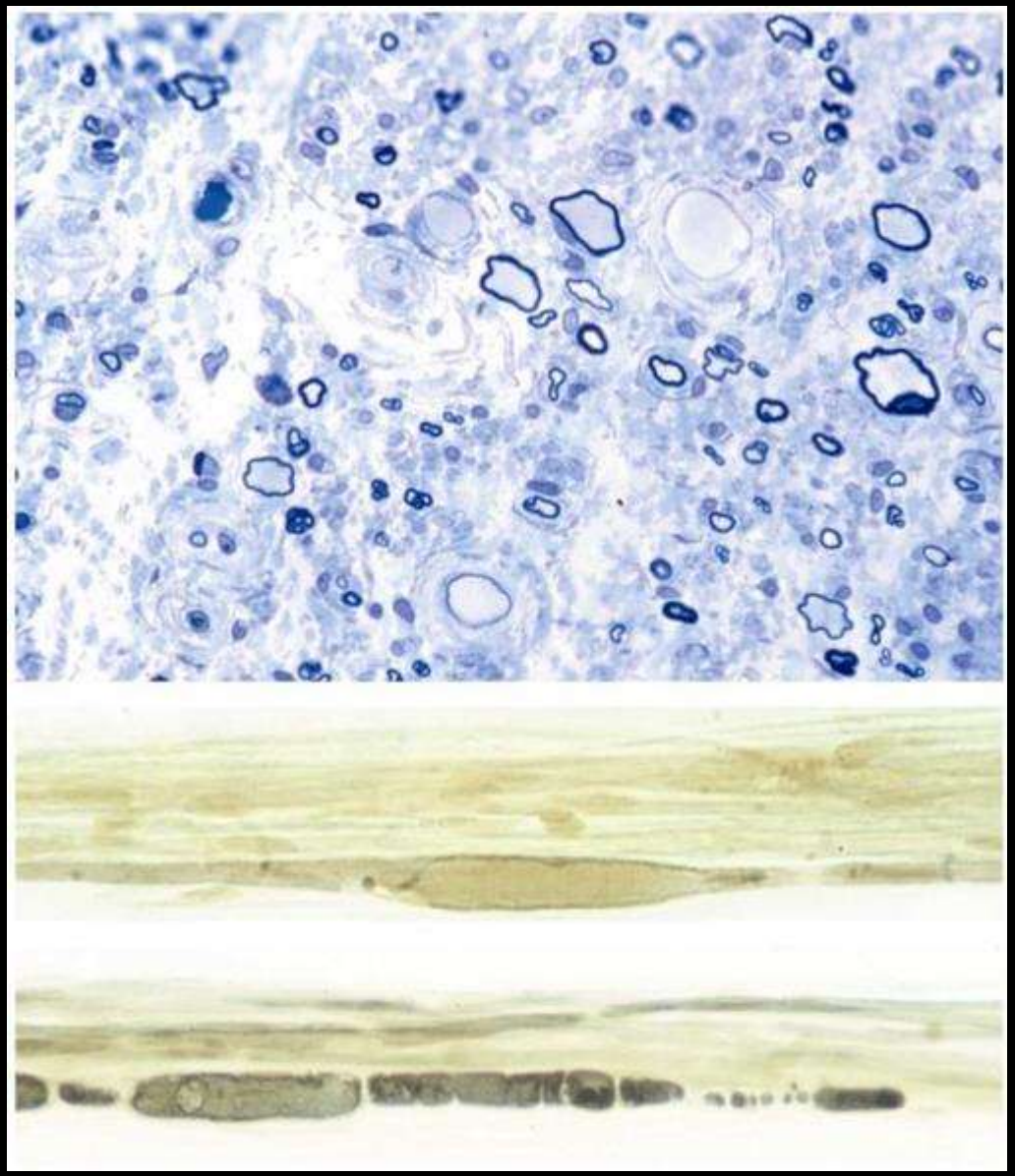
- Some conditions have stereotypic pathological patterns
  - Polyglucosan body disease
  - Axonal spheroids
    - neuroaxonal dystrophy
    - hexacarbon toxicity
    - acrylamide toxicity
  - Giant axonal dystrophy
  - Lysosomal enzyme related alterations
    - MLD
    - Fabry
    - Tangier

Polyglucosan Disease - Adult Onset



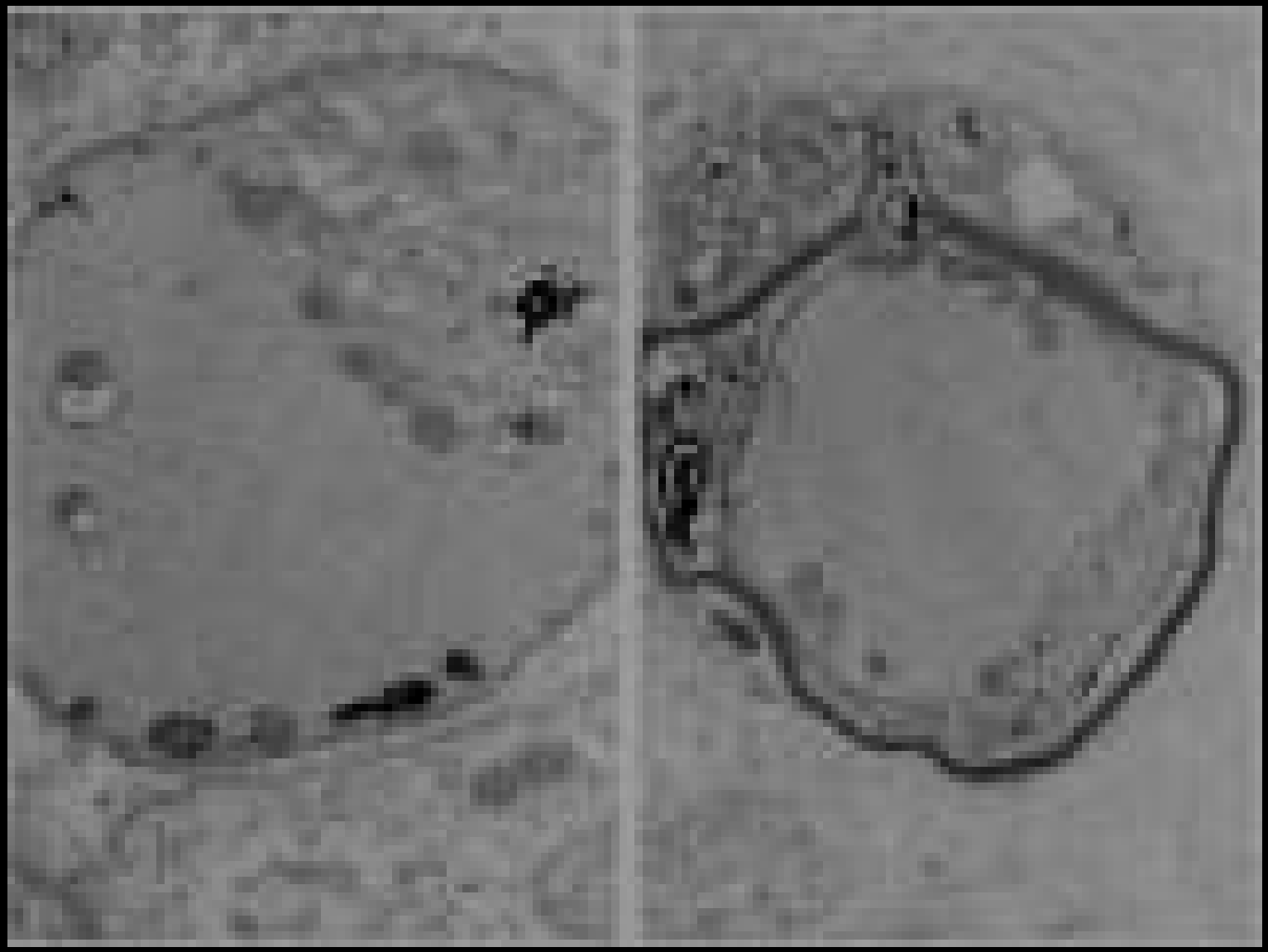
From: Klein et al, Muscle & Nerve, 2004

Giant Axonal Neuropathy



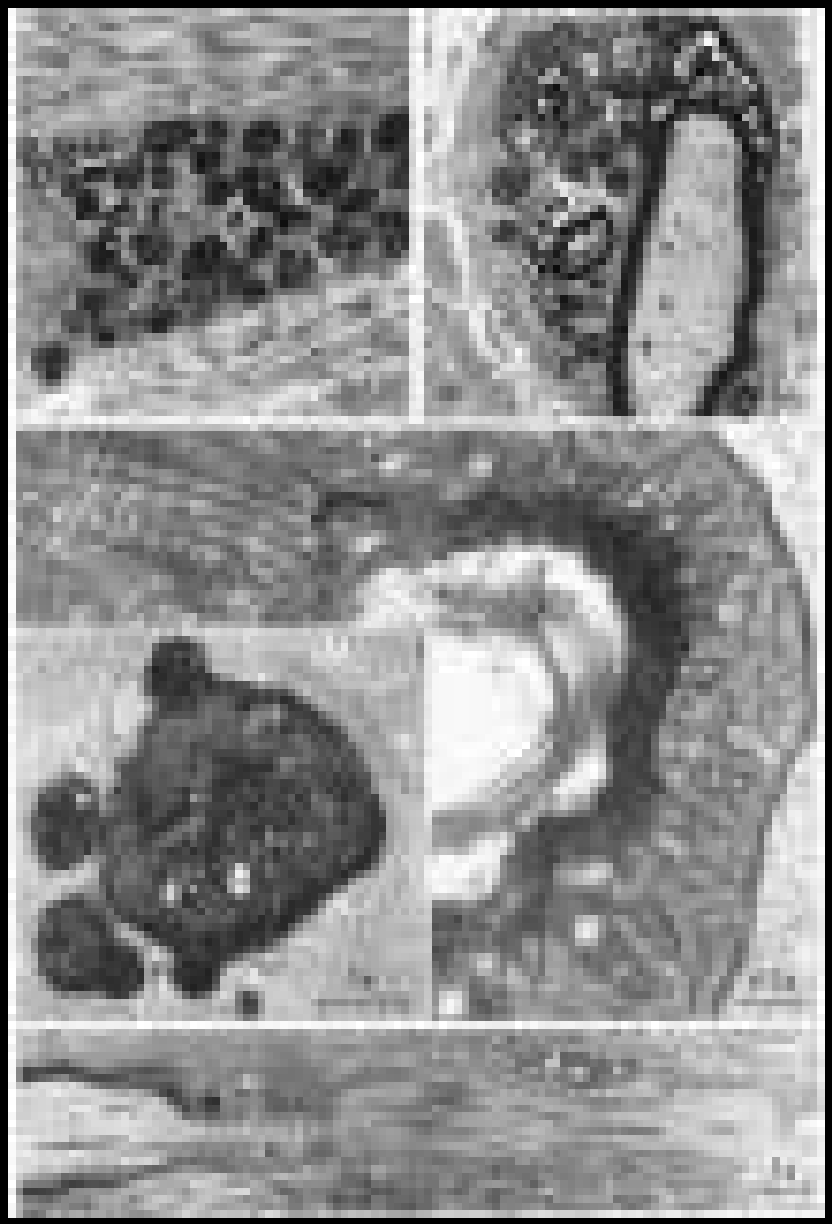
From: Dyck et al, Greenfield's Neuropathology 7th ed., 2002

Giant Axonal Neuropathy



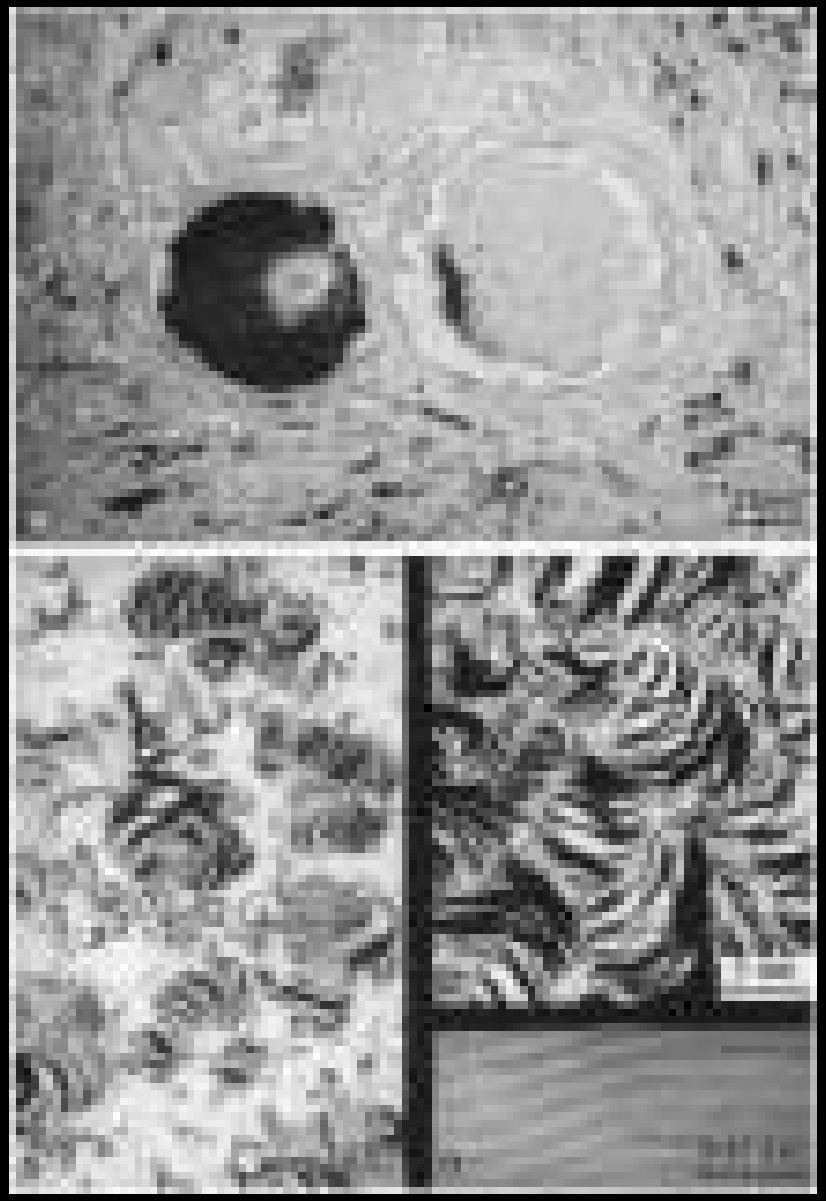
From: Dyck, Peripheral Neuropathy, 2nd ed., 1984

Metachromatic Leukodystrophy



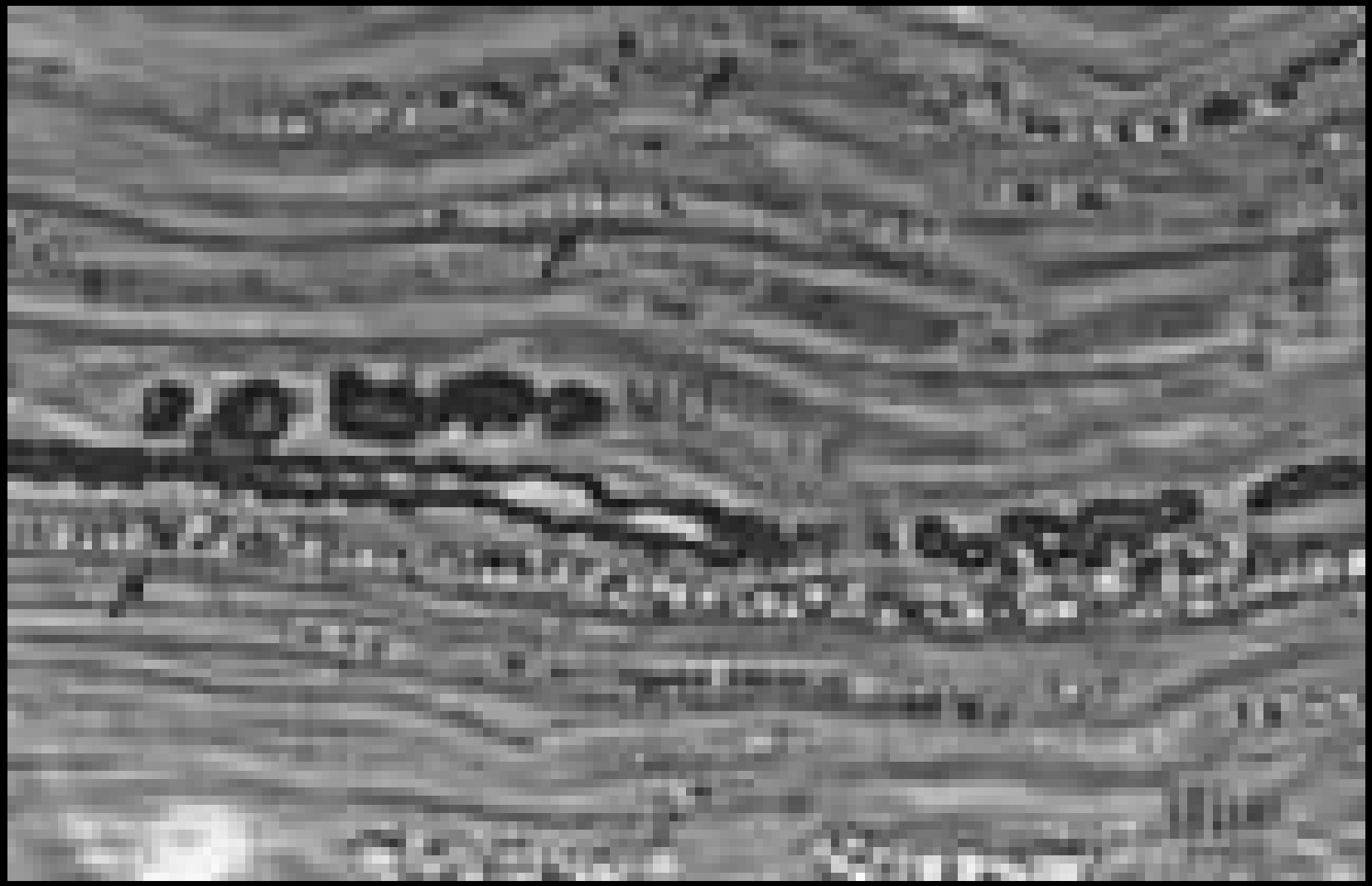
From: Dyck, New developments in electromyography and clinical neurophysiology, 1973

Fabry Disease



From: Ohnishi & Dyck, Archives of Neurology, 1974

Tangier Disease



From: Dyck et al, Journal of Neuropathology & Experimental Neurology, 1978

Comparing NCS/EMG and Nerve Biopsy

- NCS/EMG
  - provides information about largest axons only (Aαβ fibers), and not about the other fiber classes (gamma, delta, drC and sympathetic C)
  - provides information about a group of fibers (a volley) and not about individual fibers
  - can be performed on many nerves throughout the body - large sampling
  - studies are easily repeated to assess disease progression

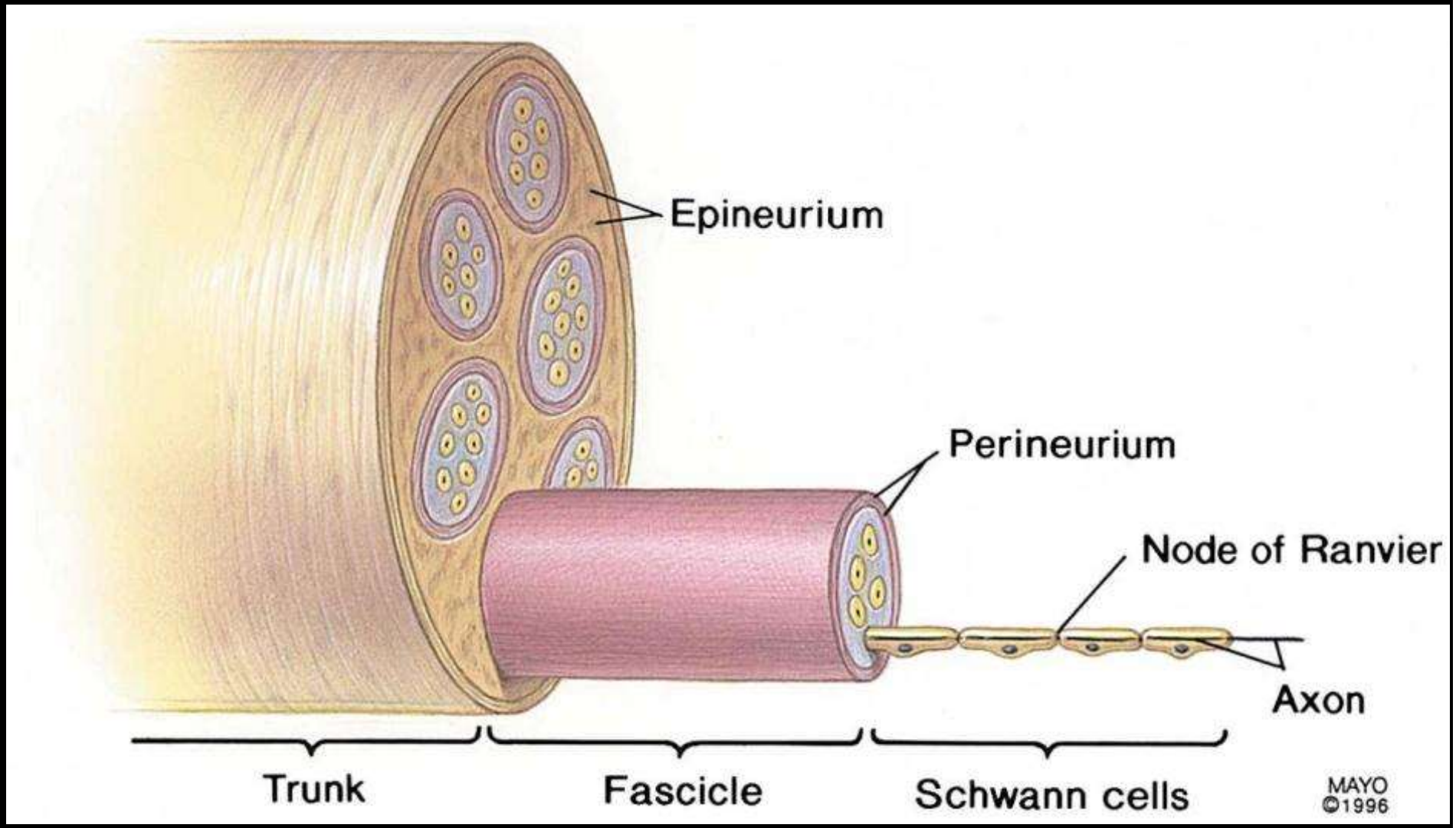
Comparing NCS/EMG and Nerve Biopsy

- Nerve Biopsy
  - provides information about all classes of nerve fibers (large and small myelinated, unmyelinated)
  - provides information about all cells (not just neurons) and sub-cellular structure
  - provides information about disconnected fibers and sprouts
  - limited to a small anatomical region
  - not easily repeatable

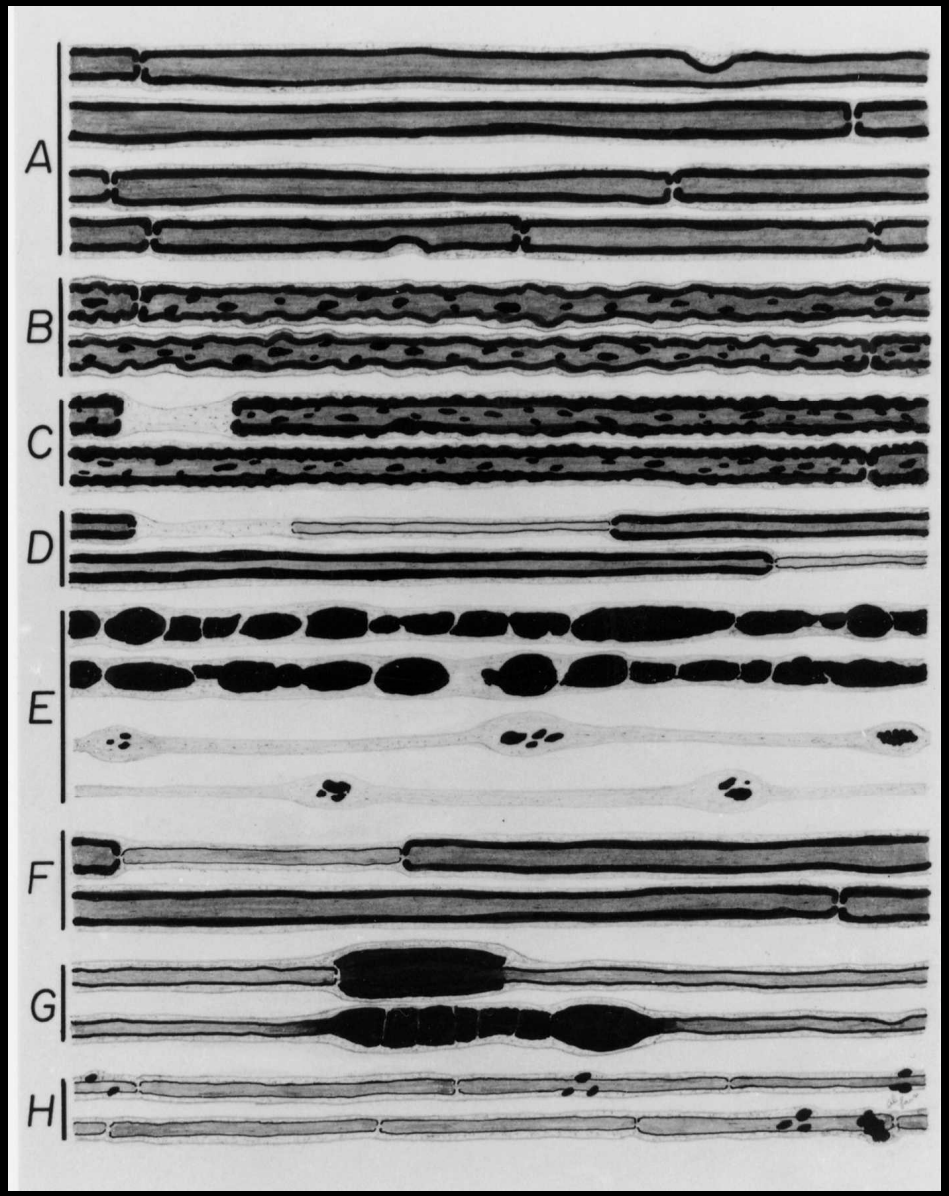
Utility of Nerve Biopsy

- Carefully selected cases
- Properly processed without artifact
- Sufficient preparations available
  - teased (most important in judging pathology for individual fibers)
  - paraffin
  - epoxy
  - immunohistochemistry
  - electron microscopy
- Access to other specialized pathologists (hematopathologists, neuropathologists, etc.)

Nerve Anatomy



Teased Fiber Conditions



A: normal

B: myelin wrinkling

C: segmental demyelination

D: segmental demyelination and remyelination

E: axonal degeneration

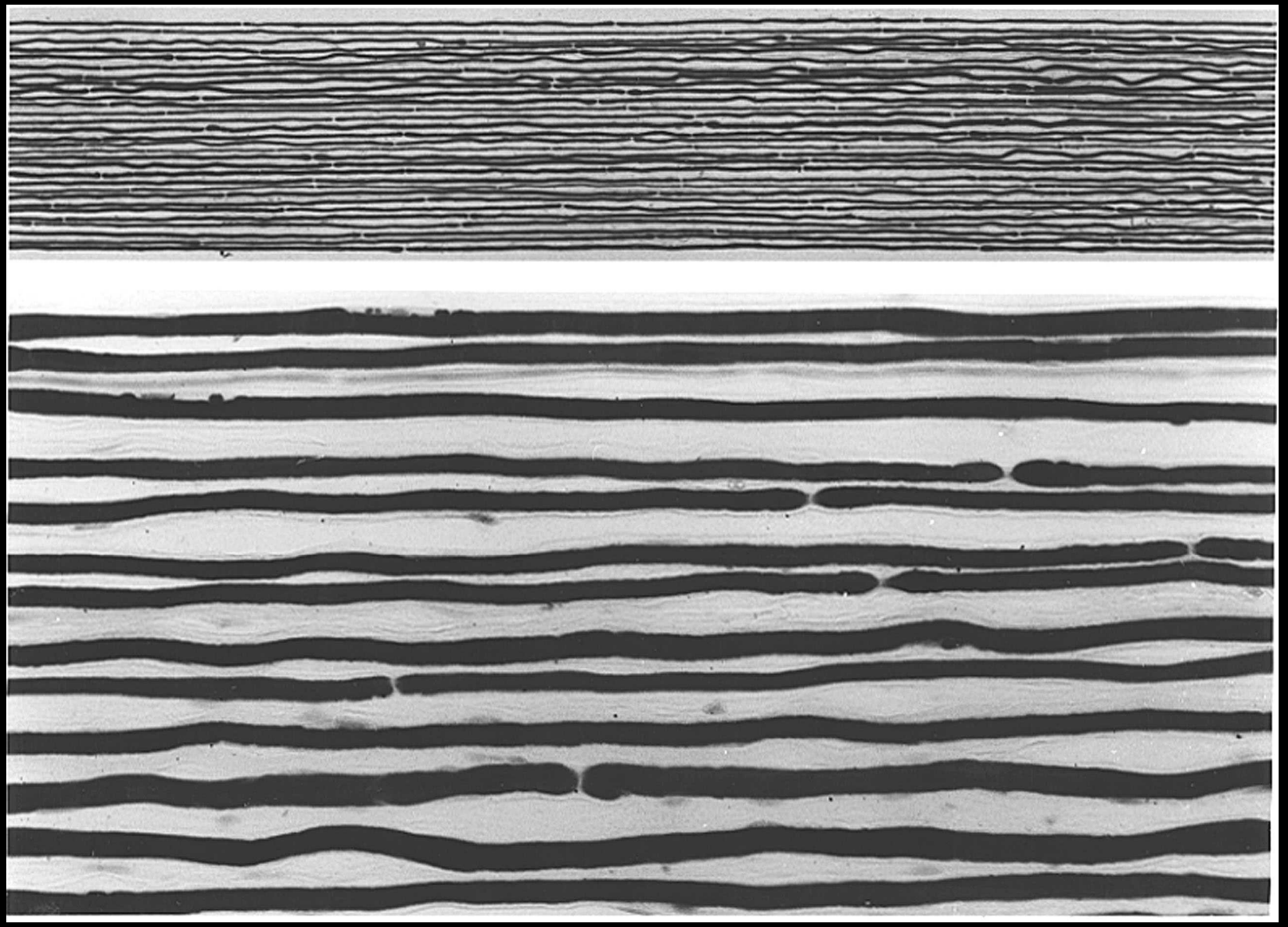
F: remyelination

G: tomacula

H: regeneration after axonal degeneration

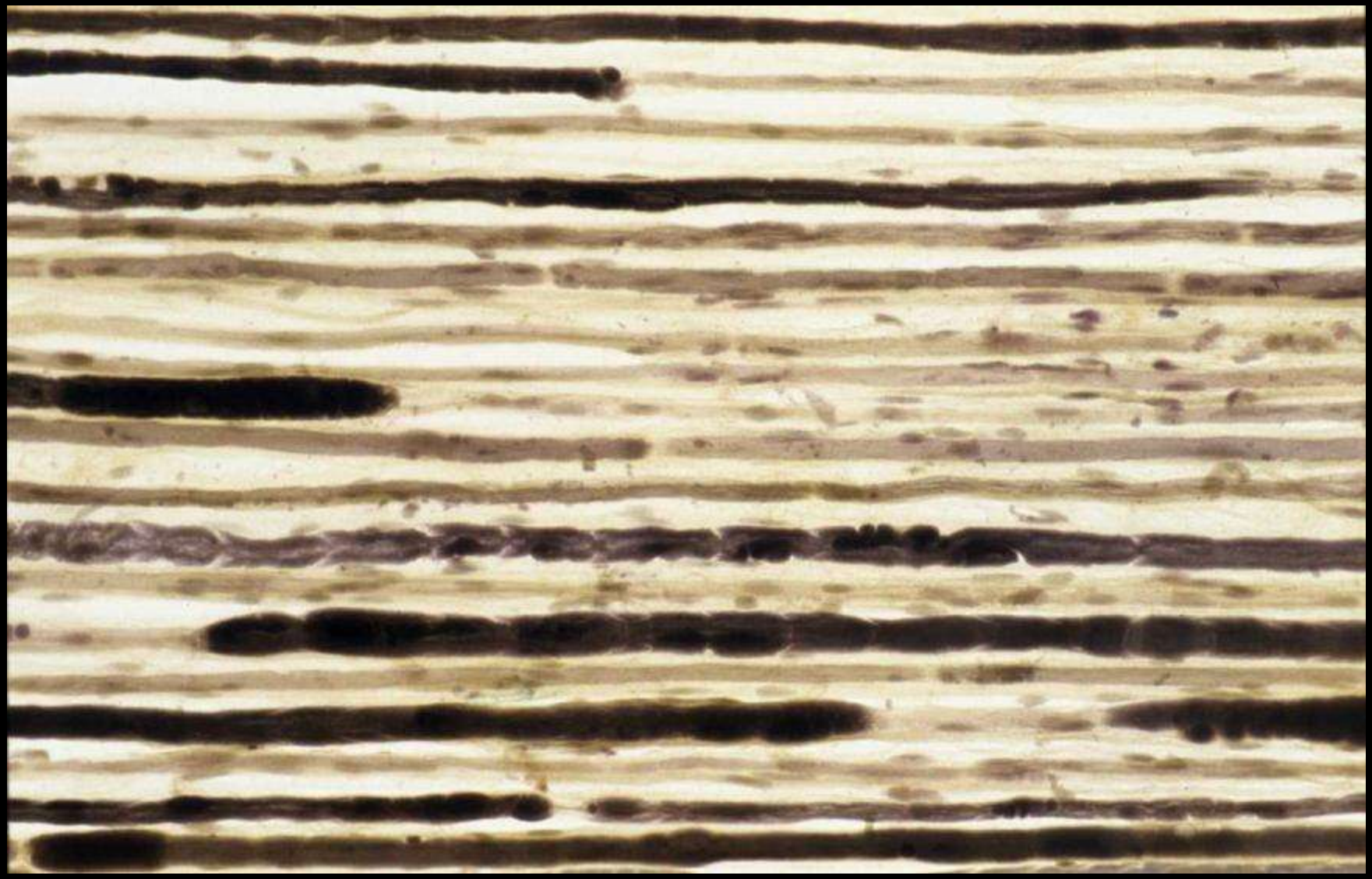
From: Dyck et al, Neurology, 1975

Teased Fibers - Condition A (normal)



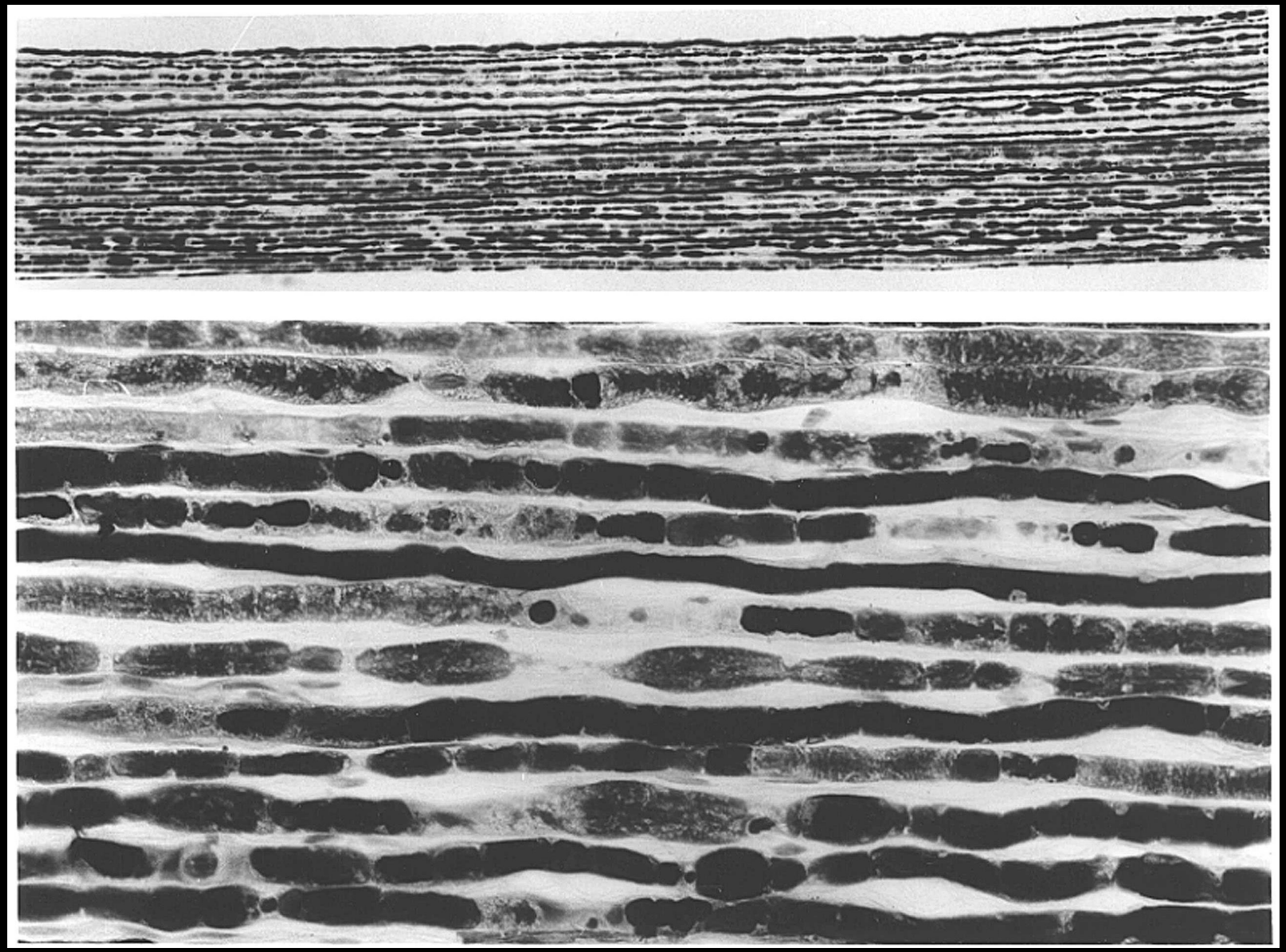
From: Dyck et al, Greenfield's Neuropathology 7th ed., 2002

Teased Fibers - Condition C and D
(segmental demyelination and remyelination)



