Peripheral Neurology: NEUROPATHY

Clinical presentation, exam, diagnosis, treatment, prognosis

JAMES GILCHRIST, MD

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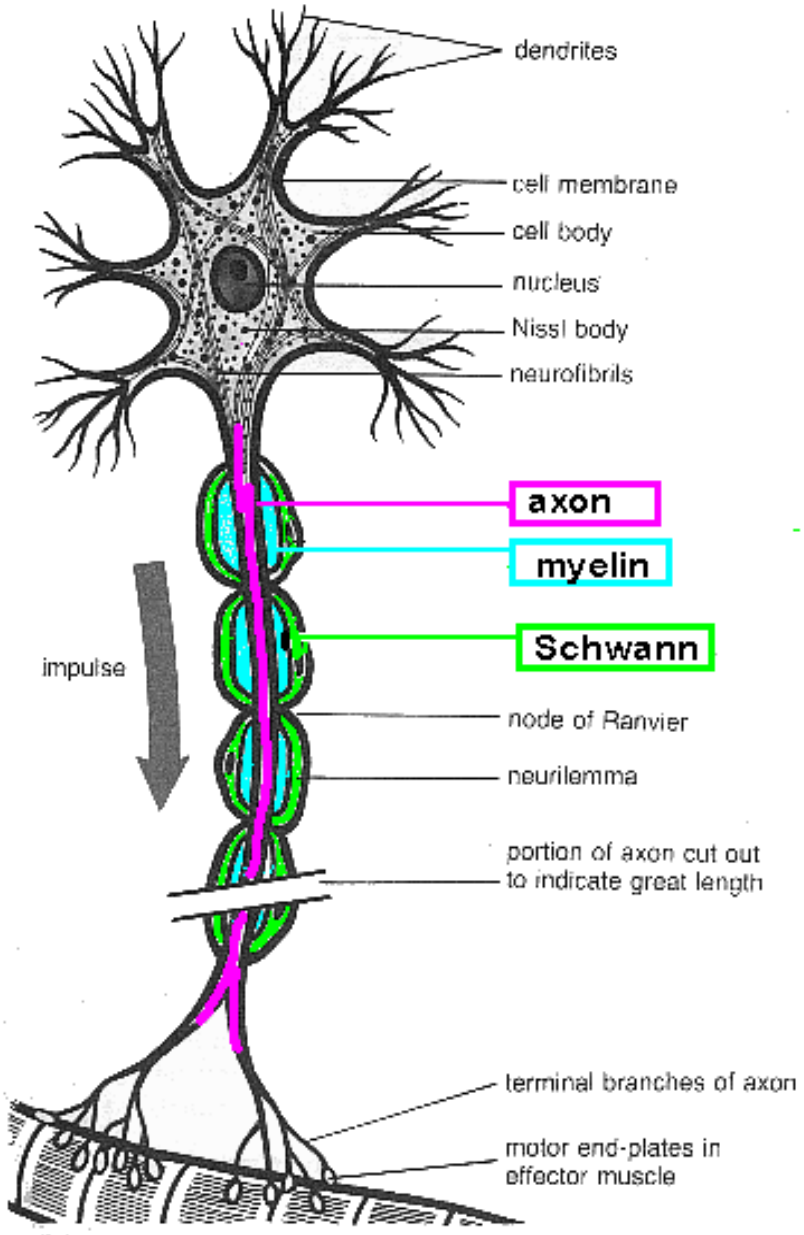
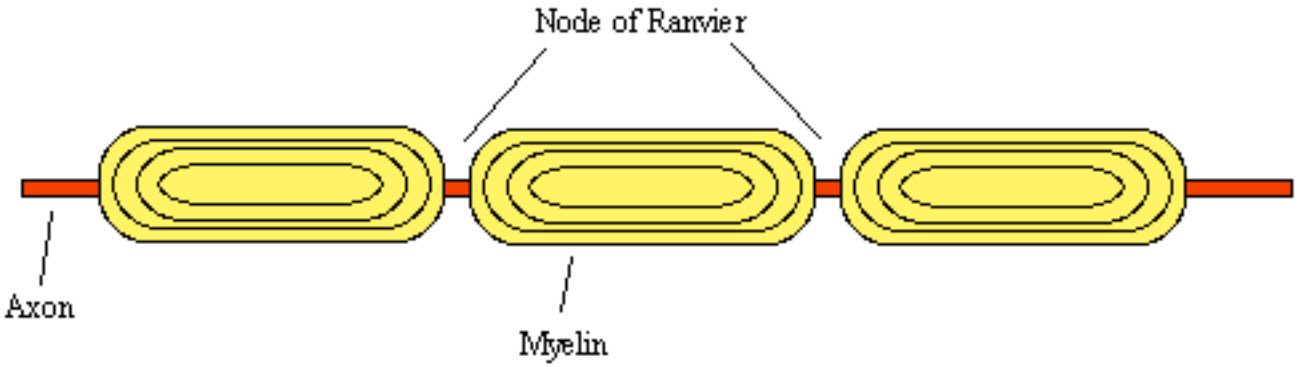
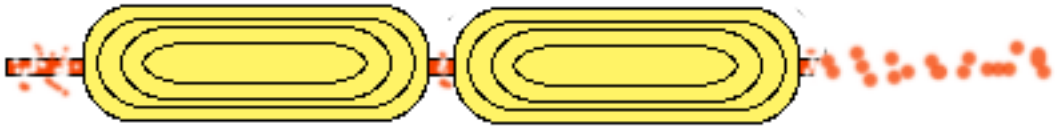
Peripheral Neuropathy

- Biology
- Epidemiology
- Clinical presentation
- Determining Etiology
- Treatment
  - Disease Altering
  - Symptomatic

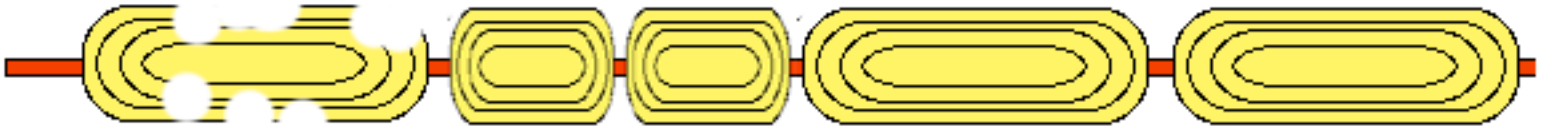

dendrites
cell membrane
cell body
nucleus
Nissl body
neurofibrils
axon
myelin
Schwann
impulse
node of Ranvier
neurilemma
portion of axon cut out
to indicate great length
terminal branches of axon
motor end-plates in
effector muscle

