Clinical and electrophysiological diagnosis in ICU acquired weakness

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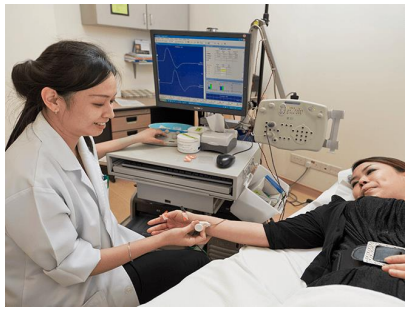
Difficulty in evaluating ICU-acquired weakness

Intubation

Sedation

Confusion



Noise

Underlying neuromuscular disorder

- Myasthenia gravis
- Motor neuron disease
- Guillain-Barre disease

ICU-acquired weakness

- Cerebral stroke
- Septic encephalopathy
- Critical illness polyneuropathy
- Critical illness myopathy

Neuromuscular differential diagnosis of Failure to wean from Ventilator”

Localization	Pre-existing	Previously Undiagnosed/New-Onset	Critical Illness Related
Spinal cord	Trauma Infarction Transverse myelitis	Acute ischemia Epidural abscess Acute transverse myelitis	Not described
Anterior horn cell	Amyotrophic lateral sclerosis Poliomyelitis (West Nile virus)	Amyotrophic lateral sclerosis (predominant diaphragm weakness) West Nile virus poliomyelitis	Hopkins syndrome
Peripheral nerve	Guillain-Barré syndrome Chronic inflammatory demyelinating polyneuropathy	Incidential Guillain-Barré syndrome Porphyria, vasculitis, toxic, compressive	Critical illness polyneuropathy
Neuromuscular junction	Myasthenia gravis Lambert-Eaton syndrome Botulism	Unmasked myasthenia gravis Atypical myasthenia gravis (predominant respiratory weakness, muscle-specific tyrosine kinase antibody) Toxic	Prolonged neuromuscular blockade
Muscle	Muscular dystrophy Polymyositis Periodic paralysis Metabolic/congenital Mitochondrial	Rhabdomyolysis Toxic myopathies Polymyositis Myotonic dystrophy Adult-onset acid maltase deficiency Pyomyositis Hypokalemic Hypophosphatemic	Critical illness myopathy

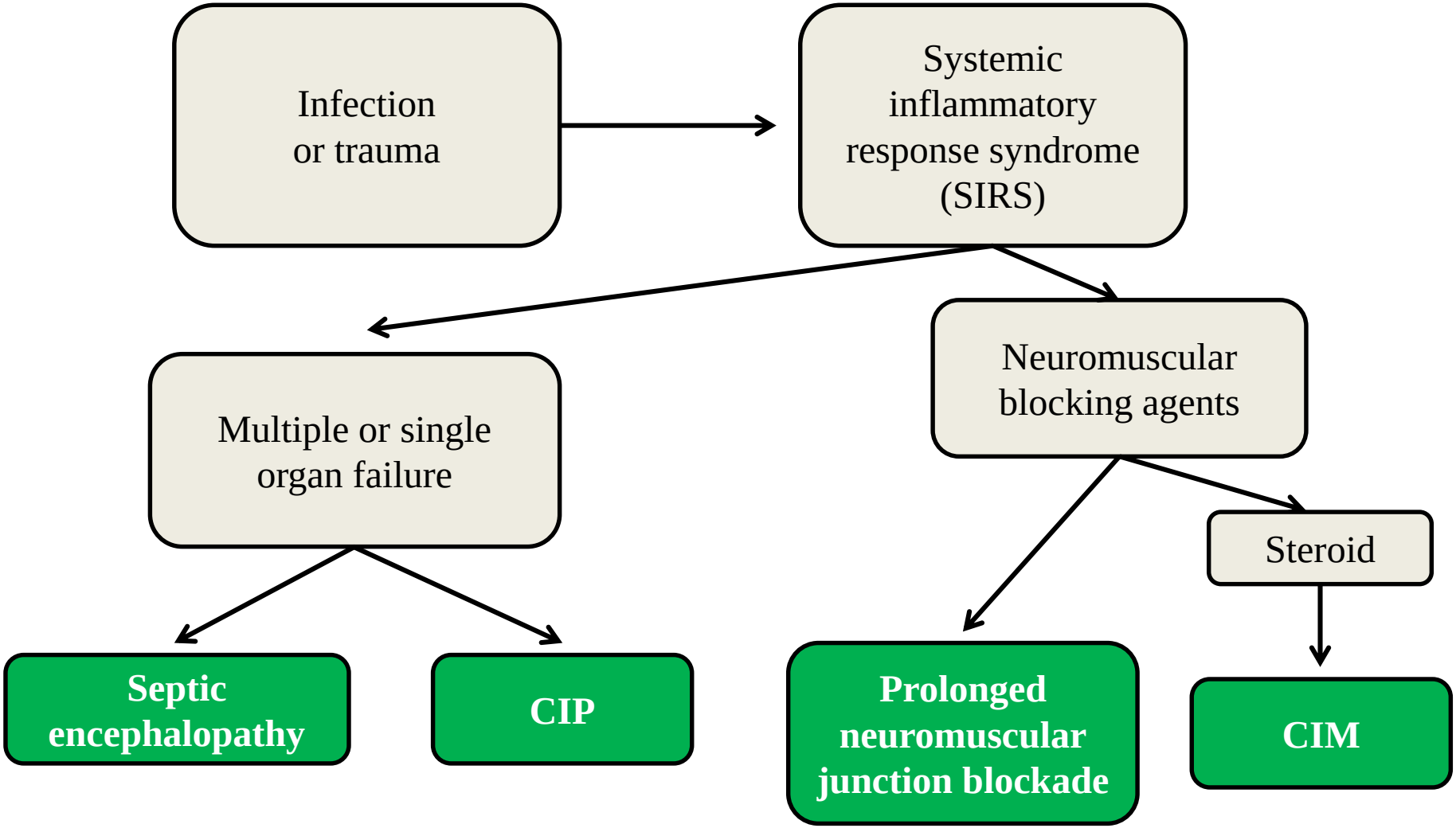
Acute Neuromuscular Weakness in the intensive care unit [1]