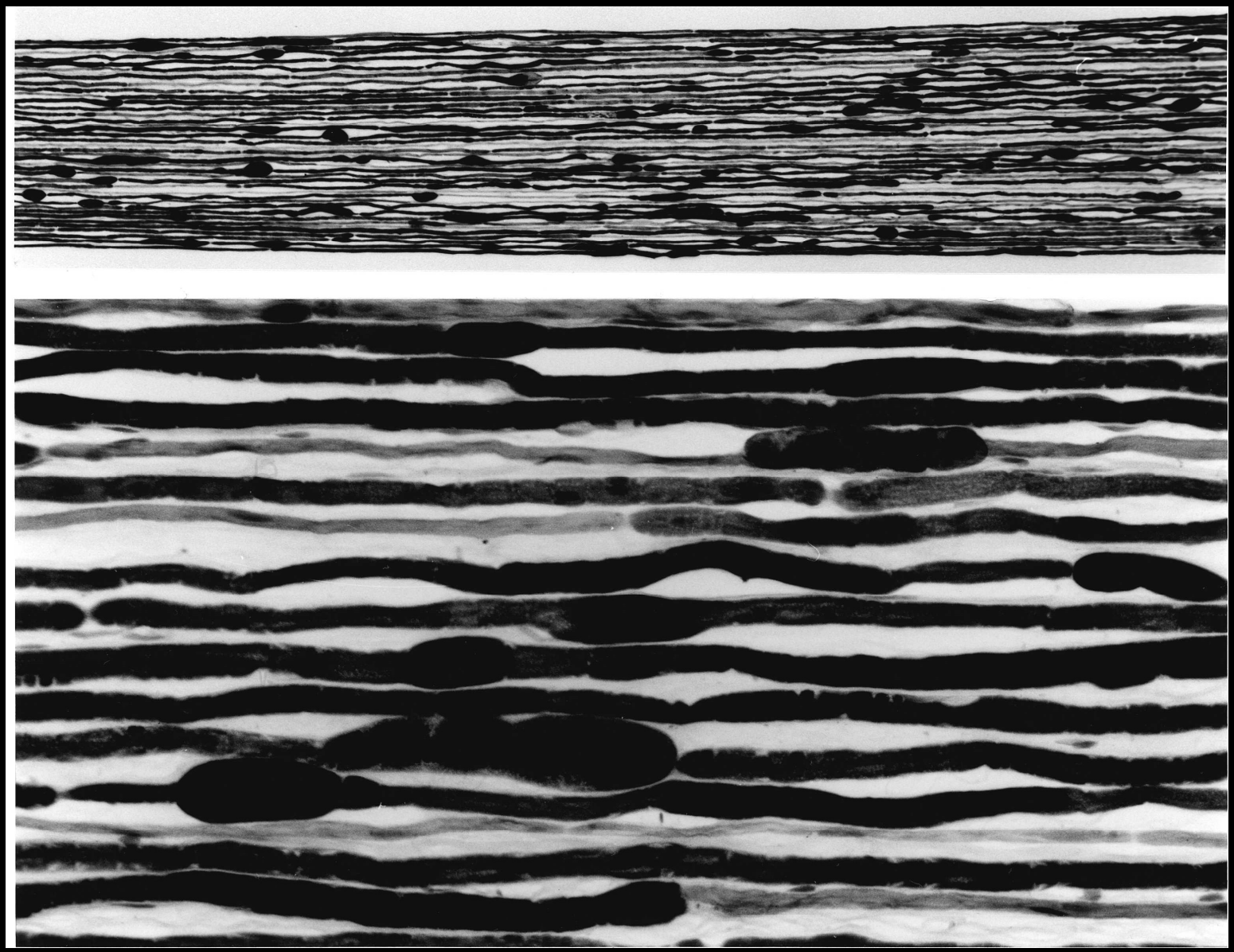
From: Dyck et al, Peripheral Neuropathy 4th ed., 2005

Teased Fibers - Condition E (axonal degeneration)



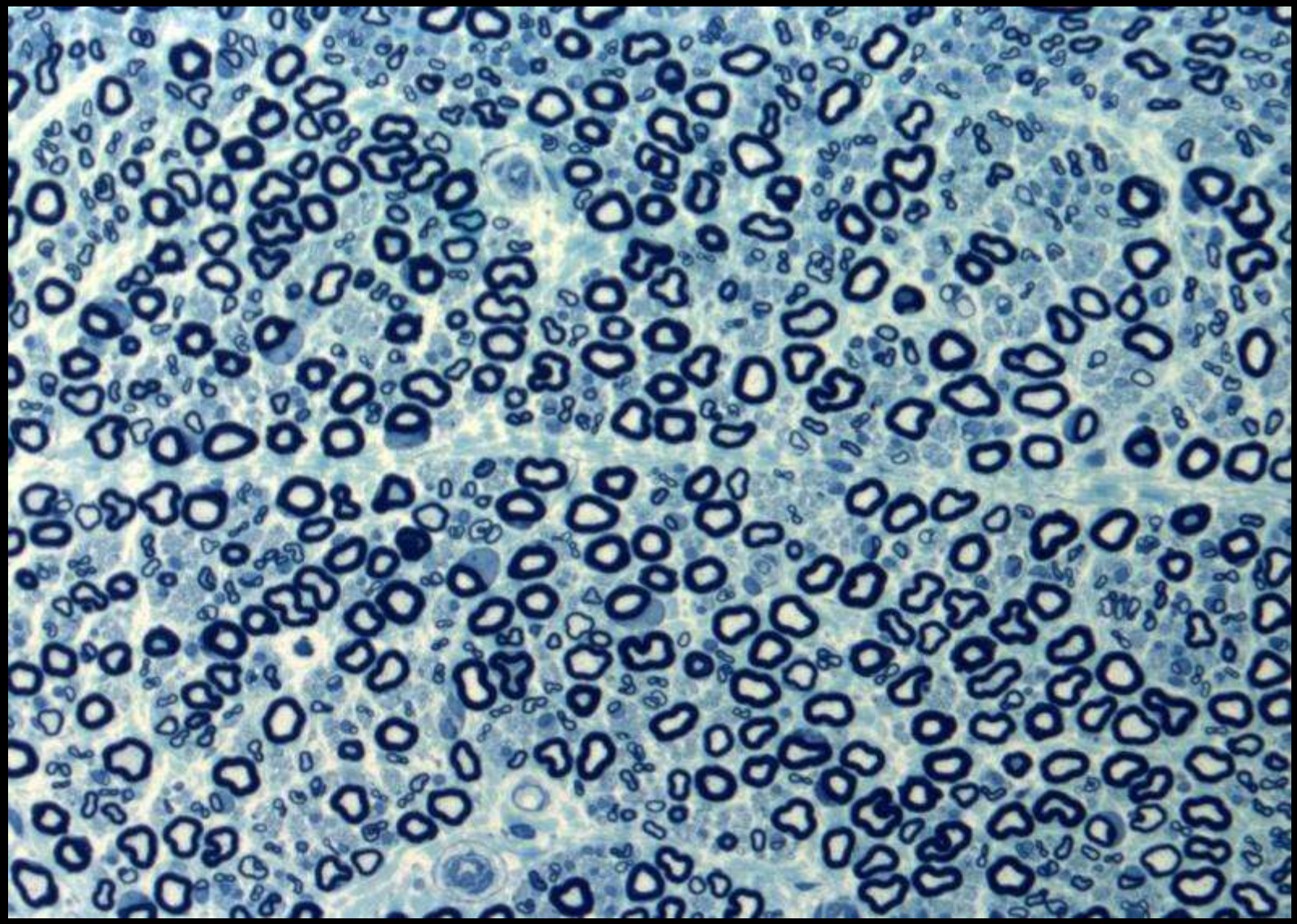
From: Dyck et al, Greenfield's Neuropathology 7th ed., 2002

Teased Fibers - Condition G (tomaculous)

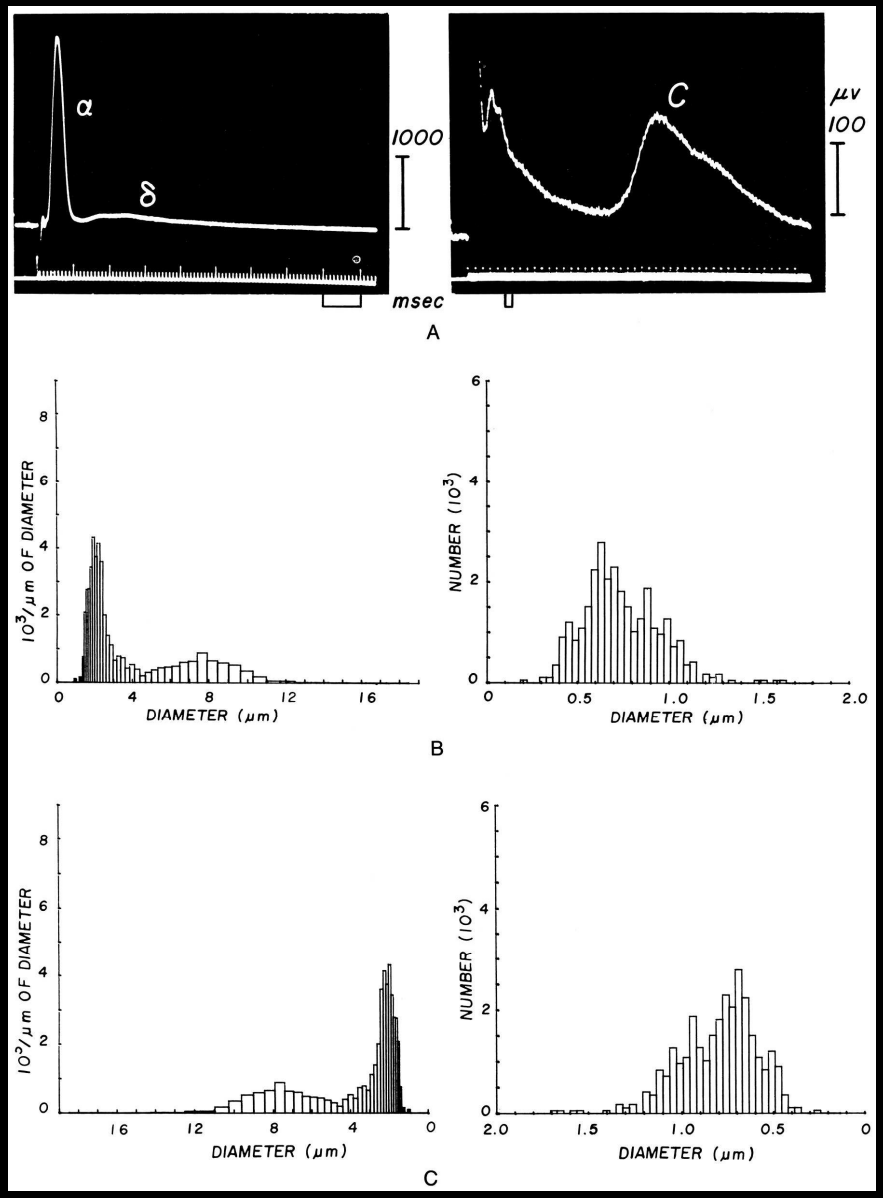


From: Dyck et al, Greenfield's Neuropathology 7th ed., 2002

Normal Nerve (bimodal distribution)
epoxy section, methylene blue



Healthy Subject



From: Lambert & Dyck, Peripheral Neuropathy 1st ed., 1975

Nerve Conduction and Underlying Fiber Alteration (3 patterns)

- Low CV and normal CMAP/SNAP
  - segmental demyelination ± remyelination
  - remyelination
  - loss of large fibers
  - fiber regeneration
- Normal CV and low CMAP/SNAP
  - decreased number of large fibers
  - axonal degeneration
- Low CV and low CMAP/SNAP
  - mixed demyelination and axonal degeneration
  - fiber regeneration
  - loss of large fibers

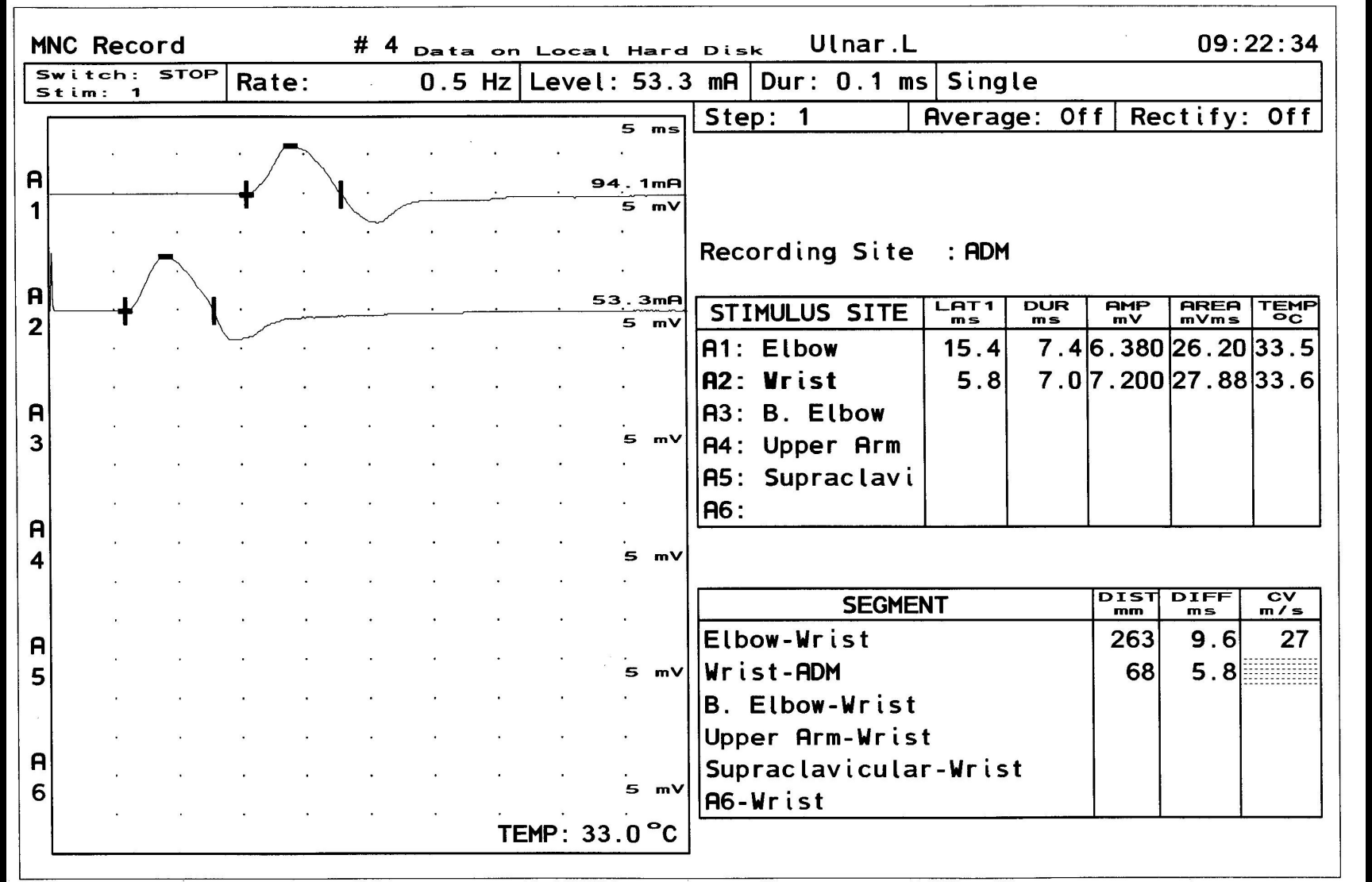
Correlation of Nerve Conduction Abnormalities and Underlying Nerve Fiber Alteration

- Low conduction velocities (normal amplitudes)
  - demyelinating conditions
  - loss of large fibers

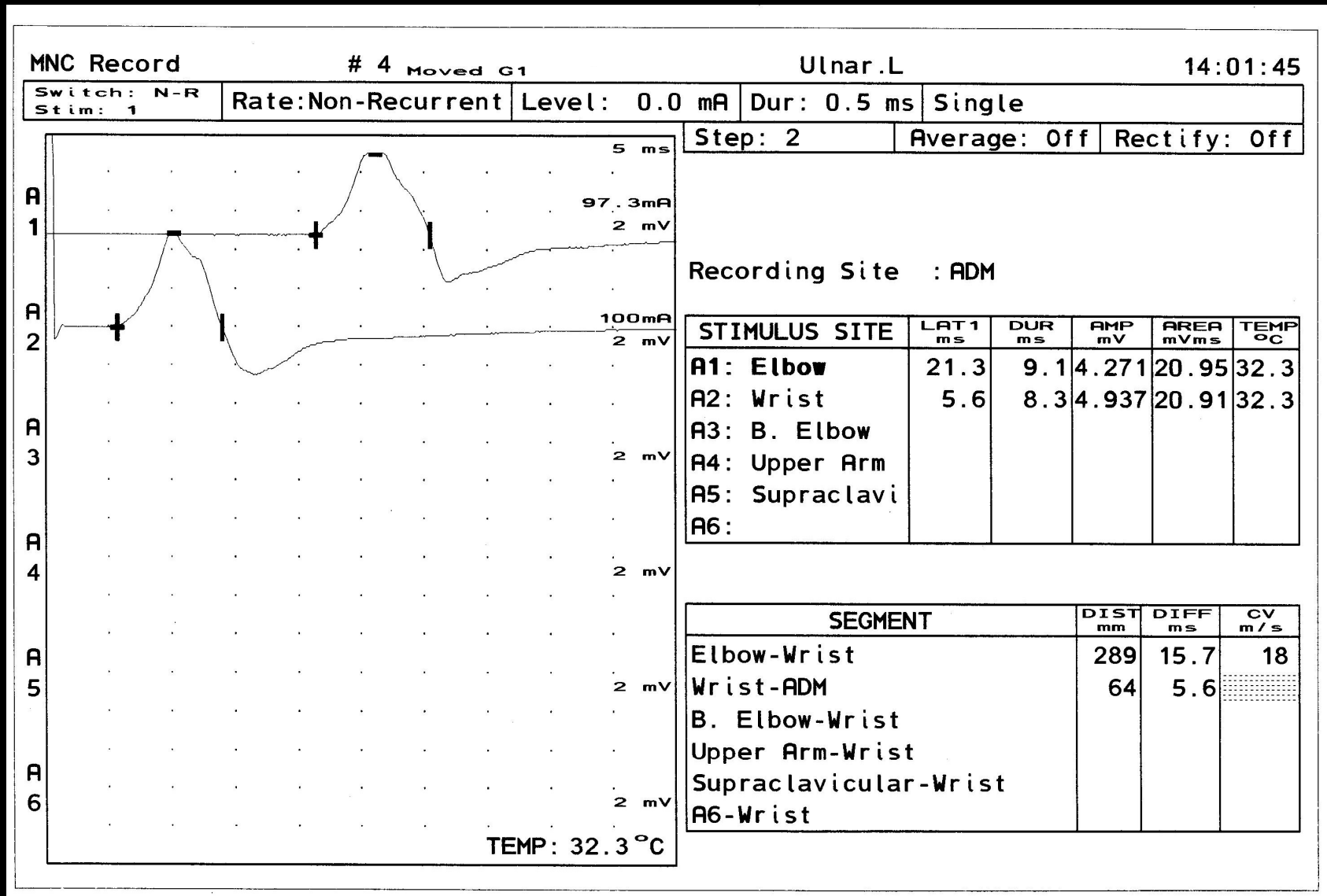
Segmental Demyelination

- Inherited
  - usually uniform slowing of CVs
  - conduction block is uncommon (exception HNPP)
- Acquired
  - temporal dispersion (unequal slowing of CVs)
  - conduction more block common
  - F-waves especially prolonged (proximal slowing)

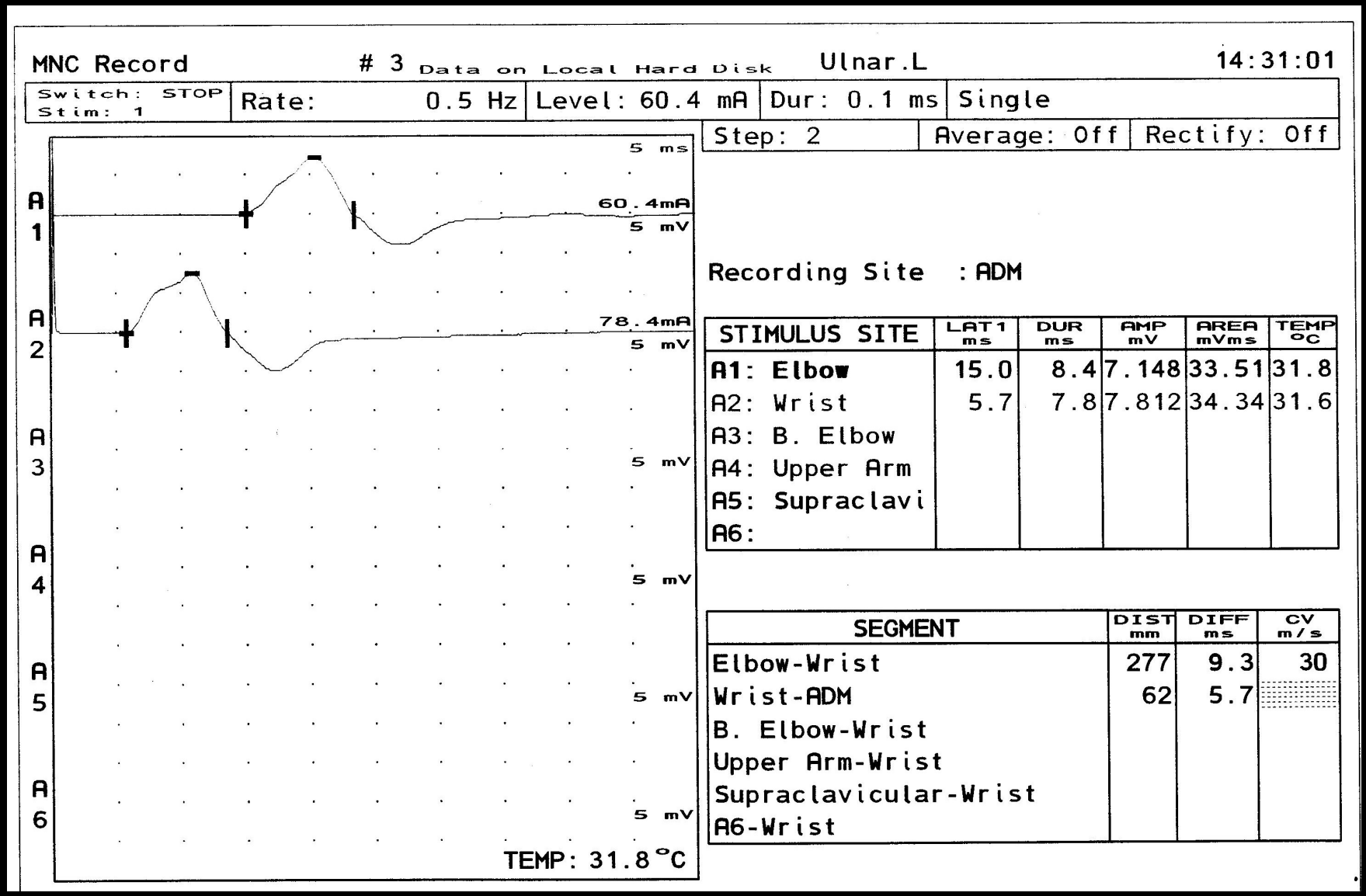
CMT-1A (HMSN-IA): uniform slowing
49 F (mother)



CMT-1A (HMSN-IA): uniform slowing
67 F (grandmother)



CMT-1A (HMSN-IA): uniform slowing
28 F (daughter)



CMT-1A (HMSN-IA)

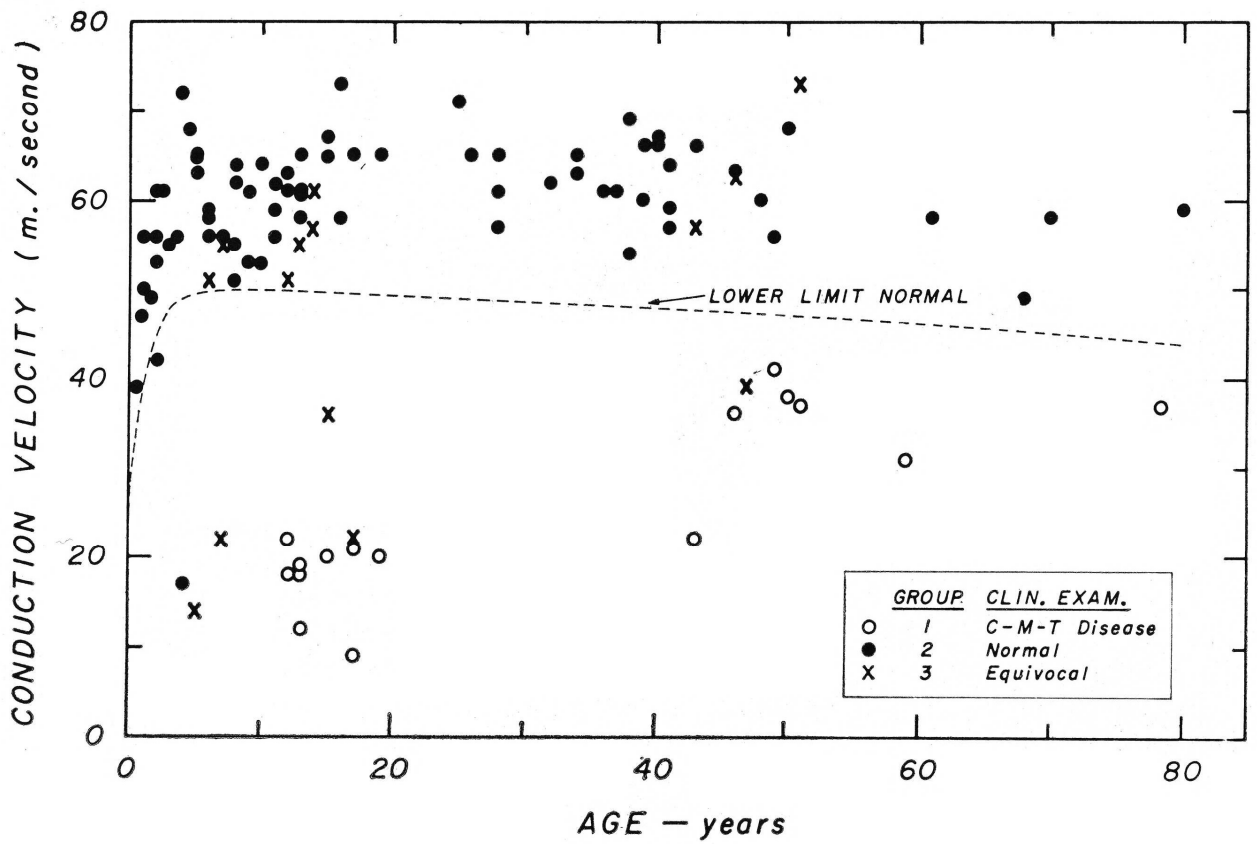
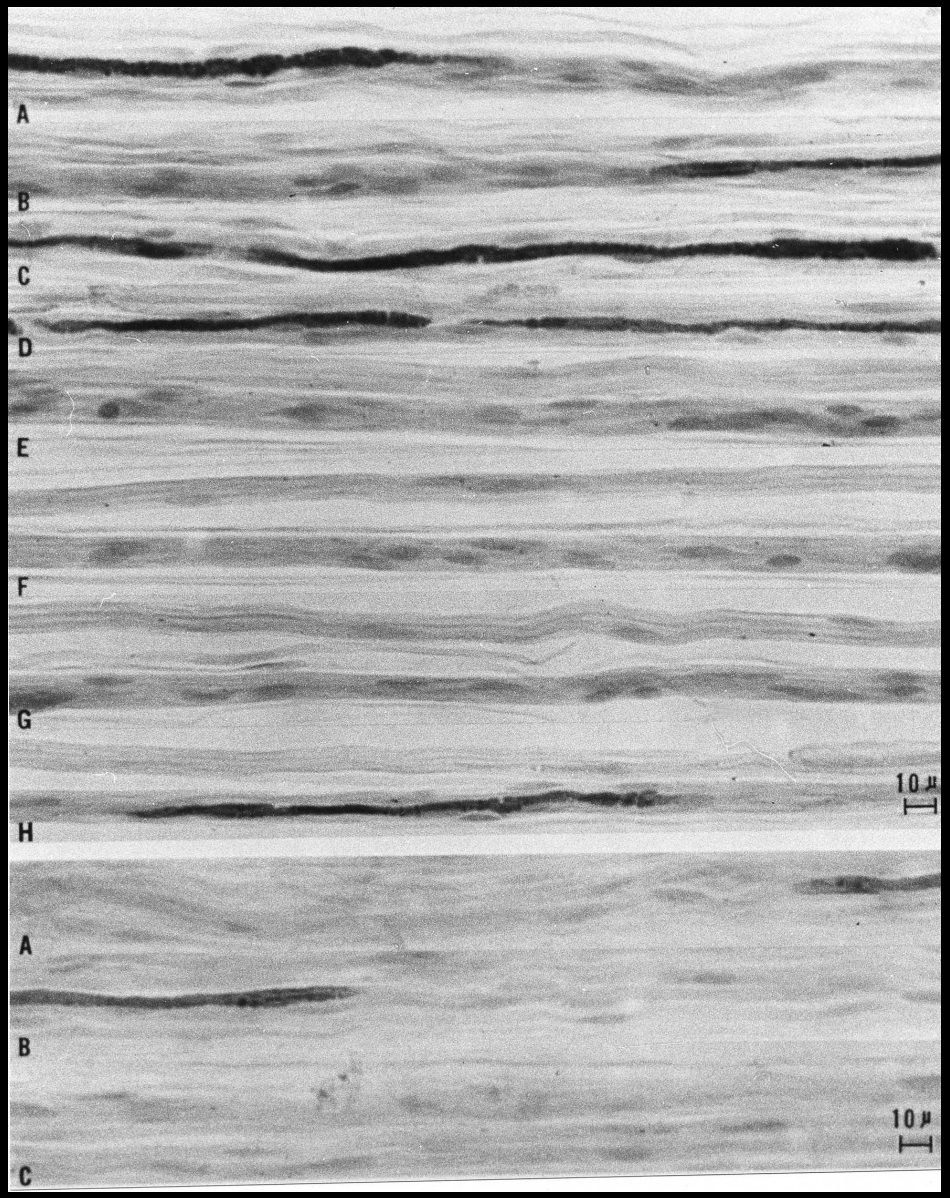


Fig. 4. Conduction velocity of motor fibers of the ulnar nerve between elbow and wrist in relation to age in the kinship studied. Each point represents 1 member of the family. The dotted line represents the lower limits of normal conduction velocity found in other studies in this laboratory. Symbols above this line represent persons with normal, those below, persons with low conduction velocities. All of the persons in group 1 (Charcot-Marie-Tooth disease diagnosed on clinical examination) had low values. Of the persons in group 2 (normal on clinical examination) only a 4-year-old boy and a 1½-year-old girl had low values. Five of 14 persons in group 3 (equivocal findings on clinical examination) had low conduction velocities.

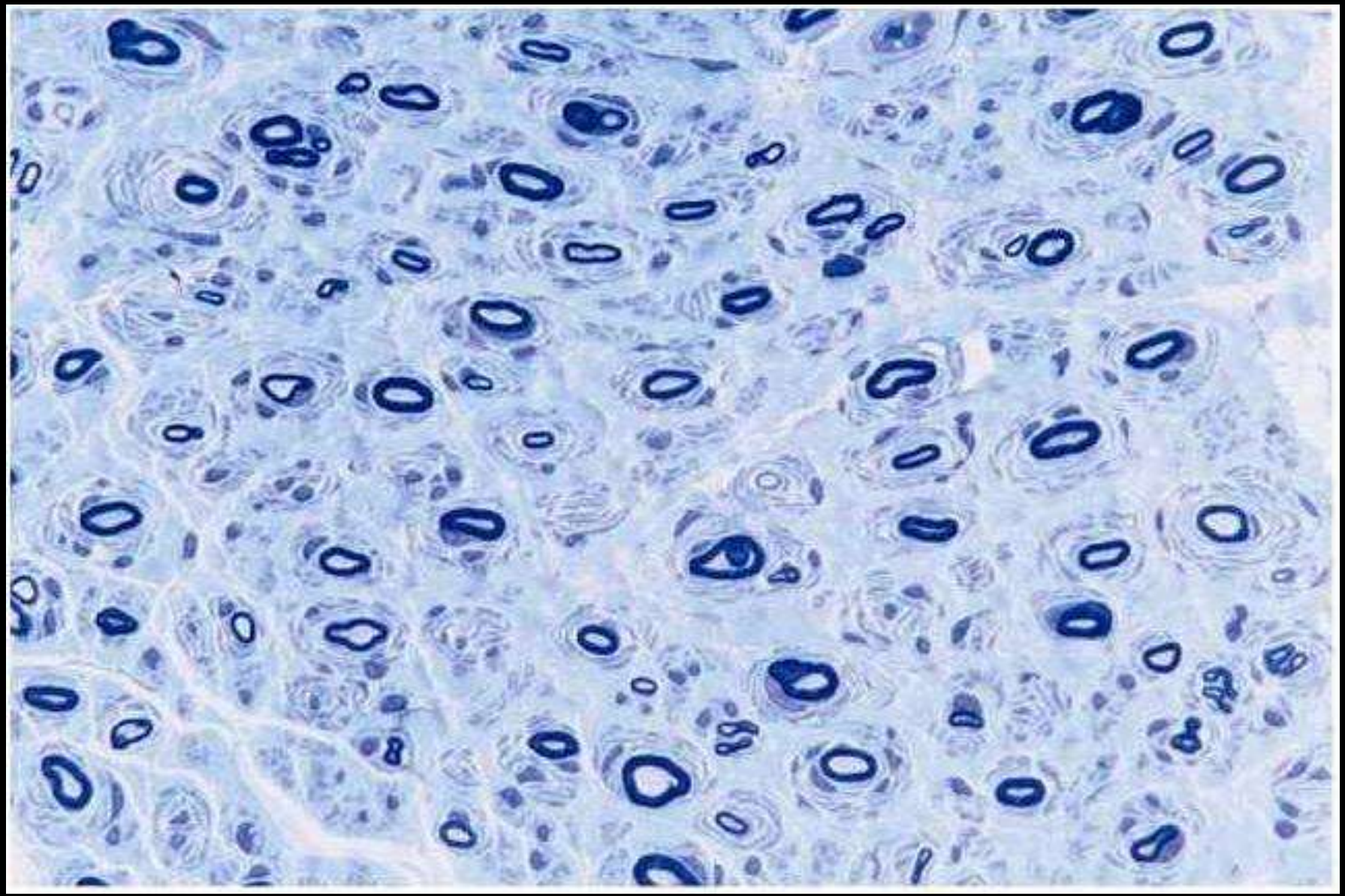
From: Dyck & Lambert et al, Neurology, 1963

CMT-1A (HMSN-IA)



From: Dyck et al, Mayo Clinic Proc., 1970

CMT-1A (HMSN-IA) (generalized pattern)



From: Dyck et al, Greenfield's Neuropathology 7th ed., 2002

Hypertrophic Inherited Neuropathy

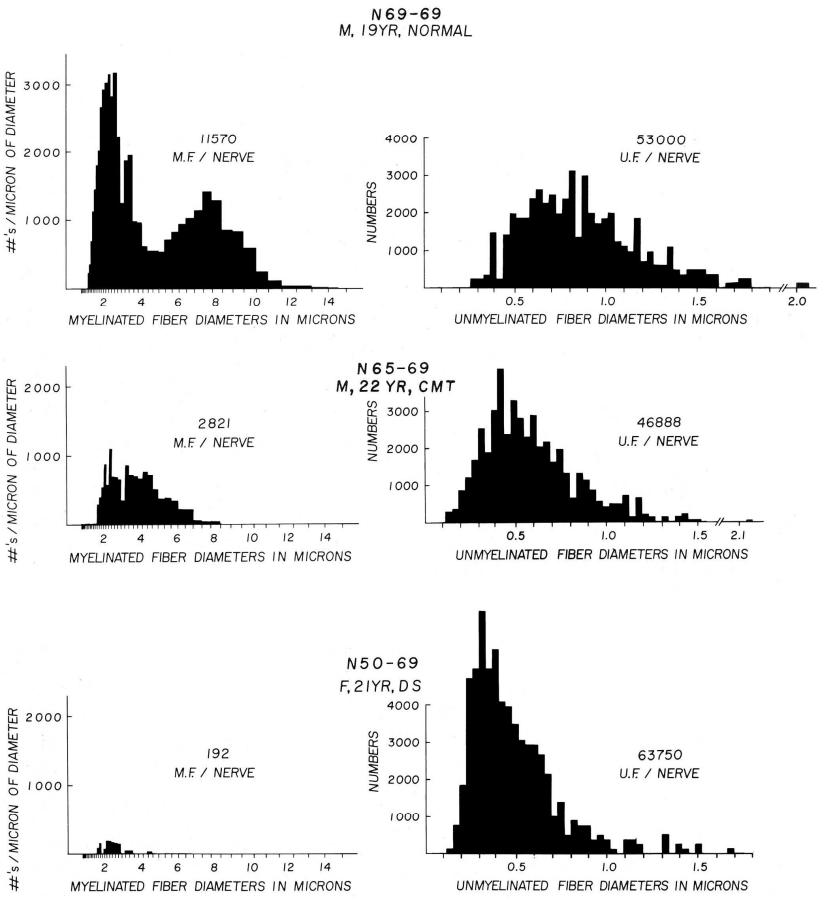


Fig. 3. Spectra of myelinated and unmyelinated fibers of healthy sural nerve of 19-year-old man *(Top)*, of sural nerve of 22-year-old man with HN-CMT *(Middle)*, and of sural nerve of 21-year-old woman with HN-DS *(Bottom)*. Note decrease in numbers and alteration in spectrum of myelinated fibers of nerve from patients. Number and spectrum of unmyelinated fibers of sural nerve of patient with HN-CMT are normal. Number of unmyelinated fibers in nerve of patient with HN-DS is slightly above normal and peak is somewhat displaced to smaller size categories.