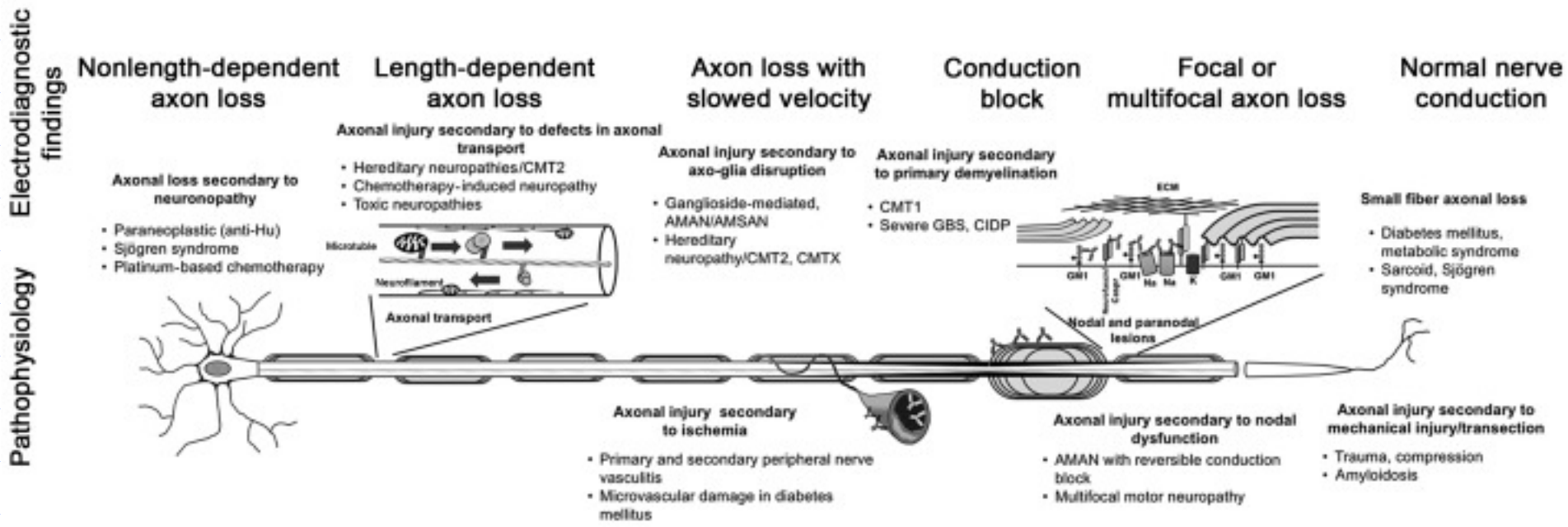


axonal neuropathy



demyelinating neuropathy





McCorquodale D, Smith AG.
Handbook Clin Neuro 161: 2019

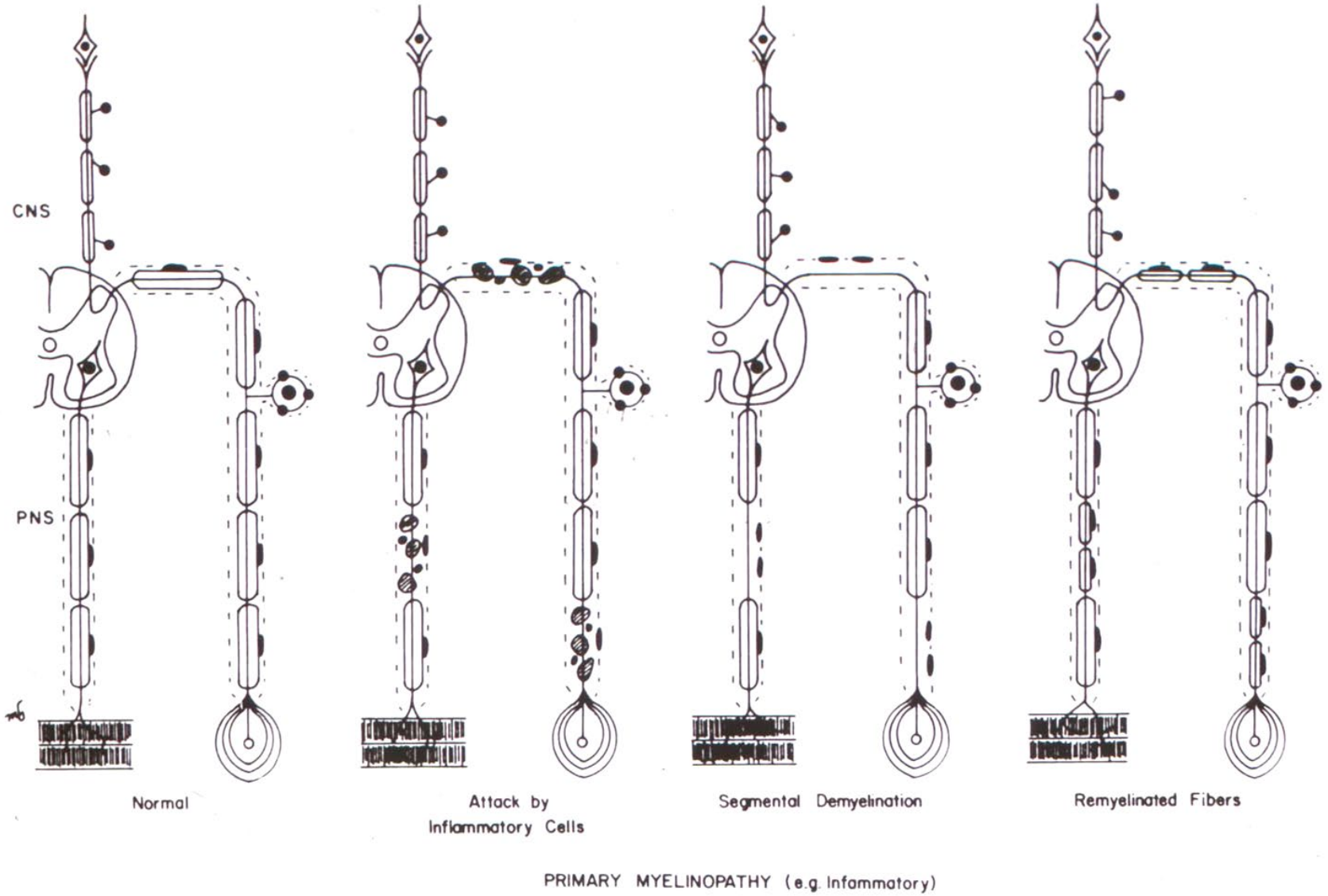
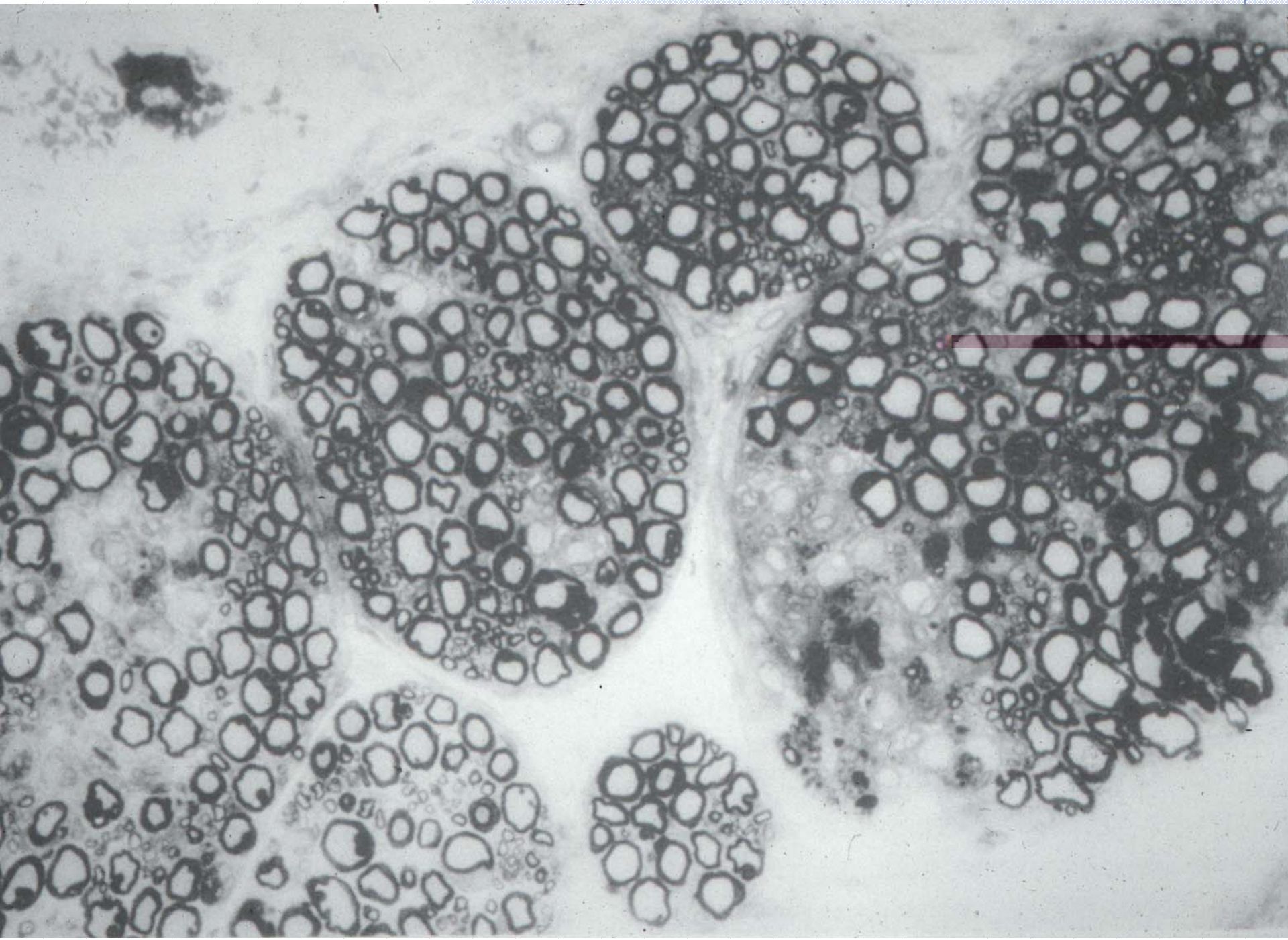
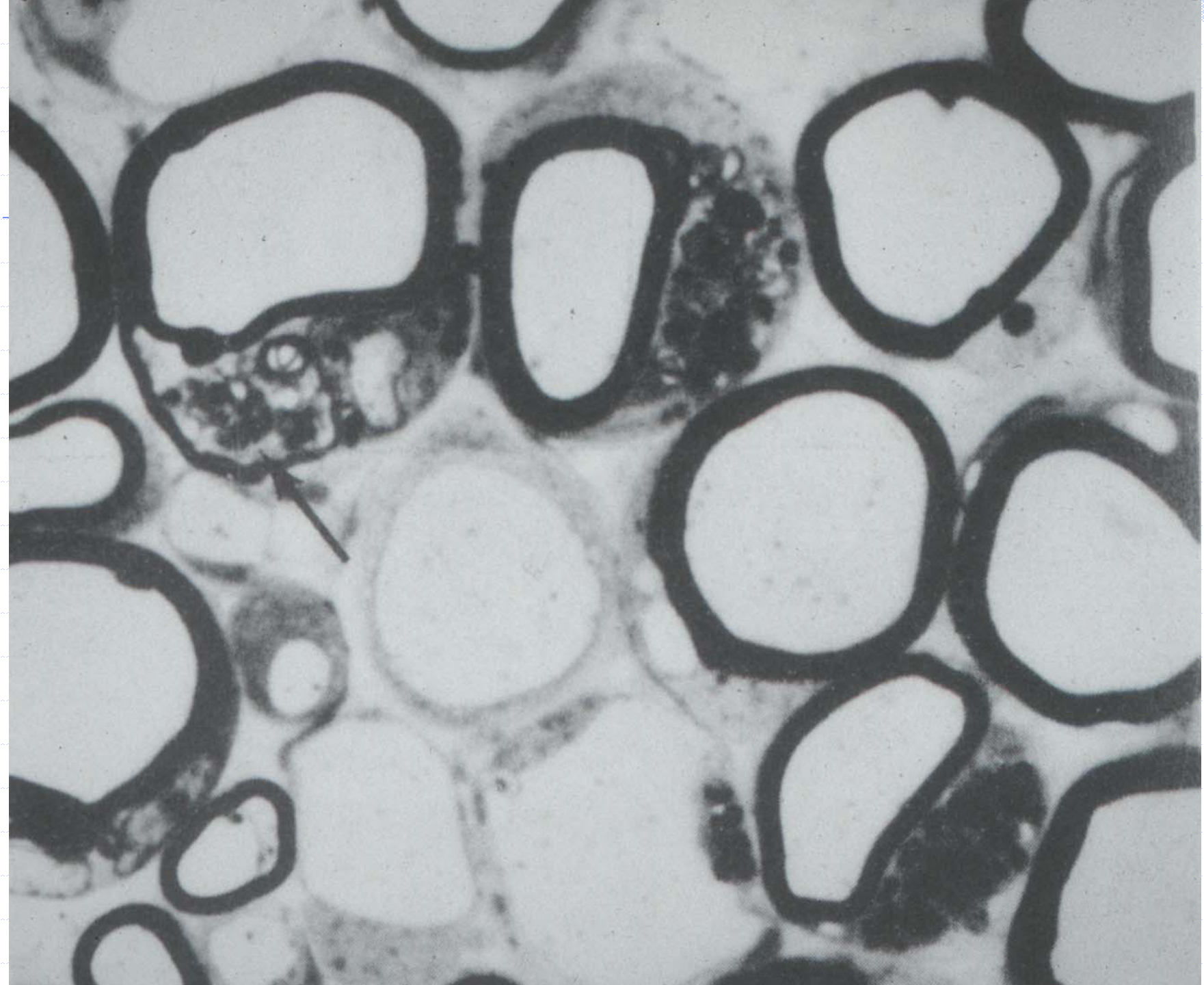
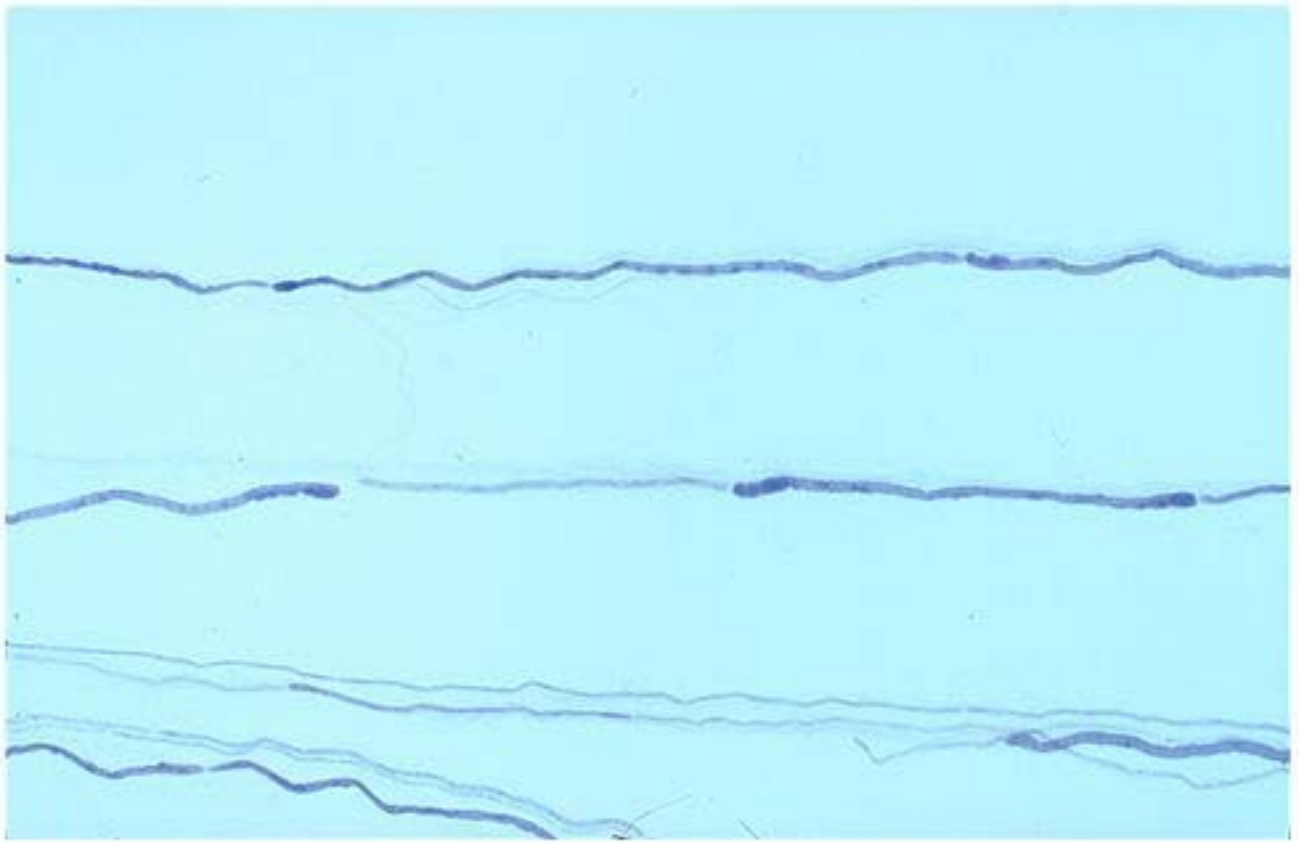


FIGURE 7. A diagram of the cardinal pathologic features of an inflammatory PNS myelinopathy. Axons are spared as is CNS myelin. Following the attack, the remaining Schwann cells divide. The denuded segments of axons are remyelinated, leaving them with shortened internodes.