- ICU-acquired weakness (ICUAW) begins within hours of ICU admission and is associated with functional disability in the longer term.

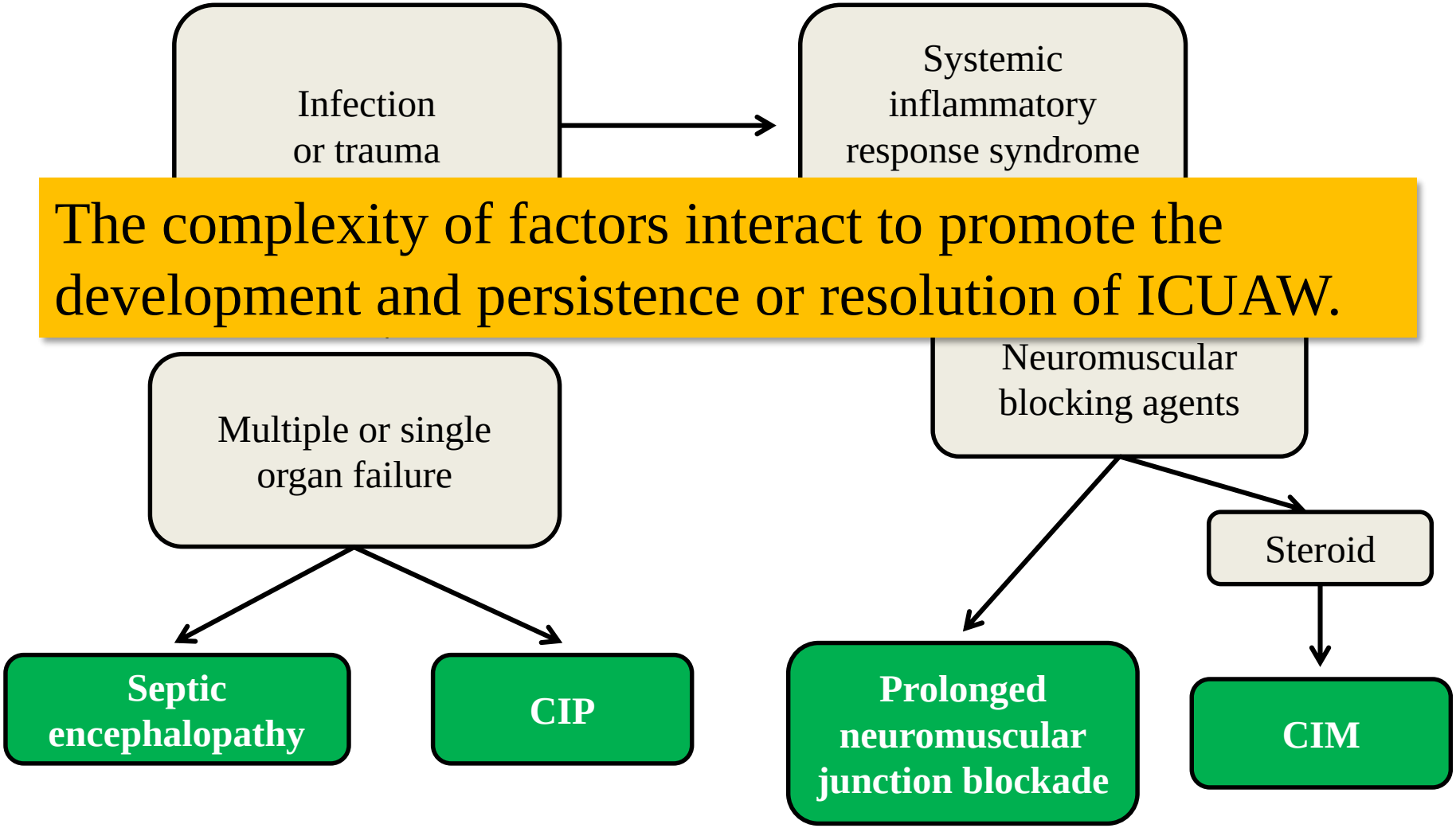
- 25-34% of patients treated for critical illness develop neuromuscular weakness due to myopathy, neuropathy, or both.