Healthy
29 M

CMT-1A (HMSN-IA)
22 M

Dejerine-Sottas (HMSN-III)
21 F

From: Dyck et al, Mayo Clinic Proc., 1970

Dejerine-Sottas (HMSN-III)

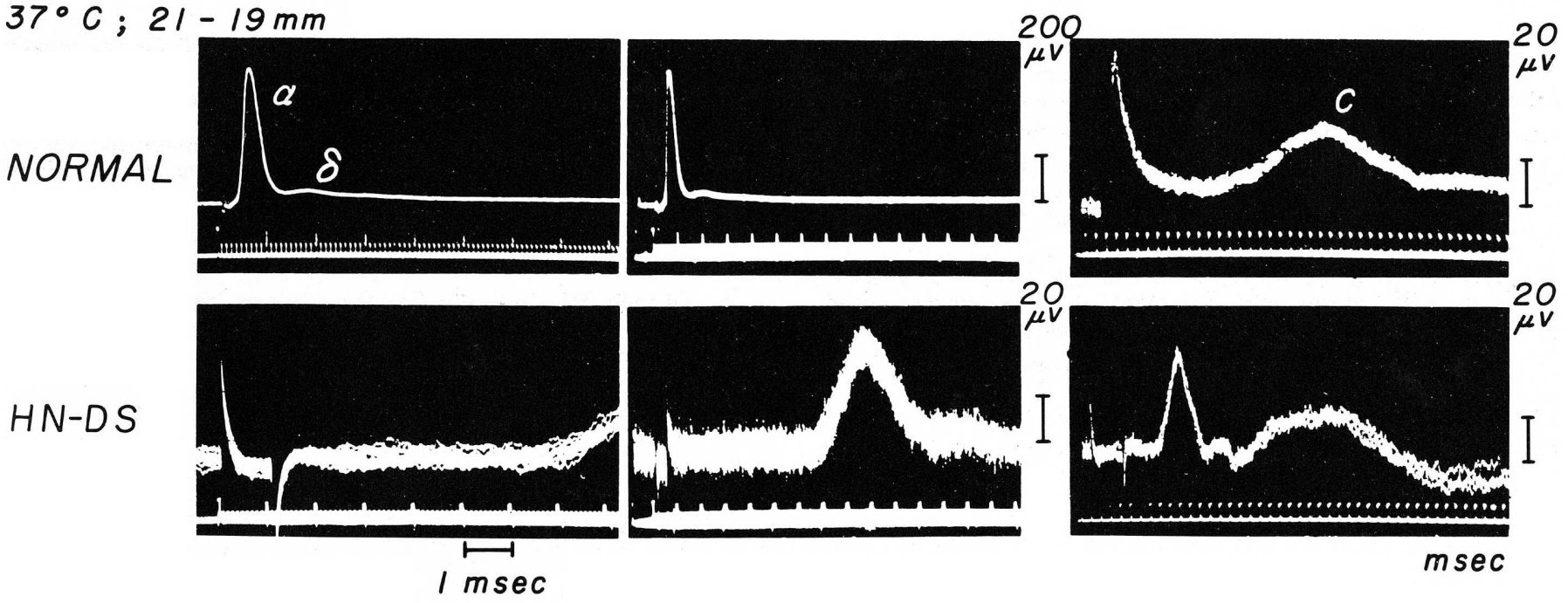
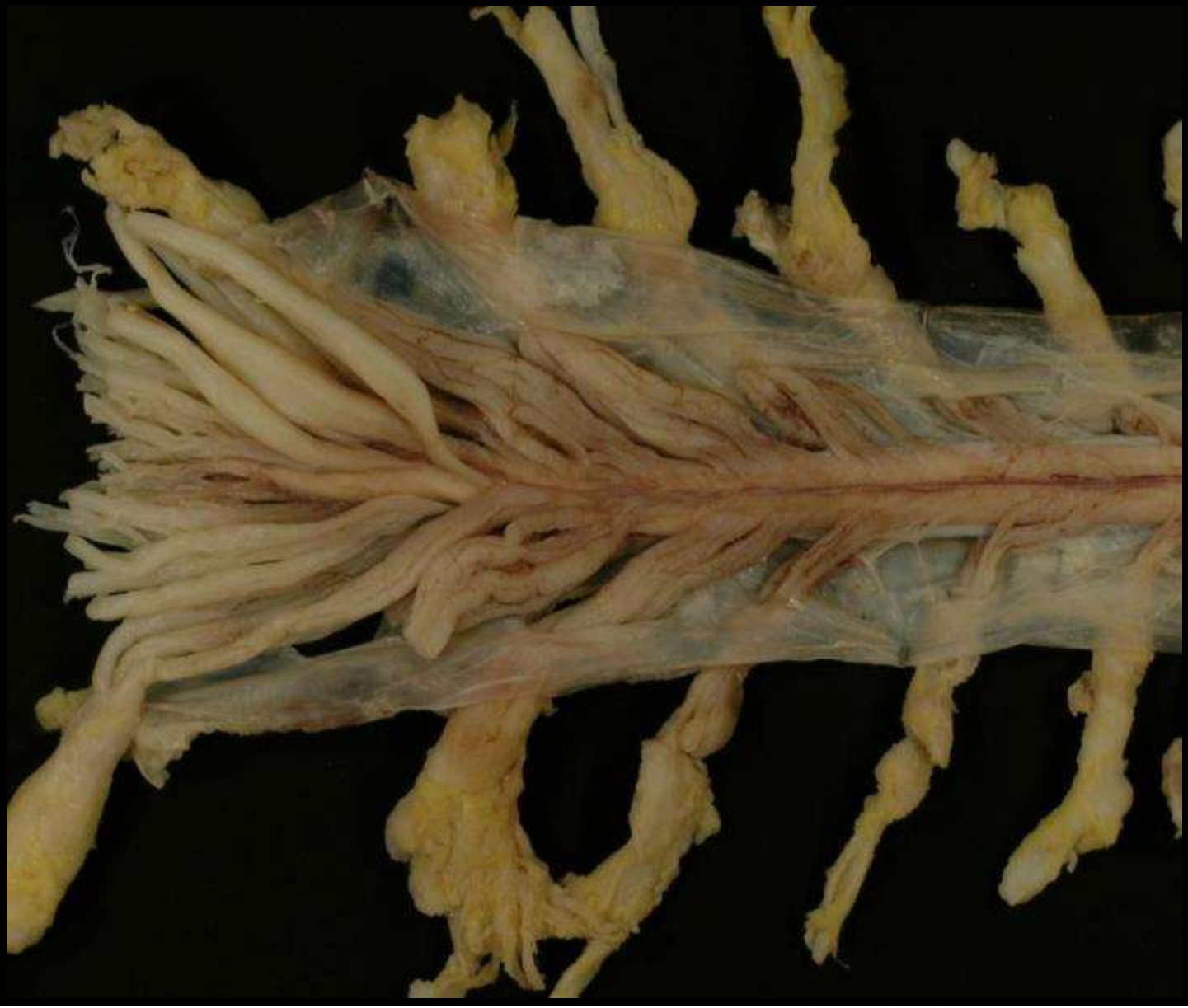


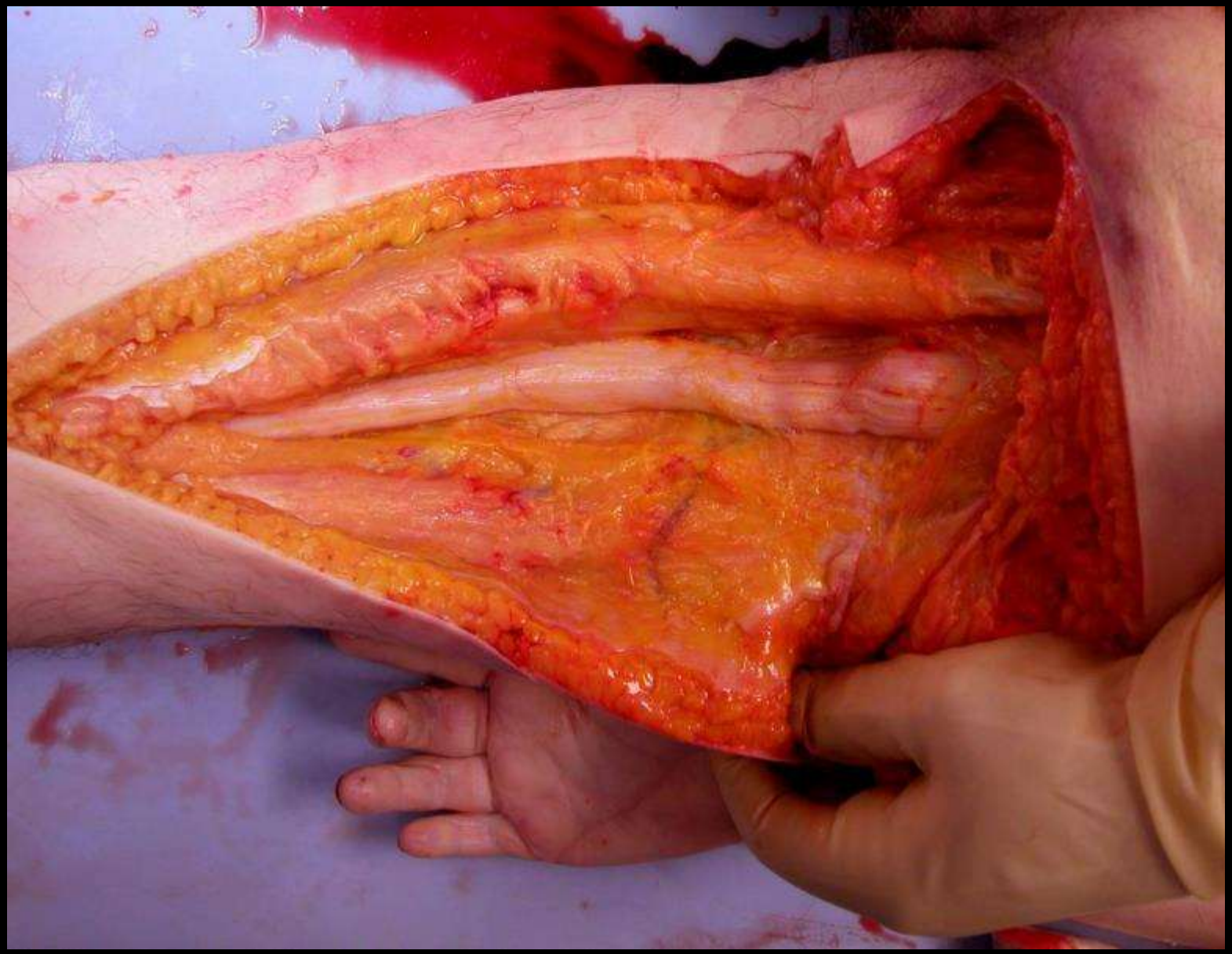
Fig. 2. Action potentials of human sural nerves in vitro.

From: Dyck & Lambert, Mayo Clinic Proc., 1971

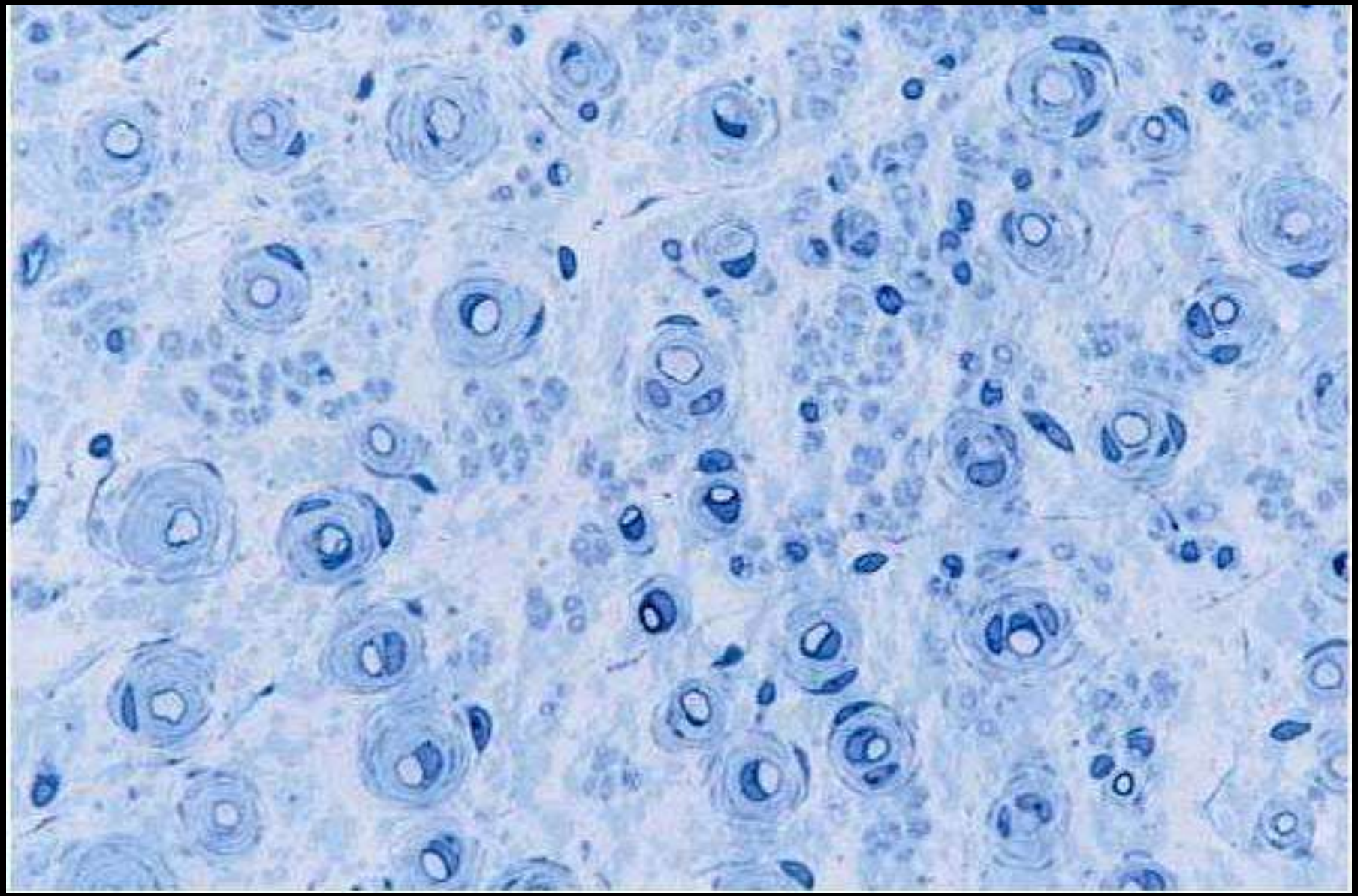
Dejerine-Sottas (HMSN-III)
Enlarged Cauda Equina



Dejerine-Sottas (HMSN-III)
Enlarged Sciatic Nerve

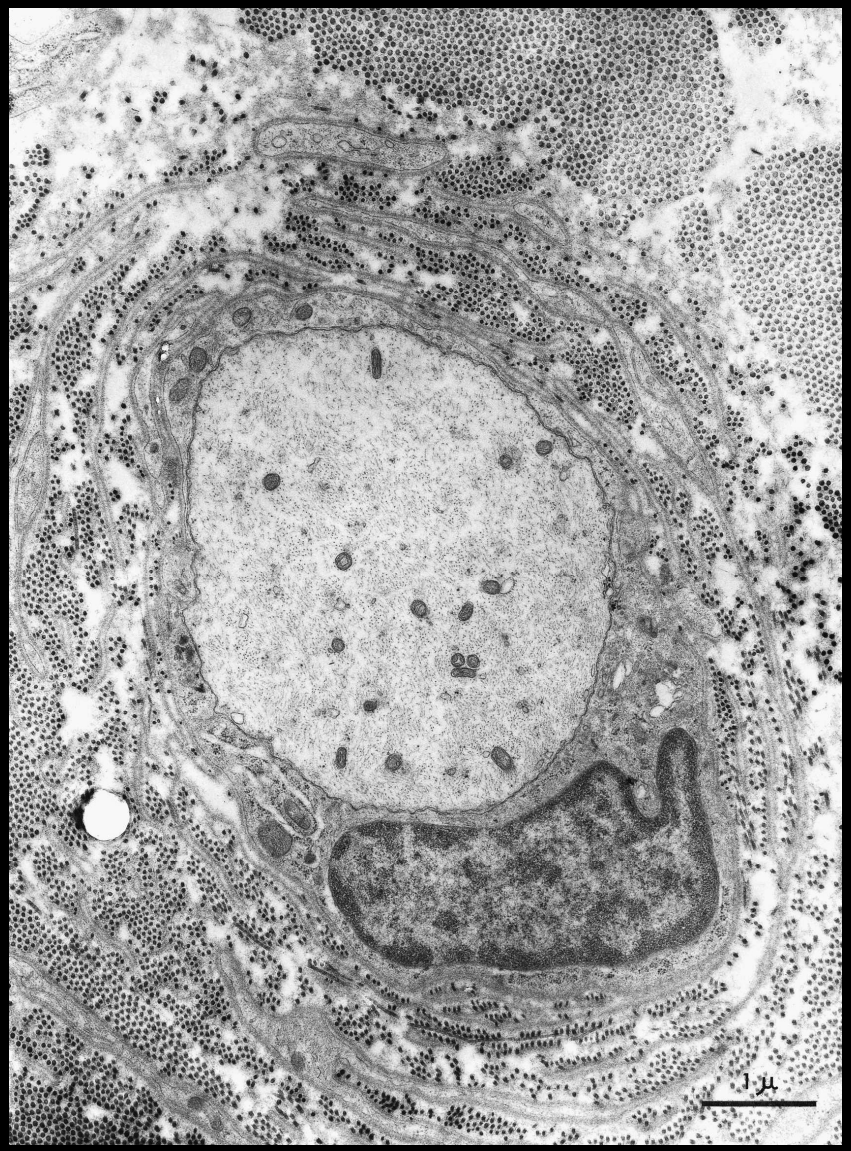


HMSN-III (generalized pattern)



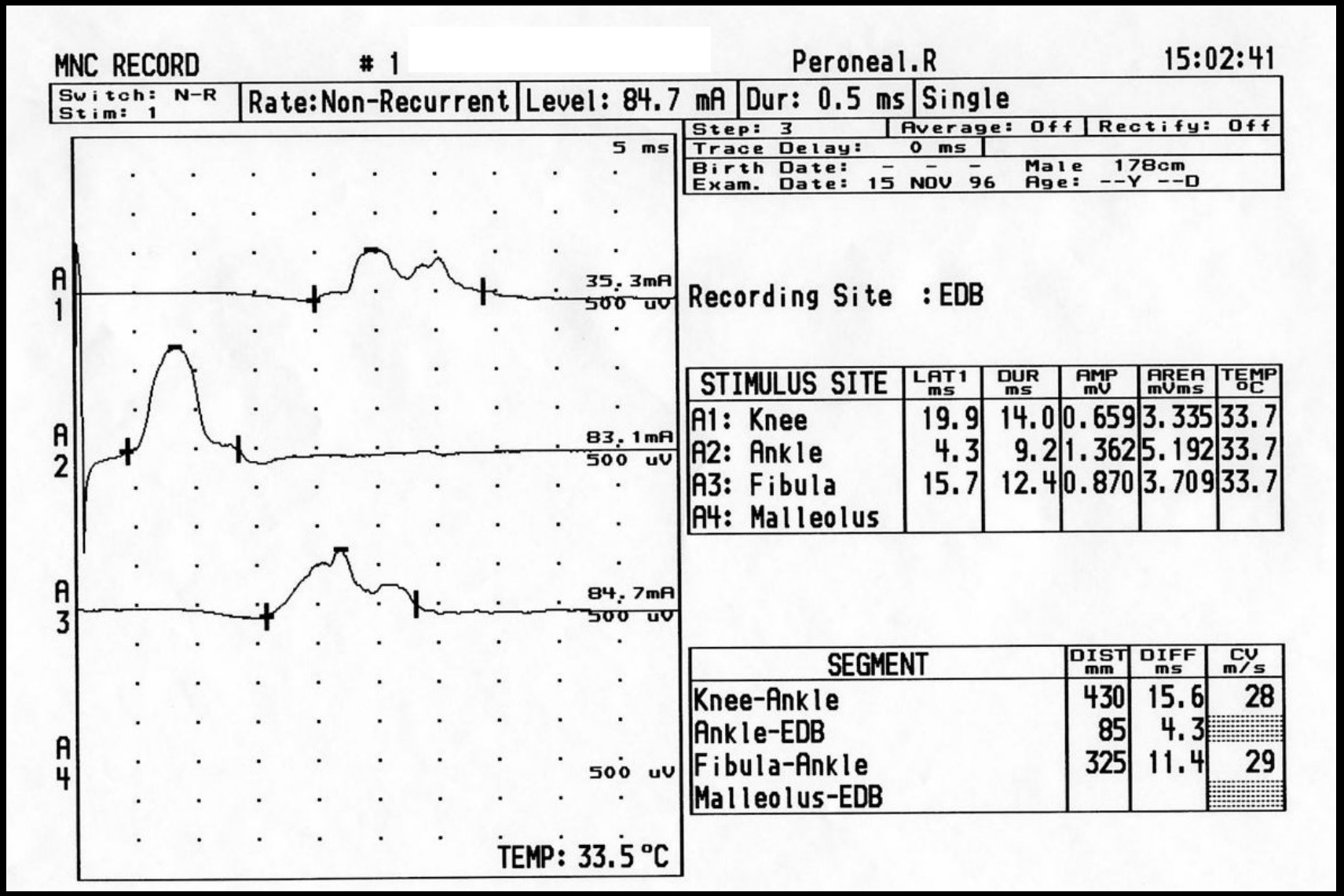
From: Dyck et al, Greenfield's Neuropathology 7th ed., 2002

Onion Bulb - Demyelinated Axon (Dejerine-Sottas, HMSN-III)



From: Dyck & Gomez, Mayo Clinic Proc., 1968

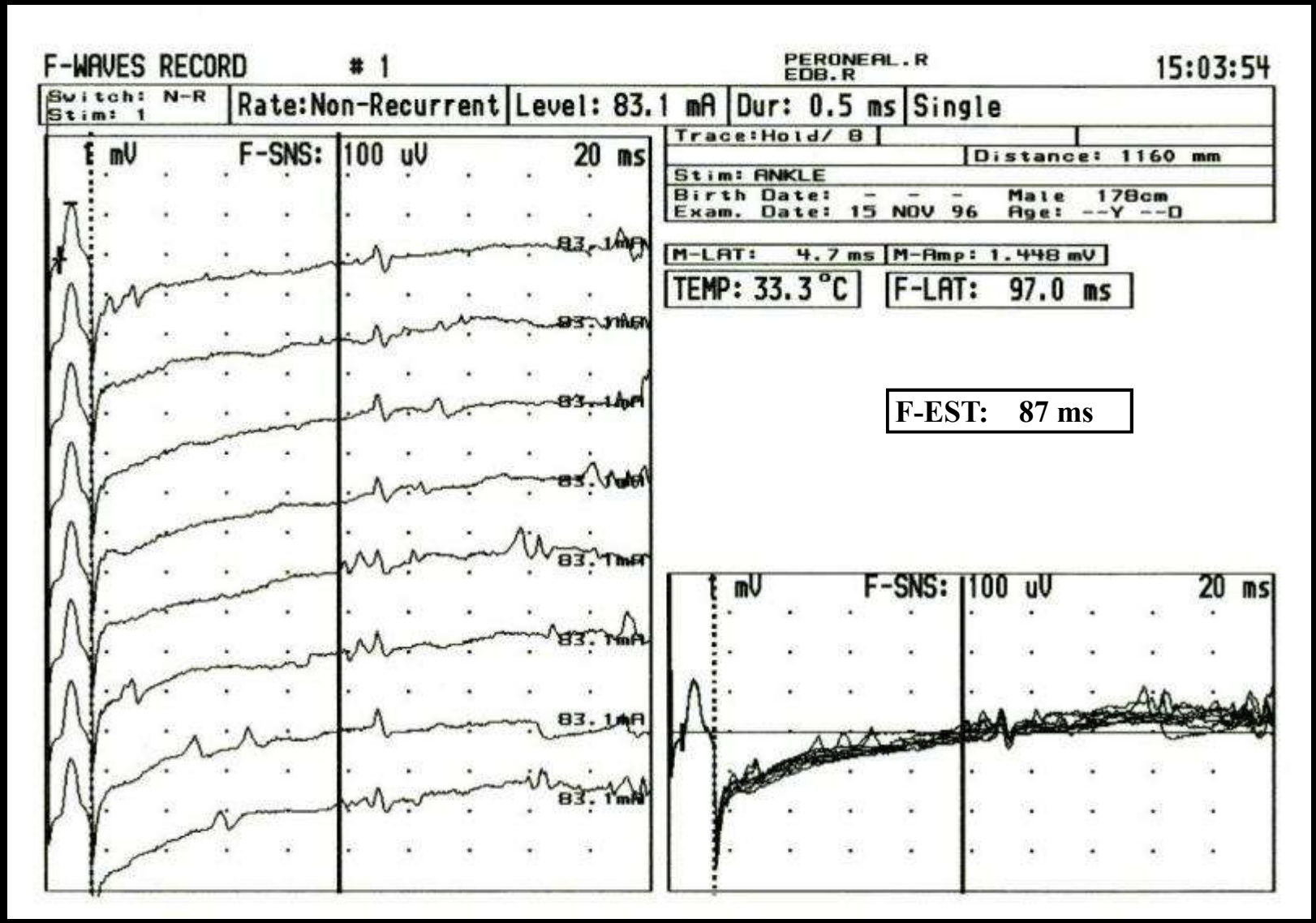
CIDP, 55 M
temporal dispersion and CB



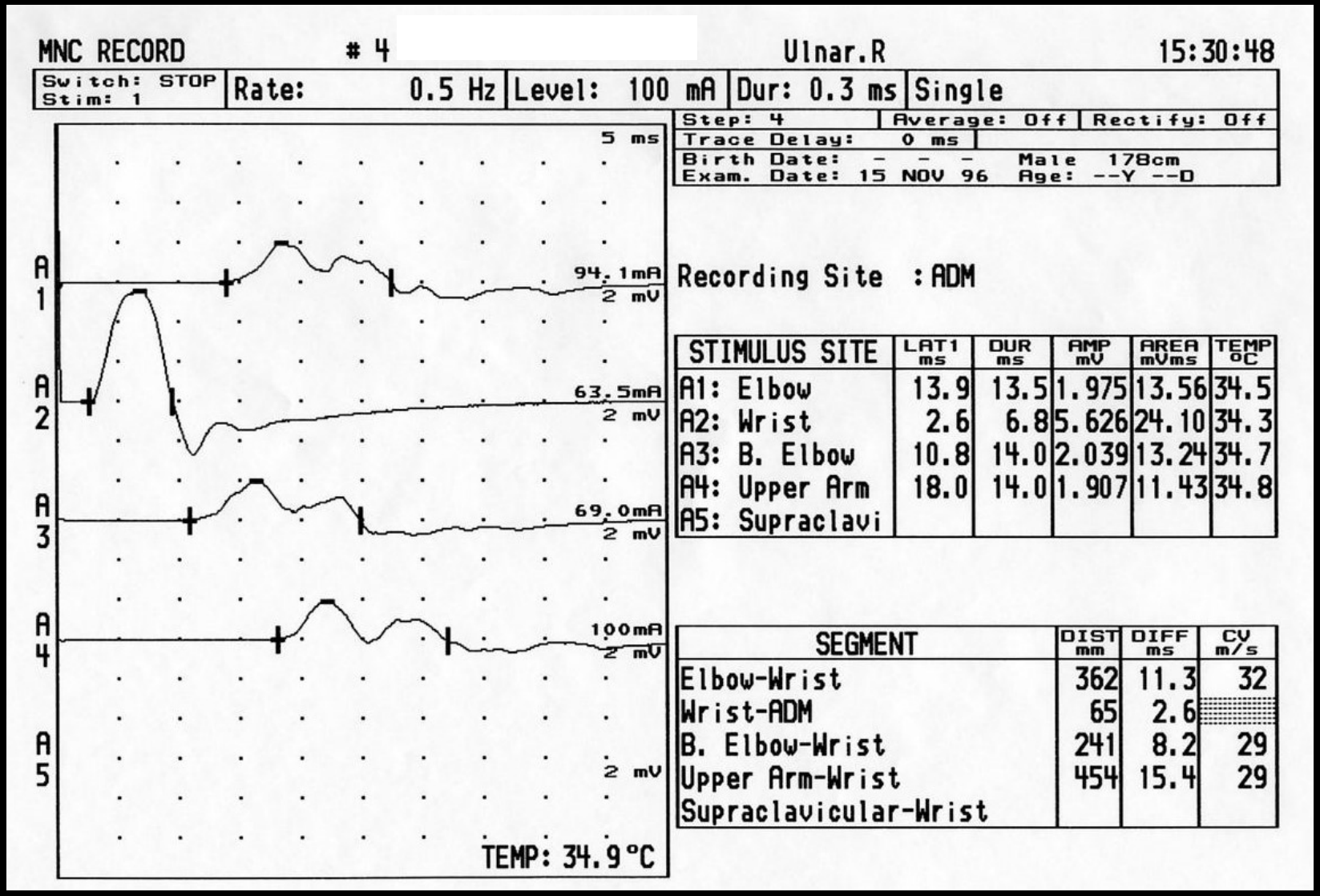
STIMULUS SITE	LAT1 ms	DUR ms	AMP mV	AREA mVms	TEMP °C
A1: Knee	19.9	14.0	0.659	3.335	33.7
A2: Ankle	4.3	9.2	1.362	5.192	33.7
A3: Fibula	15.7	12.4	0.870	3.709	33.7
A4: Malleolus					

SEGMENT	DIST mm	DIFF ms	CV m/s
Knee-Ankle	430	15.6	28
Ankle-EDB	85	4.3	
Fibula-Ankle	325	11.4	29
Malleolus-EDB			

CIDP, 55 M
prolonged F latency



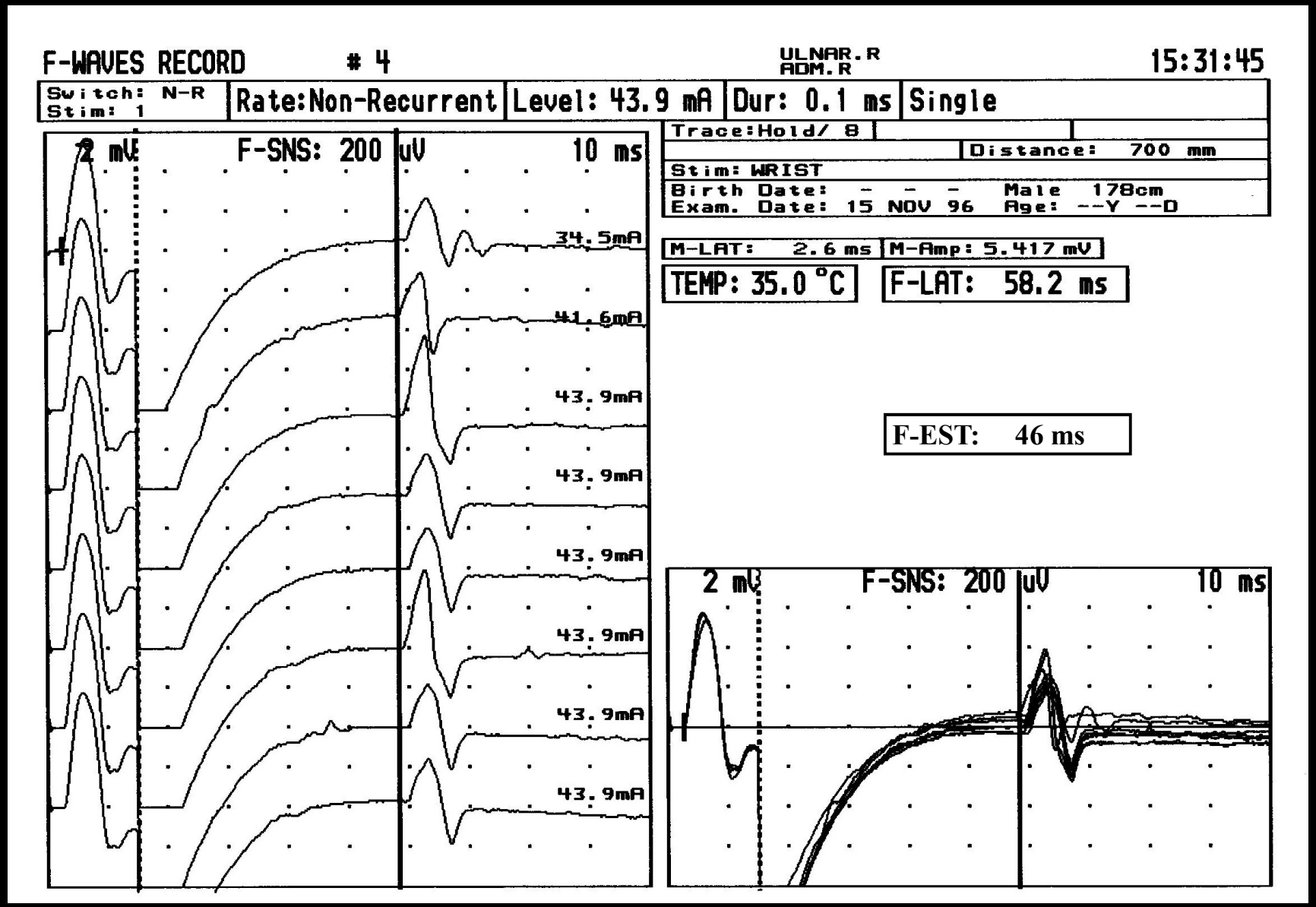
CIDP, 55 M
temporal dispersion and CB



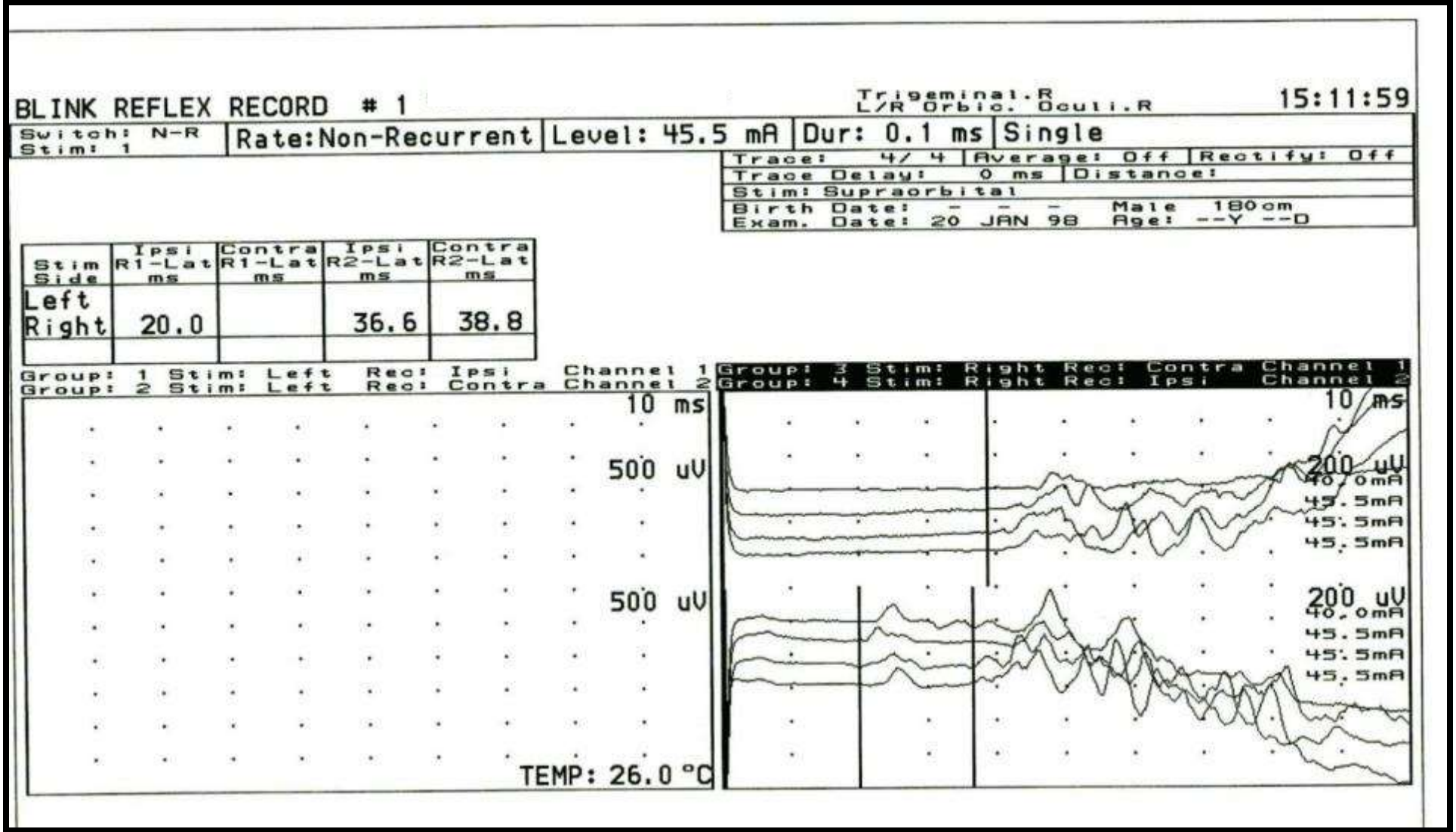
STIMULUS SITE	LAT1 ms	DUR ms	AMP mV	AREA mVms	TEMP °C
A1: Elbow	13.9	13.5	1.975	13.56	34.5
A2: Wrist	2.6	6.8	5.626	24.10	34.3
A3: B. Elbow	10.8	14.0	2.039	13.24	34.7
A4: Upper Arm	18.0	14.0	1.907	11.43	34.8
A5: Supraclavi					

SEGMENT	DIST mm	DIFF ms	CV m/s
Elbow-Wrist	362	11.3	32
Wrist-ADM	65	2.6	
B. Elbow-Wrist	241	8.2	29
Upper Arm-Wrist	454	15.4	29
Supraclavicular-Wrist			

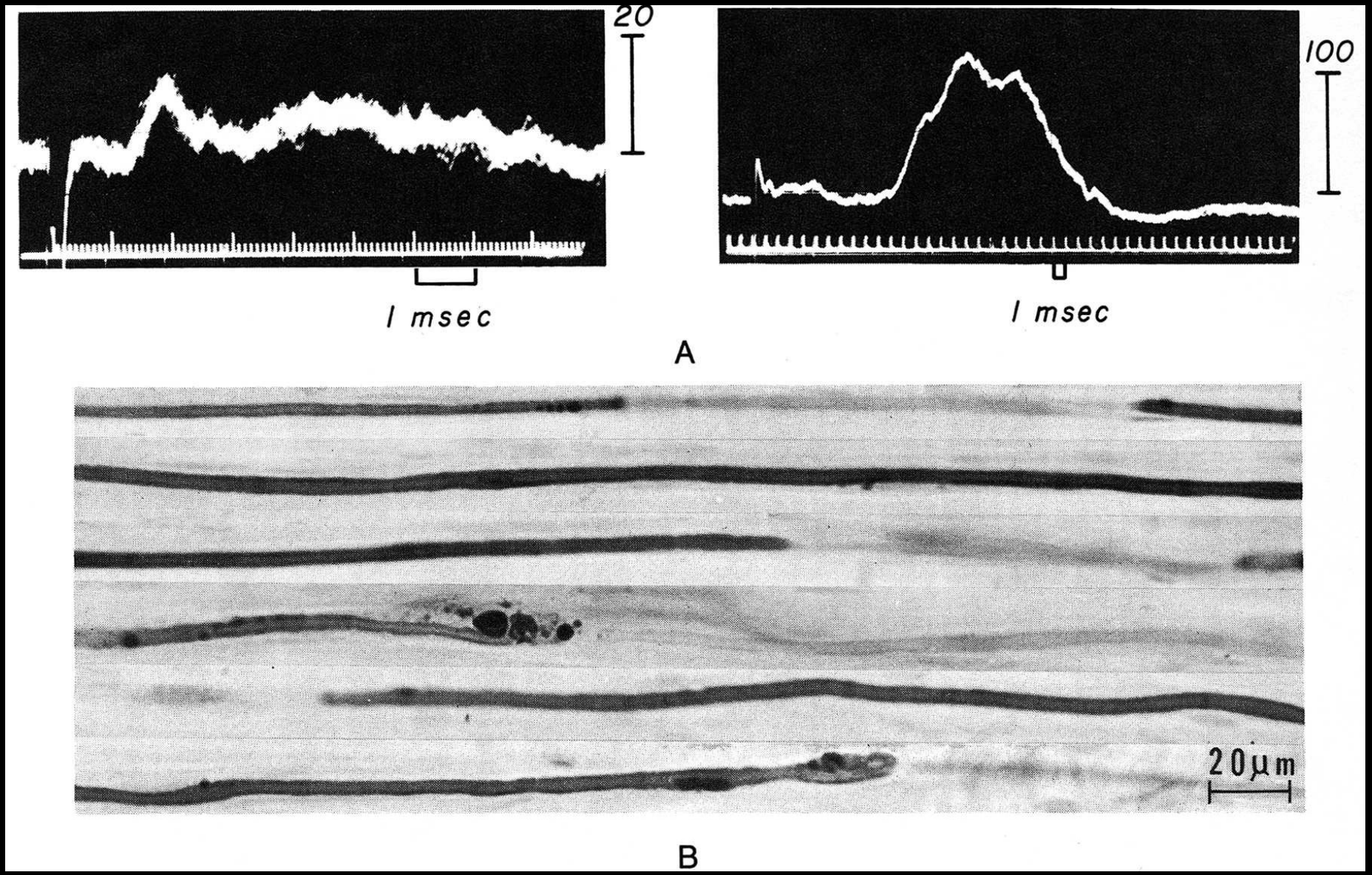
CIDP, 55 M


F-WAVES RECORD
4
ULNAR.R
ADM.R
15:31:45
Switch: N-R
Stim: 1
Rate:Non-Recurrent
Level: 43.9 mA
Dur: 0.1 ms
Single
Trace:Hold/ 8
Distance: 700 mm
Stim: WRIST
Birth Date: - - - Male 178cm
Exam. Date: 15 NOV 96 Age: --Y --D
M-LAT: 2.6 ms
M-Amp: 5.417 mV
TEMP: 35.0 °C
F-LAT: 58.2 ms
F-EST: 46 ms
2 mV
F-SNS: 200 uV
10 ms
34.5mA
41.6mA
43.9mA
43.9mA
43.9mA
43.9mA
43.9mA
43.9mA
2 mV
F-SNS: 200 uV
10 ms