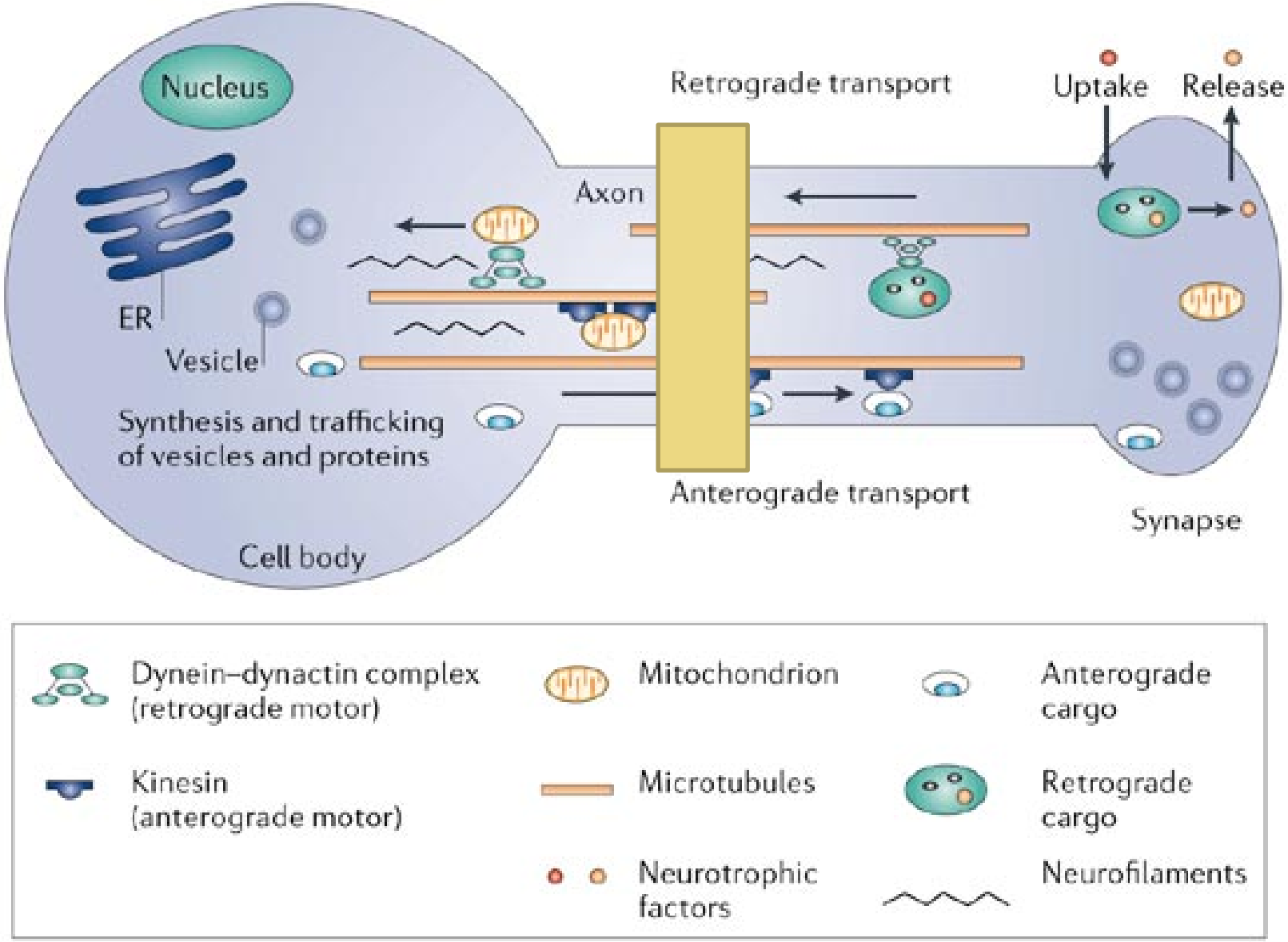




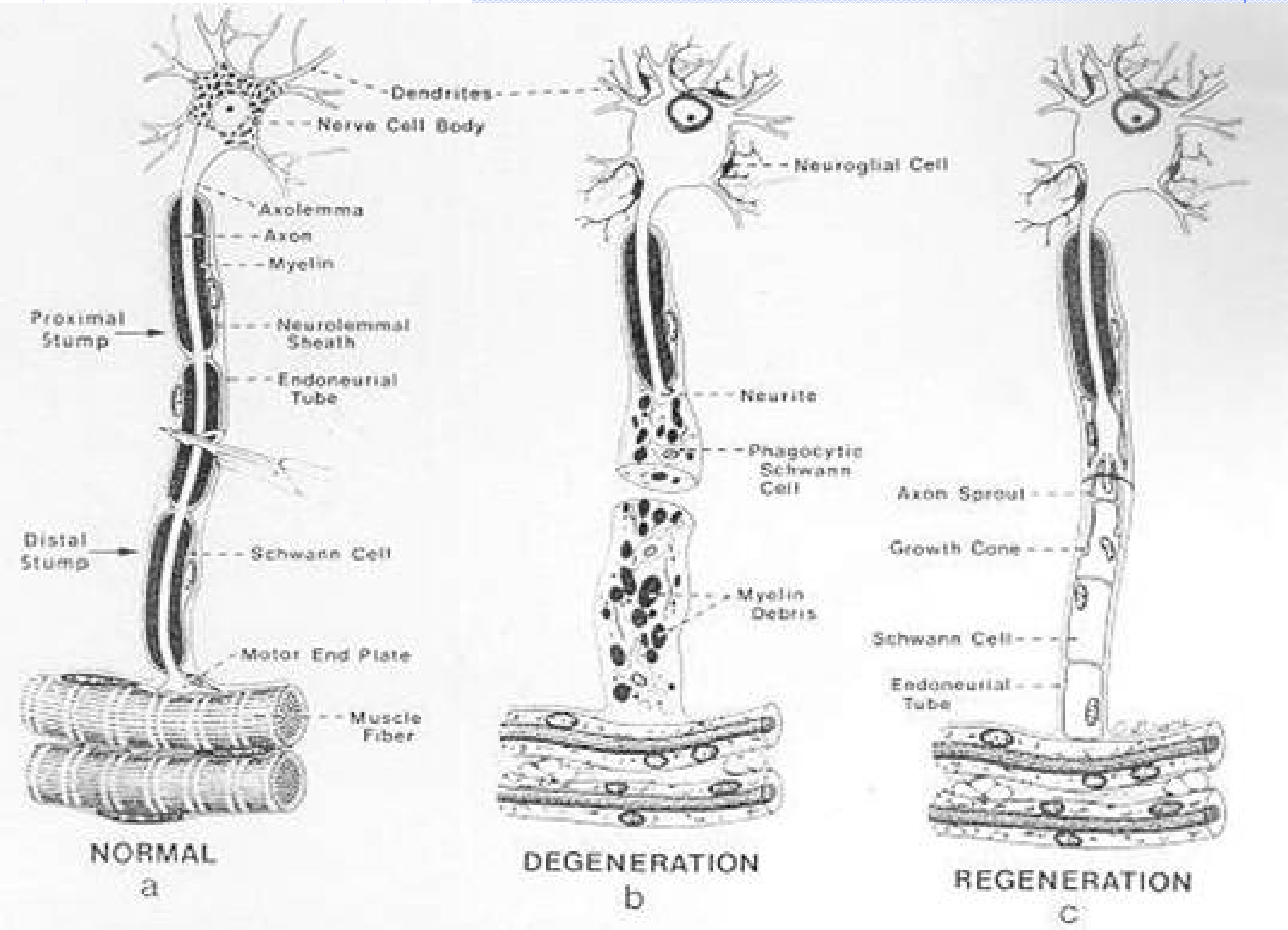
Demyelinating neuropathy

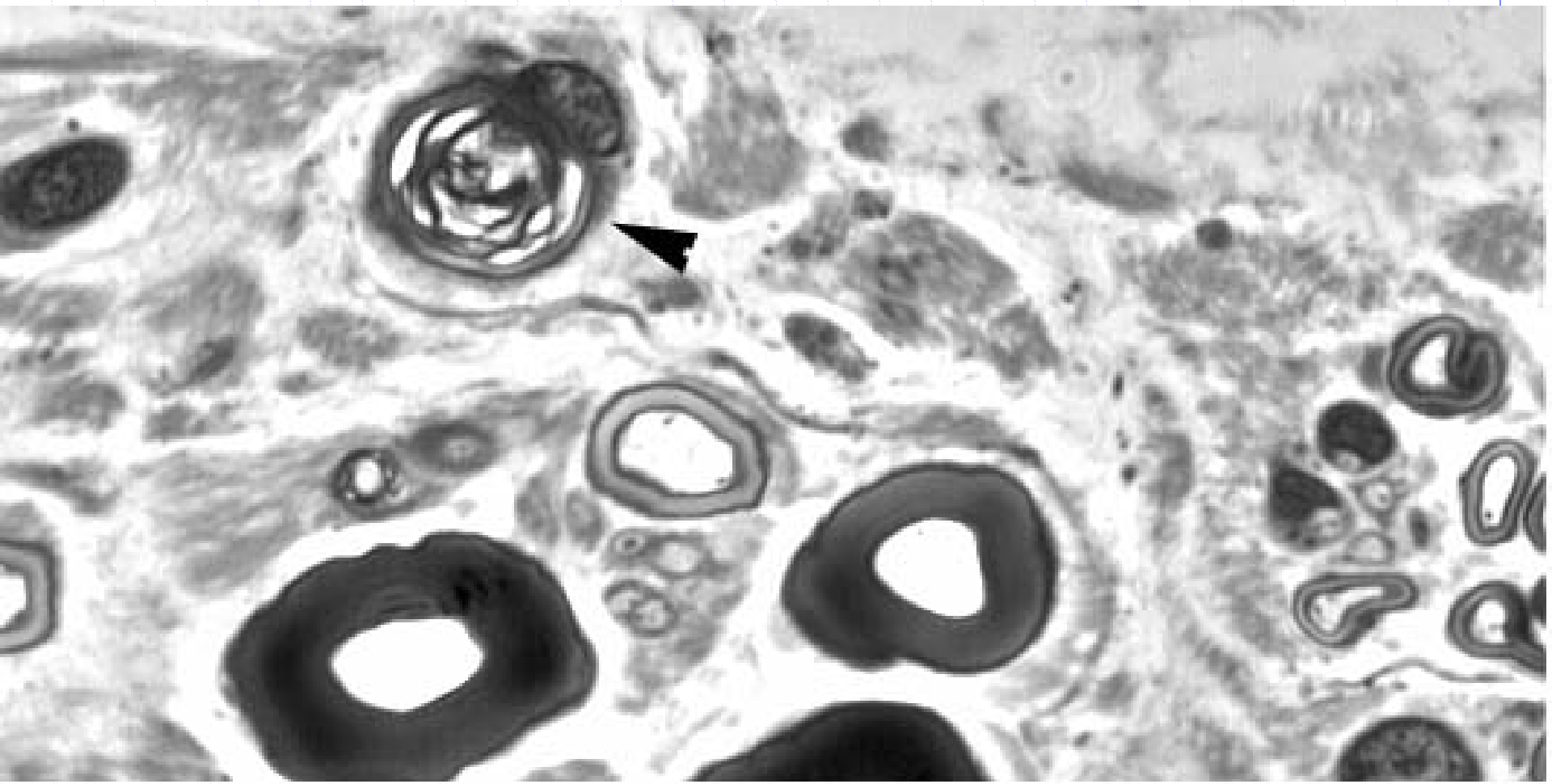


Teased fiber preparation

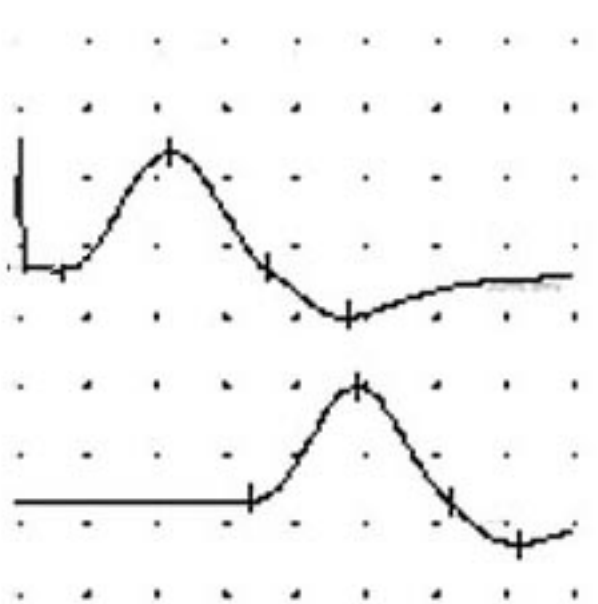


Slow anterograde: 1-2 mm/day
Fast anterograde: 200-400 mm/day
Retrograde transport: 100-200 mm/day

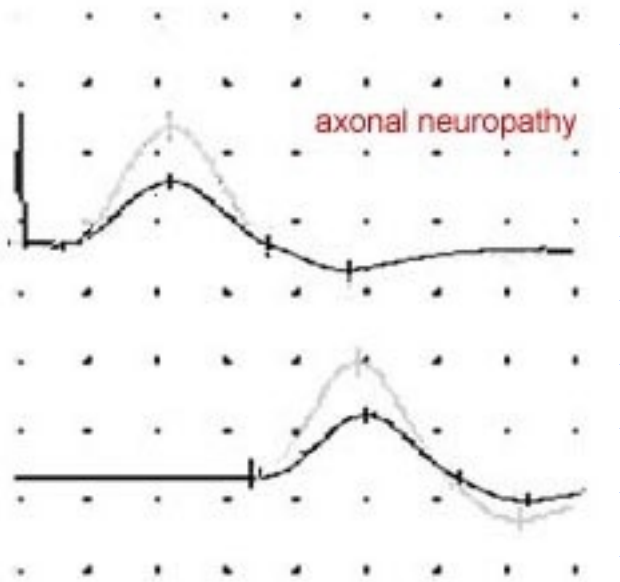

Dendrites
Nerve Cell Body
Axolemma
Axon
Myelin
Proximal Stump
Neurolemmal Sheath
Endoneurial Tube
Distal Stump
Schwann Cell
Motor End Plate
Muscle Fiber
NORMAL
a
Neuroglial Cell
Neurite
Phagocytic Schwann Cell
Myelin Debris
DEGENERATION
b
Axon Sprout
Growth Cone
Schwann Cell
Endoneurial Tube
REGENERATION
c