- Electrodiagnostic studies are abnormal in up to 80% in some studies.

Initial concept of ICU-acquired weakness



Initial concept of ICU-acquired weakness



The complexity of factors interact to promote the development and persistence or resolution of ICUAW.

ICU-acquired weakness:

critical illness polyneuropathy and critical illness myopathy

Historical review (1)

Characteristic axonal loss of motor and sensory fibers to the toxic effect of sepsis

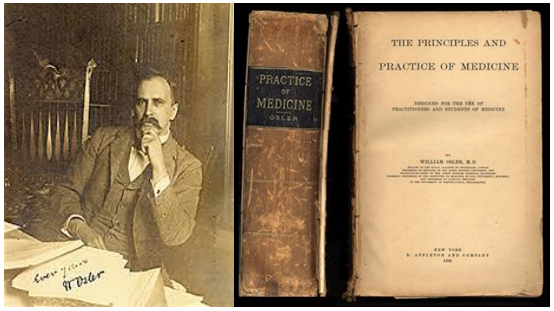
In 1984, Bolton et al
: "critical illness polyneuropathy"

In 1977, Bischoff et al: severe polyneuropathy attributed to gentamicin sulfate

In 1971, Henderson et al: polyneuropathy in patients with burns

In 1961, Mertens: "coma-related disseminated polyneuropathies"

In 1892, Osler: "rapid loss of flesh" with prolonged sepsis



Historical review (2)

- The muscles can be primarily involved without the nerves necessarily being affected.

- In 1996, Lacomis D et al. reported
  critical illness myopathy in patients
  with excessive dosages of iv corticosteroids.

- Increasing evidence in ICU has shown that critical illness polyneuropathy and myopathy frequently occur concomitantly.

The prevalence of CIP/CIM

- Critical illness polyneuropathy
  - 1/3 in the most severe critically ill patients
  - Up to 100% in patients with multiple organ failure

- Critical illness myopathy
  - 36% of patients who need mechanical ventilation for severe asthma
  - about 70% of patients who are admitted to ICU for at least 7 days

- The epidemiology tends to correlated with the duration and the severity of basic diseases.

Diagnostic criteria of CIP

Panel 1: Diagnostic criteria for critical illness polyneuropathy

1 The patient is critically ill (multiorgan dysfunction and failures)
2 Limb weakness or difficulty weaning patient from ventilator after non-neuromuscular causes such as heart and lung disease have been excluded
3 Electrophysiological evidence of axonal motor and sensory polyneuropathy
4 Absence of a decremental response on repetitive nerve stimulation

Definite diagnosis of critical illness polyneuropathy is established if all four criteria are fulfilled. Probable diagnosis of critical illness polyneuropathy is established if criteria 1, 3, and 4 are fulfilled. Diagnosis of intensive care unit-acquired weakness is established if only criteria 1 and 2 are fulfilled. Modified from Bolton,[11] by permission of John Wiley & Sons.

Lancet Neurol 2005; 10:931–941.

Table 2. Diagnostic criteria for critical illness polyneuropathy*

1. The patient is critically ill (sepsis and multiple organ failure, SIRS)
2. Difficulty weaning patient from ventilator after nonneuromuscular causes such as heart and lung disease have been excluded
3. Possible limb weakness
4. Electrophysiologic evidence of axonal motor and sensory polyneuropathy

**These diagnostic criteria are now well established, but in certain circumstances other acute axonal polyneuropathies, such as those due to thiamine deficiency, porphyria, etc., should be excluded (with permission from Bolton[27]).*

Muscle Nerve 2005;32:140-163

Critical Illness Polyneuropathy

- No unifying molecular mechanism(s) has been identified to explain the development, progression, and/or recovery from CIP.