CIDP, 51 M

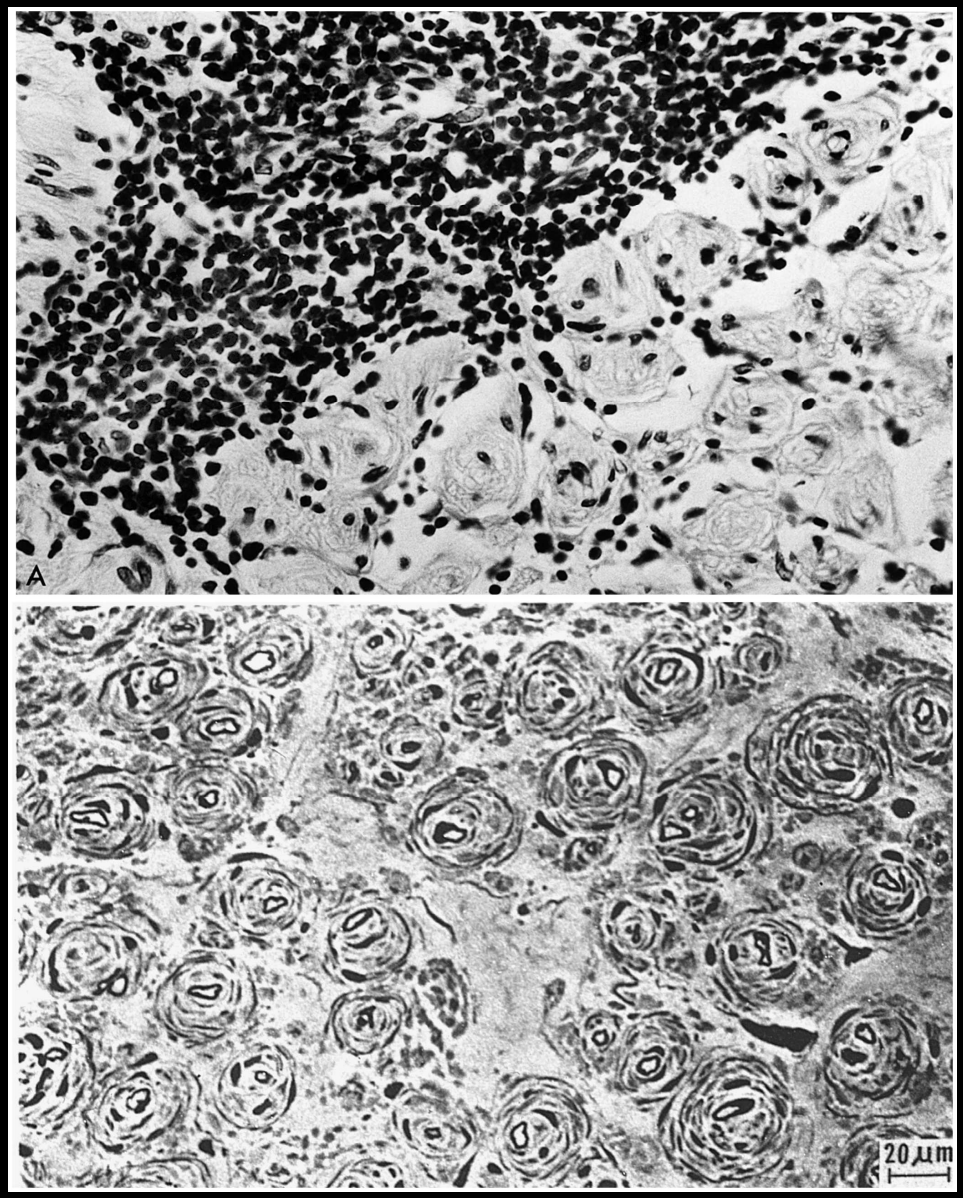

BLINK REFLEX RECORD # 1
Trigeminal.R
L/R Orbic. Ocul.R
15:11:59
Switch: N-R
Stim: 1
Rate:Non-Recurrent
Level: 45.5 mA
Dur: 0.1 ms
Single
Trace: 4/ 4
Average: Off
Rectify: Off
Trace Delay: 0 ms
Distance:
Stim: Supraorbital
Birth Date: - - -
Male 180cm
Exam. Date: 20 JAN 98
Age: --Y --D
Stim Side
Ipsi R1-Lat ms
Contra R1-Lat ms
Ipsi R2-Lat ms
Contra R2-Lat ms
Left
Right
20.0
36.6
38.8
Group: 1 Stim: Left Rec: Ipsi Channel 1
Group: 2 Stim: Left Rec: Contra Channel 2
10 ms
500 uV
500 uV
TEMP: 26.0 °C
Group: 3 Stim: Right Rec: Contra Channel 1
Group: 4 Stim: Right Rec: Ipsi Channel 2
10 ms
200 uV
40.0mA
45.5mA
45.5mA
45.5mA
200 uV
40.0mA
45.5mA
45.5mA
45.5mA

CIDP



From: Lambert & Dyck, Peripheral Neuropathy 1st ed., 1975

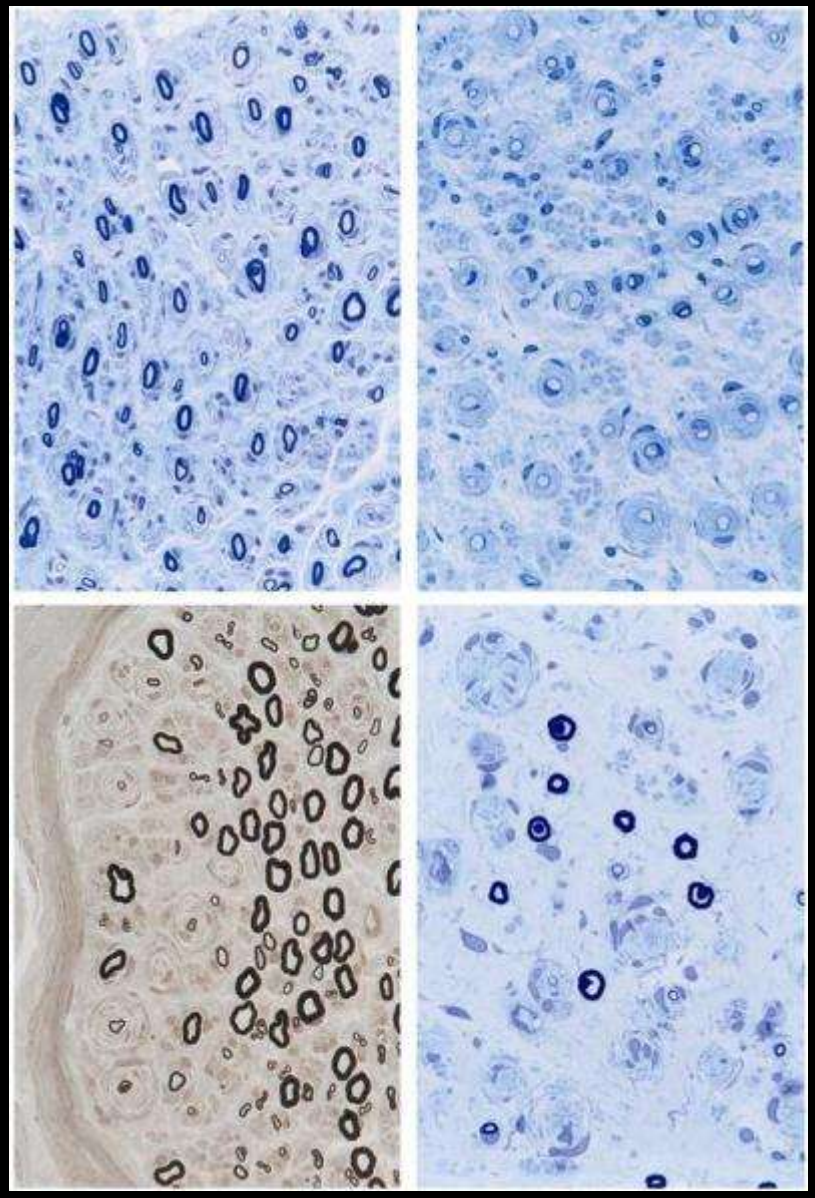
CIDP



From: Dyck et al, Mayo Clinic Proc., 1975

Onion Bulb Patterns

CMT-1A (HMSN-IA)
(generalized pattern)



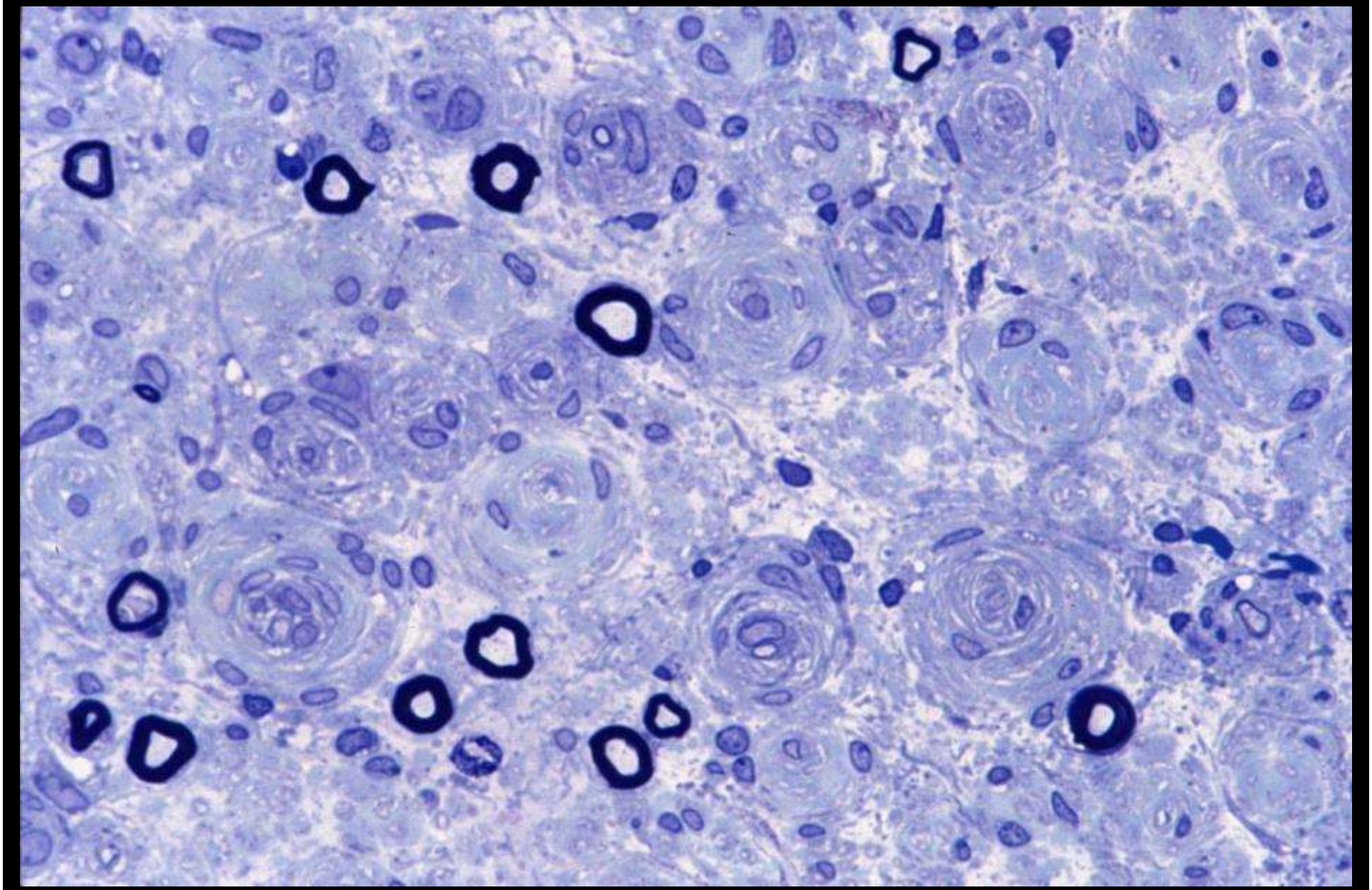
HMSN-III
(generalized pattern)

Inherited Neuropathy
(focal pattern)

CIDP
(mixed pattern)

From: Dyck et al, Greenfield's Neuropathology 7th ed., 2002

CIDP (mixed pattern)



Pattern of Onion Bulbs

n=131	Acquired Neuropathy	Inherited Neuropathy	Significance
Generalized OB	17	34	$p < 0.0001$
Focal OB	17	9	NS
Mixed OB	48	6	$p < 0.0001$

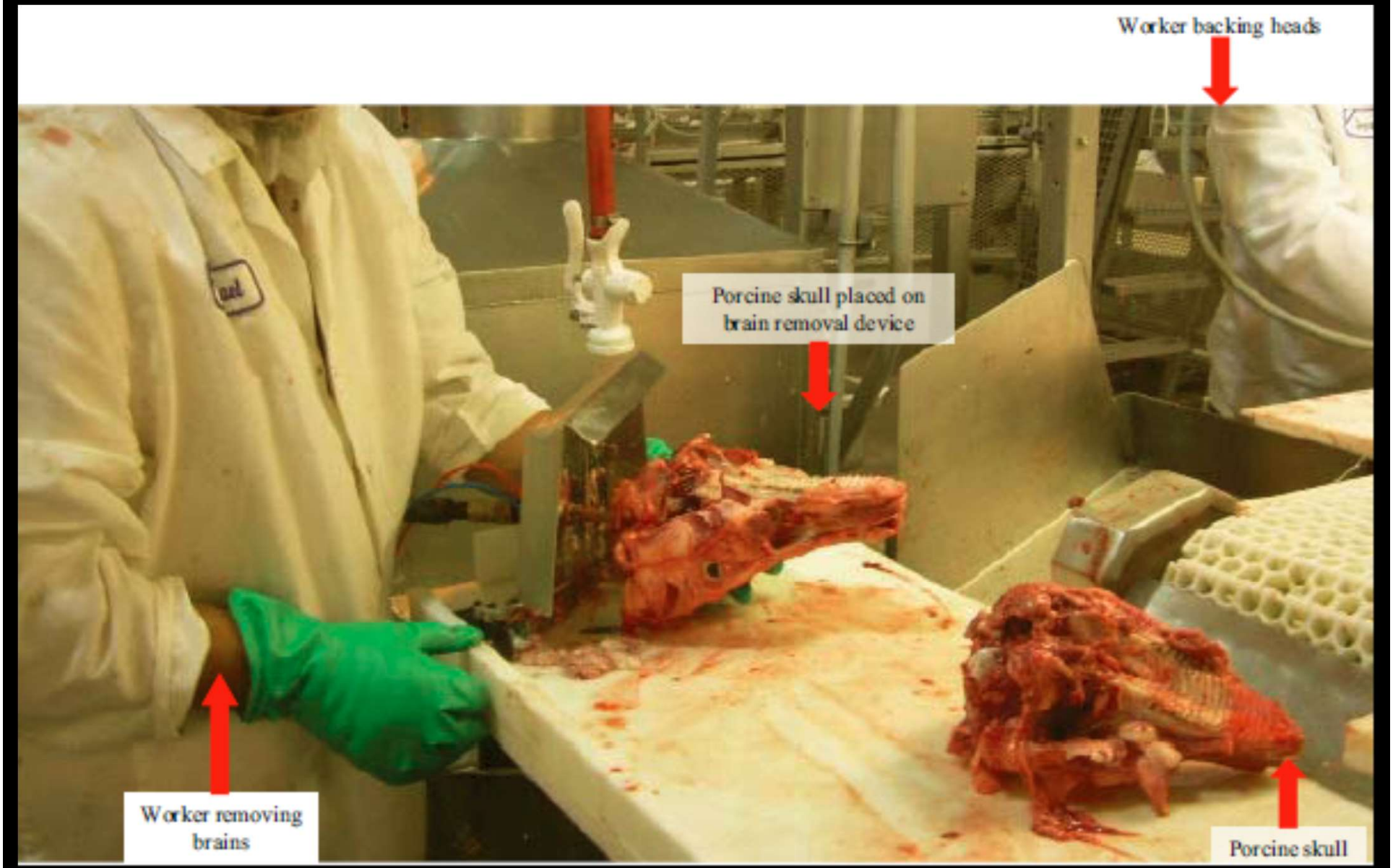
- Mixed OB are highly suggestive of acquired demyelinating neuropathy and may explain temporal dispersion.
- Generalized OB may explain uniform slowing in inherited neuropathy.

Inflammatory polyradiculoneuropathy
occurring in pork processing workers

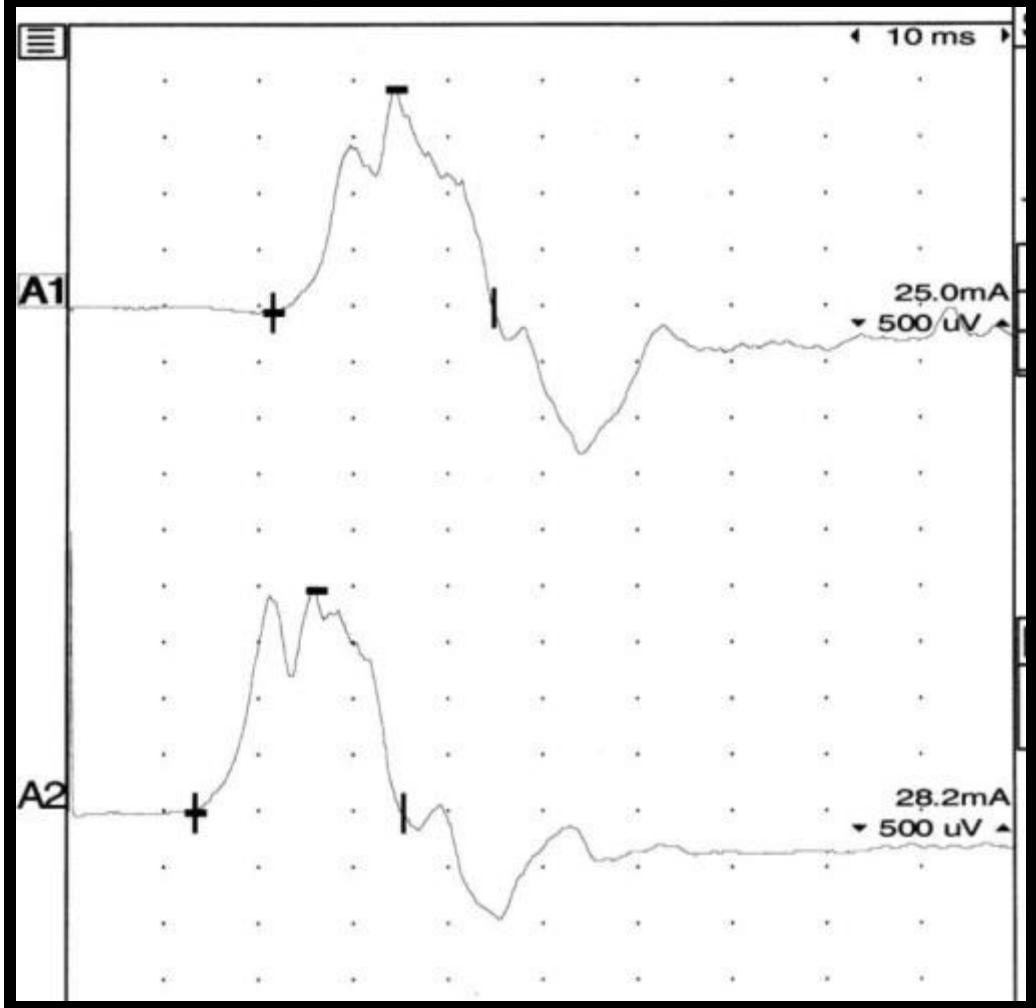
An outbreak of neurological autoimmunity with polyradiculoneuropathy in workers exposed to aerosolised porcine neural tissue: a descriptive study

Daniel H Lachance, Vanda A Lennon, Sean J Pittock, Jennifer A Tracy, Karl N Krecke, Kimberly K Amrami, Eric M Poeschla, Robert Orenstein, Bernd W Scheithauer, James J Sejvar, Stacy Holzbauer, Aaron S DeVries, P James B Dyck

Lancet Neurol 2010;9:55-66


Worker backing heads
Porcine skull placed on brain removal device
Worker removing brains
Porcine skull

Inflammatory polyradiculoneuropathy occurring in pork processing workers

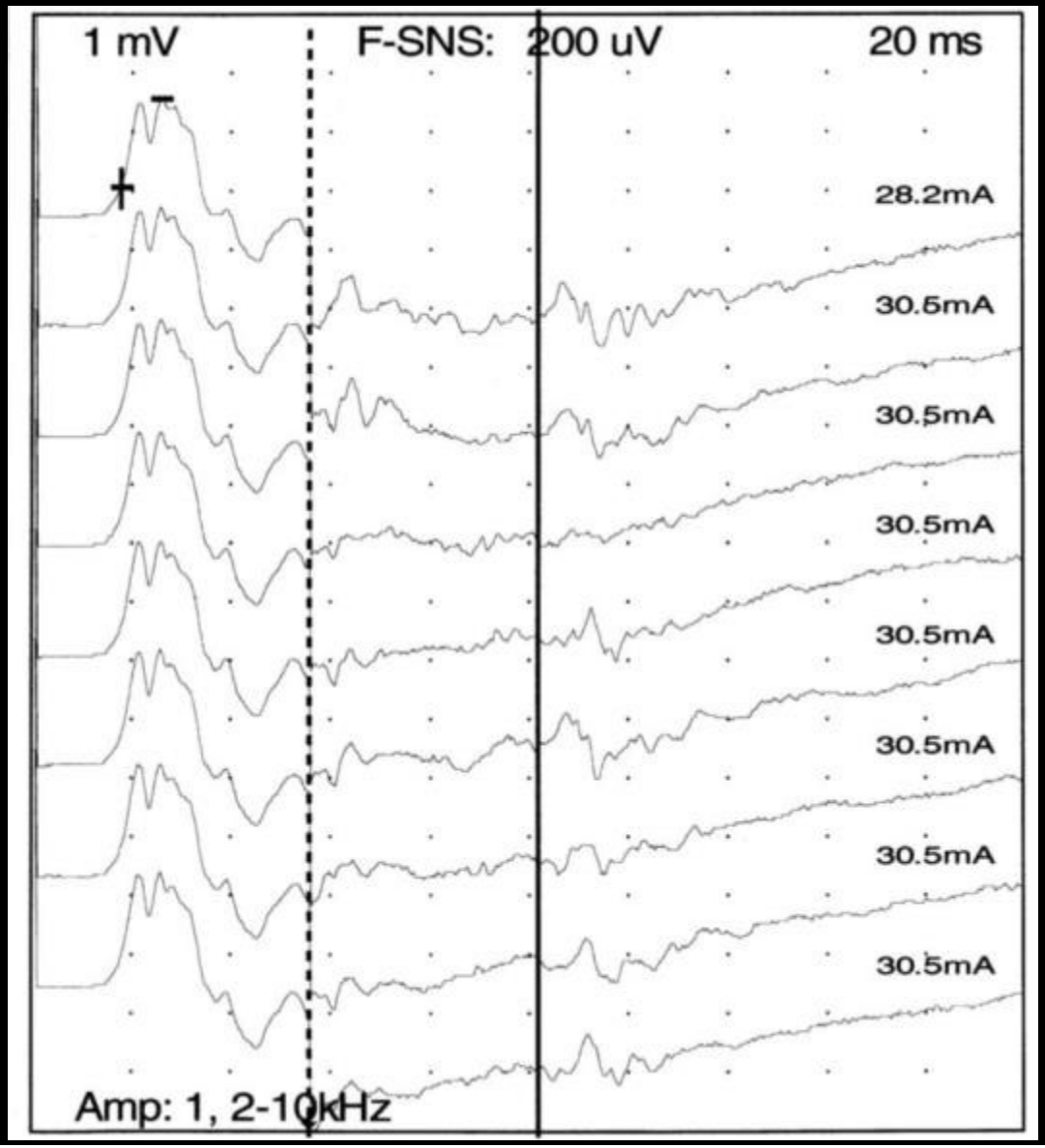


30 M

Right Tibial Study
Recording site: Abductor hallucis

Stimulus Site	Lat 1 ms	Dur ms	Amp mV	CV m/s
A1: Knee	21.3	23.5	2.0	45
A2: Ankle	13.2	21.9	2.0	

Inflammatory polyradiculoneuropathy occurring in pork processing workers

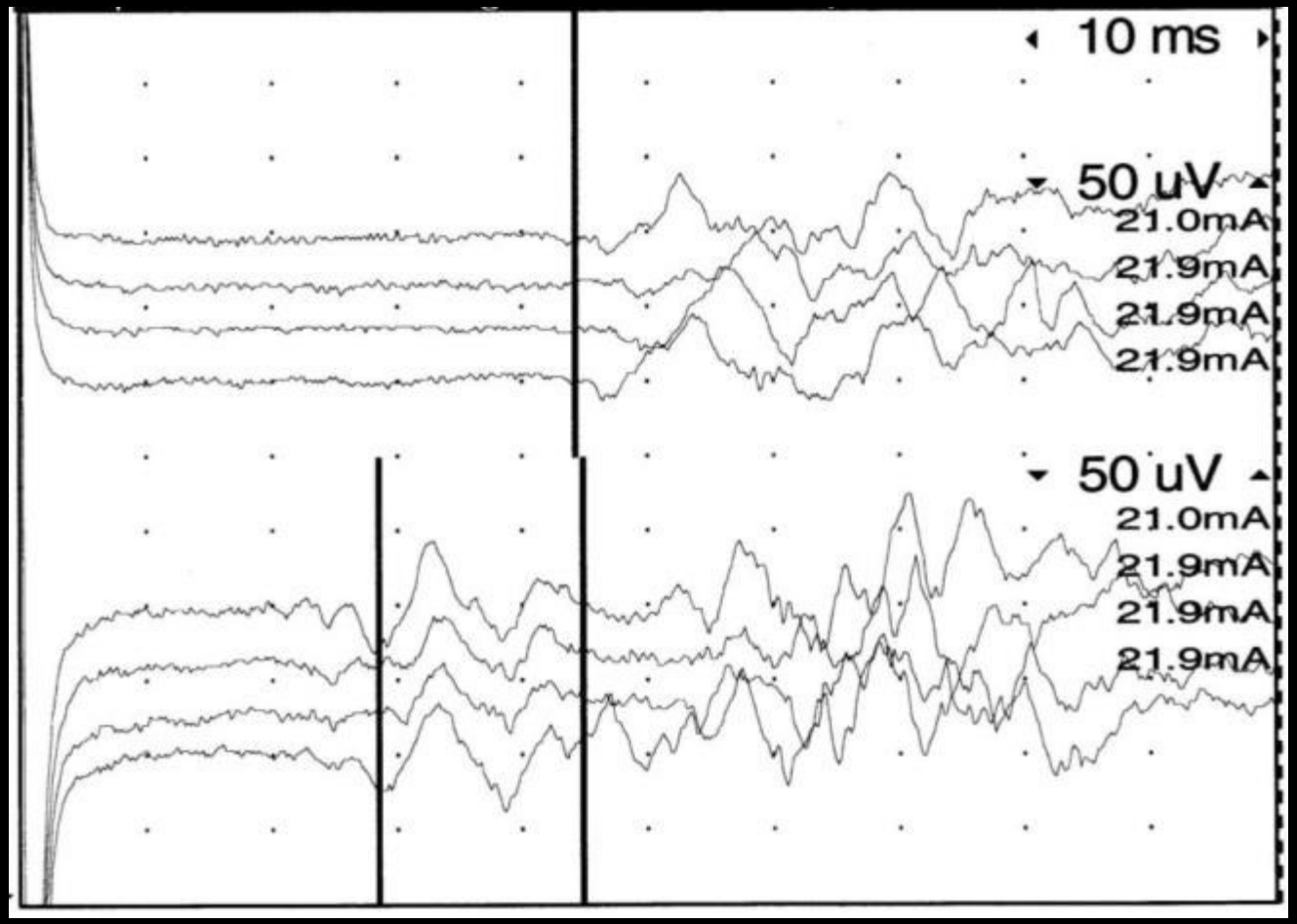


30 M

Right Tibial F-Wave Study
Recording site: Abductor hallucis

F-Lat: 101.8 ms
F-EST = 58.5 ms

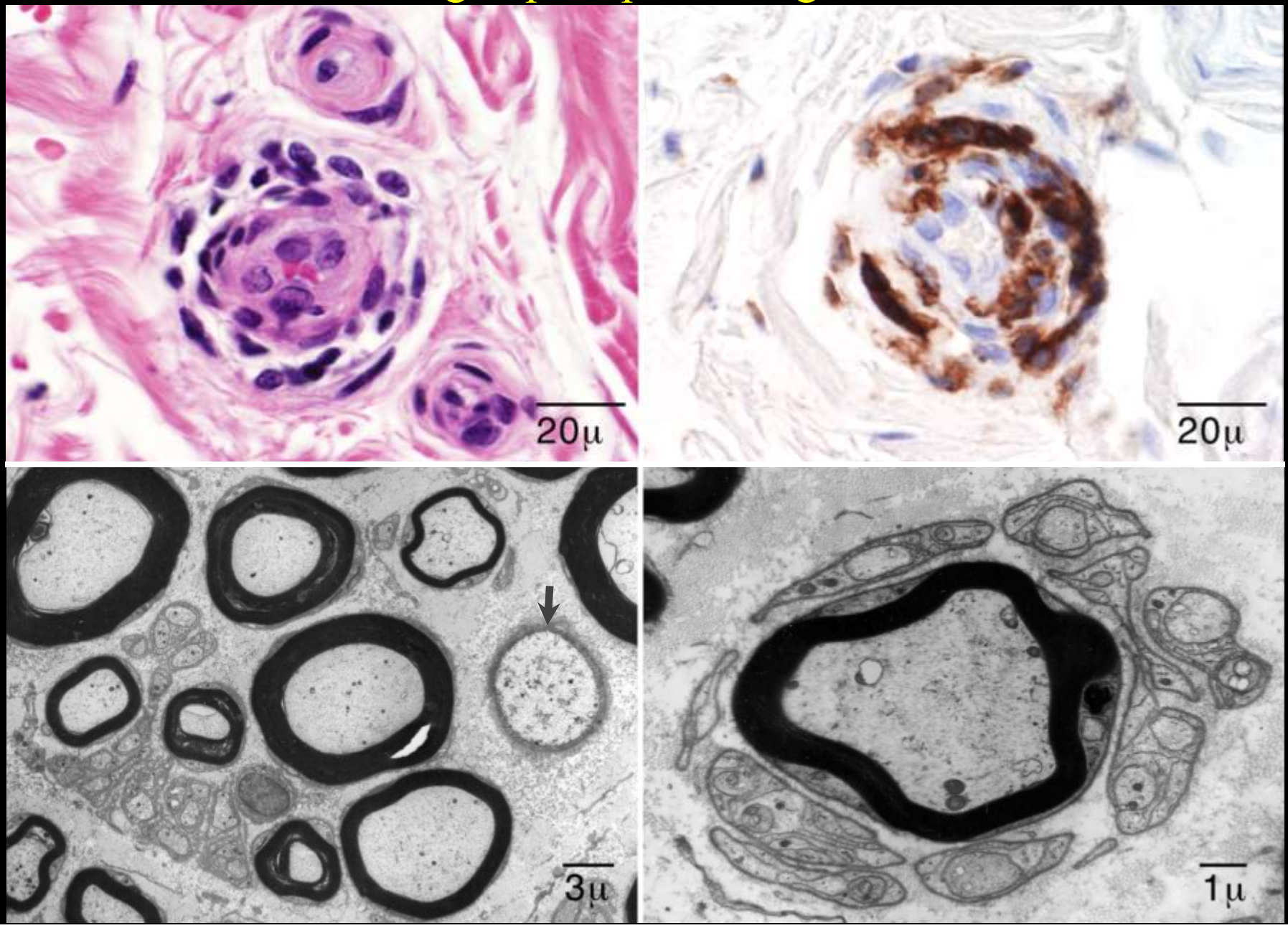
Inflammatory polyradiculoneuropathy occurring in pork processing workers



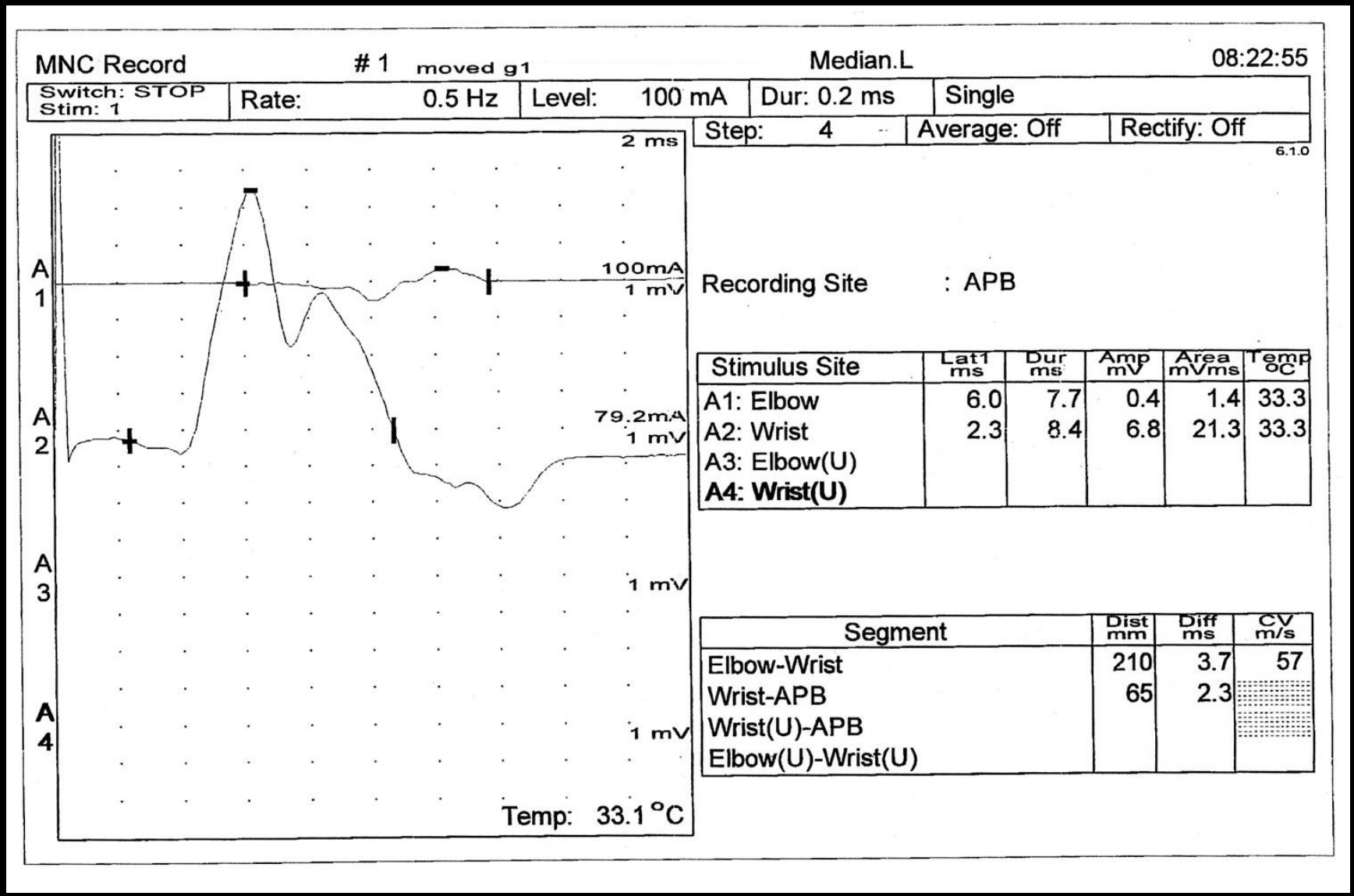
51 F
Right Trigeminal Study
Recording site: Supraorbital

Stim Side	Ipsi R1-Lat ms	Ipsi R2-Lat ms	Contra R2-Lat ms
Right	28.4	44.8	44.2

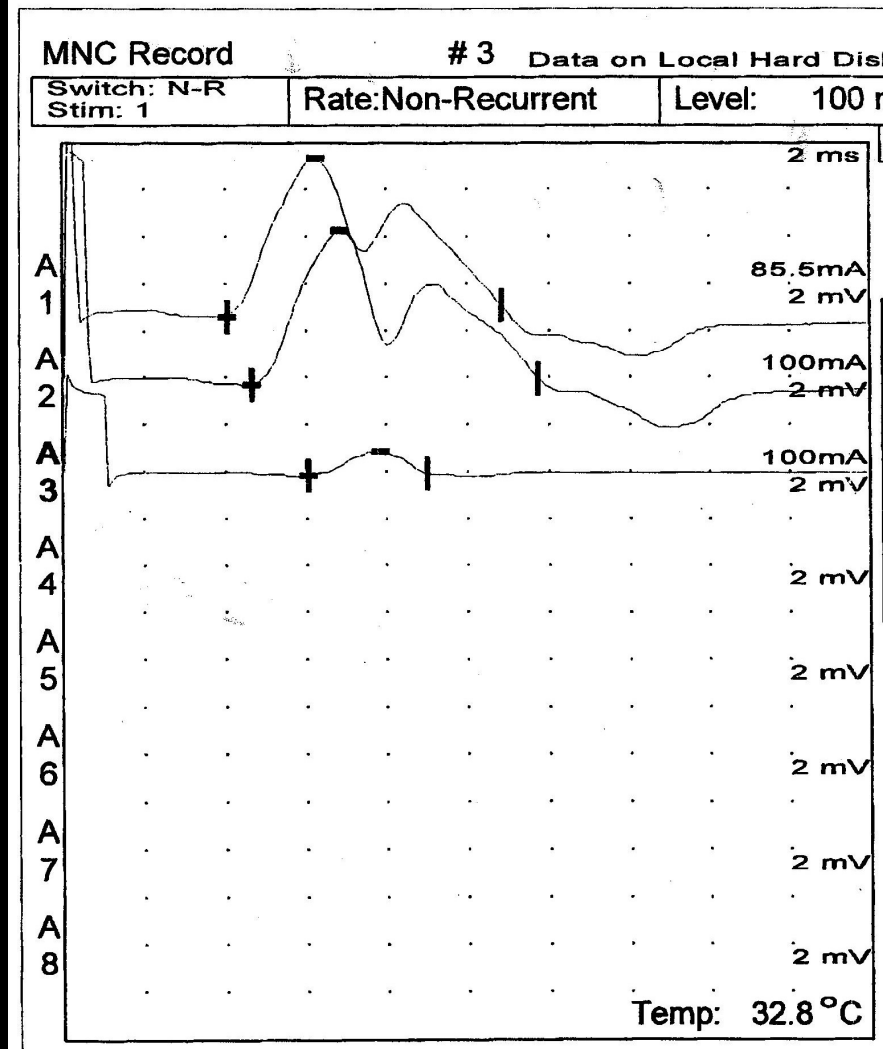
Inflammatory polyradiculoneuropathy occurring in pork processing workers