Nerve conduction studies

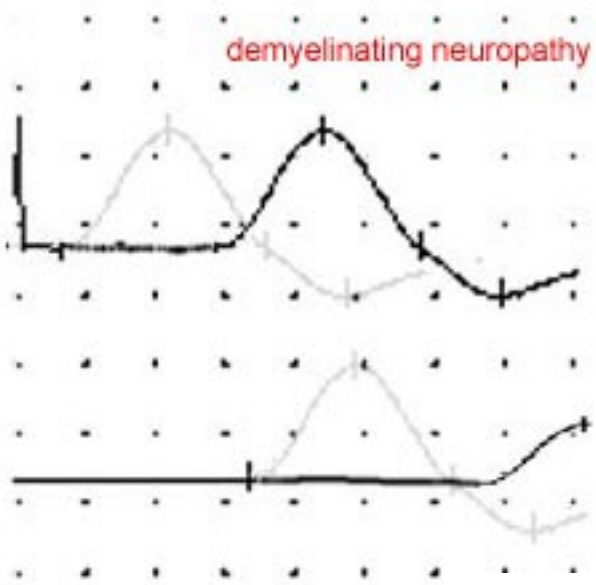


Axonal neuropathy

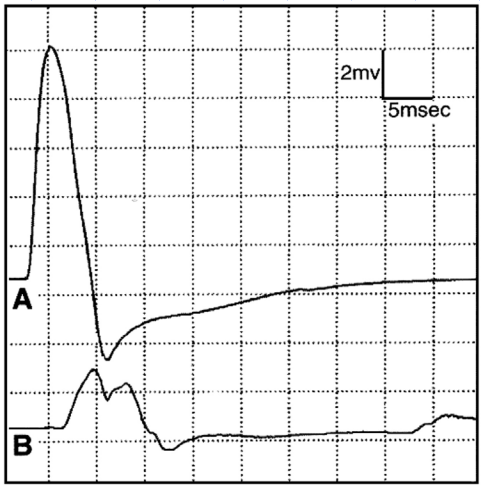


Low amplitude
Normal latency
Normal conduction velocity

Demyelinating neuropathy



Delayed latency, slow conduction velocity

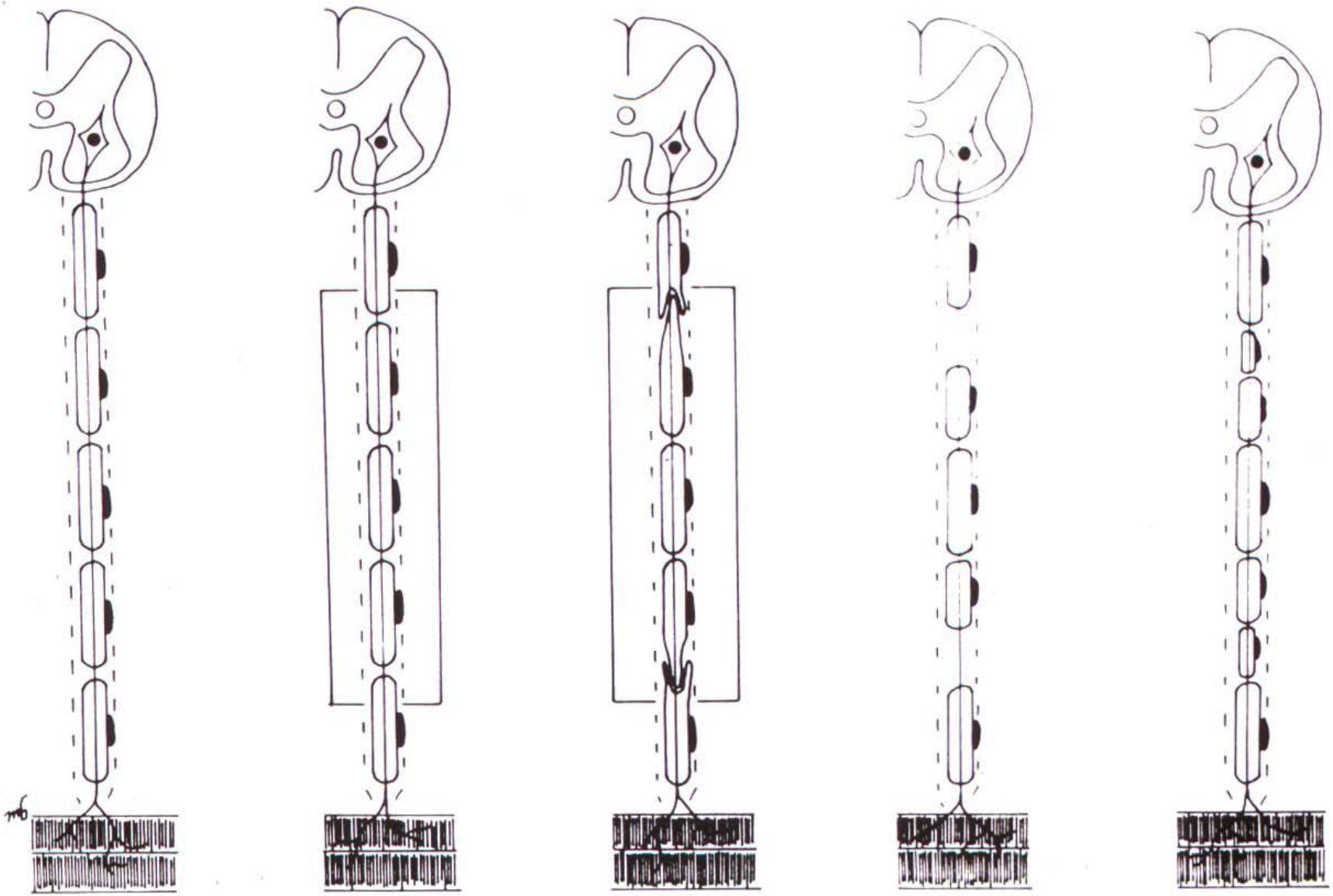


Conduction block

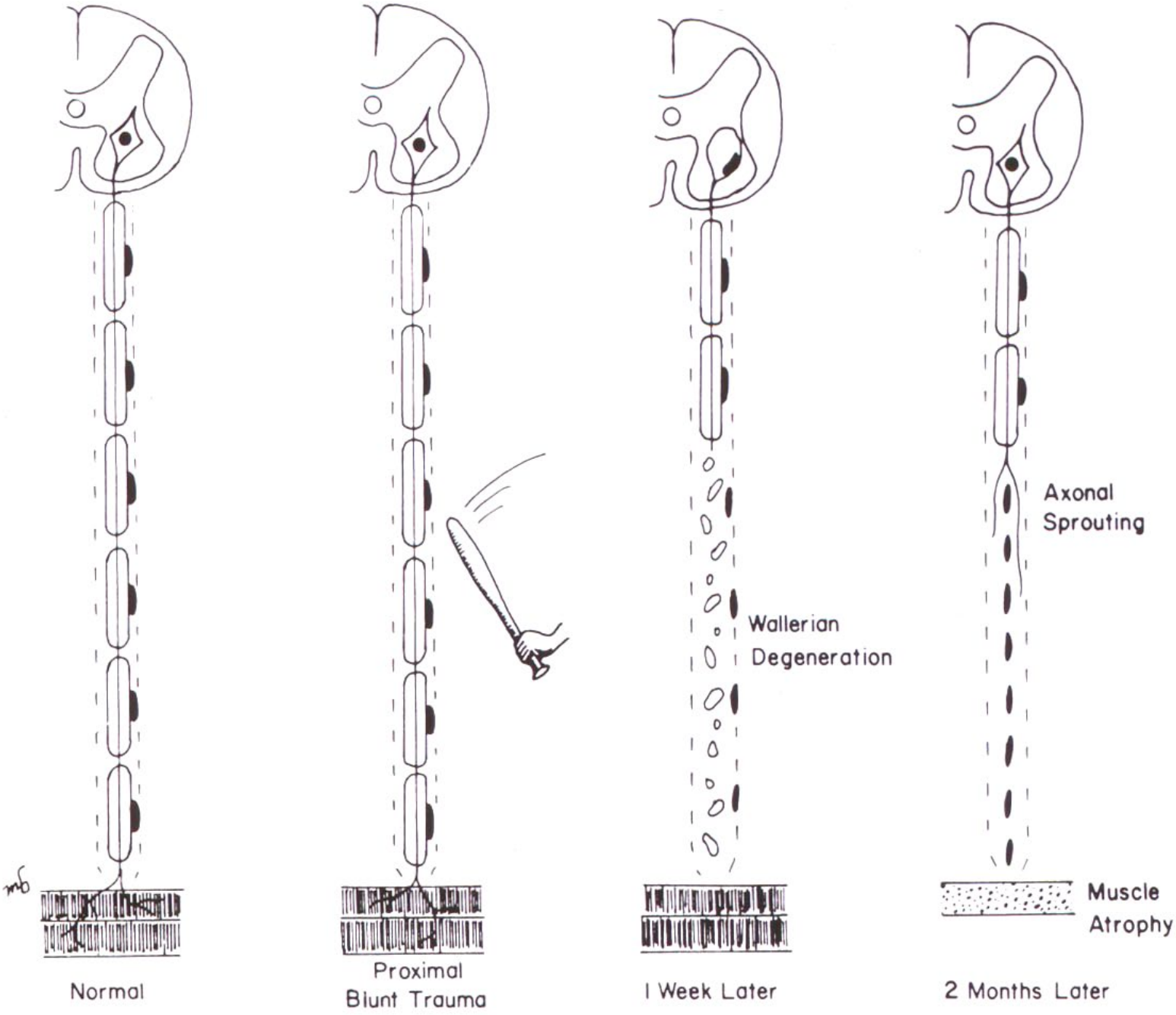
Temporal dispersion

Classes of Nerve Injury (Mononeuropathy)

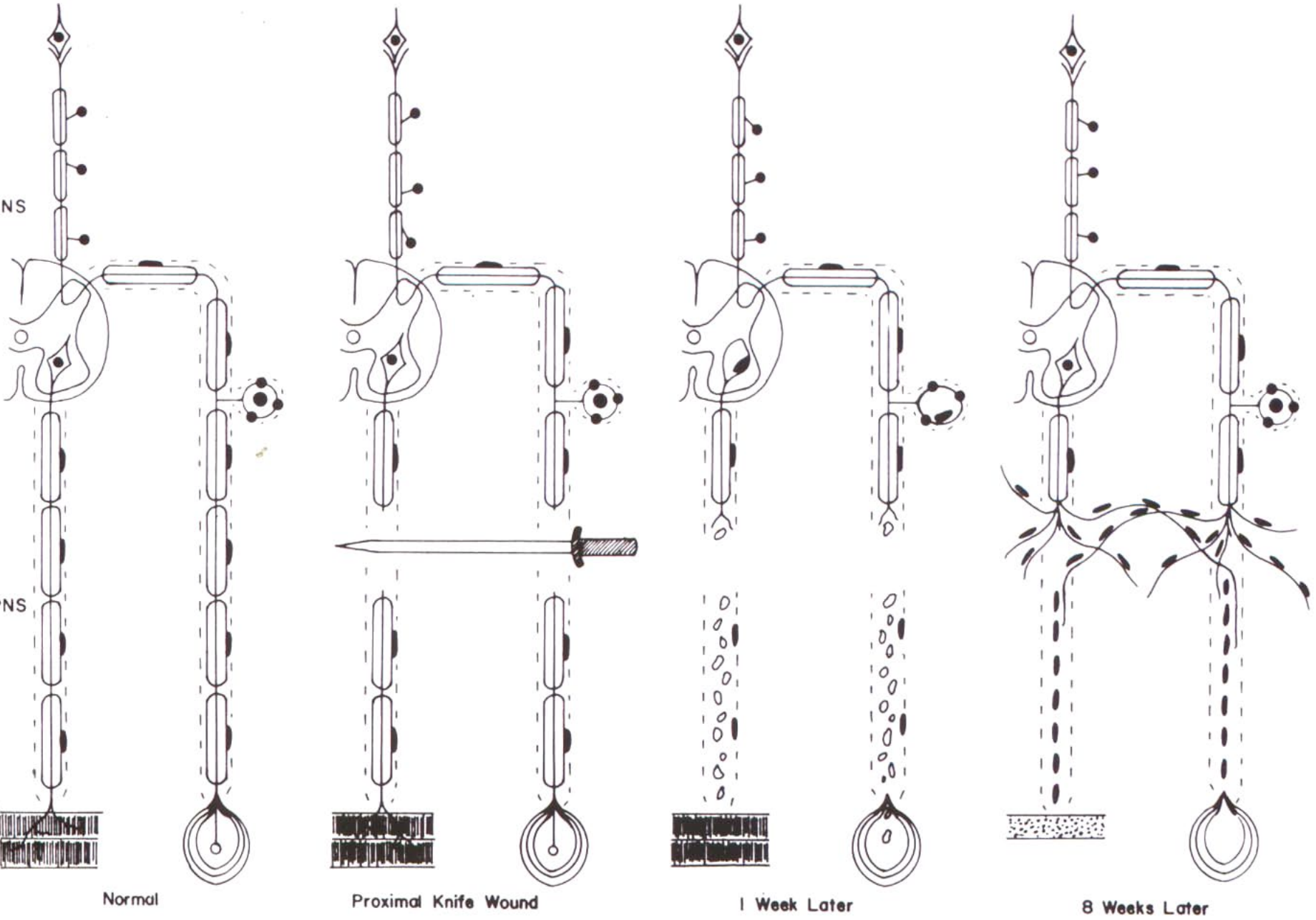
- Class 1: NEUROPRAXIA
- Class 2: AXONOTMESIS
- Class 3: NEUROTMESIS



CLASS I — ACUTE NERVE INJURY
(e.g. Compression)



CLASS 2 NERVE INJURY



DEGENERATION & ABBERANT REGENERATION
IN (CLASS 3) NERVE INJURY

Epidemiology

- A study of 4191 subjects over age 55
  - 17% had symptoms suggestive of PN