Multifocal Motor Neuropathy, 51 F
conduction block



Multifocal Motor Neuropathy, 51 F
conduction block



MNC Record # 3 Data on Local Hard Disk Median.L 08:25:55

Switch: N-R Stim: 1	Rate:Non-Recurrent	Level: 100 mA	Dur: 1 ms	Single
		Step: 3	Average: Off	Rectify: Off

6.1.0

Recording Site : APB

Stimulus Site	Lat1 ms	Dur ms	Amp mV	Area mVms	Temp °C
A1: SITE 1	4.0	6.8	6.8	20.9	33.1
A2: SITE 2	4.6	7.1	6.7	21.1	33.0
A3: SITE 3	6.0	2.9	1.1	1.4	32.9
A4: SITE 4					
A5: SITE 5					
A6: SITE 6					
A7: SITE 7					
A8: SITE 8					

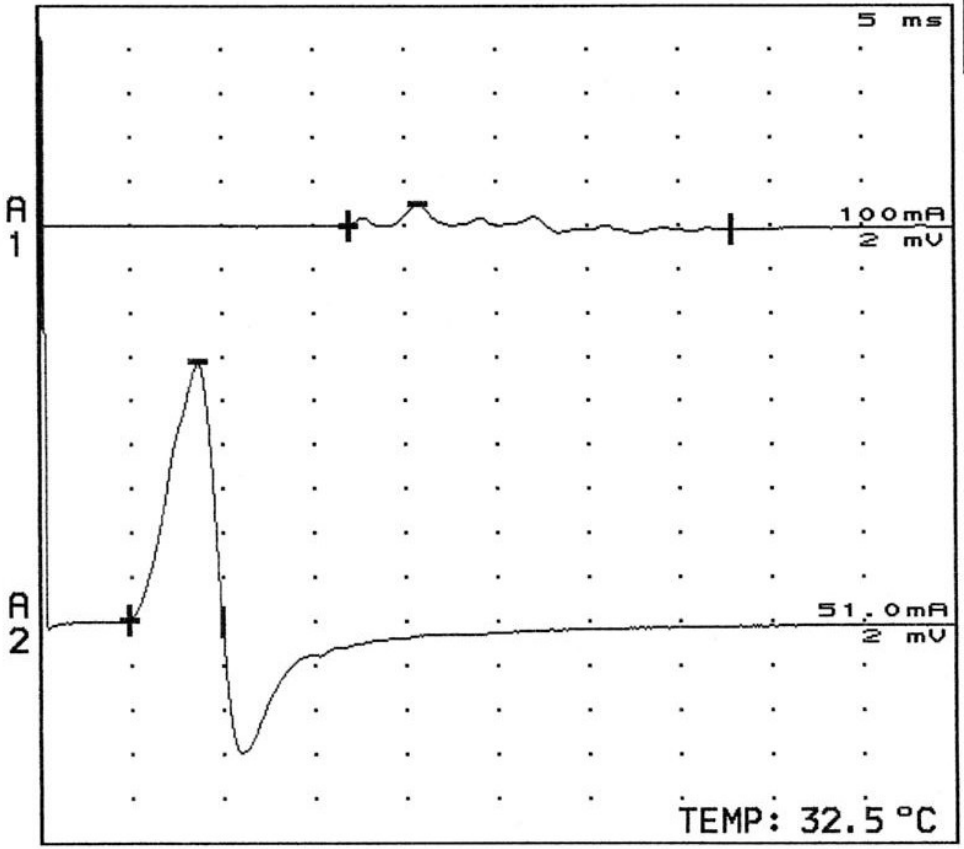
Segment	Dist mm	Diff ms
SITE 1-APB	64	4.0
SITE 2-SITE 1	85	0.6
SITE 3-SITE 2	111	1.4
SITE 4-SITE 3		
SITE 5-SITE 4		
SITE 6-SITE 5		
SITE 7-SITE 6		
SITE 8-SITE 7		

Multifocal Motor Neuropathy, 53 M
conduction block

MNC RECORD # 2 Tibial.L 13:29:14

Switch: STOP Stim: 1	Rate: 0.5 Hz	Level: 50.2 mA	Dur: 0.5 ms	Single

Step: 2	Average: Off	Rectify: Off
Trace Delay: 0 ms		
Birth Date: - - -	Male 173cm	
Exam. Date: 17 JAN 97	Age: --Y --D	

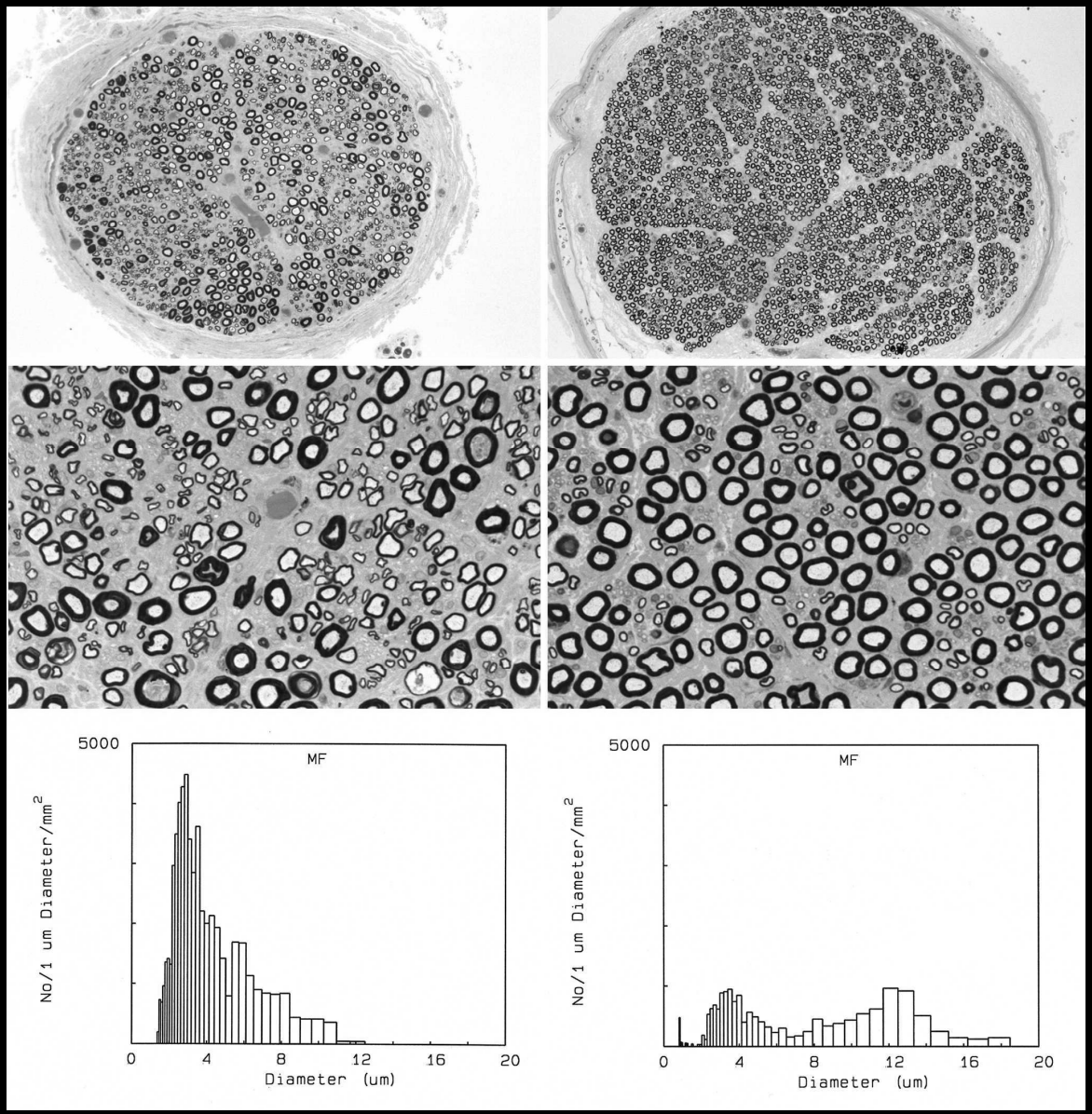


Recording Site : AH

STIMULUS SITE	LAT1 ms	DUR ms	AMP mV	AREA mVms	TEMP °C
A1: Knee	16.9	20.9	0.964	5.256	32.6
A2: Ankle	4.8	5.1	11.71	30.48	32.6

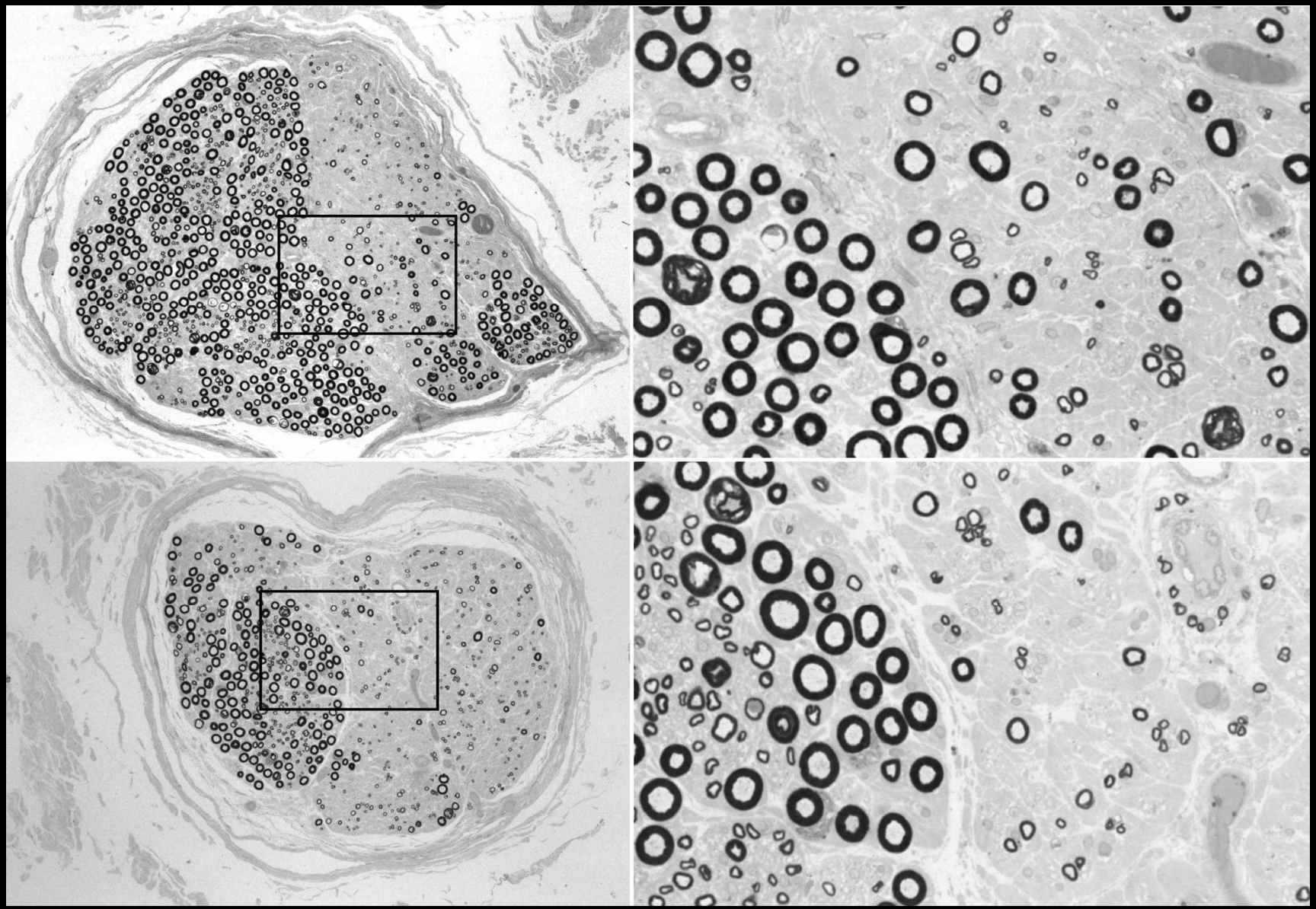
SEGMENT	DIST mm	DIFF ms	CV m/s
Knee-Ankle	408	12.1	34
Ankle-AH	82	4.8	

Multifocal Motor Neuropathy



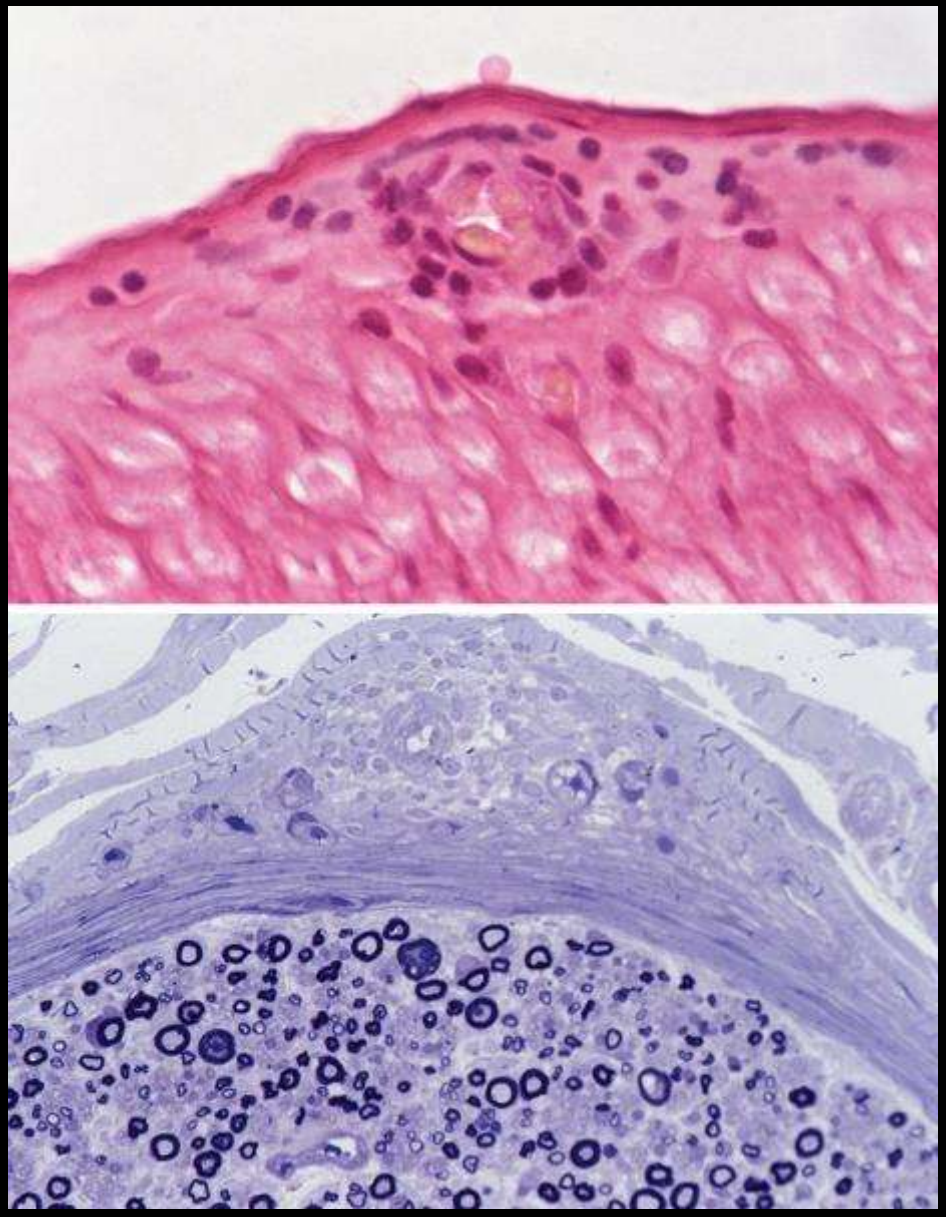
From: Taylor & PJB Dyck, Neuropathology & Experimental Neurology, 2004

Multifocal Motor Neuropathy (multifocal fiber loss)



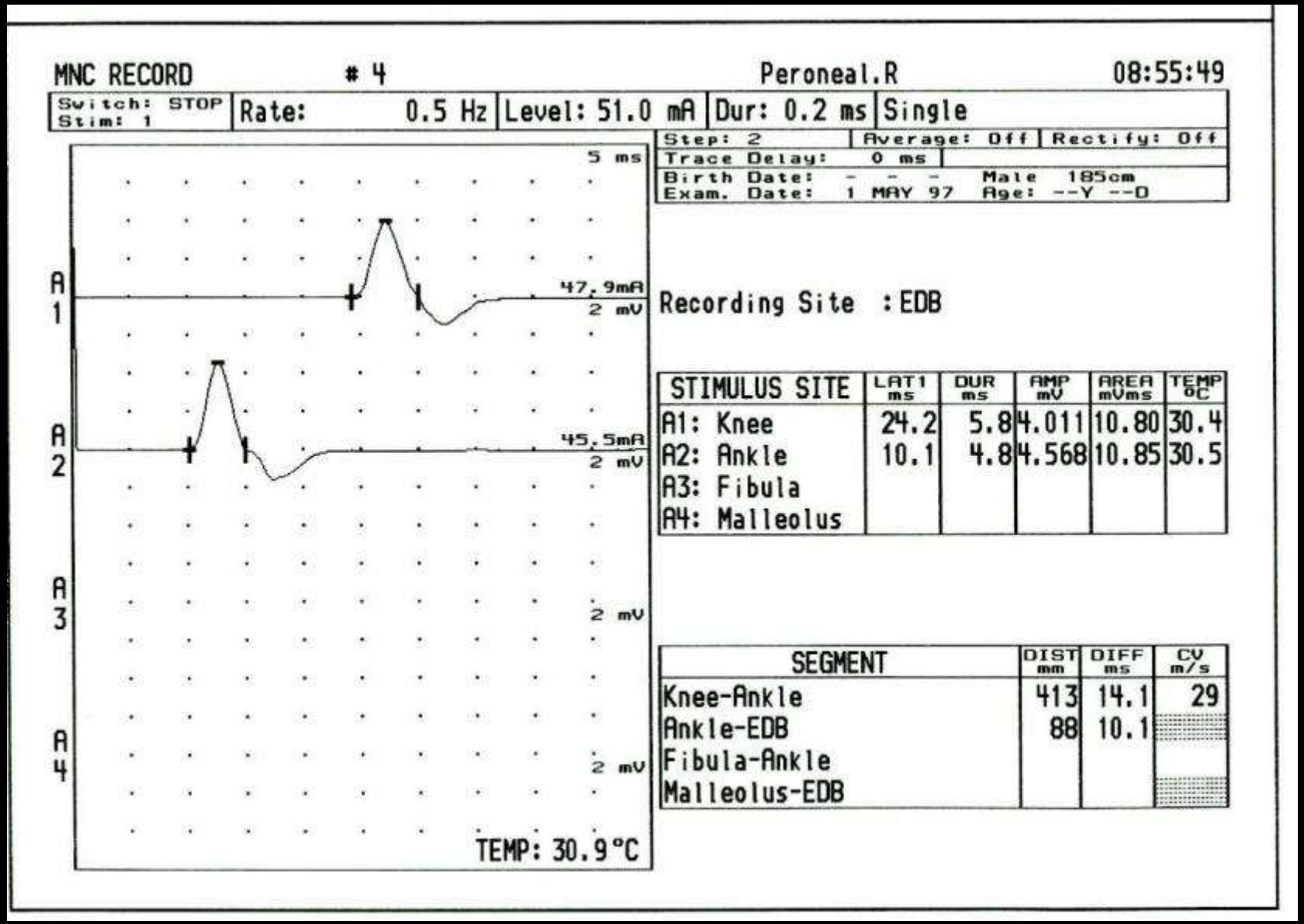
From: Taylor & PJB Dyck, Neuropathology & Experimental Neurology, 2004

Minimal Perivascular Inflammation in MMN

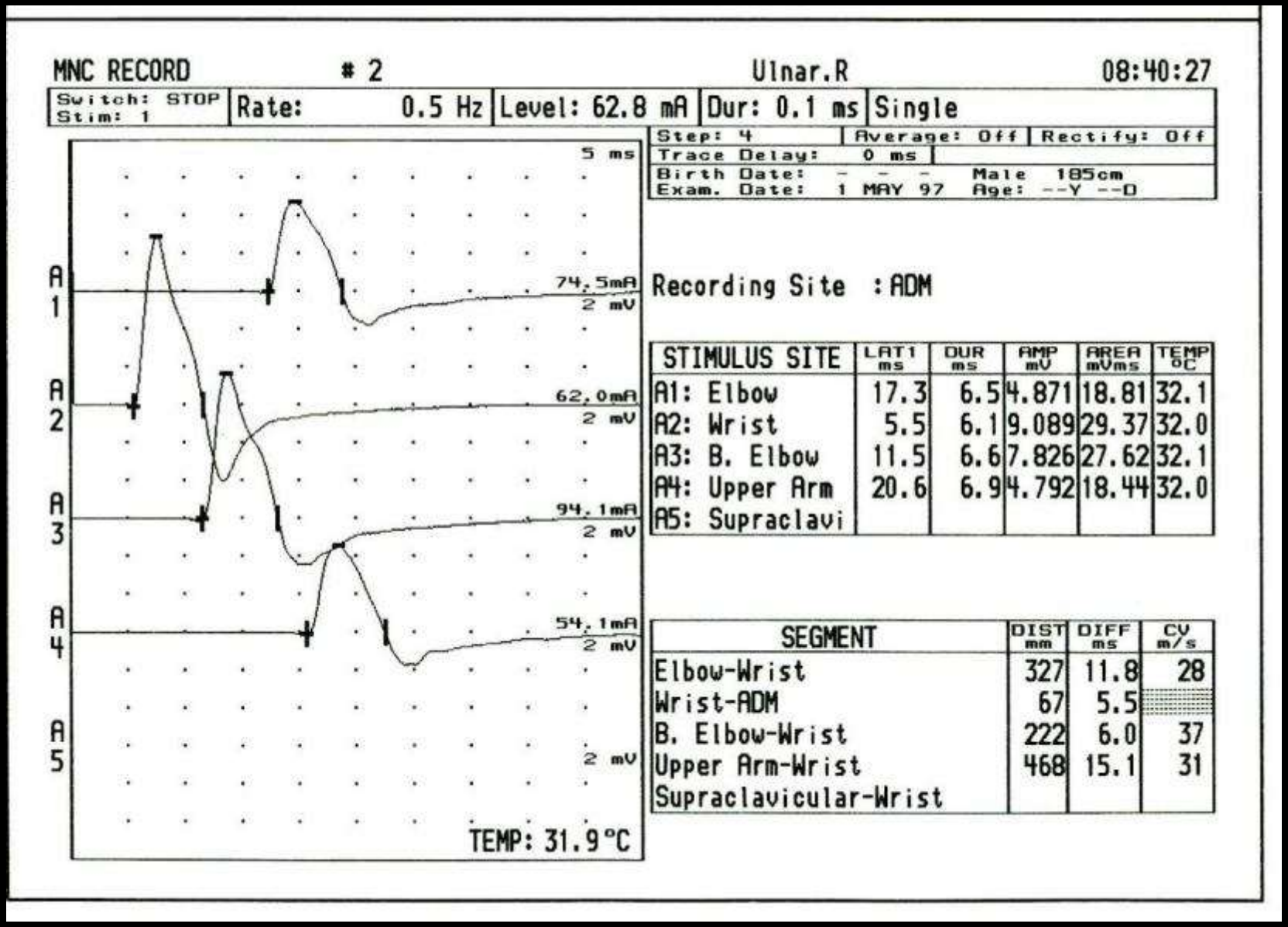


Taylor et al, 2004

HNPP, 61 M

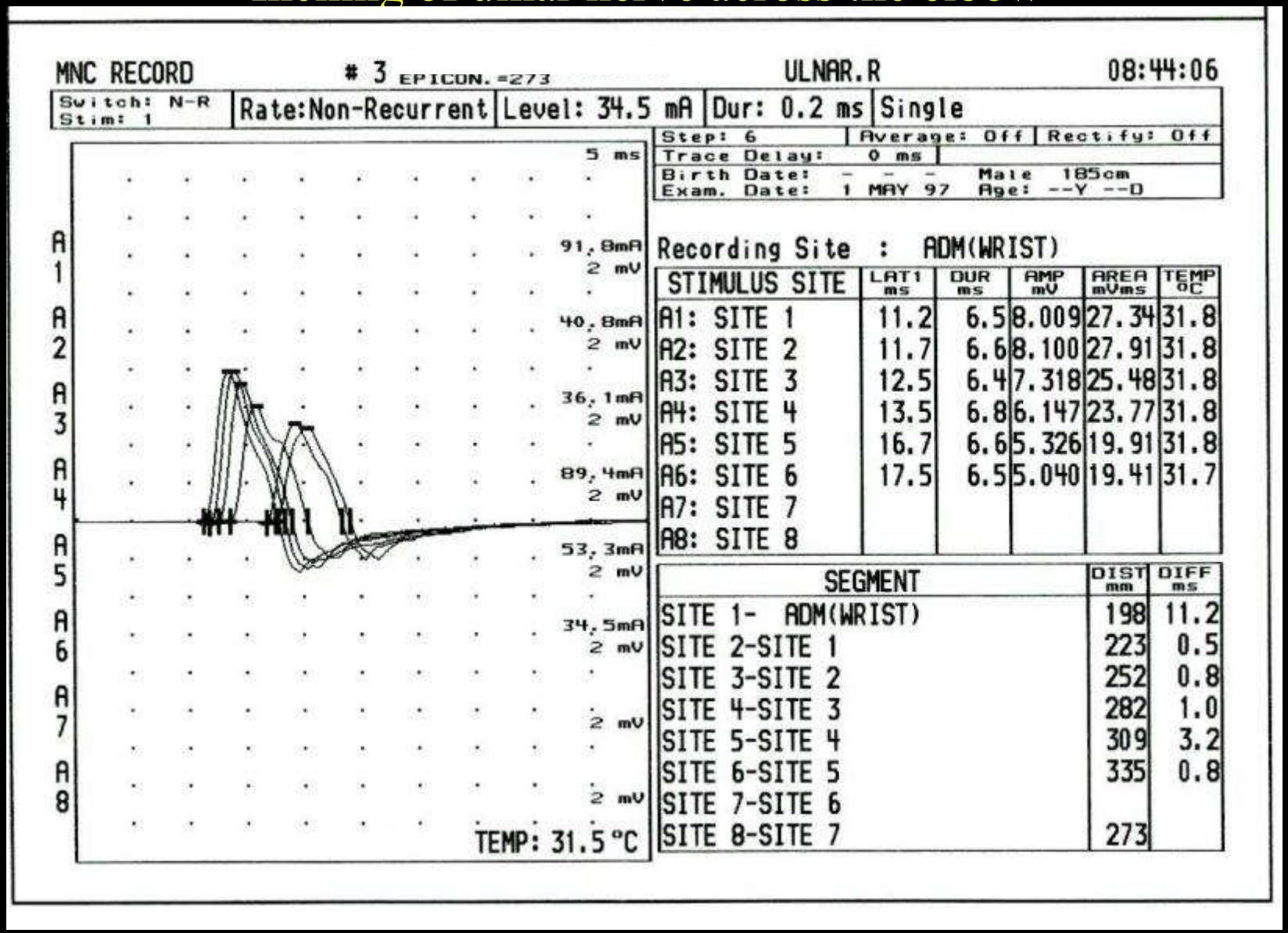

MNC RECORD
4
Peroneal.R
08:55:49
Switch: STOP
Stim: 1
Rate: 0.5 Hz
Level: 51.0 mA
Dur: 0.2 ms
Single
Step: 2
Average: Off
Rectify: Off
Trace Delay: 0 ms
Birth Date: - - -
Male 185cm
Exam. Date: 1 MAY 97
Age: --Y --D
5 ms
A1
47.9mA
2 mV
A2
45.5mA
2 mV
A3
2 mV
A4
2 mV
TEMP: 30.9°C
Recording Site : EDB
STIMULUS SITE | LAT1 ms | DUR ms | AMP mV | AREA mVms | TEMP °C
A1: Knee | 24.2 | 5.8 | 4.011 | 10.80 | 30.4
A2: Ankle | 10.1 | 4.8 | 4.568 | 10.85 | 30.5
A3: Fibula
A4: Malleolus
SEGMENT | DIST mm | DIFF ms | CV m/s
Knee-Ankle | 413 | 14.1 | 29
Ankle-EDB | 88 | 10.1
Fibula-Ankle
Malleolus-EDB

HNPP, 61 M

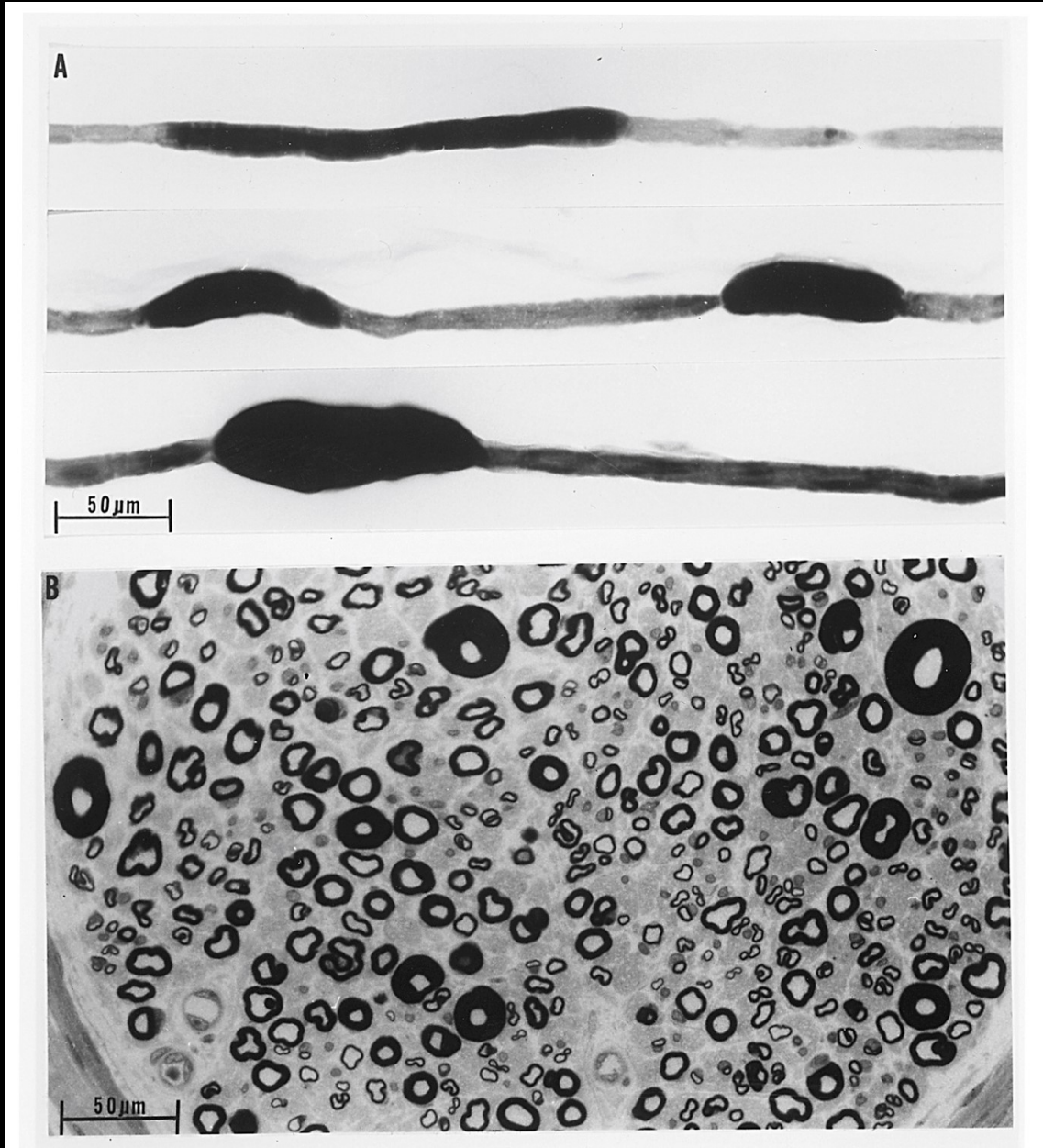

MNC RECORD
2
Ulnar.R
08:40:27
Switch: STOP
Stim: 1
Rate: 0.5 Hz
Level: 62.8 mA
Dur: 0.1 ms
Single
Step: 4
Average: Off
Rectify: Off
Trace Delay: 0 ms
Birth Date: - - -
Male 185cm
Exam. Date: 1 MAY 97
Age: --Y --D
5 ms
A1
74.5mA
2 mV
A2
62.0mA
2 mV
A3
94.1mA
2 mV
A4
54.1mA
2 mV
A5
2 mV
TEMP: 31.9°C
Recording Site : ADM
STIMULUS SITE | LAT1 ms | DUR ms | AMP mV | AREA mVms | TEMP °C
A1: Elbow | 17.3 | 6.5 | 4.871 | 18.81 | 32.1
A2: Wrist | 5.5 | 6.1 | 9.089 | 29.37 | 32.0
A3: B. Elbow | 11.5 | 6.6 | 7.826 | 27.62 | 32.1
A4: Upper Arm | 20.6 | 6.9 | 4.792 | 18.44 | 32.0
A5: Supraclavi
SEGMENT | DIST mm | DIFF ms | CV m/s
Elbow-Wrist | 327 | 11.8 | 28
Wrist-ADM | 67 | 5.5
B. Elbow-Wrist | 222 | 6.0 | 37
Upper Arm-Wrist | 468 | 15.1 | 31
Supraclavicular-Wrist

HNPP, 61 M

Inching of ulnar nerve across the elbow



HNPP (tomaculae)



From: Crum, Sorenson, Abad & PJB Dyck, Muscle and Nerve, 2000

Polyneuropathy Associated with Hypothyroidism

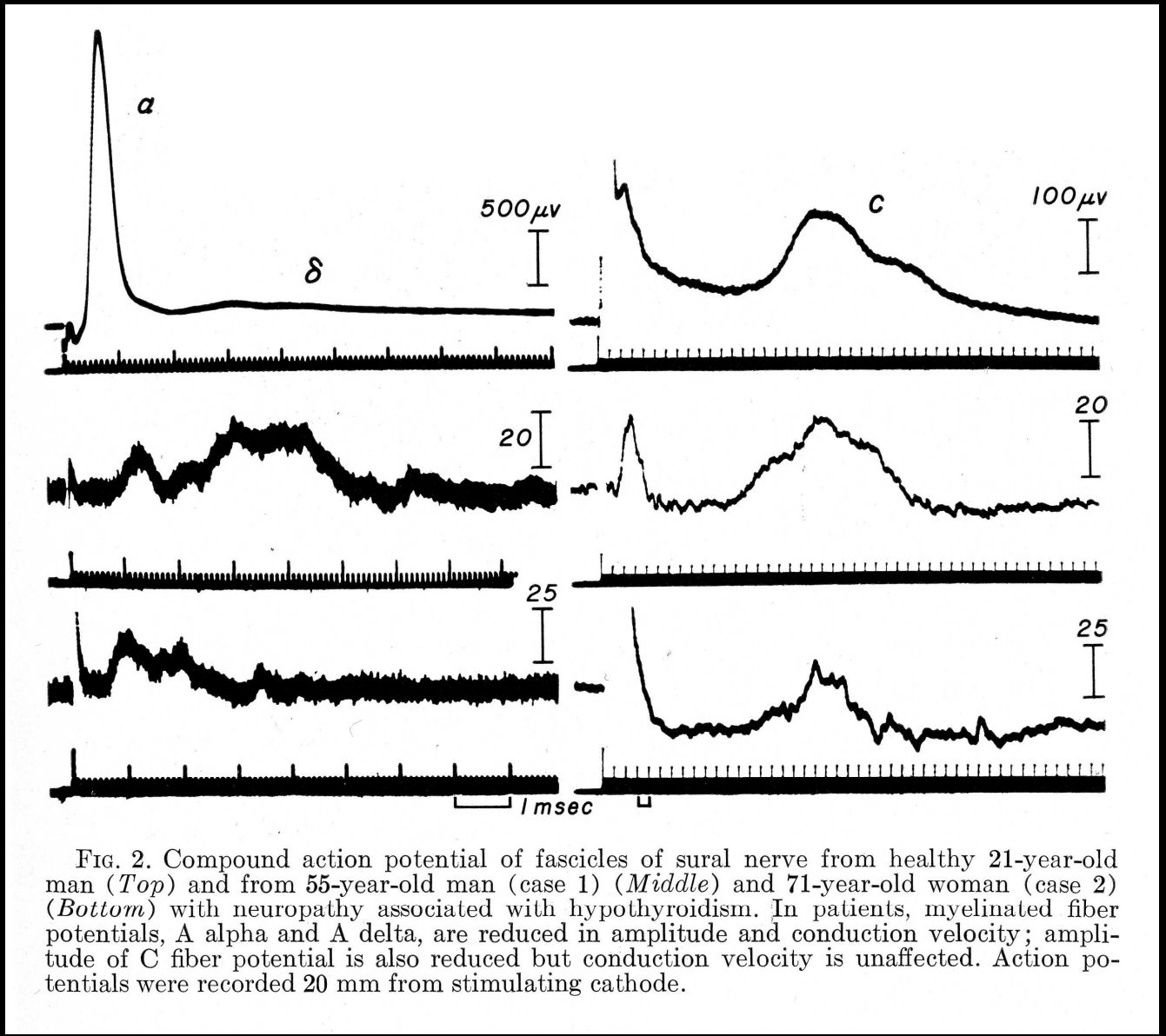


FIG. 2. Compound action potential of fascicles of sural nerve from healthy 21-year-old man (*Top*) and from 55-year-old man (case 1) (*Middle*) and 71-year-old woman (case 2) (*Bottom*) with neuropathy associated with hypothyroidism. In patients, myelinated fiber potentials, A alpha and A delta, are reduced in amplitude and conduction velocity; amplitude of C fiber potential is also reduced but conduction velocity is unaffected. Action potentials were recorded 20 mm from stimulating cathode.