  - 7% had one exam finding
  - 4% had two exam findings
- A study of Type 2 diabetics
  - After 10 years 42% had PN
- Studies of patients with HIV
  - Up to 63% have evidence of PN

Epidemiology

Impact of peripheral neuropathy

- 25% of medical costs in diabetics

  (estimated yearly at $10 billion)

- Major contributor to falls in the elderly

Symptoms/signs

DISTAL>proximal

Sensory

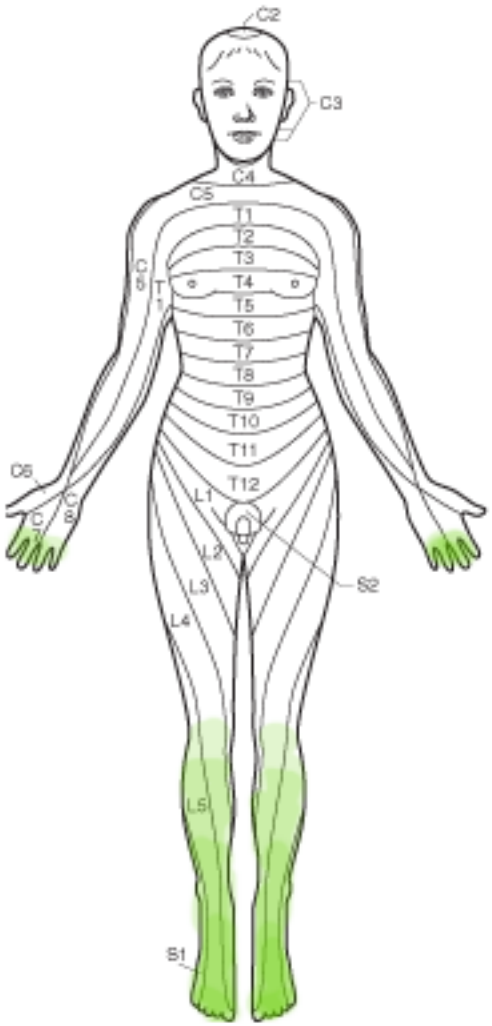
- Sensory loss
  - Small fiber-pin, temp
  - Large fiber-position
- Paresthesia
- Pain
- Ataxia
- Hyporeflexia

Motor

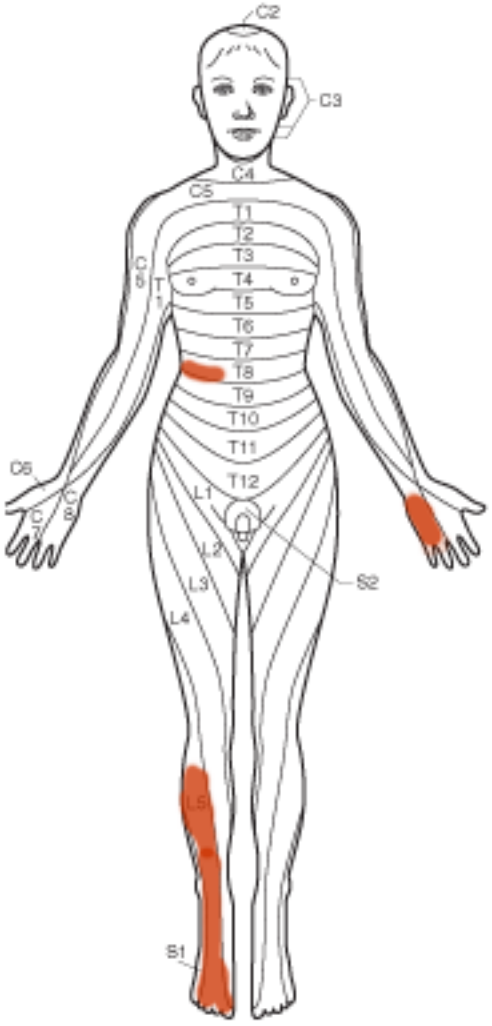
- Weakness
- Atrophy
- Cramping
- Fasciculations

Autonomic

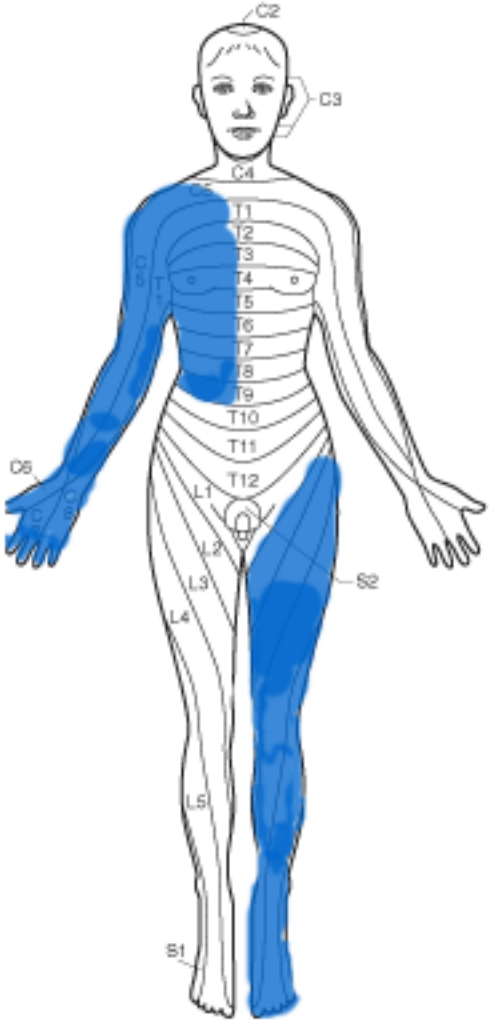
- Hypo/hyper hydrosis
- Orthostasis
- Bladder, bowel
- Skin, hair changes



POLYNEUROPATHY



MONONEUROPATHY MULTIPLEX



GANGLIONOPATHY

Distal Symmetric Polyneuropathy

Endocrine diseases
Diabetes mellitus
Hypothyroidism
Acromegaly

Nutritional diseases
Alcoholism
Vitamin B_{12} deficiency
Folate deficiency
Whipple's disease
Postgastrectomy syndrome
Gastric surgery for obesity
Thiamine deficiency

Hypophosphatemia
Critical illness neuropathy
Uremia
Connective tissue diseases
Rheumatoid arthritis
Polyarteritis nodosa
SLE
Churg-Strauss vasculitis
Cryoglobulinemia
Amyloidosis
Celiac disease

Carcinomatous / Lymphomatous axonal sensorimotor polyneuropathy
Paraproteinemia
Infectious diseases
Acquired immunodeficiency syndrome
Lyme disease
Leprosy

Sarcoidosis

Toxic neuropathy
Acrylamide
Carbon disulfide
Dichlorophenoxyacetic acid
Ethylene oxide
Hexacarbons
Carbon monoxide
Organophosphorus esters
Glue sniffing

Metal neuropathy
Chronic arsenic intoxication
Mercury
Gold
Thallium

Drugs causing neuropathy

Axonal

Vincristine
Paclitaxel (Taxol)
Nitrous oxide
Colchicine
Isoniazid
Hydralazine
Metronidazole (Flagyl)
Pyridoxine
Didanosine
Lithium
Alpha interferon
Dapsone
Phenytoin (Dilantin)
Cimetidine
Disulfiram (Antabuse)
Chloroquine
Ethambutol
Amitriptyline (Elavil, Endep)

? statins

Demyelinating

Amiodarone (Cordarone)
Chloroquine
Suramin
Gold

Neuronopathy

Thalidomide (Synovir)
Cisplatin (Platinol)

Pyridoxine

Work-up for mild (sensory) PN

- Fasting glucose (Hgb A1C, ?GTT)
- Methylmalonic acid, Vit B12
- TSH, BUN, Cr
- Lyme, ESR, RF, ANA
- SPEP, IFE
- Copper

  (Anemia or myelopathy)
- Transglutaminase Antibodies

  (Diarrhea or rash)

Diabetic neuropathies

- Distal symmetric polyneuropathy
  - Likely both metabolic and vascular
  - Glycemic control
  - Glucose intolerance
- Radiculoplexoneuropathy (amyotrophy)
  - Mostly Type 2 (male predominance)
  - Due to microvasculitis
- Cranial neuropathies
- Mononeuropathies
- Thoracolumbar radiculopathies

When to go beyond basic studies

- Rapid progression
- Significant weakness or ataxia
- Unusual pattern of symptoms/deficits
  - Asymmetry
  - Arms > Legs or Proximal ≥ distal
  - Motor only
  - Cranial nerve involvement
- Preserved Reflexes
- Family History

When to go beyond basic studies

- Rapid progression *
- Significant weakness or ataxia *
- Unusual pattern of symptoms/deficits
  - Asymmetry
  - Arms > Legs or Proximal ≥ distal *
  - Motor only
  - Cranial nerve involvement *
- Preserved Reflexes
- Family History *

* May be demyelinating

Demyelinating neuropathies

- Charcot-Marie-Tooth disease type 1
- Hereditary Neuropathy with Pressure Palsies
- Acute Inflammatory (AIDP, "GBS")
  - Post infectious (viral, campylobacter)
  - Post vaccinal
  - HIV (seroconversion)
  - ? Lyme
- Chronic Inflammatory (CIDP)
  - Monoclonal Gammopathies
  - Lymphoproliferative disorders

Chronic Demyelinating Polyneuropathies

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

- Acquired
- Relapsing or progressive
- Proximal AND distal weakness, areflexia
- NCS: demyelinating
- Responsive to immuno-modulation
- Elevated CSF protein

Charcot-Marie-Tooth disease (CMT)

- Inherited, usually dominant (types 1 and 2)
- Type 1: "demyelinating"
  Type 2: "axonal"
- NCS only difference
- Slowly progressive
- Distal weakness and sensory loss. DTRs variable
- Not responsive to steroids

NEUROLOGY (Ny) 1982;32:592-6

The electrodiagnostic distinctions between chronic familial and acquired demyelinative neuropathies

Richard A. Lewis, M.D., and Austin J. Sumner, M.D.

Table. Motor and sensory conduction studies (mean ± SEM)

	Familial	Acquired	Normal
Motor conduction studies			
Median nerve	n = 18	n = 40	n = 30
Distal latency (msec)	9.9 ± 0.5	7.9 ± 0.9	3.5 ± 0.1
Conduction velocity (m/sec)	17.6 ± 0.9	29.9 ± 2.0	56.5 ± 0.5
Ulnar nerve	n = 13	n = 40	n = 30
Distal latency	8.1 ± 0.7	6.0 ± 0.5	2.8 ± 0.1
Conduction velocity	15.6 ± 1.2	29.9 ± 1.9	54.2 ± 0.5
Sensory conduction studies			
Median nerve	n = 7	n = 14	n = 30
Amplitude (μV)	2.3 ± 0.5	7.5 ± 2.3	17.3 ± 1.2
Latency	7.1 ± 0.4	4.2 ±0.6	2.7 ± 0.1

Familial vs Acquired demyelinating polyneuropathies

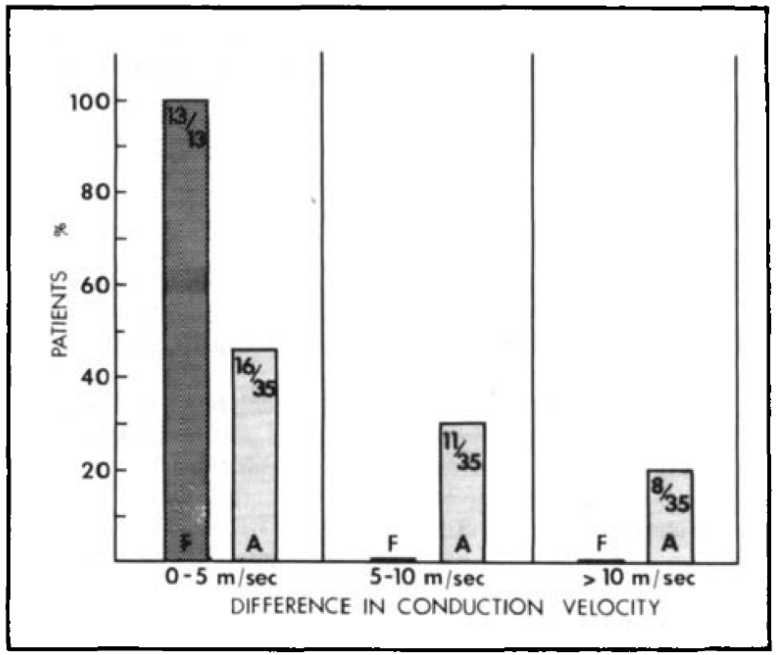
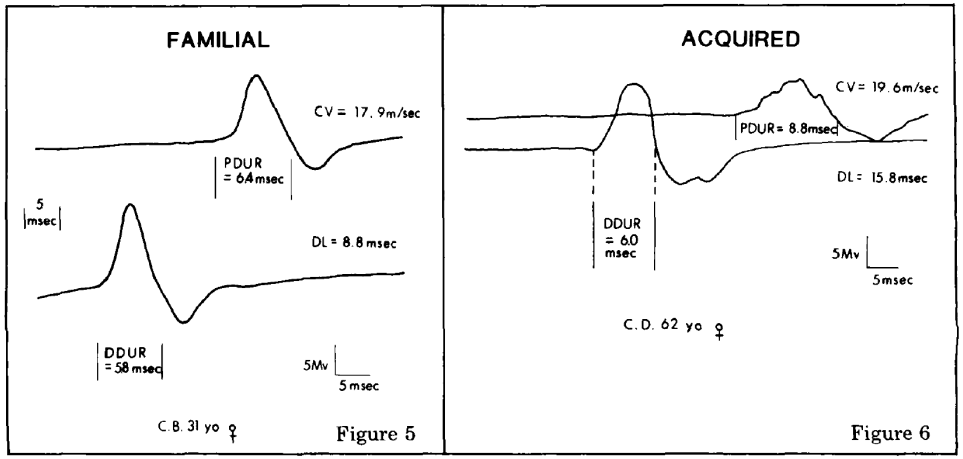


Figure 4. Bar graph comparing forearm motor CV between ulnar and median nerves.



Lewis, Sumner. Neurology 1982

The advent of Genetic Testing

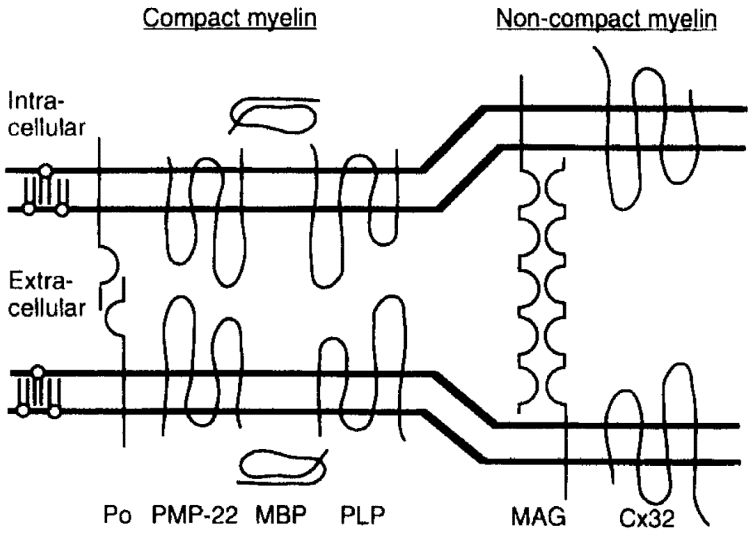


FIGURE 1. Localization of myelin components in the mammalian CNS and PNS myelin sheaths. Mutations in PMP22 (CMT-1A, HNPP), P0 (CMT-1B), and Cx32 (CMT-X) are known to cause inherited neuropathies. Intracellular and extracellular refer to the cytoplasm of the myelinating Schwann cell. (Figure kindly provided by Dr. Steven Scherer.[92])

Table 1. Electrophysiological findings of inherited demyelinating neuropathies.

Inherited disorders with uniform conduction slowing
Charcot–Marie–Tooth 1A
Charcot–Marie–Tooth 1B
Dejerine–Sottas
Metachromatic leukodystrophy
Cockayne's disease
Krabbe's disease
Inherited disorders with multifocal conduction slowing
Hereditary neuropathy with liability to pressure palsies
Charcot–Marie–Tooth X
Adrenomyeloneuropathy
Pelizeus–Merzbacher disease with proteolipid protein null mutation
Refsum's disease

Lewis, Sumner, Shy. M&N 2000

Conclusion

- NCS important in establishing demyelination.
- Conduction block, temporal dispersion and asymmetry are not unique to CIDP.
- Understanding of different electrodiagnostic patterns of inherited neuropathies is important.
- Family history, genetic testing, response to therapy are important features of diagnosis.