Healthy
21 M

Hypothyroidism
55 M

Hypothyroidism
71 F

From: Dyck & Lambert, Journal of Neuropathology & Experimental Neurology, 1970

Polyneuropathy Associated with Hypothyroidism

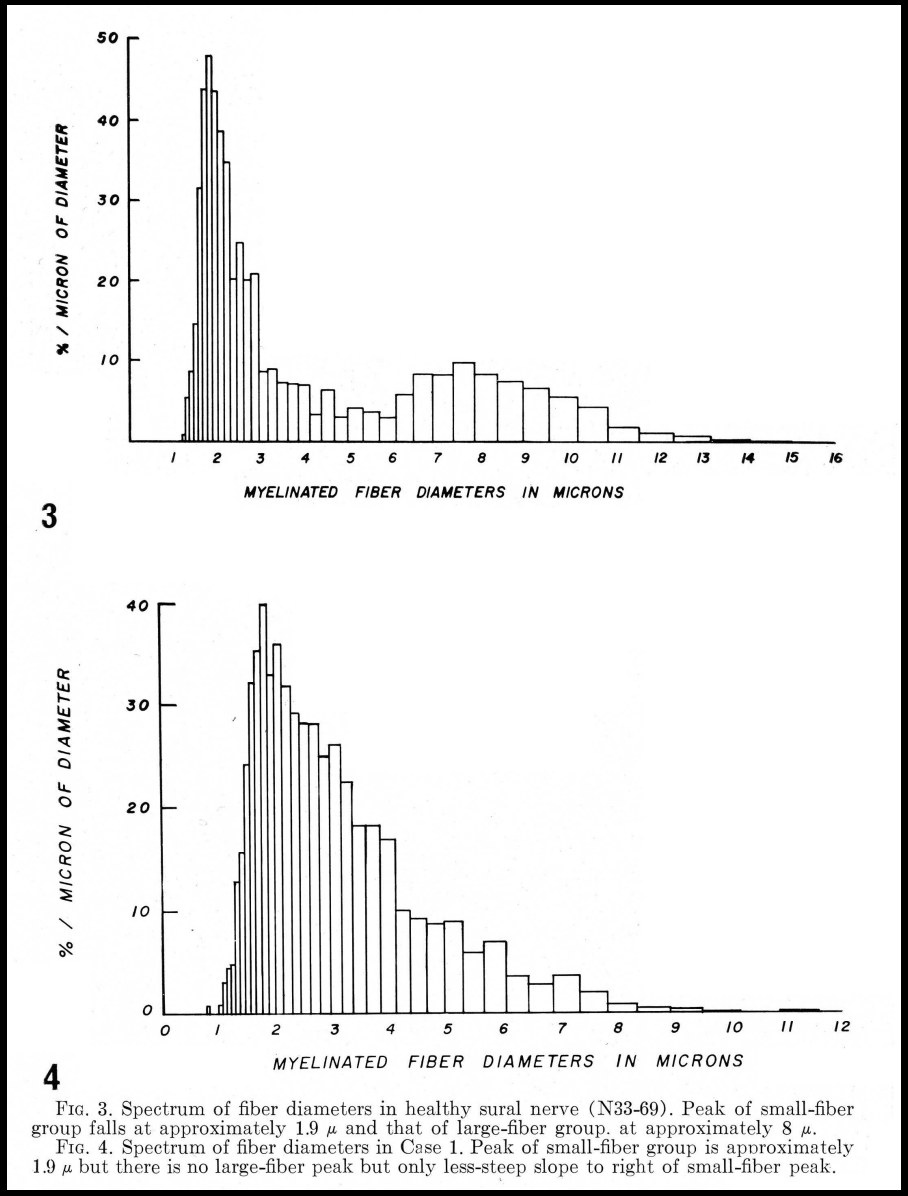


FIG. 3. Spectrum of fiber diameters in healthy sural nerve (N33-69). Peak of small-fiber group falls at approximately 1.9 μ and that of large-fiber group. at approximately 8 μ.

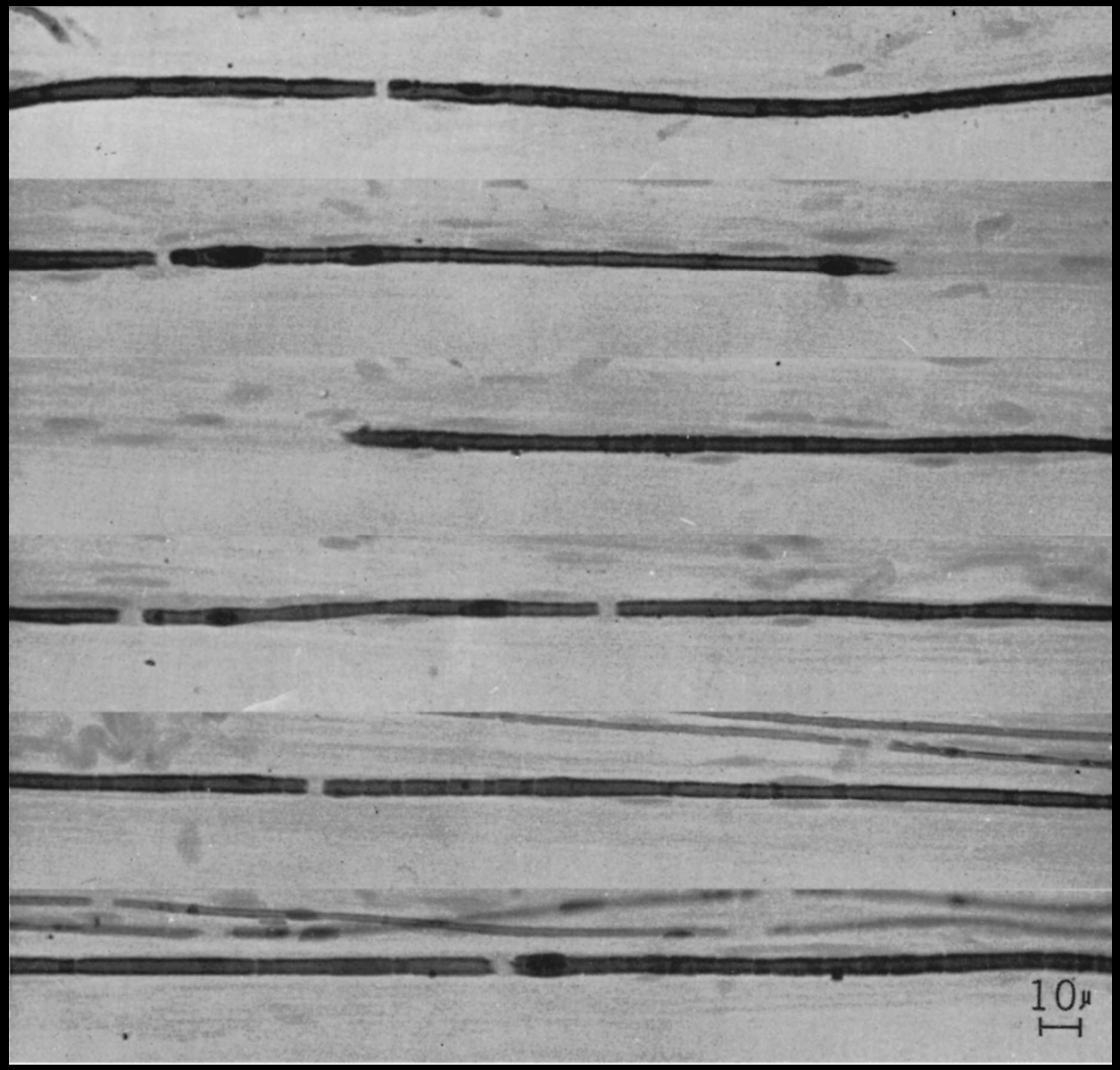
FIG. 4. Spectrum of fiber diameters in Case 1. Peak of small-fiber group is approximately 1.9 μ but there is no large-fiber peak but only less-steep slope to right of small-fiber peak.

Healthy sural nerve

Hypothyroidism

From: Dyck & Lambert, Journal of Neuropathology & Experimental Neurology, 1970

Polyneuropathy Associated with Hypothyroidism



From: Dyck & Lambert, Journal of Neuropathology & Experimental Neurology, 1970

Polyneuropathy Associated with Hypothyroidism

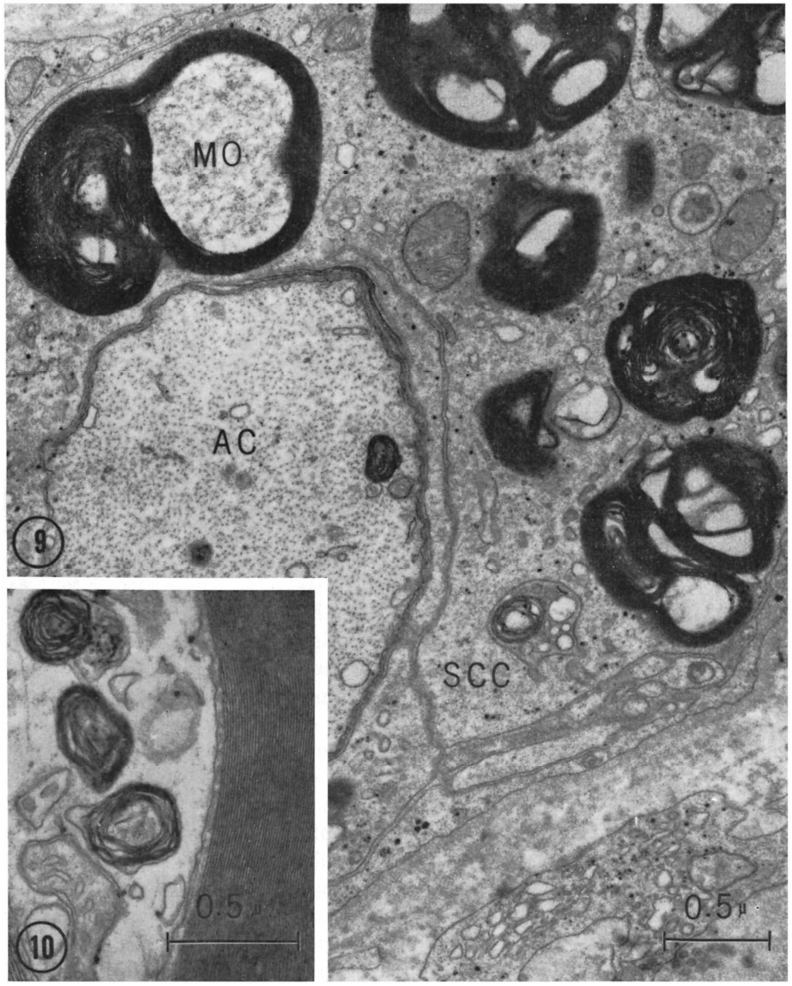


FIG. 9. Demyelinated internode of myelinated fiber from sural nerve in Case 1. Demyelinated internode (axis cylinder = *AC*) is surrounded by abundant Schwann cell cytoplasm (*SCC*) which contains myelin ovoids (*MO*) of various sizes, mitochondria, and endoplasmic reticulum; × 31,600.

FIG. 10. Portion of myelinated fiber from sural nerve in Case 1, showing degenerative changes within axis cylinder. Although myelin is intact, contents of axis cylinder are altered and lamellar bodies are present; × 39,520.

From: Dyck & Lambert, Journal of Neuropathology & Experimental Neurology, 1970

Polyneuropathy Associated with Hypothyroidism

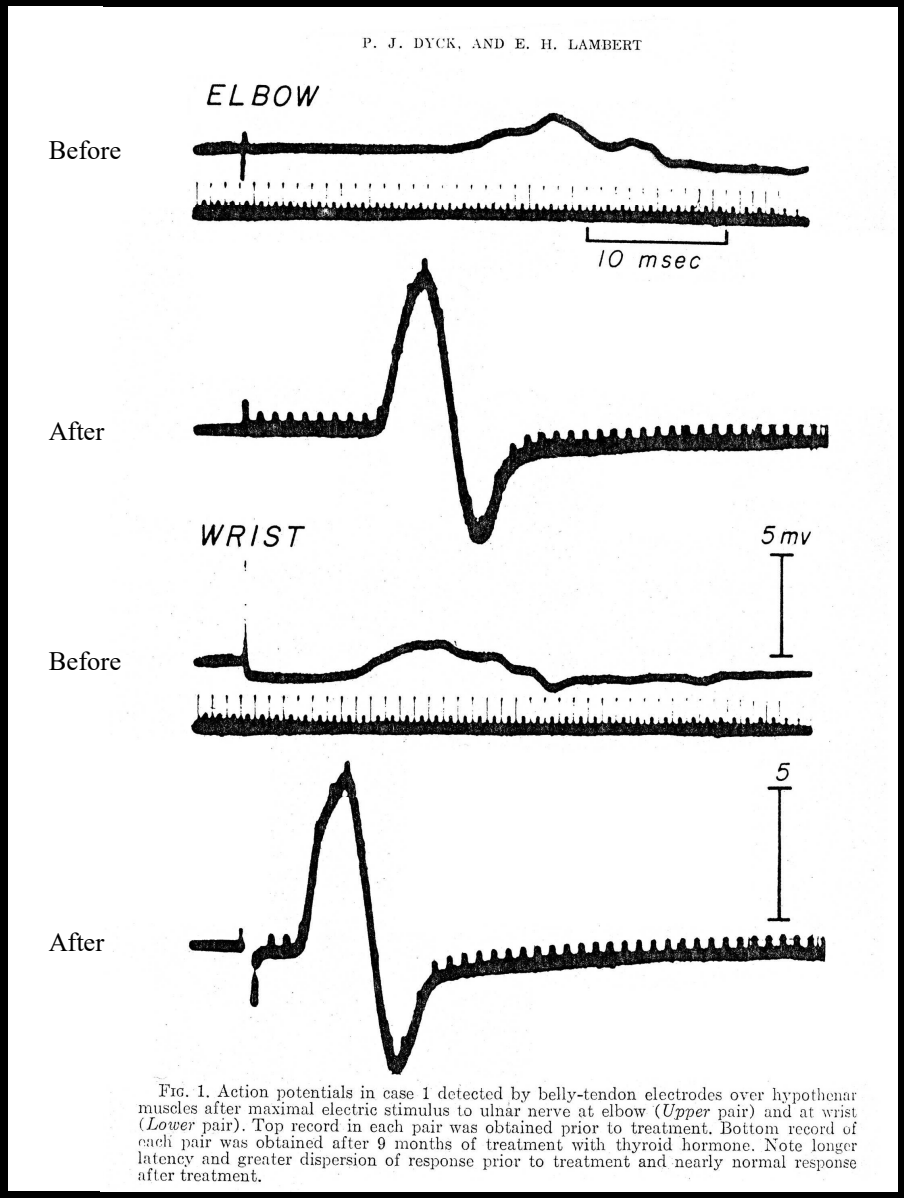


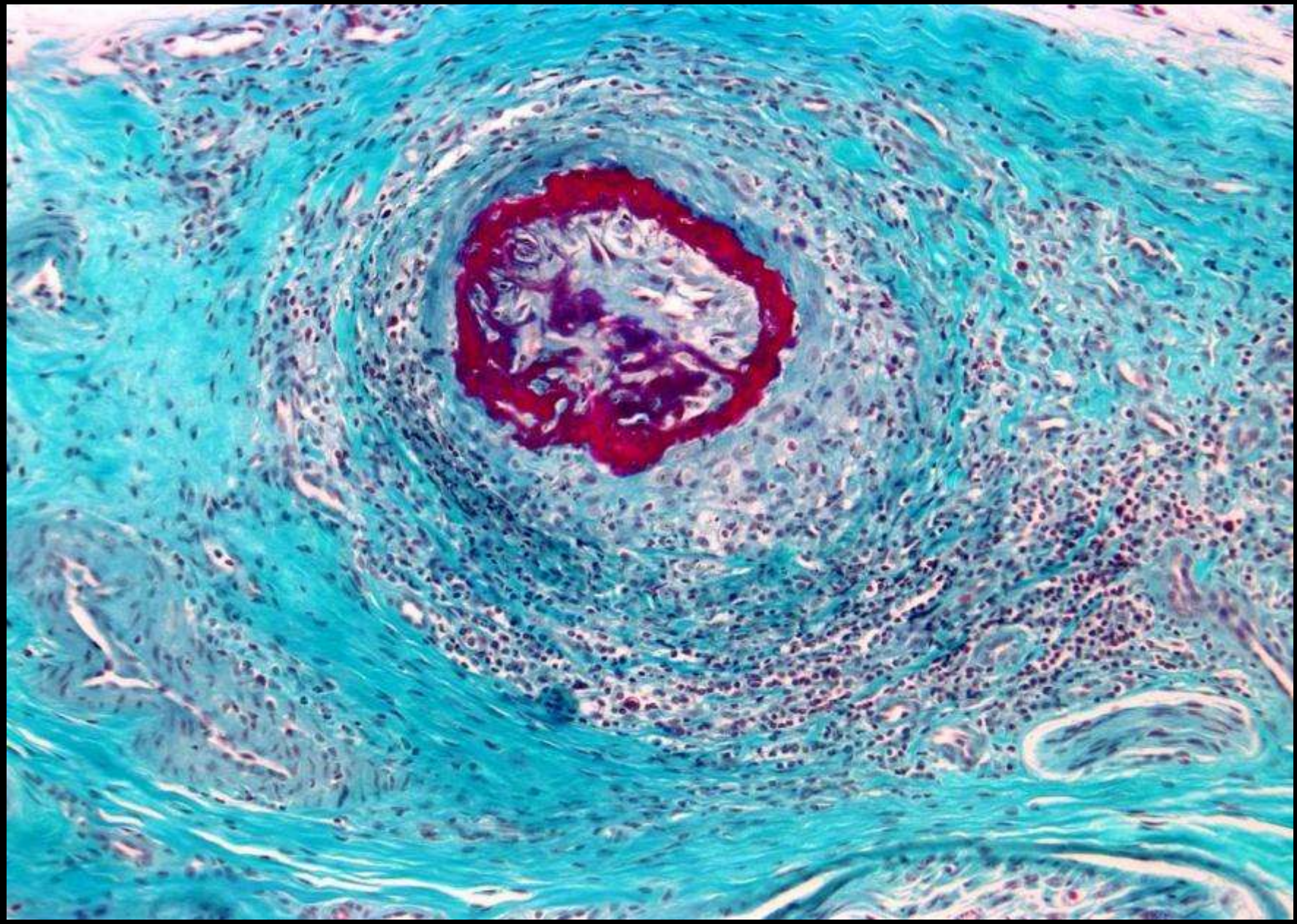
FIG. 1. Action potentials in case 1 detected by belly-tendon electrodes over hypothenar muscles after maximal electric stimulus to ulnar nerve at elbow (*Upper* pair) and at wrist (*Lower* pair). Top record in each pair was obtained prior to treatment. Bottom record of each pair was obtained after 9 months of treatment with thyroid hormone. Note longer latency and greater dispersion of response prior to treatment and nearly normal response after treatment.

From: Dyck & Lambert, Journal of Neuropathology & Experimental Neurology, 1970

Correlation of Nerve Conduction Abnormalities and Underlying Nerve Fiber Alteration

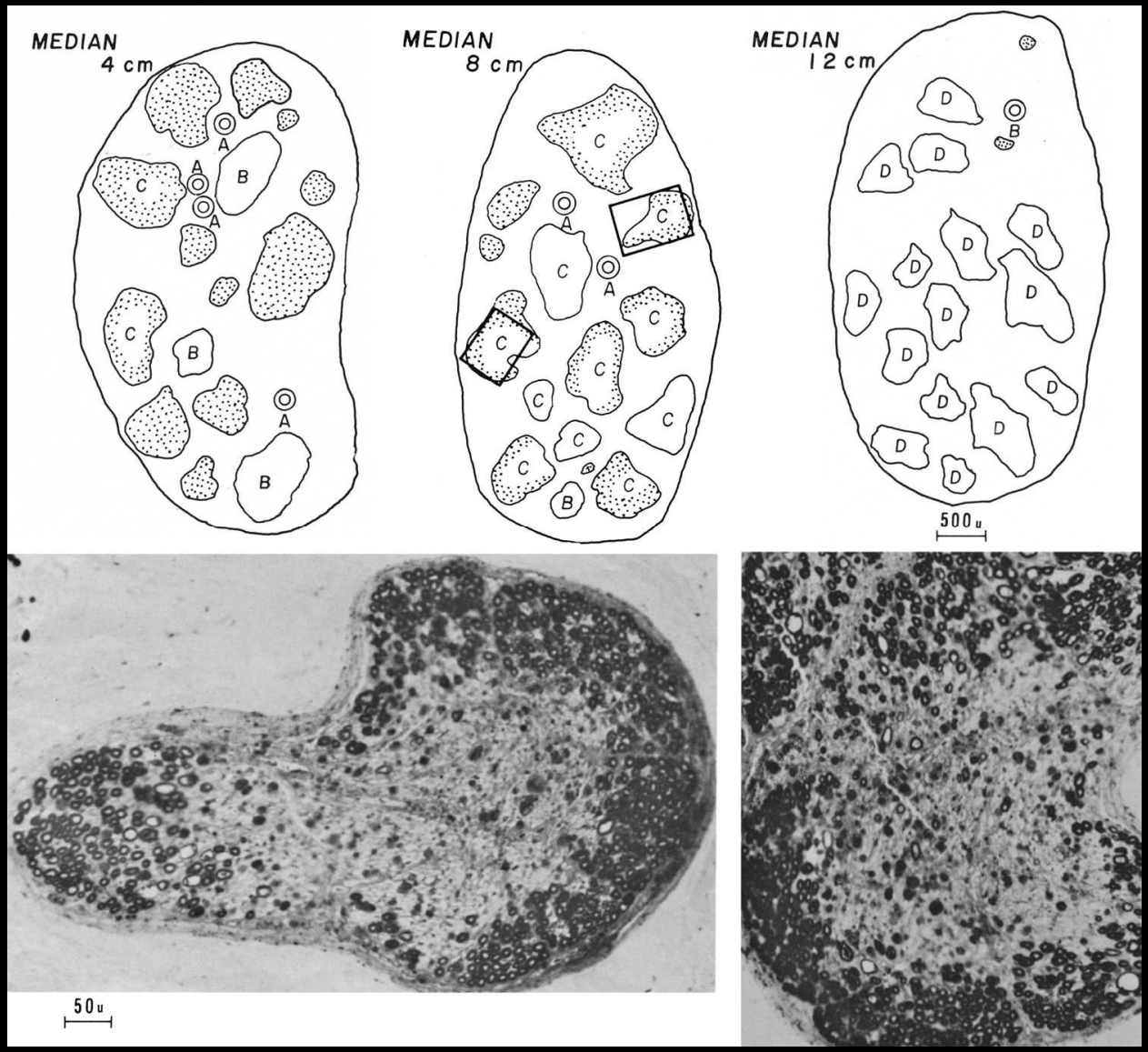
- Low CMAP/SNAP (normal CV)
  - axonal degeneration
  - loss of large fibers

Necrotizing Vasculitis with Fibrinoid Necrosis



From: Burns, Schaublin and PJB Dyck, Vasculitic Neuropathies, Neurologic Clinics, 2007

Rheumatoid Arthritis and Necrotizing Angiopathic Neuropathy
central fascicular fiber loss



From: Dyck et al, Mayo Clinic Proc., 1972

Friedreich's Ataxia

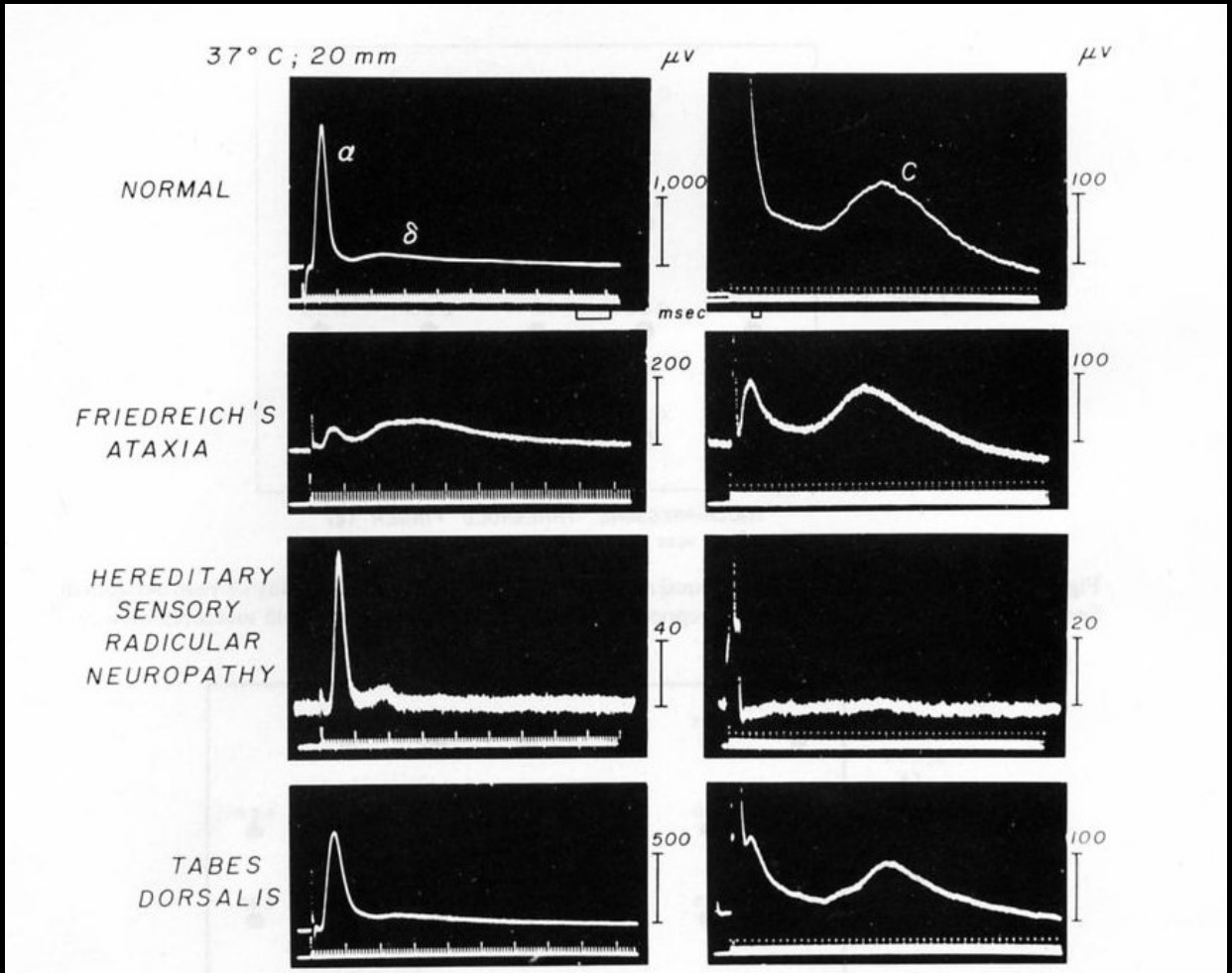
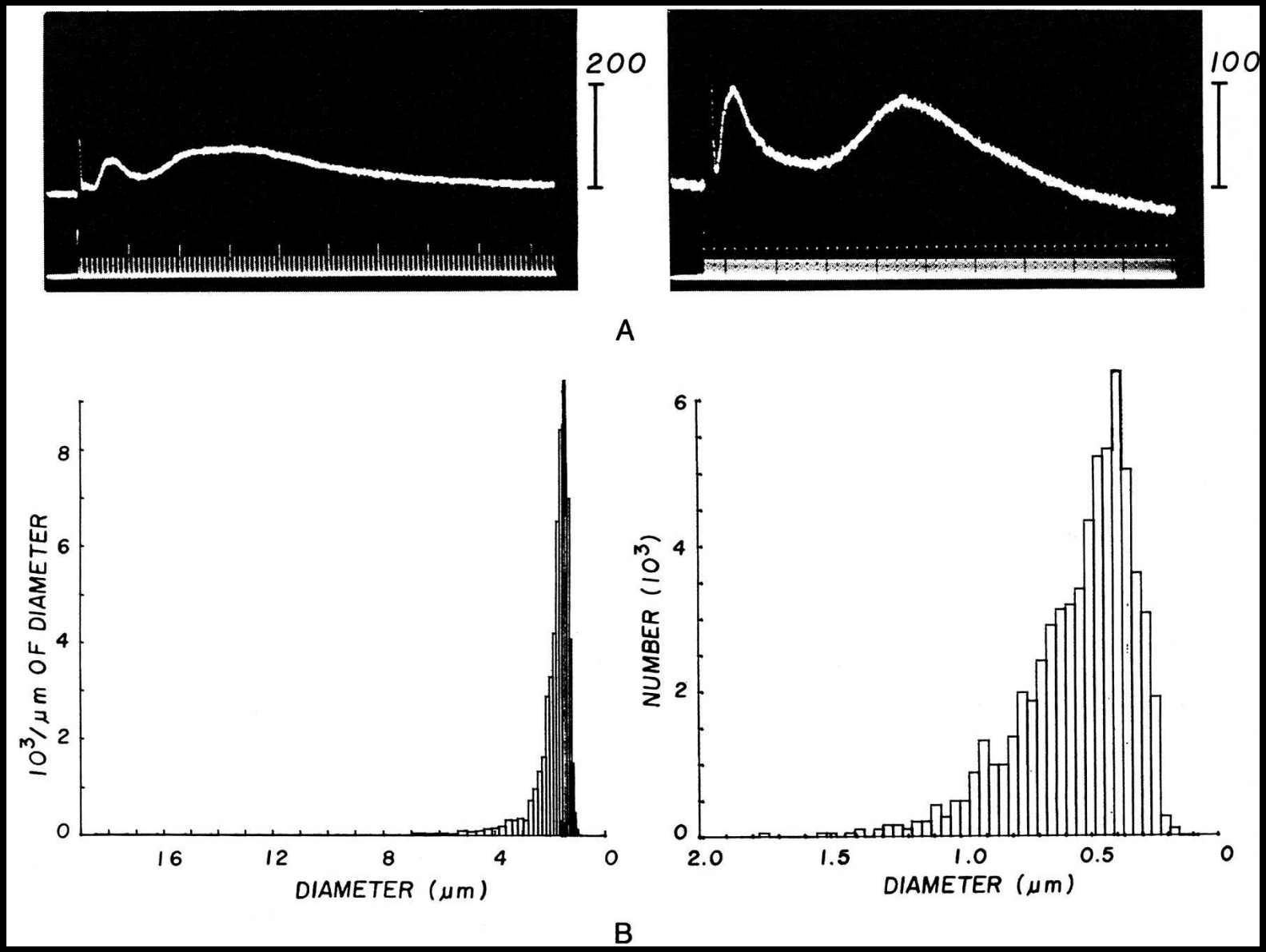


Fig. 18. Compound action potentials of sural nerve from a healthy person and from patients with Friedreich's ataxia, hereditary sensory radicular neuropathy and tabes dorsalis. Note great reduction in amplitude of A alpha potential in Friedreich's ataxia, the reduction in amplitude of all three peaks in hereditary sensory radicular neuropathy (greatest in the C potential, less in the A delta and least in the A alpha) and lack of abnormality in tabes dorsalis.

From: Dyck & Lambert et al, Handbook of Electroencephalography and Clinical Neurophysiology

Friedreich's Ataxia

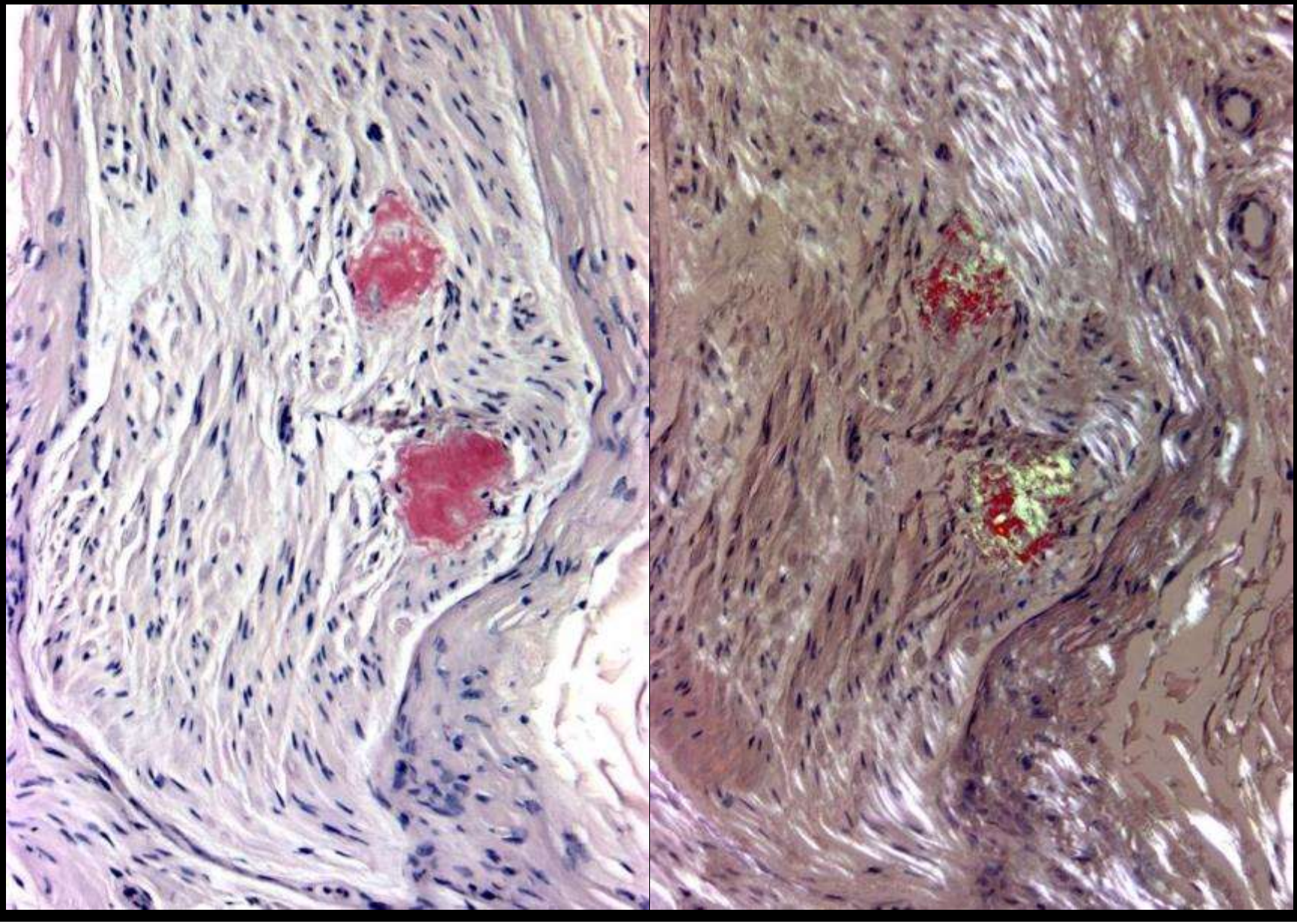


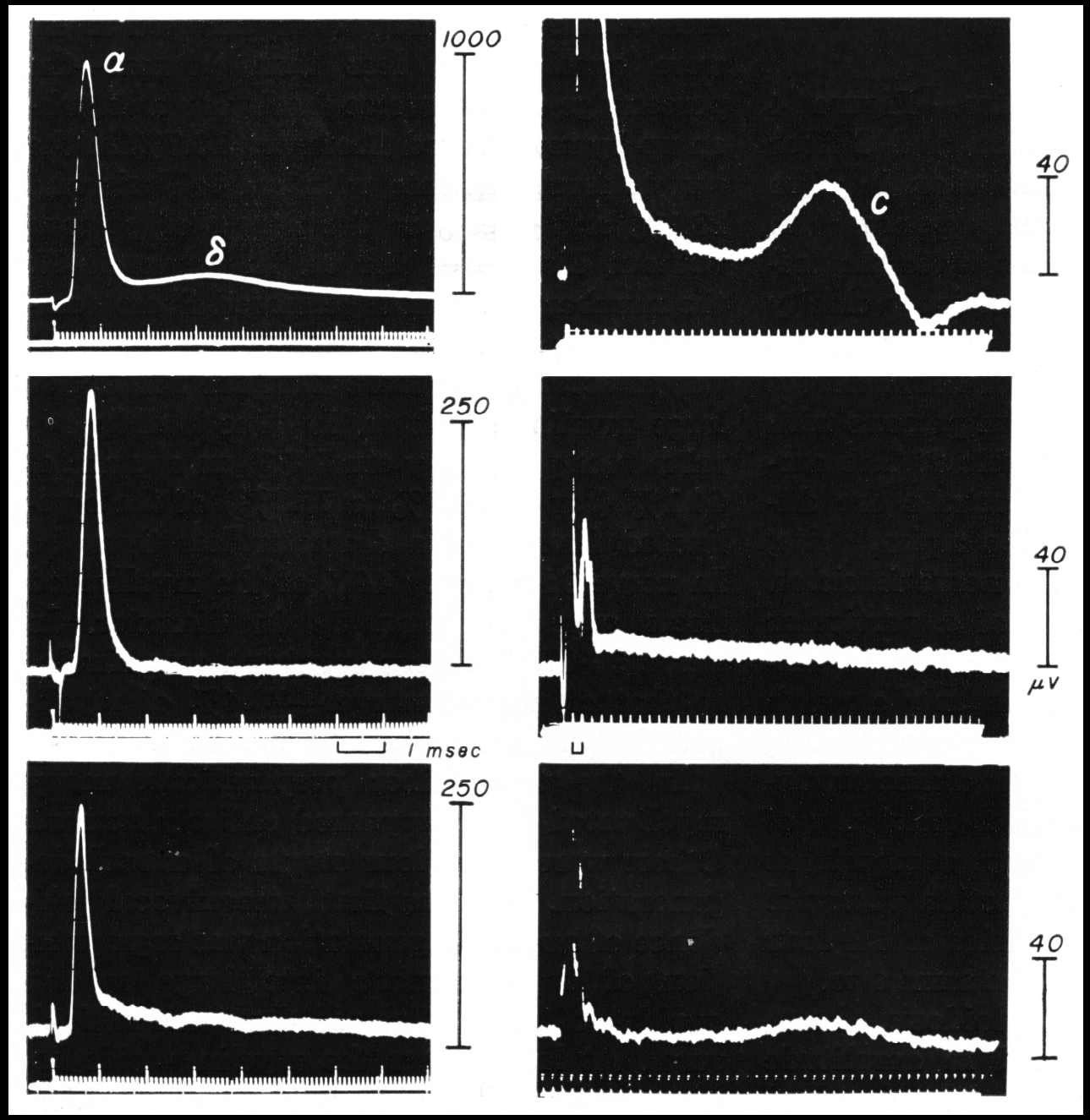
From: Lambert & Dyck, Peripheral Neuropathy 1st ed., 1975

Amyloid

congo red

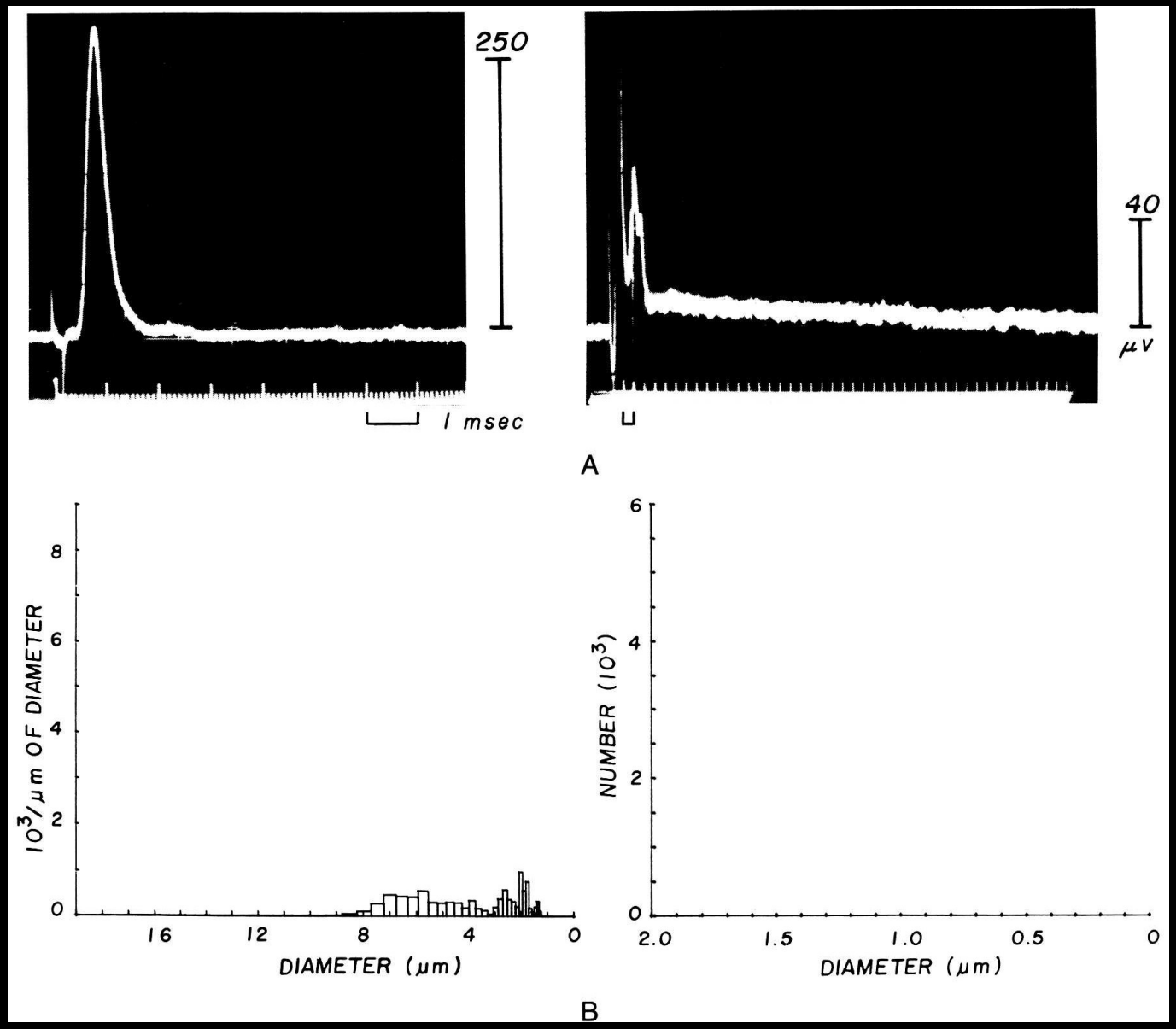
apple-green birefringence



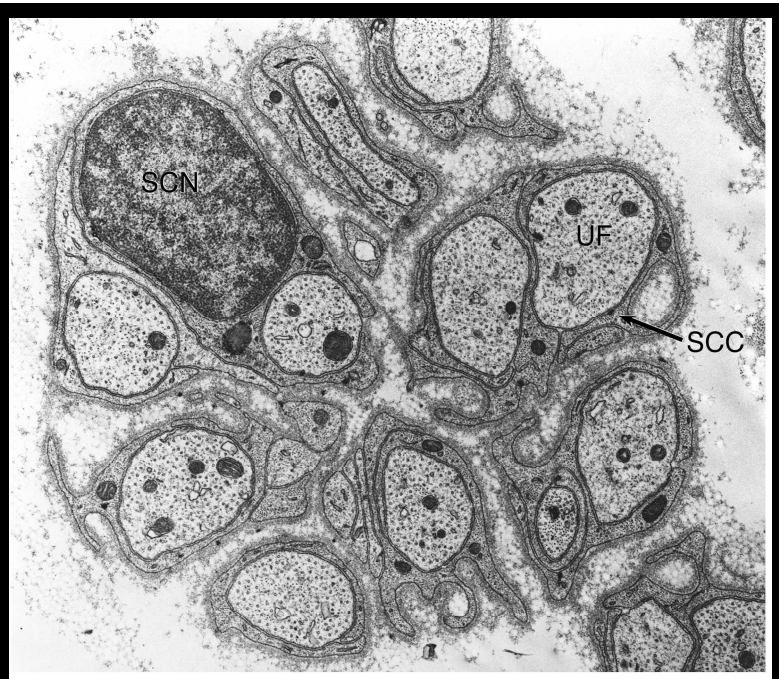


From: Dyck & Lambert, Archives of Neurology, 1969

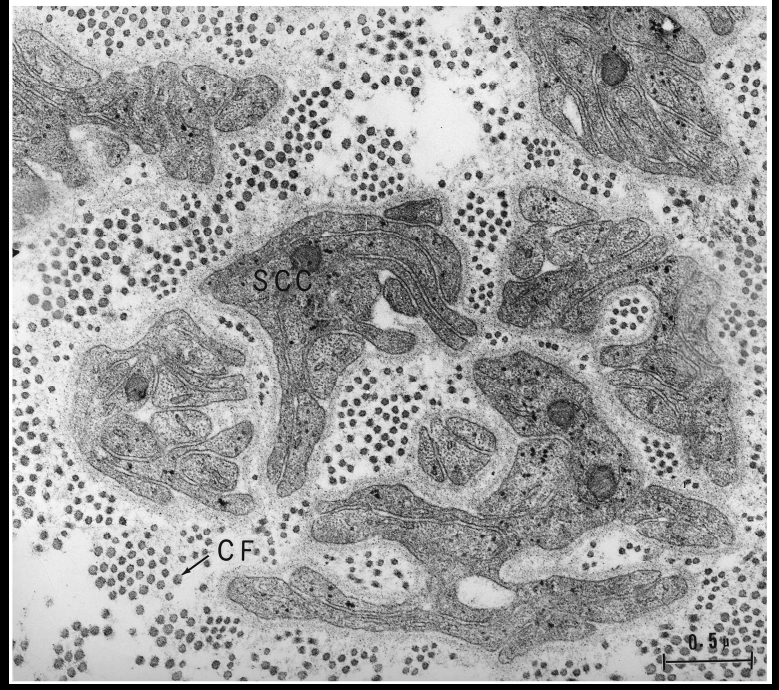
Amyloid



From: Lambert & Dyck, Peripheral Neuropathy 1st ed., 1975



Healthy subject



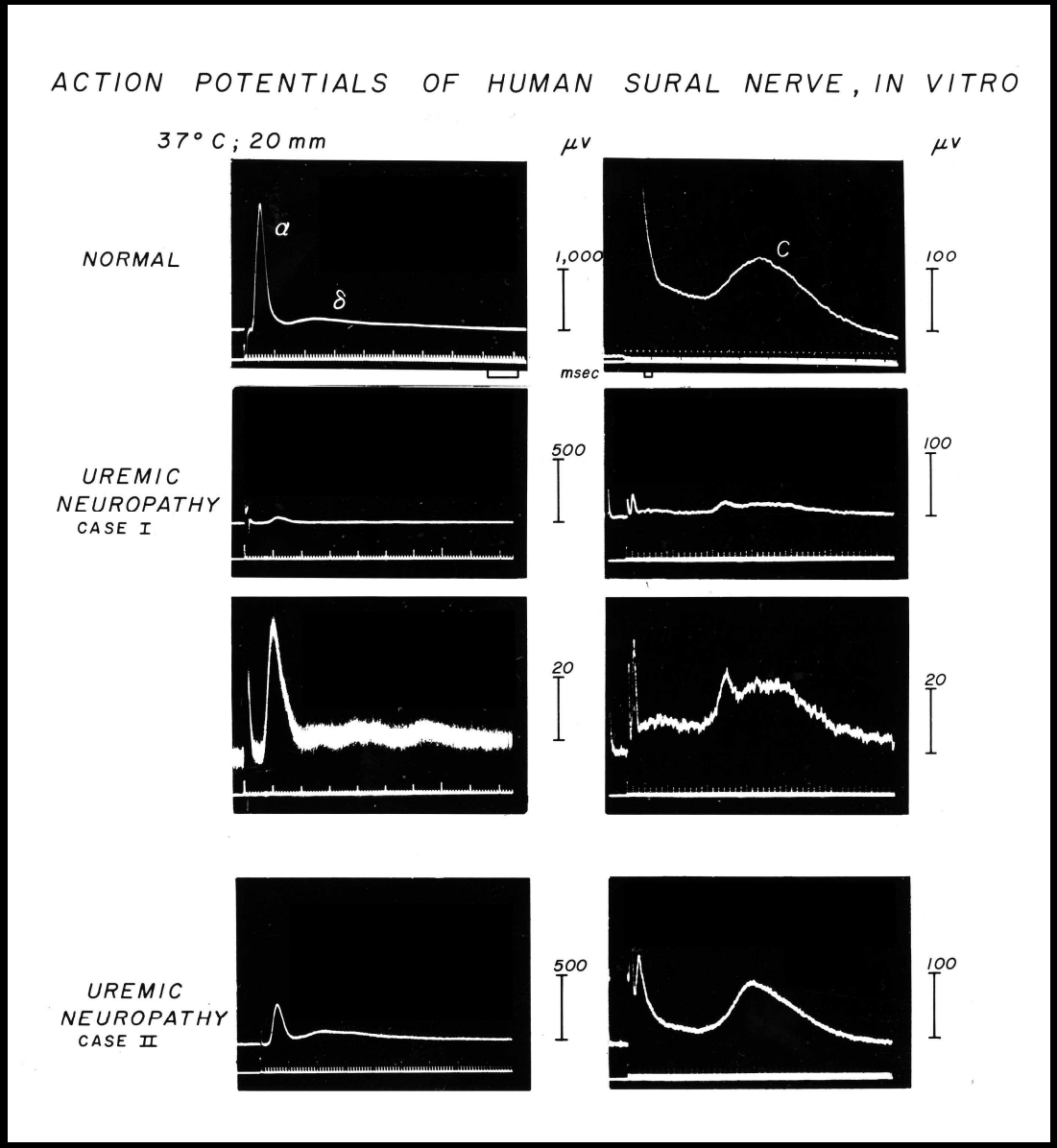
Amyloid

From: Dyck & Lambert, Archives of Neurology, 1969

Correlation of Nerve Conduction Abnormalities and Underlying Nerve Fiber Alteration

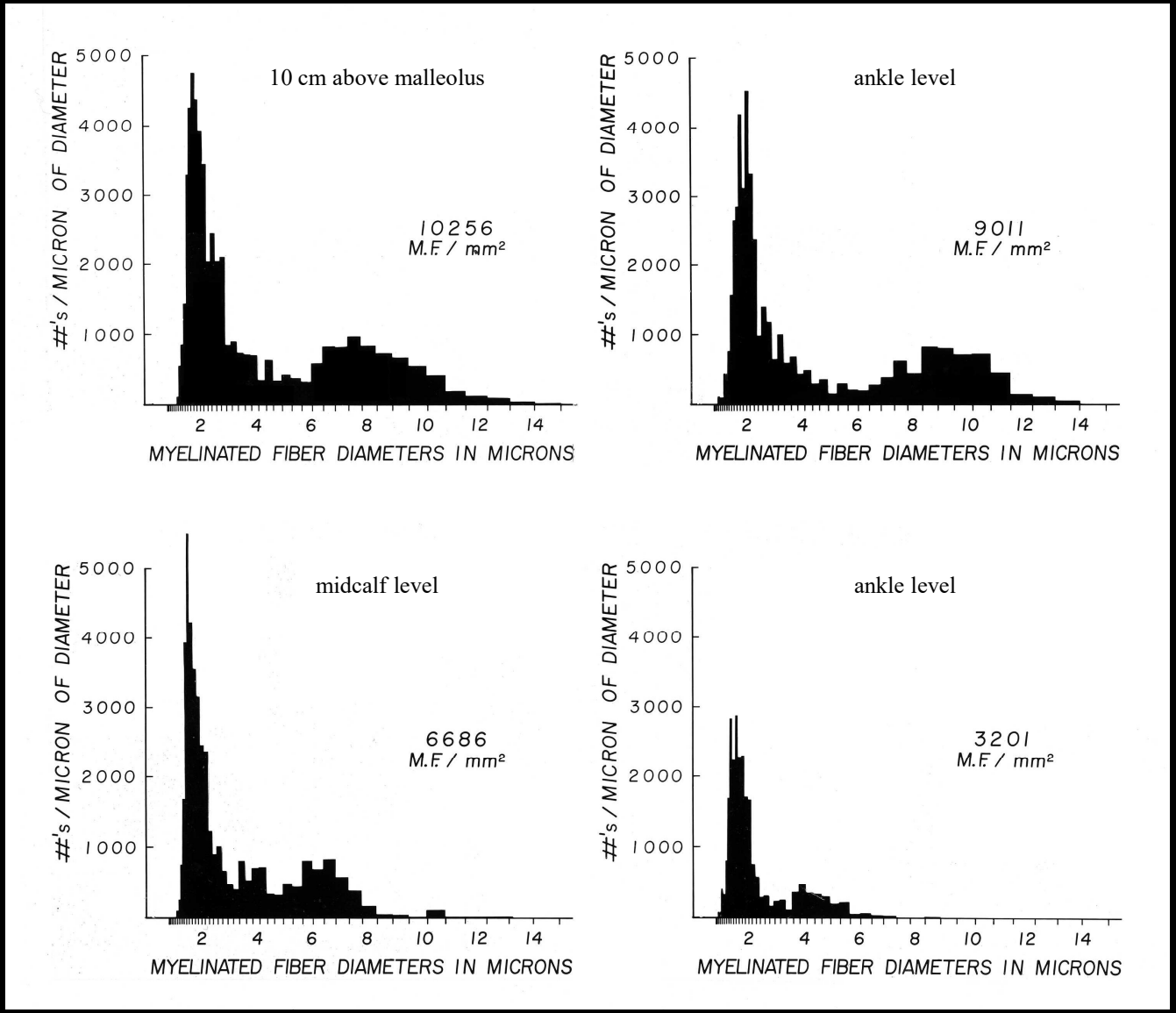
- Low CMAP/SNAP and low CVs
  - mixed axonal degeneration and demyelination
  - loss of large fibers
  - regeneration

Uremic Neuropathy



From: Dyck et al, Mayo Clinic Proc., 1971

Uremic Neuropathy
Myelinated Fiber Diameter in Sural Nerve

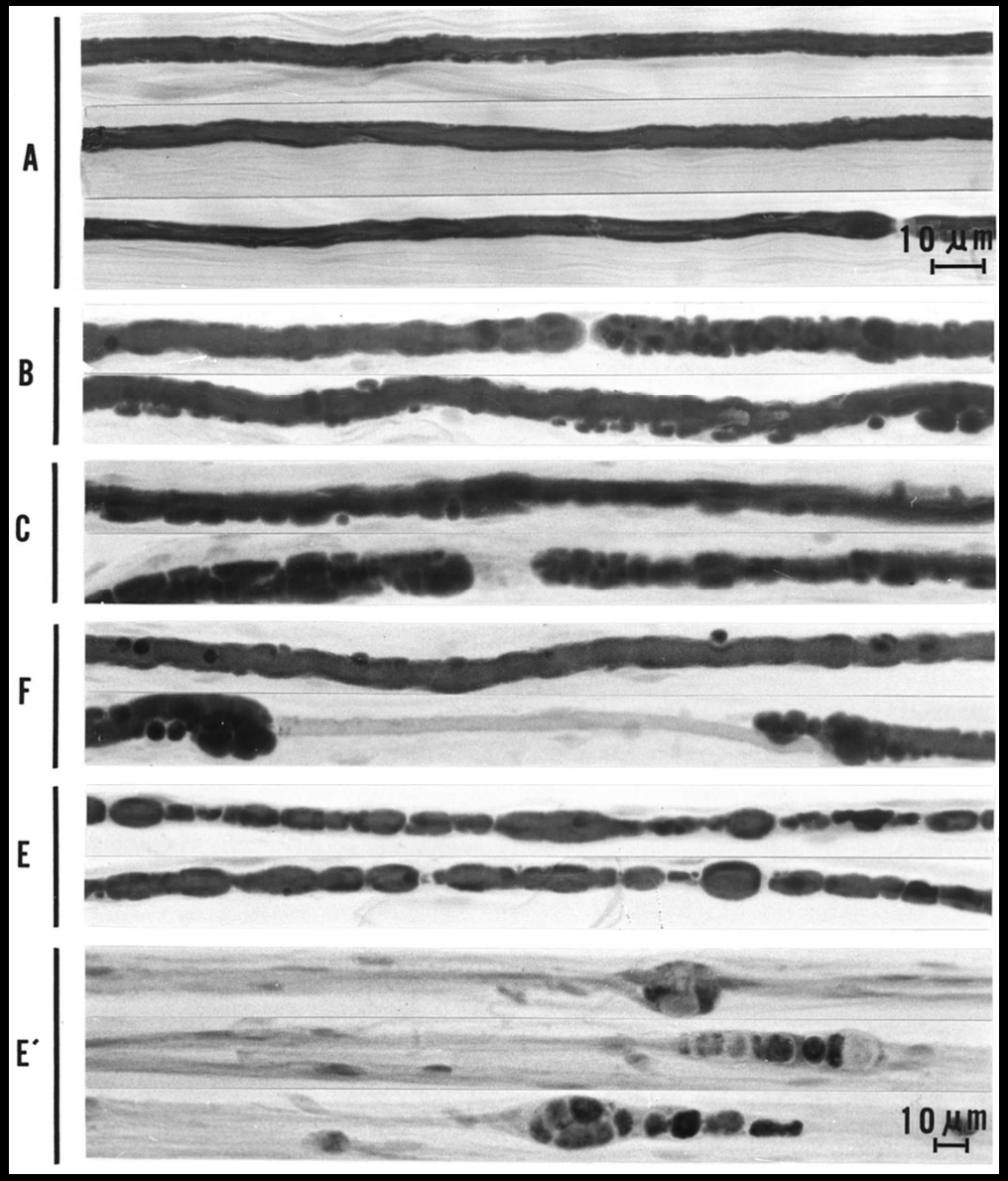


Healthy
23 year old

Uremic
neuropathy
24 M

From: Dyck et al, Mayo Clinic Proc., 1971

Uremic Neuropathy



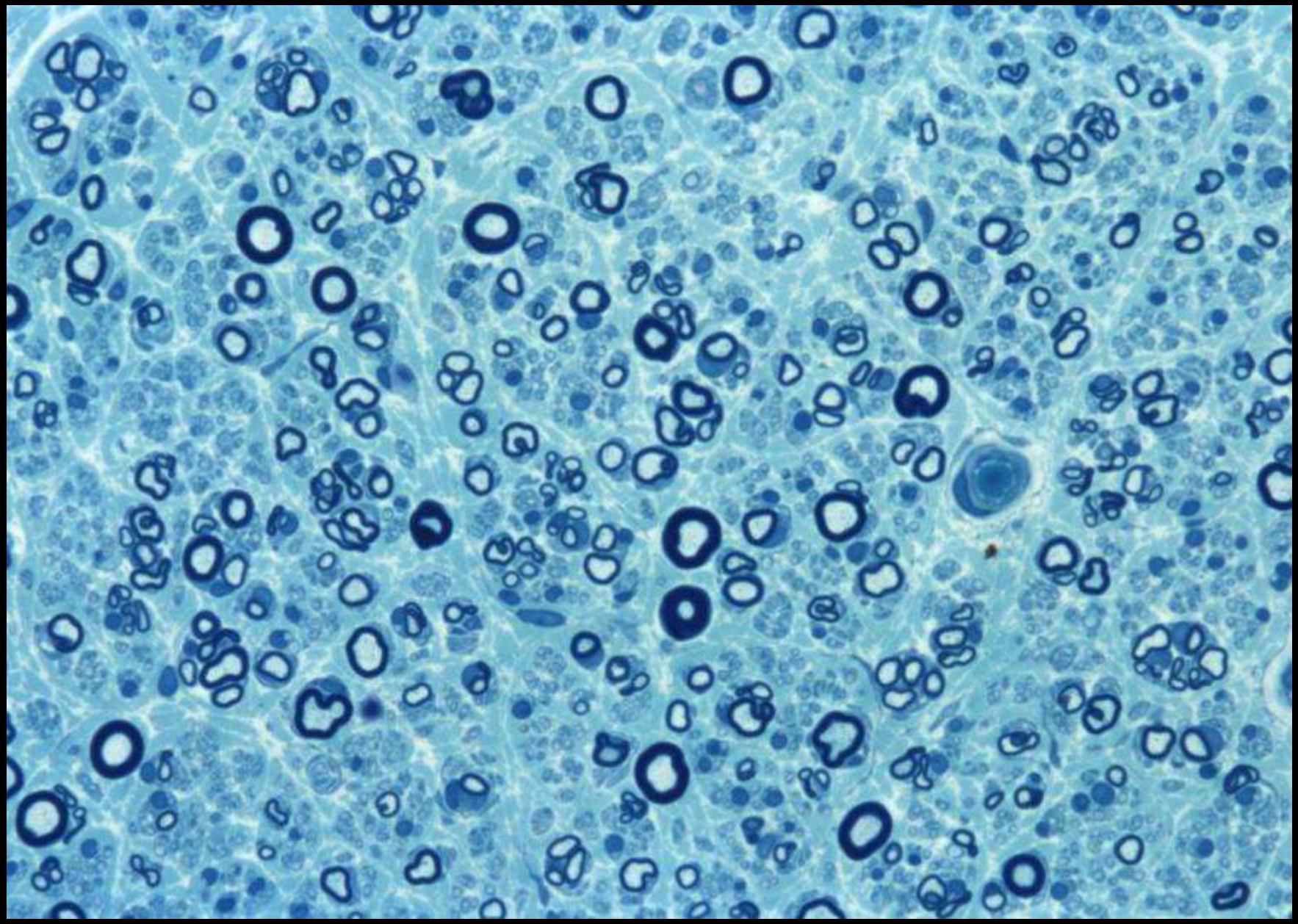
From: Dyck et al, Mayo Clinic Proc., 1971

Fiber Regeneration

48 M with mildly low CVs and prolonged F latencies

Stimulate (Record)	A (mV/μV)	CV (m/s)	DL (ms)	F (ms)
Median motor (APB)	10.6 (>4)	46 (>48)	4.0 (<4.5)	37.1 (<32)
Median sensory (Index)	18 (>15)	44 (>56)	3.4 (<3.6)	
Ulnar motor (ADM)	8.9 (>6.0)	50 (>51)	3.0 (<3.6)	36.9 (<32)
Ulnar sensory (Fifth)	12 (>10)	48 (>54)	3.4 (<3.1)	
Peroneal motor (EDB)	1.0 (>2)	34 (>41)	4.8 (<6.6)	78.2 (<58)
Sural sensory (Ankle)	0	-	NR	
Tibial motor (AH)	2.1 (>4)	31 (>40)	5.6 (<6.1)	78.2 (<58)

Regenerating Clusters – Loss of Large Fibers



Introduction to Fascicular Nerve Biopsies

- Whole distal cutaneous biopsies appropriate for most neuropathies.
- For asymmetric, motor predominant, focal or proximal neuropathies, a distal cutaneous nerve biopsy will miss the pathological process.
- Fascicular biopsies at the site of focal MRI lesions may be useful and have therapeutic implications.

Case 1

- 62 year old woman with pain and tingling of bottom of her left foot; unable to walk on tiptoes.
- Neurological examination and EMG showed a left tibial neuropathy.
- MRI showed increased T_2 signal and enlargement of the tibial nerve at the popliteal fossa.
- Whole sural and then fascicular tibial nerve biopsies were obtained.

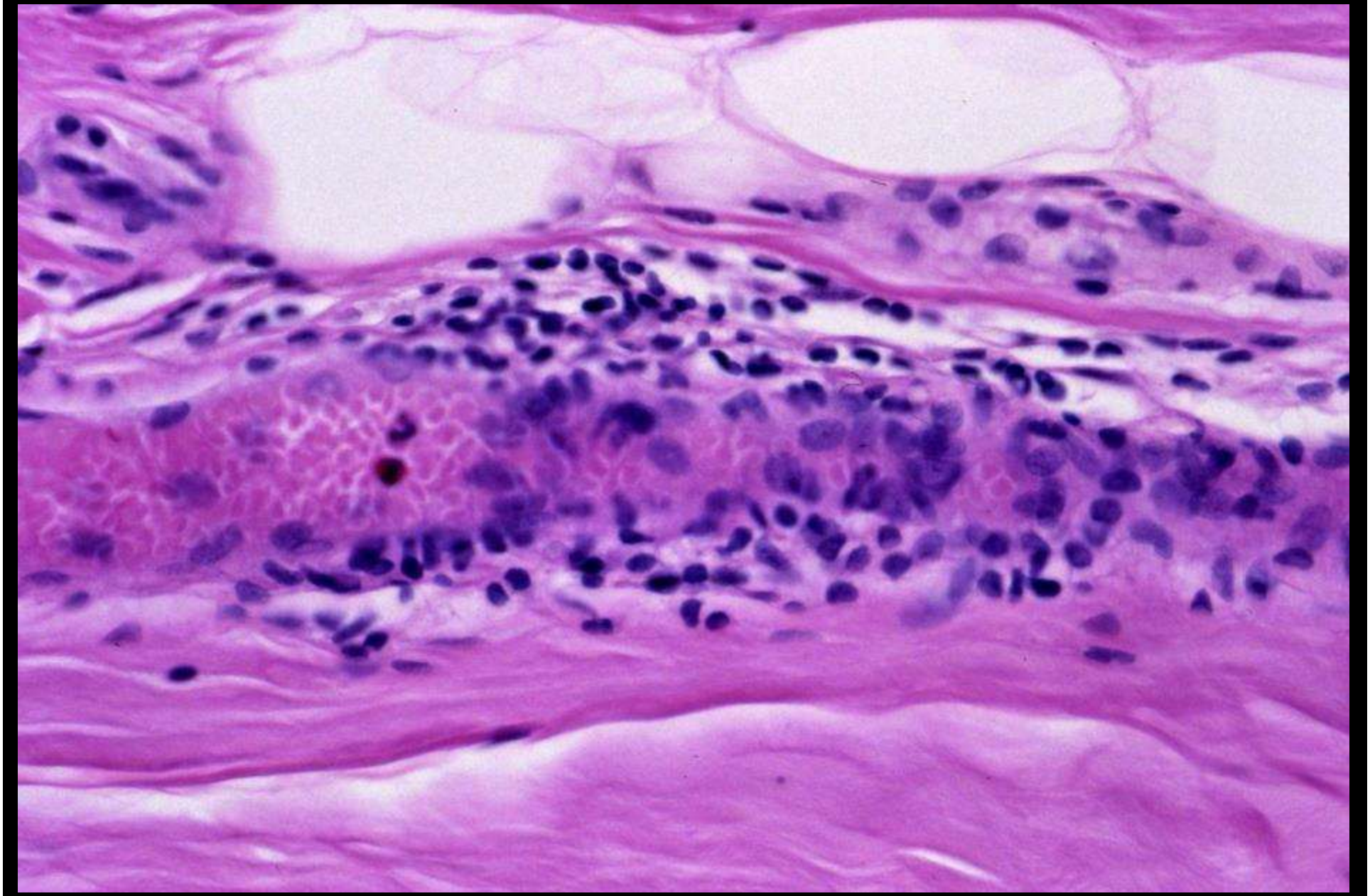
Nerve Conduction Studies

Stimulate (Record)	A (mV/μV)	CV (m/s)	DL (ms)	F (ms)
R. Peroneal motor (EDB)	3.2 (>2)	51 (>41)	4.0 (<6.6)	
L. Peroneal motor (EDB)	5.3 (>2)	47 (>41)	4.4 (<6.6)	44 (<58)
R. Sural sensory (Ankle)	13 (>0)			3.4 (<4.5)
L. Sural sensory (Ankle)	5 (>0)	52 (>40)	3.5 (<4.5)	
R. Tibial motor (AH)	13.4 (>4)	47 (>40)	3.6 (<6.1)	43.8 (<58)
L. Tibial motor (AH)	0 (>4)		NR	

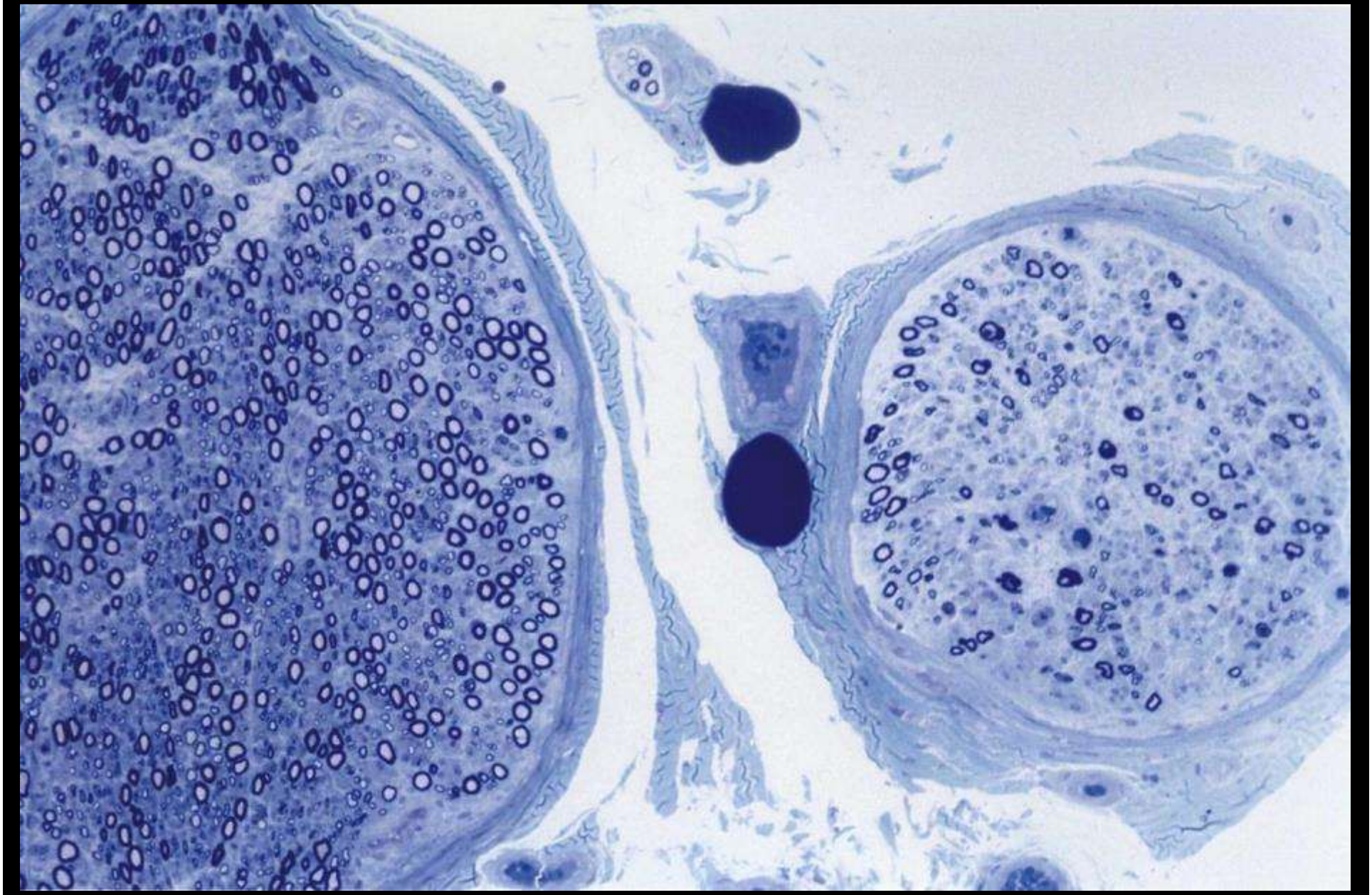
EMG

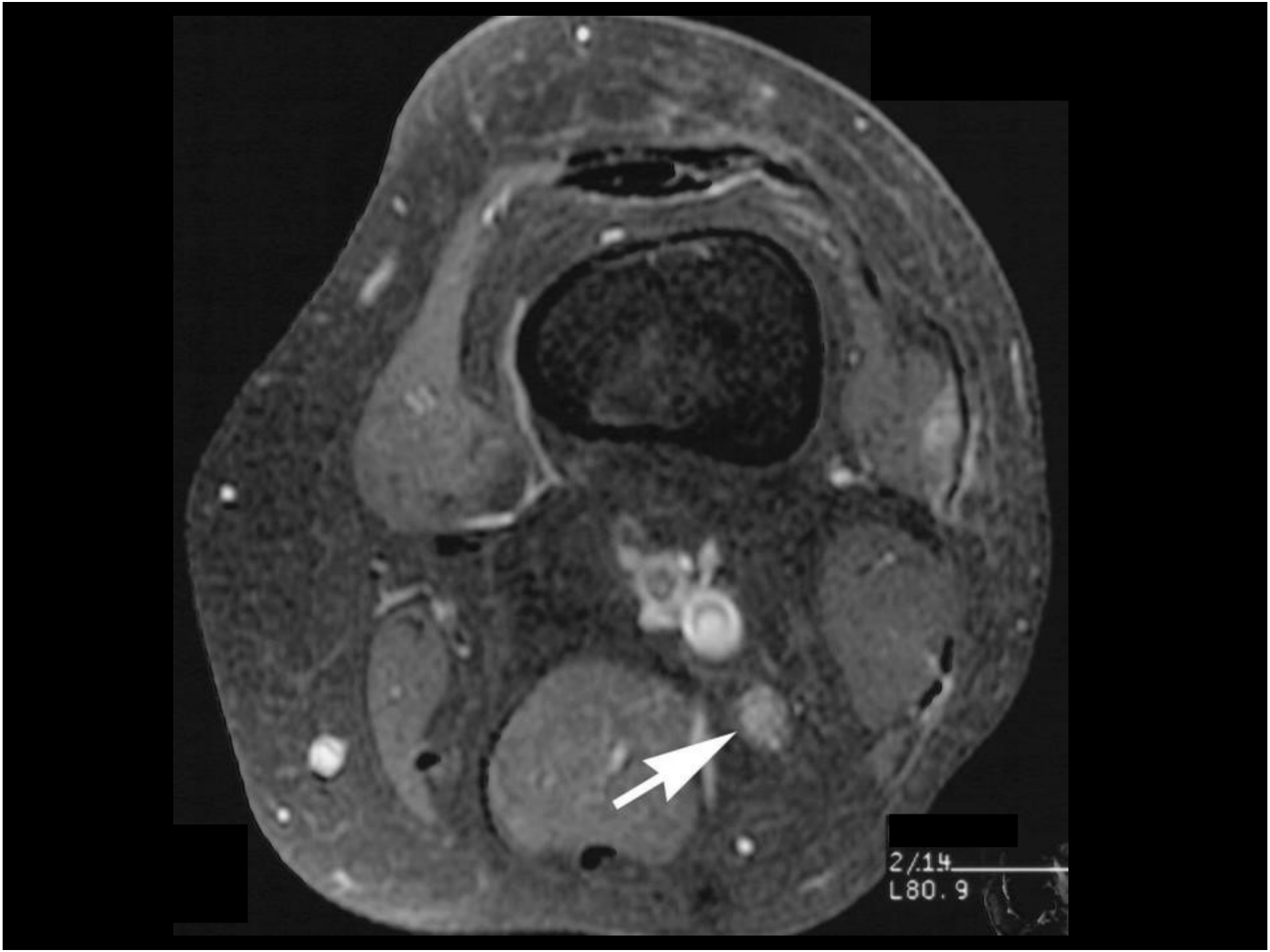
Muscle	Insertional activity	Fibrillation	Fasciculation	MUP
R. Gastrocnemius medialis	Normal	0	0	Normal
L. Abductor hallucis	Increased	+++	0	none
L. Gastrocnemius medialis	Increased	++	0	2 + big
L. Gluteus maximus	Normal	0	0	Normal
L. Peroneus longus	Normal	0	0	Normal
L. Semimembranosus	Normal	0	0	Normal
L. Tibialis anterior	Normal	0	0	Normal
L. Paraspinal lumbar (lower)	Normal	0	0	Normal
L. Biceps fem. (short head)	Normal	0	0	Normal

Sural



Sural

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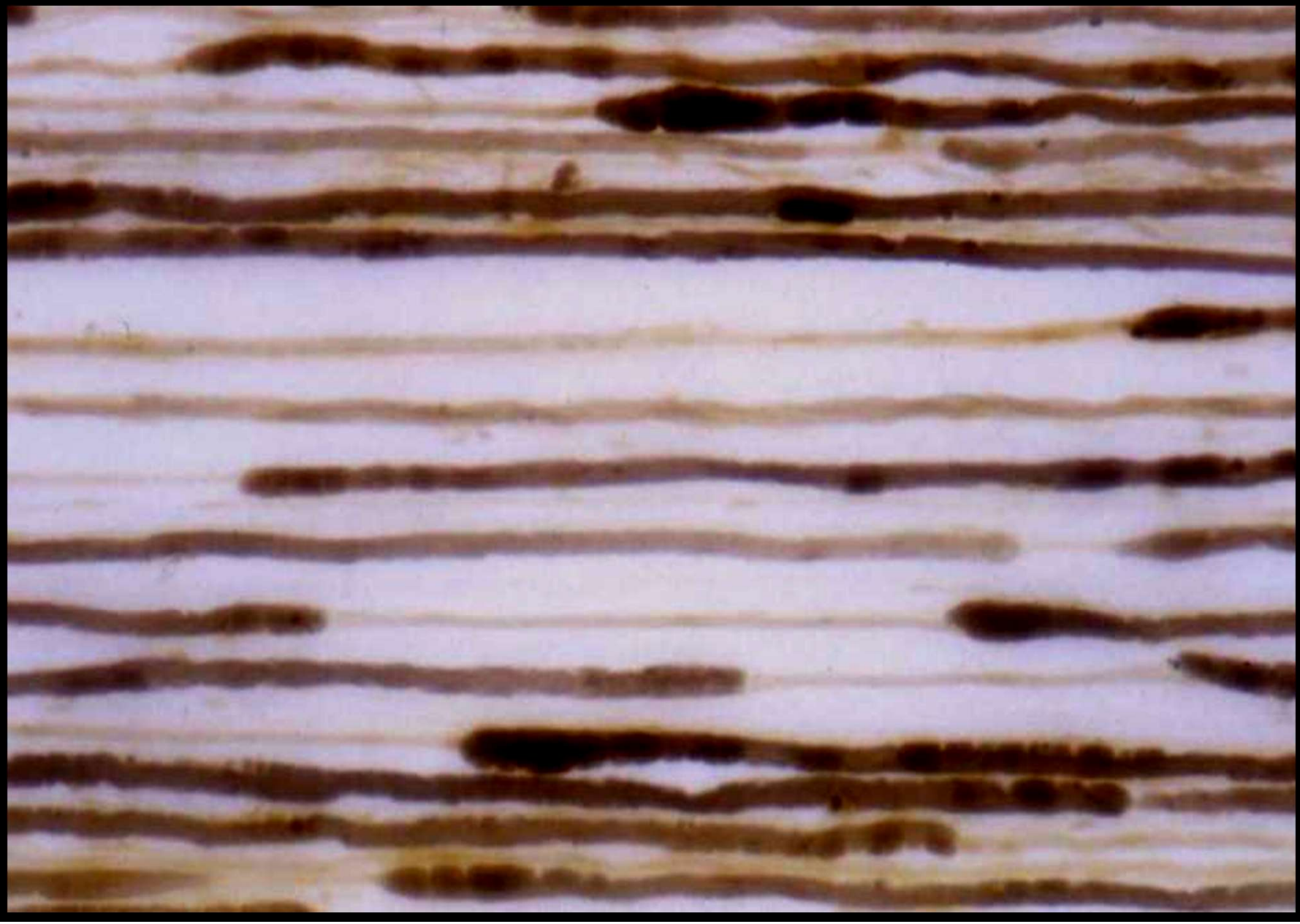
L80.9