When to go beyond basic studies

- Rapid progression
- Significant weakness or ataxia
- Unusual pattern of symptoms/deficits
  - Asymmetry *
  - Arms > Legs or Proximal ≥ distal
  - Motor only
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- Preserved Reflexes
- Family History

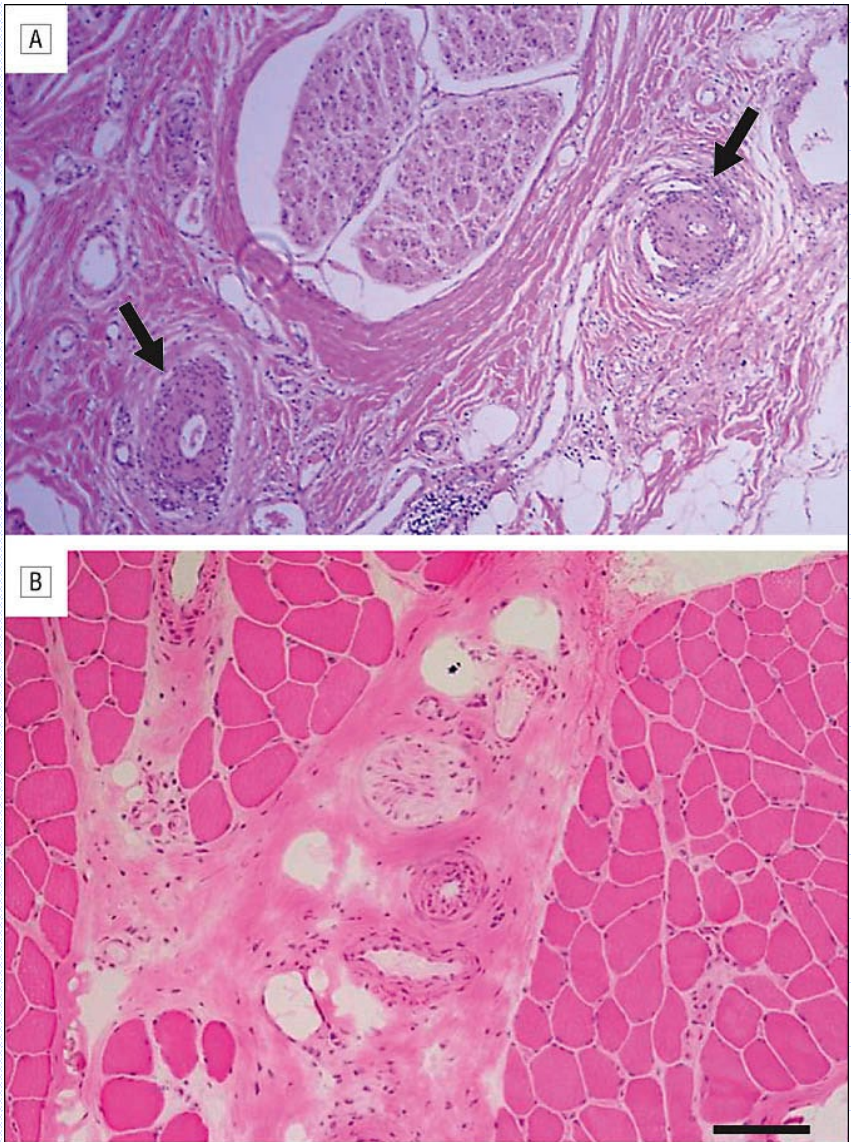
Differential diagnosis of Mononeuropathy Multiplex

- Diabetes
- Vasculitis
- Infections (Lyme, Leprosy, Hep C)
- Infiltrative (Sarcoid, amyloid, neoplastic)
- Inflammatory (Perineuritis)
- Demyelinating (Multifocal CIDP, MMN, MADSAM)
- Hereditary (HNPP)

Mononeuropathy multiplex

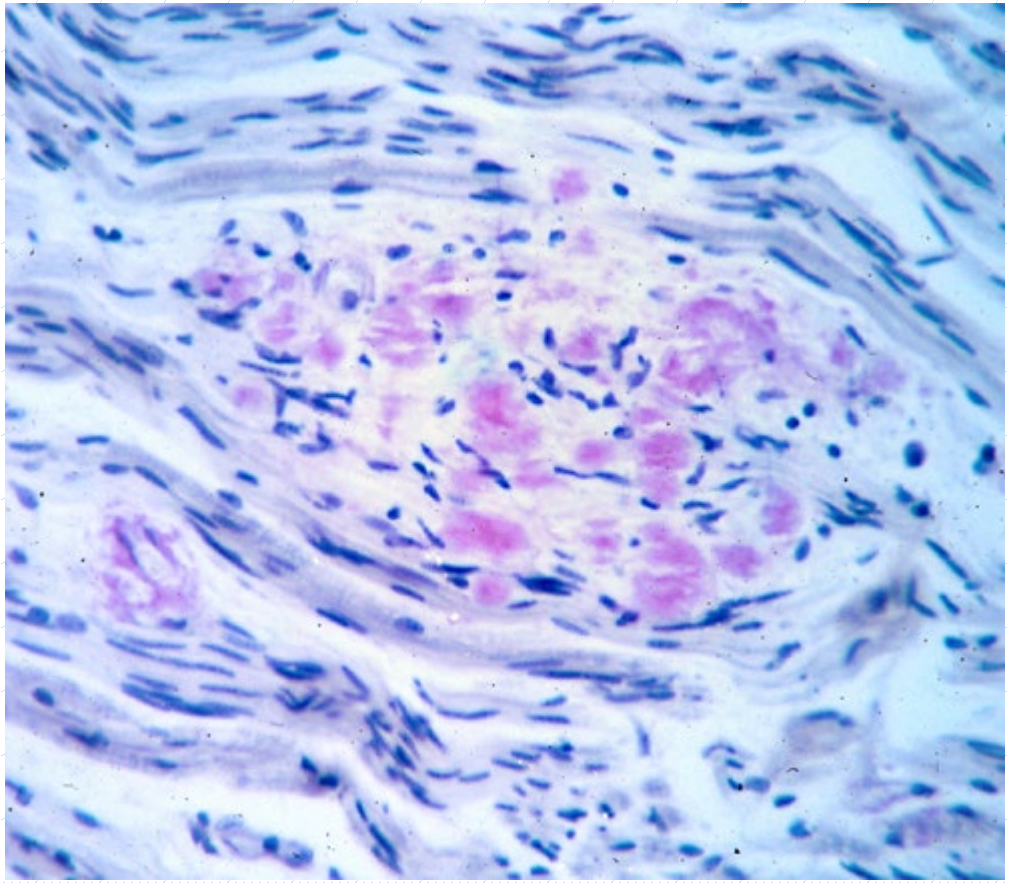
Vasculitis

Amyloidosis



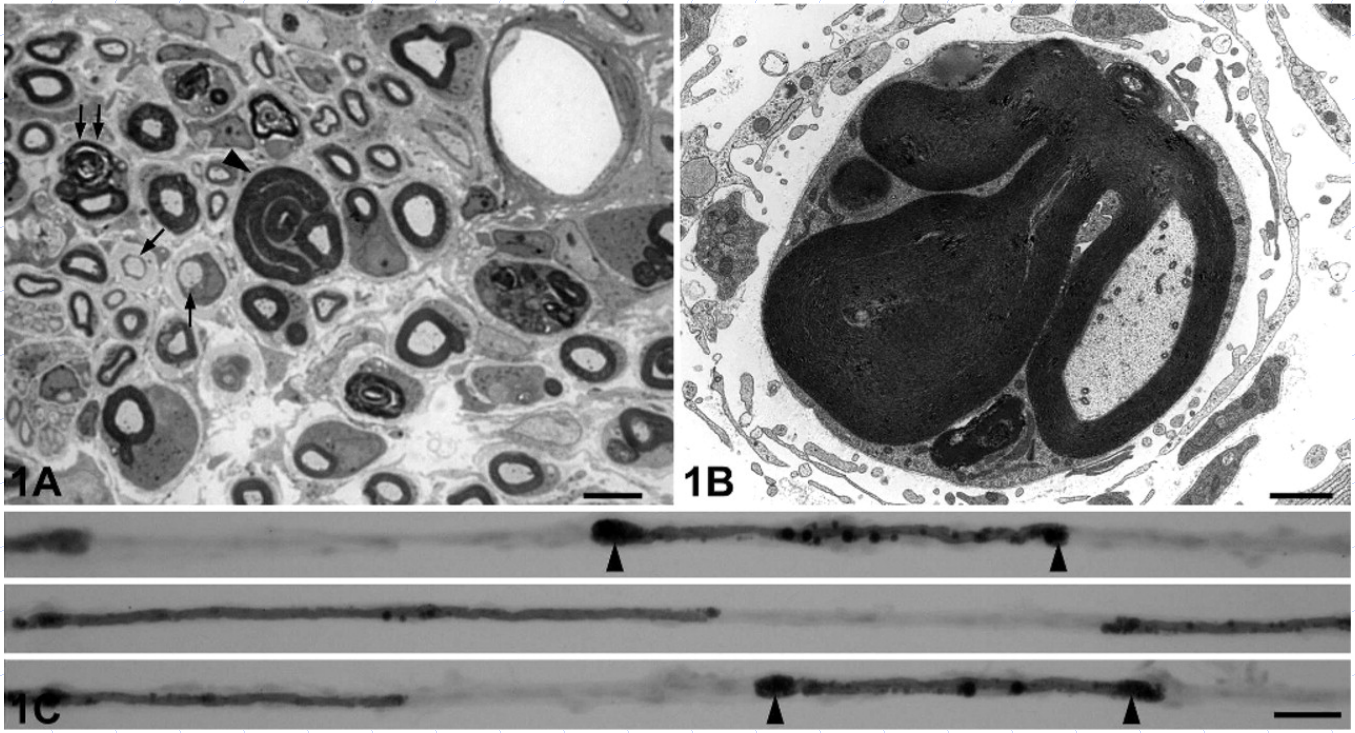
Mononeuropathy multiplex

Amyloid



Mononeuropathy multiplex

HNPP: Tomaculous neuropathy



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  - Motor only *
  - Cranial nerve involvement
- Preserved Reflexes
- Family History

Proximal or pure motor neuropathy

- Amyotrophic Lateral Sclerosis
- Spinal Bulbar Atrophy (Kennedy disease)
- Spinal Muscular Atrophy
- Paraproteinemia
- Lead intoxication
- Porphyria
- Multifocal Motor Neuropathy
- Diabetic amyotrophy
- Brachial Plexitis

When to go beyond basic studies

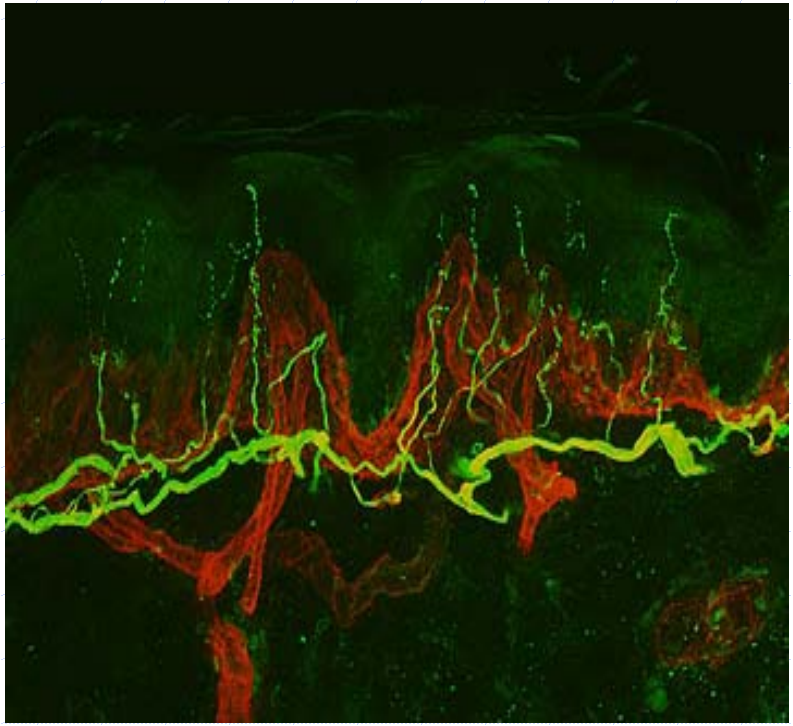
- Rapid progression
- Significant weakness or ataxia
- Unusual pattern of symptoms/deficits
  - Asymmetry
  - Arms > Legs
  - Cranial nerve involvement
- Preserved Reflexes *
- Family History

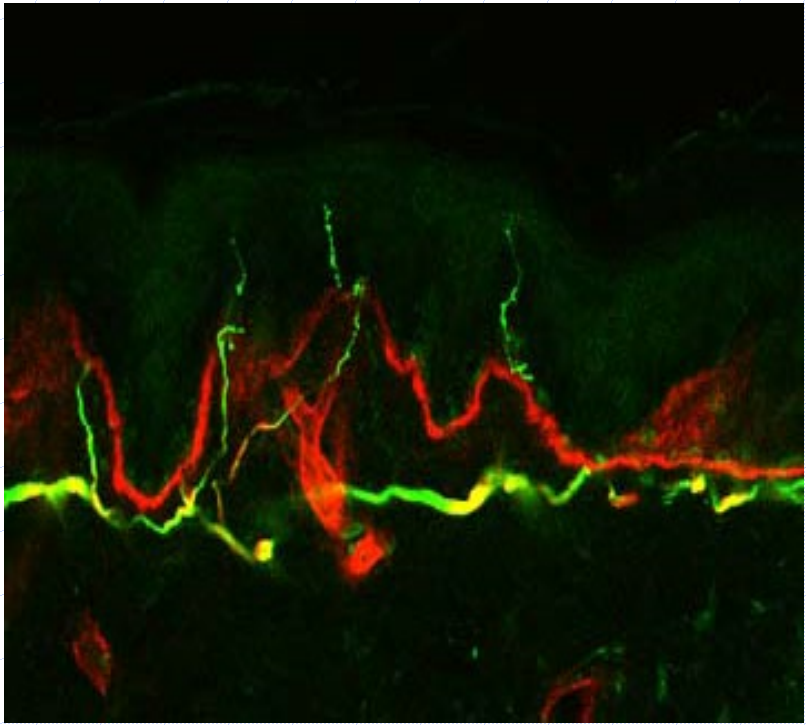
Small fiber neuropathy

- Diabetes, glucose intolerance
- Alcoholic
- HIV
- Hep C
- Amyloid
- Vasculitis, Lupus, Sjogrens
- Sarcoid
- Idiopathic

Normal Nerve Conduction Studies: no large fiber involvement

Small fiber neuropathy





Epidermal Nerve fiber density using paraxonal antibody PGP9.5

Diagnostic testing beyond lab work (summary)

- "Garden variety"- NCS
- Acute- CSF, NCS, biopsy if not demyelinating
- Multifocal- NCS, antibody testing, biopsy
- Demyelinating- NCS, CSF, genetic studies
- Small fiber- skin biopsy

Disease altering treatment: Demyelinating neuropathies

AIDP (GBS)

- Plasmapheresis
- IVIG

CIDP

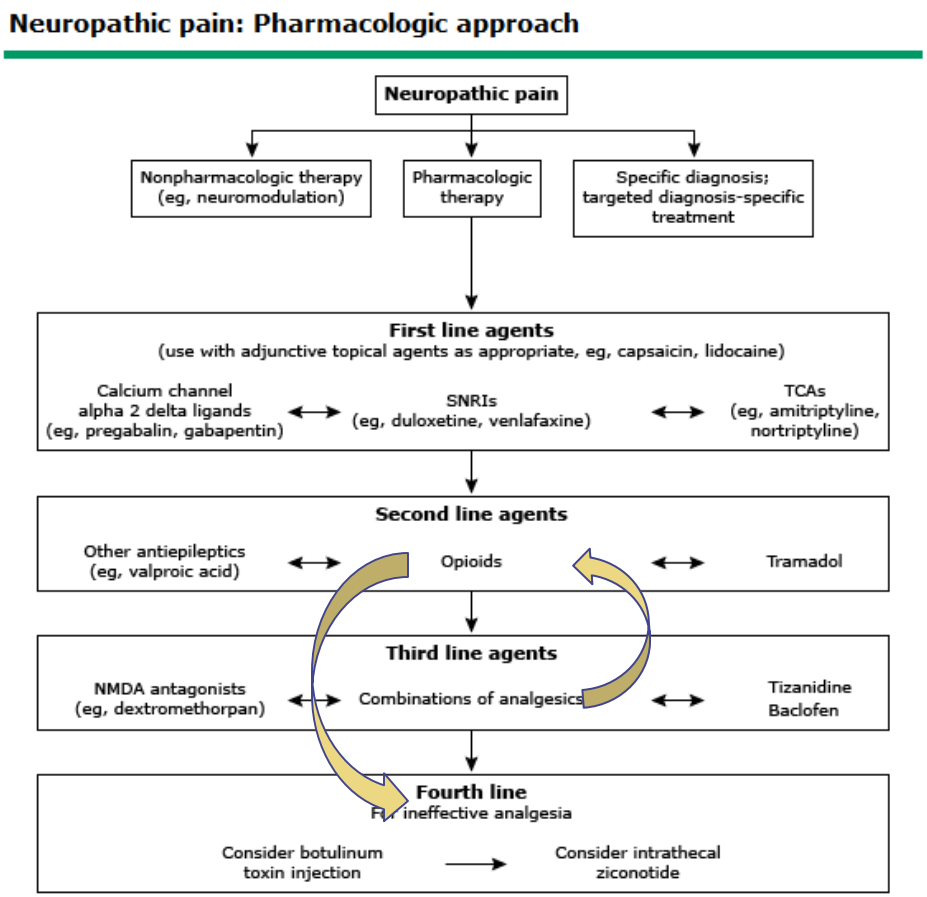
- IVIG
- Steroids
- Plasmapheresis
- ? Azathioprine
- ? Cytoxan
- ? Rituxan

Disease altering treatment

Vasculitis, perineuritis

- Steroids
- Cytoxan
- ?Azathioprine
- ?IVIG

Symptomatic treatment for neuropathic pain



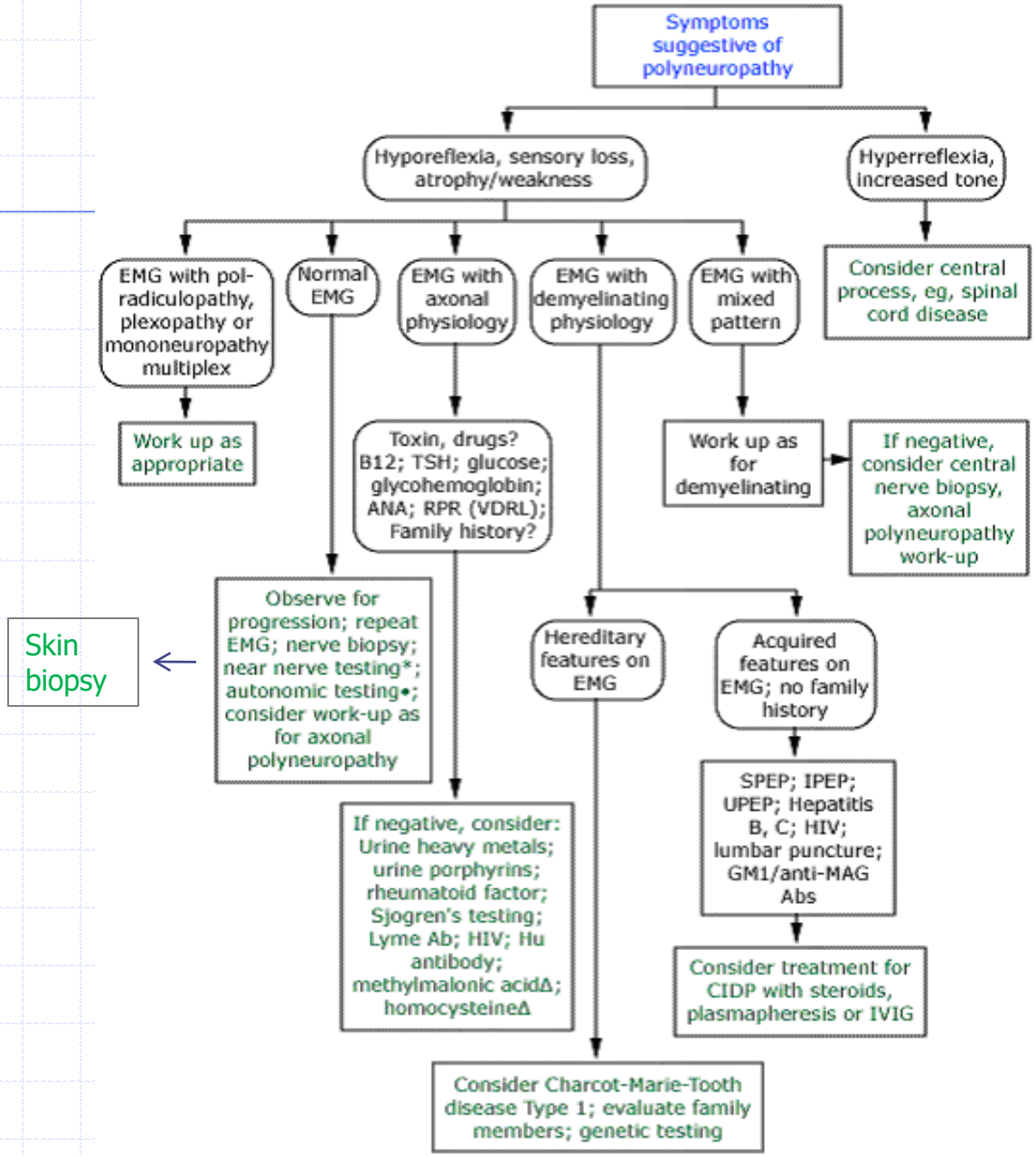
Topical Agents:
Lidocaine 4%, 5%
Capsaicin

Intravenous ketamine

Symptomatic treatment for neuropathic pain

Anticonvulsants

- Gabapentin (Neurontin)
- Pregabalin (Lyrica)
- Carbamazepine (Tegretol)
- Valproic Acid (Depakote)
- Phenytoin (Dilantin)
- Topiramate (Topamax)
- Oxcarbezepine (Trileptal)
- Lamotrigine (Lamictal)
- Leviteracetam (Keppra)


Symptoms suggestive of polyneuropathy
Hyporeflexia, sensory loss, atrophy/weakness
Hyperreflexia, increased tone
Consider central process, eg, spinal cord disease
EMG with pol-radiculopathy, plexopathy or mononeuropathy multiplex
Normal EMG
EMG with axonal physiology
EMG with demyelinating physiology
EMG with mixed pattern
Work up as appropriate
Toxin, drugs? B12; TSH; glucose; glycohemoglobin; ANA; RPR (VDRL); Family history?
Work up as for demyelinating
If negative, consider central nerve biopsy, axonal polyneuropathy work-up
Skin biopsy
Observe for progression; repeat EMG; nerve biopsy; near nerve testing*; autonomic testing•; consider work-up as for axonal polyneuropathy
Hereditary features on EMG
Acquired features on EMG; no family history
If negative, consider: Urine heavy metals; urine porphyrins; rheumatoid factor; Sjogren's testing; Lyme Ab; HIV; Hu antibody; methylmalonic acidΔ; homocysteineΔ
SPEP; IPEP; UPEP; Hepatitis B, C; HIV; lumbar puncture; GM1/anti-MAG Abs
Consider treatment for CIDP with steroids, plasmapheresis or IVIG
Consider Charcot-Marie-Tooth disease Type 1; evaluate family members; genetic testing