Fascicular Tibial
Teased Fibers - Demyelination



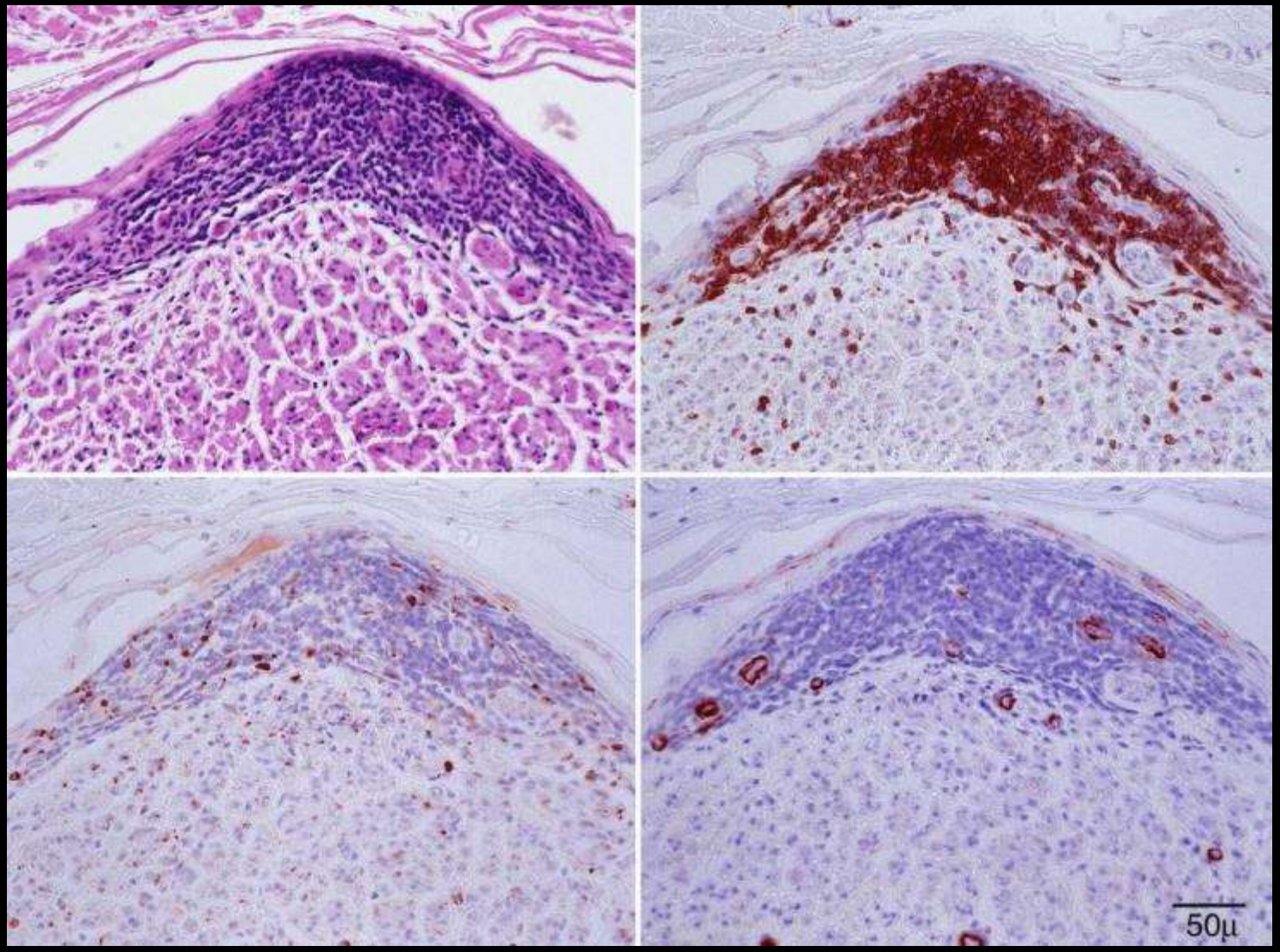
Fascicular Tibial

H&E

CD45

CD68

SMACTIN

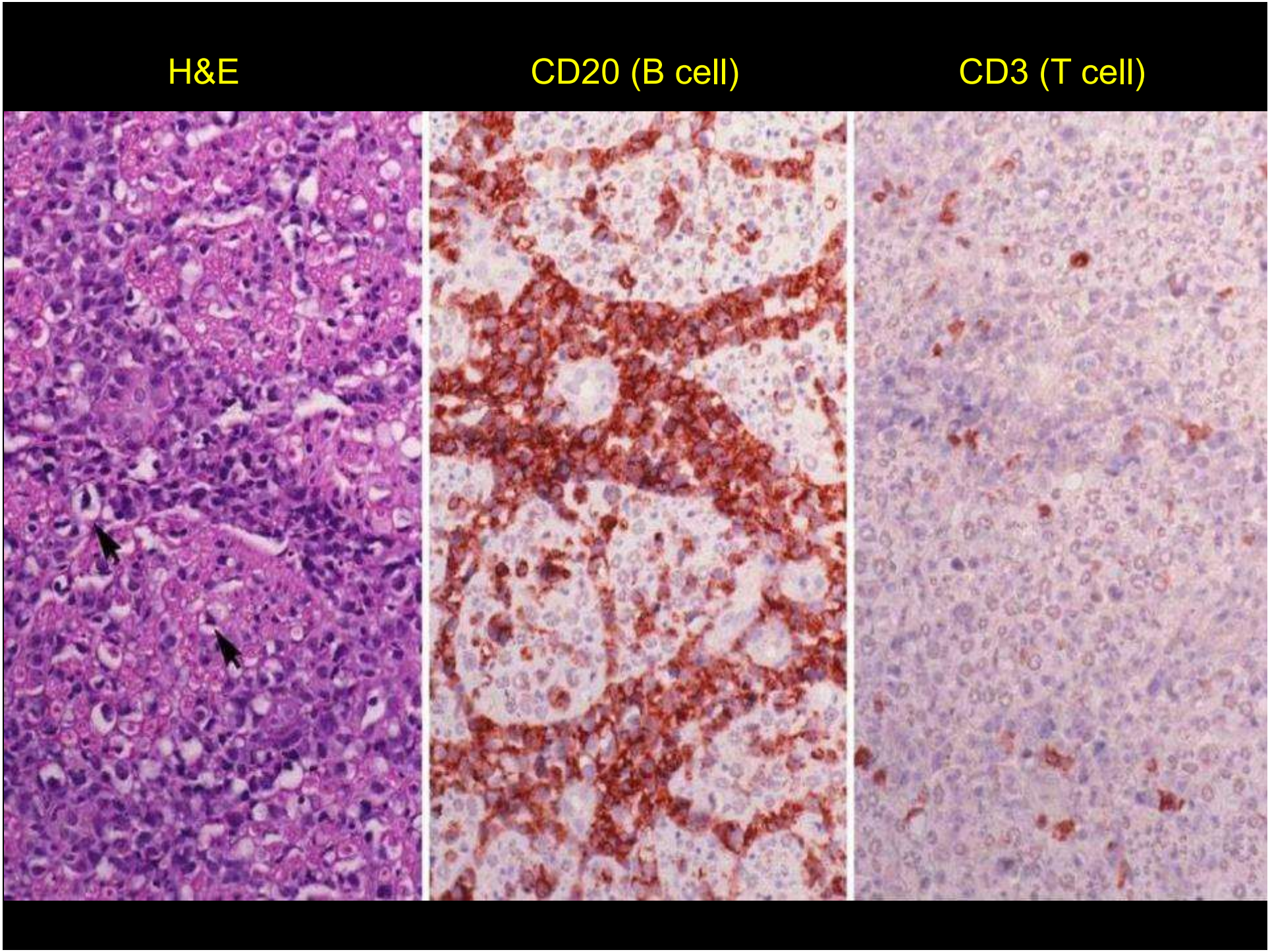


Case 1

- Pathology: inflammatory demyelination
- Diagnosis: chronic immune demyelinating mononeuropathy (CIDM)
- Treatment: PLEX

Case 2

- 37 year old man with subacute lower extremity pain and weakness (L>R).
- Hx of large B-cell lymphoma; treated with intrathecal methotrexate for lymphoma of the leptomeninges (CSF cytology negative).
- NCS/EMG showed bilateral lumbosacral plexopathy.
- MRI showed increased T_2 signal and enlargement of sciatic nerves and LS plexus.
- Whole sural nerve biopsy and then fascicular sciatic biopsy were obtained.


H&E
CD20 (B cell)
CD3 (T cell)

Case 2

- Pathology and diagnosis: B-cell lymphoma of nerve
- Treatment: high-dose chemotherapy followed by stem cell rescue
- Marked improvement – went back to being a martial arts instructor

Sparring with an invisible opponent

Martial arts expert battles rare and difficult cancer with the help of a team of Mayo experts

By anyone's standards, Greg Nelson is tough. The founder, owner and head coach at the Minnesota Martial Arts Academy in Minneapolis, Greg is one of the top martial artists in the world. He's also a former gymnast and collegiate wrestler. He expects a great deal from his body, and is familiar with the aches and pains that come with intense training and competition.

But in the spring of 2002, Greg began experiencing pain unlike any he'd known before. It started in his back and eventually moved down his body.

"I was taking pain medication, but it didn't do anything to relieve my symptoms," he says. "And I was incredibly rundown."

Greg's physician ran him through a battery of tests. On Memorial Day 2002, a CAT scan revealed that Greg had stage IV non-Hodgkin's lymphoma. The cancer had spread to his liver and spleen. The news was a shock, but there was a measure of relief in finally having an opponent to fight.

"Once we knew what was wrong, we were prepared to deal with it," says Greg's wife, Vee. "Not knowing was the hard part."

Greg immediately started a six-month course of chemotherapy, and was overjoyed when his back pain disappeared. After his fifth month of chemotherapy, tests revealed that his cancer had gone into remission.

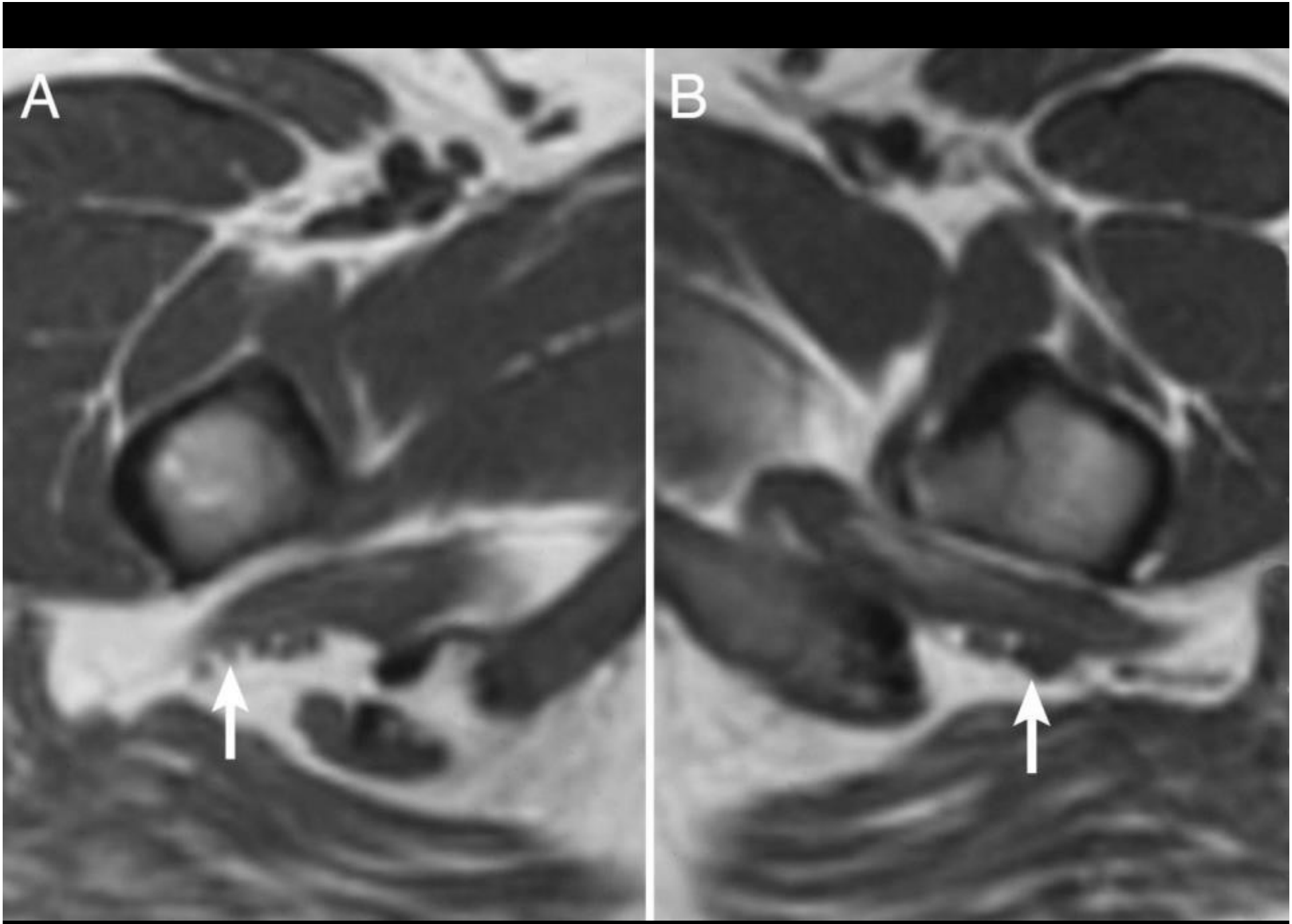
Greg thought he'd wrestled another opponent into submission. But he would soon learn his battle with cancer was only beginning. A new pain emerged. And finding the cause this time was even more difficult. Coming up with a diagnosis would take a great deal of detective work by a team of Mayo Clinic specialists.

Unraveling a mystery

When the new pain emerged, it moved down Greg's body, and his muscles began to weaken. The 38-year-old, who just a year earlier had been winning gold medals in international jujitsu competitions, came to rely on a cane to help him walk. At home, he would drop to the floor and crawl from room to room rather than walk on legs that throbbed with pain.

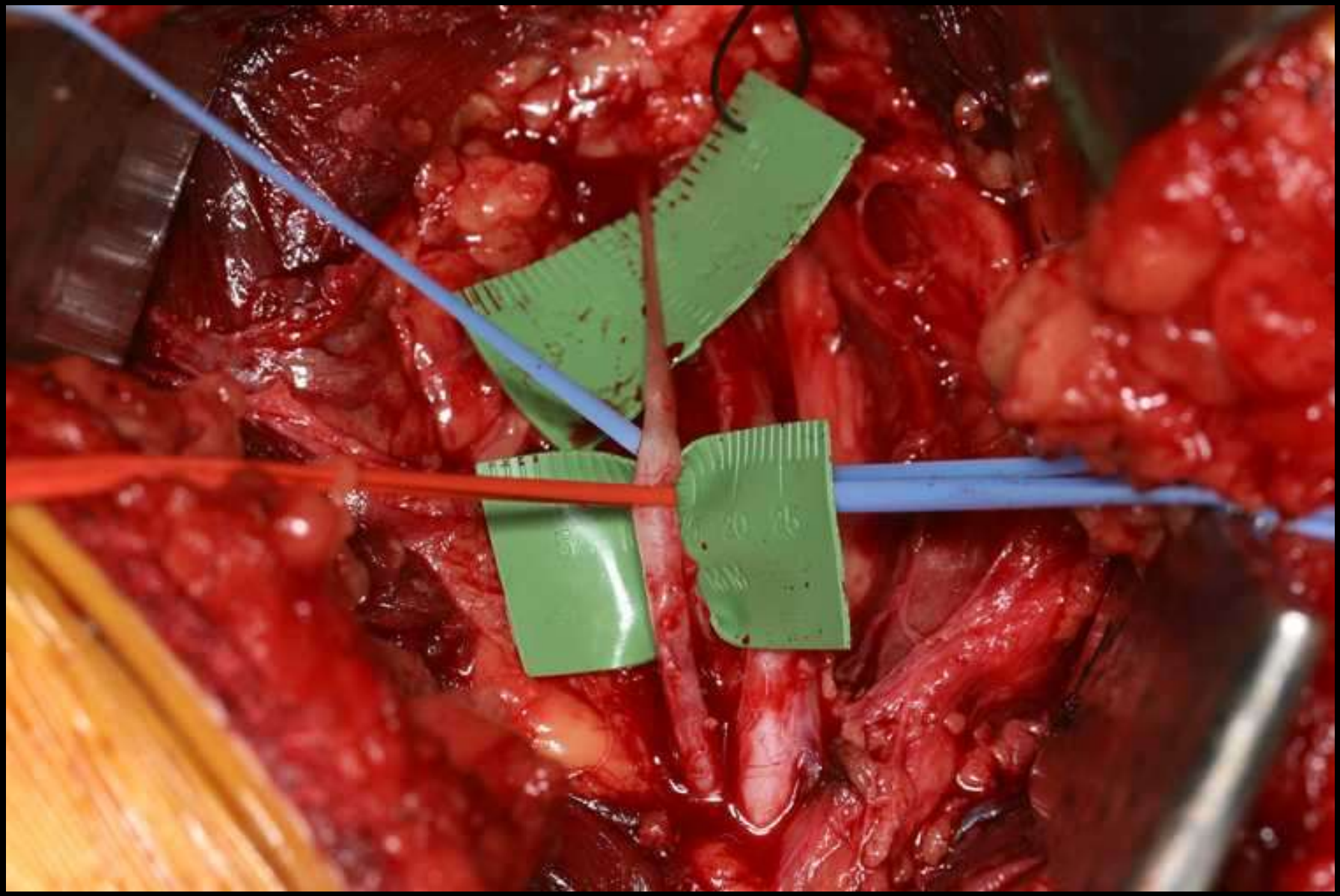
Case 3

- 16 year old girl with 5 years of left foot drop and numbness. No pain.
- Neurological examination and EMG showed a left sciatic neuropathy, peroneal more than tibial.
- MRI showed mild proximal sciatic nerve enlargement and increased T_2 signal.
- A left fascicular sciatic biopsy was performed.



From: Hahn, Mauermann, PJB Dyck & Keegan, Neurology, 2007

Perineurioma



From: R Spinner

Perineurioma

Perineurioma

H&E

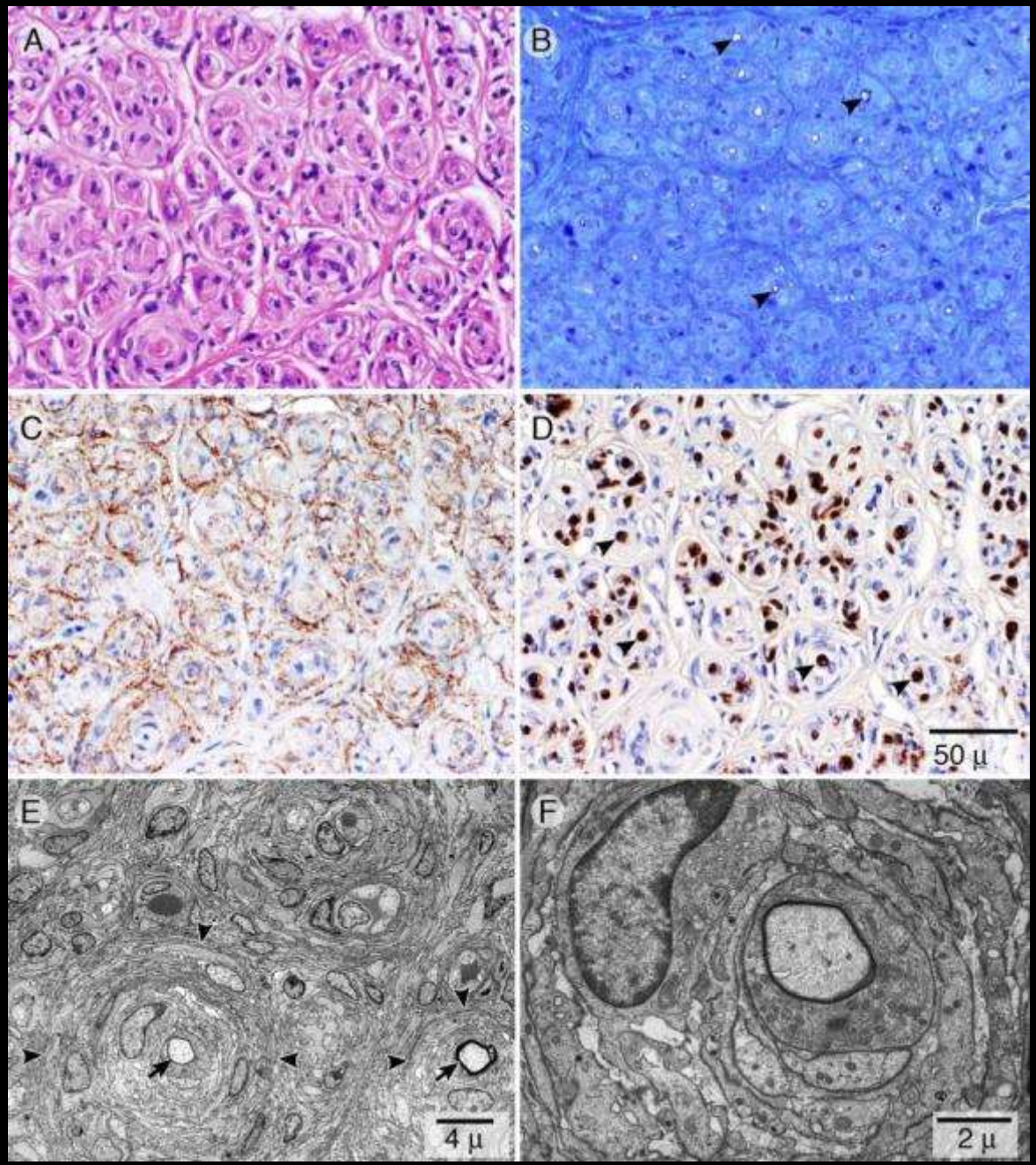
MB

EMA

S-100

EM

EM



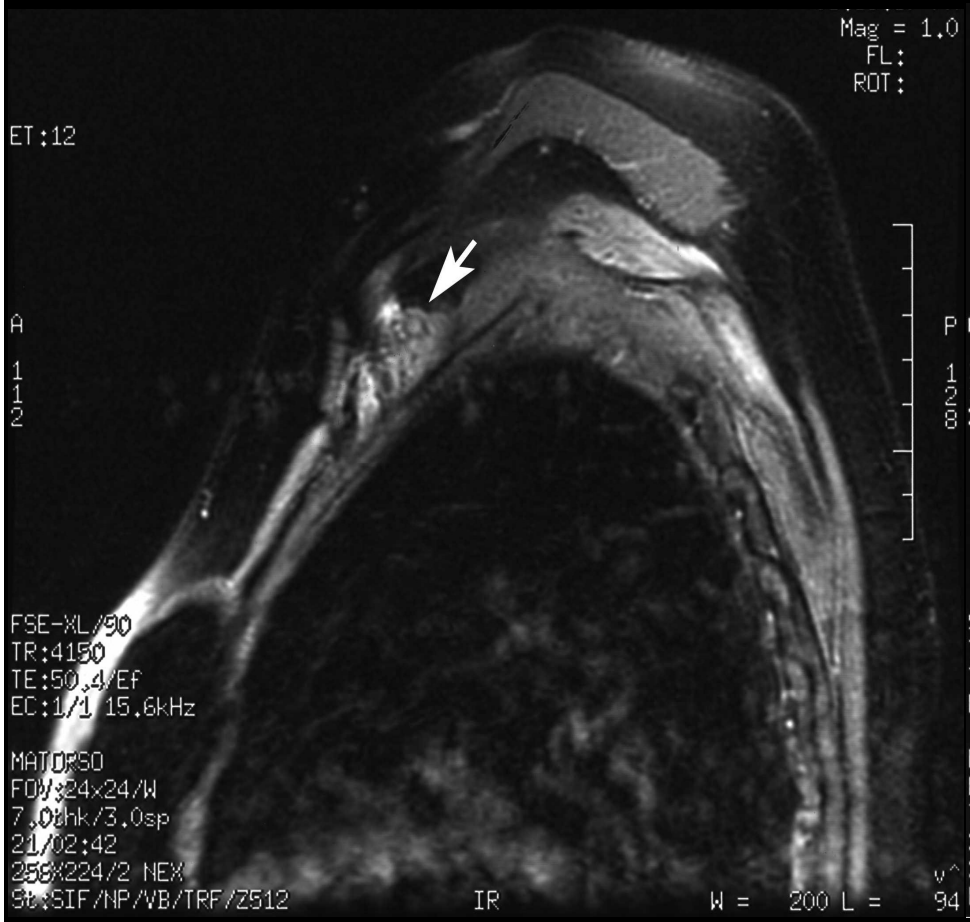
From: Hahn, Mauermann, PJB Dyck & Keegan, Neurology, 2007

Case 3

- Pathology and diagnosis: Perineurioma

Case 4

- 71 year old woman with gradual onset (over 4 years) of left thumb numbness, proximal and then distal arm weakness.
- History of breast cancer (24 years earlier) treated with chemotherapy.
- Examination and EMG showed a severe left brachial plexopathy.
- MRI showed increased size and enhancement of the left brachial plexus.
- A left brachial plexus biopsy was obtained.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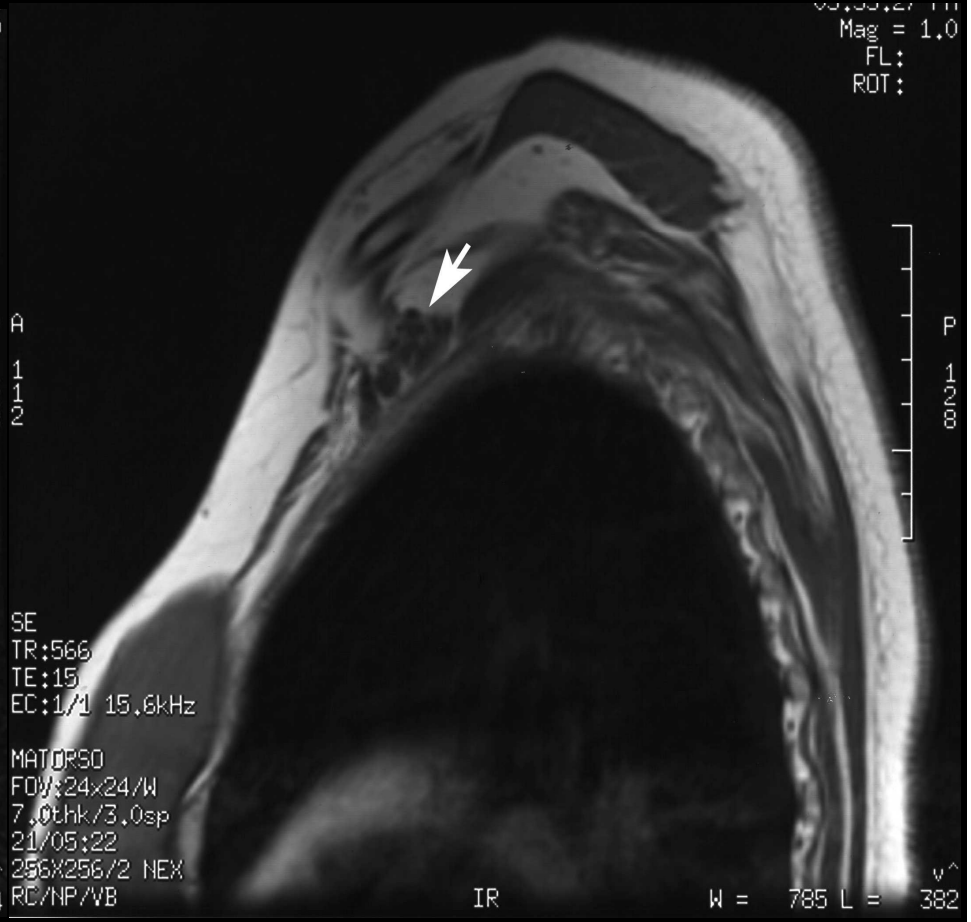
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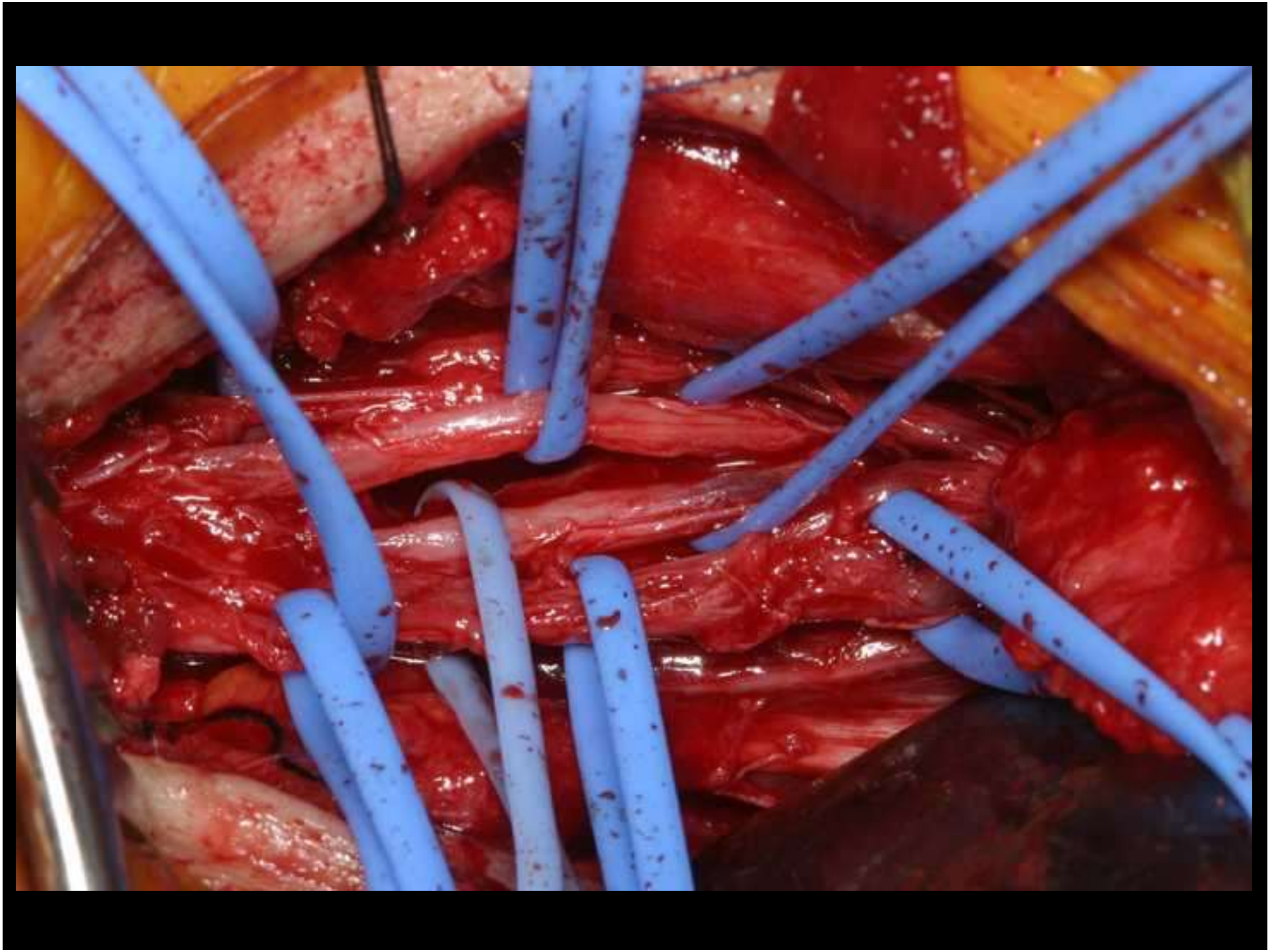
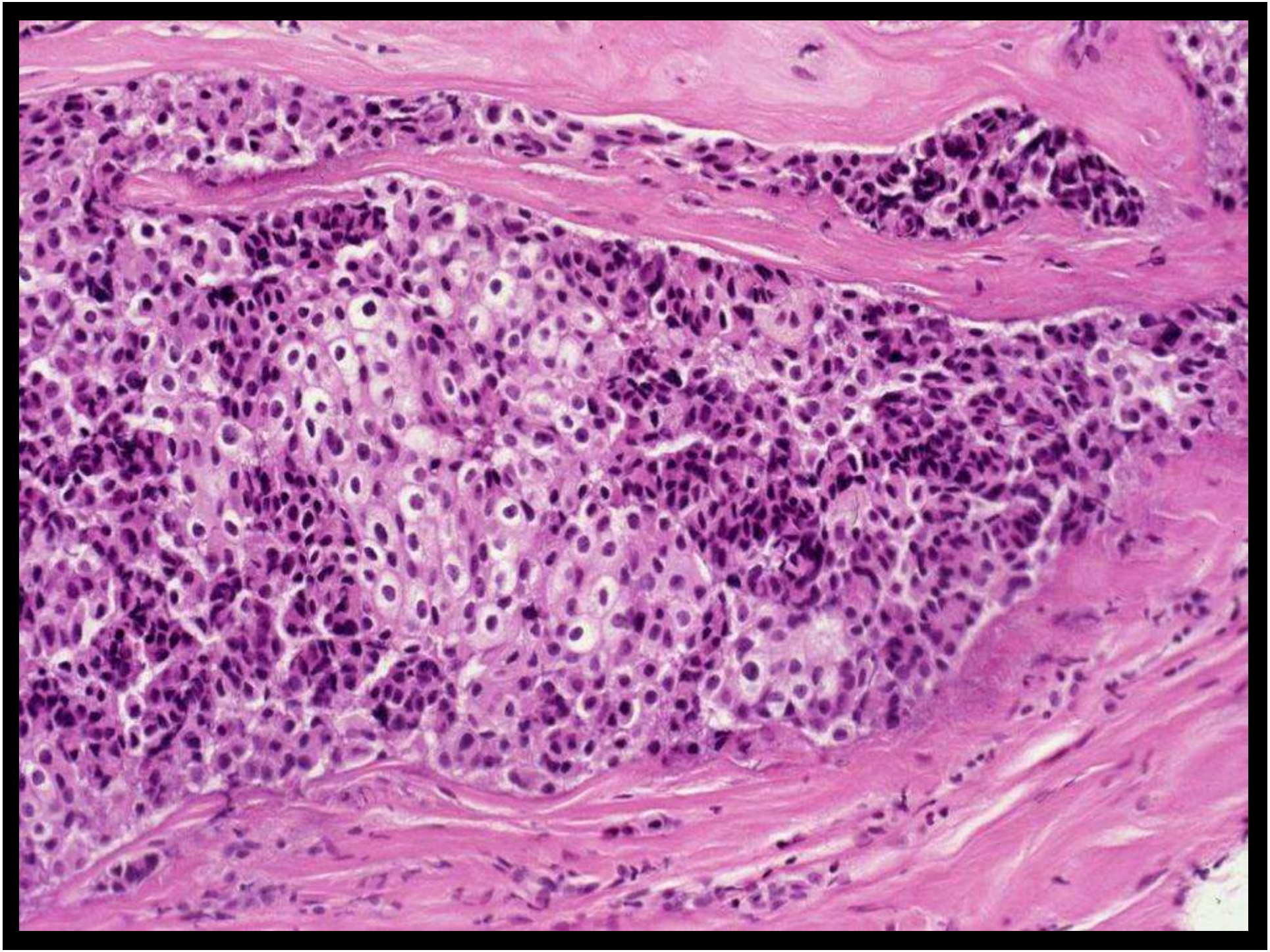




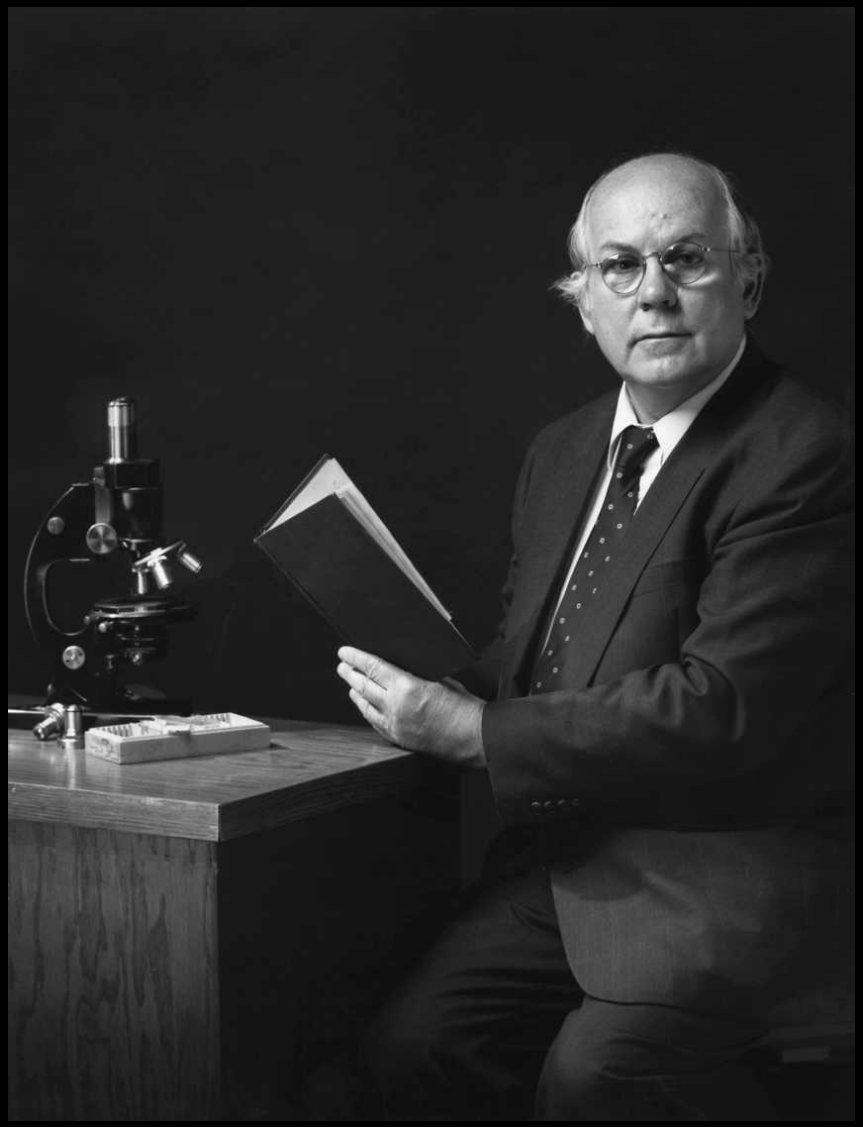
Case 4

- Pathology: adenocarcinoma of brachial plexus
- Diagnosis: metastatic breast cancer

Conclusions

- Nerve conduction studies and nerve biopsies are both clinically useful and give complimentary information.
- There is still a place for nerve biopsies in clinical practice, but they should be performed at institutions with expertise in nerve pathology.
- With improved imaging, fascicular nerve biopsies from the site of a radiological lesion are becoming increasingly important.

Acknowledgements



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