- Nerve biopsy
  - Most sensory nerves in early biopsies (median, 15 day of sepsis) look normal, despite having reduced SNAPs.
  - In contrast, late biopsies (median, 56 day) demonstrate axonal neuropathy—but this is not pathognomonic of CIP.
  - Even in patients who die with CIP, examination of the obturator, cervical, and lumbosacral roots at autopsy fail to demonstrate histologic pathological features that would characterize CIP.

Differentiation between CIP and GBS

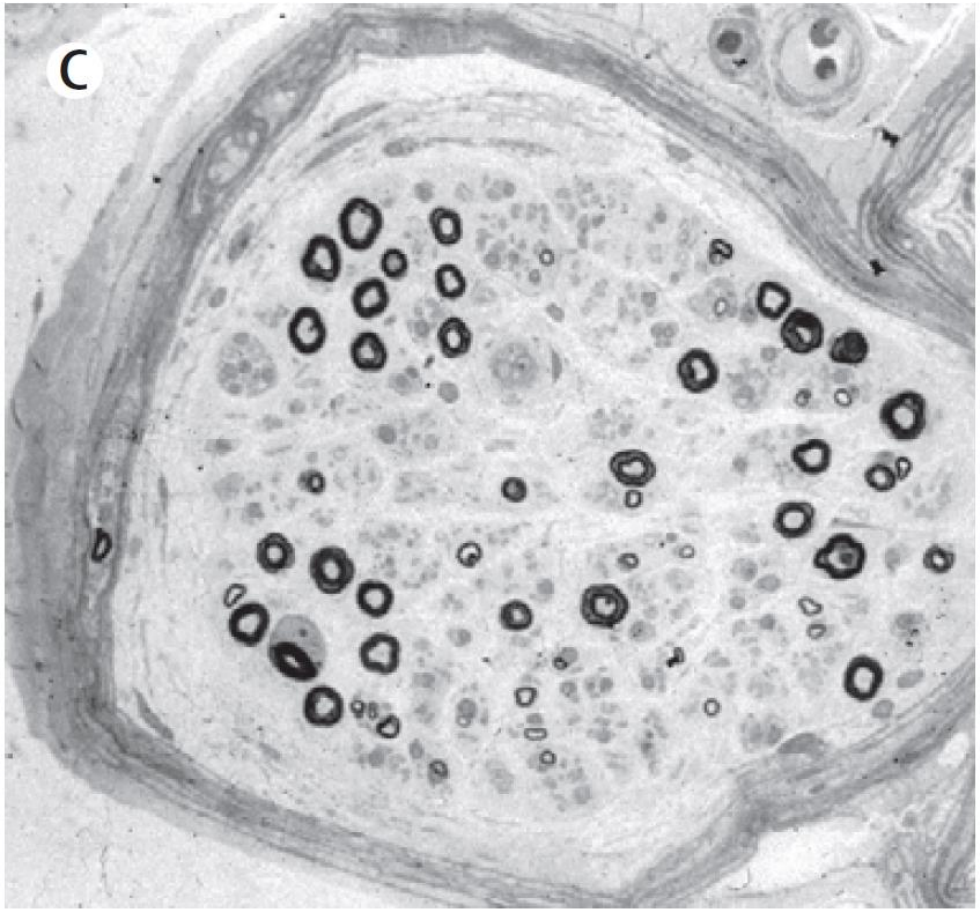
	CIP	Guillain-Barré syndrome
Prodromal conditions	Sepsis and multiple organ failure	Gastrointestinal or respiratory infection
Clinical presentation	Onset of the disorder usually after intensive care unit admission	Onset of the disorder usually before intensive care unit admission
	Often characterized by fairly symmetric limb muscle weakness sparing cranial nerves;	Infections precede the onset of progressive weakness and sensory disturbances
	Sensory deficits less prominent	Frequent cranial nerve involvement
Cerebrospinal fluid	Usually normal	Albuminocytologic dissociation
Electrophysiology	Axonal motor & sensory polyneuropathy	Demyelinating polyneuropathy or unresponsive nerves, abundant spontaneous activity Axonal motor & sensory polyneuropathy
Magnetic resonance imaging	No significant findings	Occasional enhancement of spinal nerve roots
Biopsy	Primarily axonal degeneration of distal peripheral nerves without inflammation	Primarily demyelinating process with inflammation, or motor/sensory axonal degeneration, or motor axonal degeneration only
Treatment	No specific therapy, usually anti-septic treatment	Plasmapheresis, intravenous immune globulin
Outcome	Recovery may be spontaneous and of variable timing; 50% of patients with full recovery	Usually > 75% complete recovery

Neural Regen Res. 2014;9:101-110

Pathology of CIP

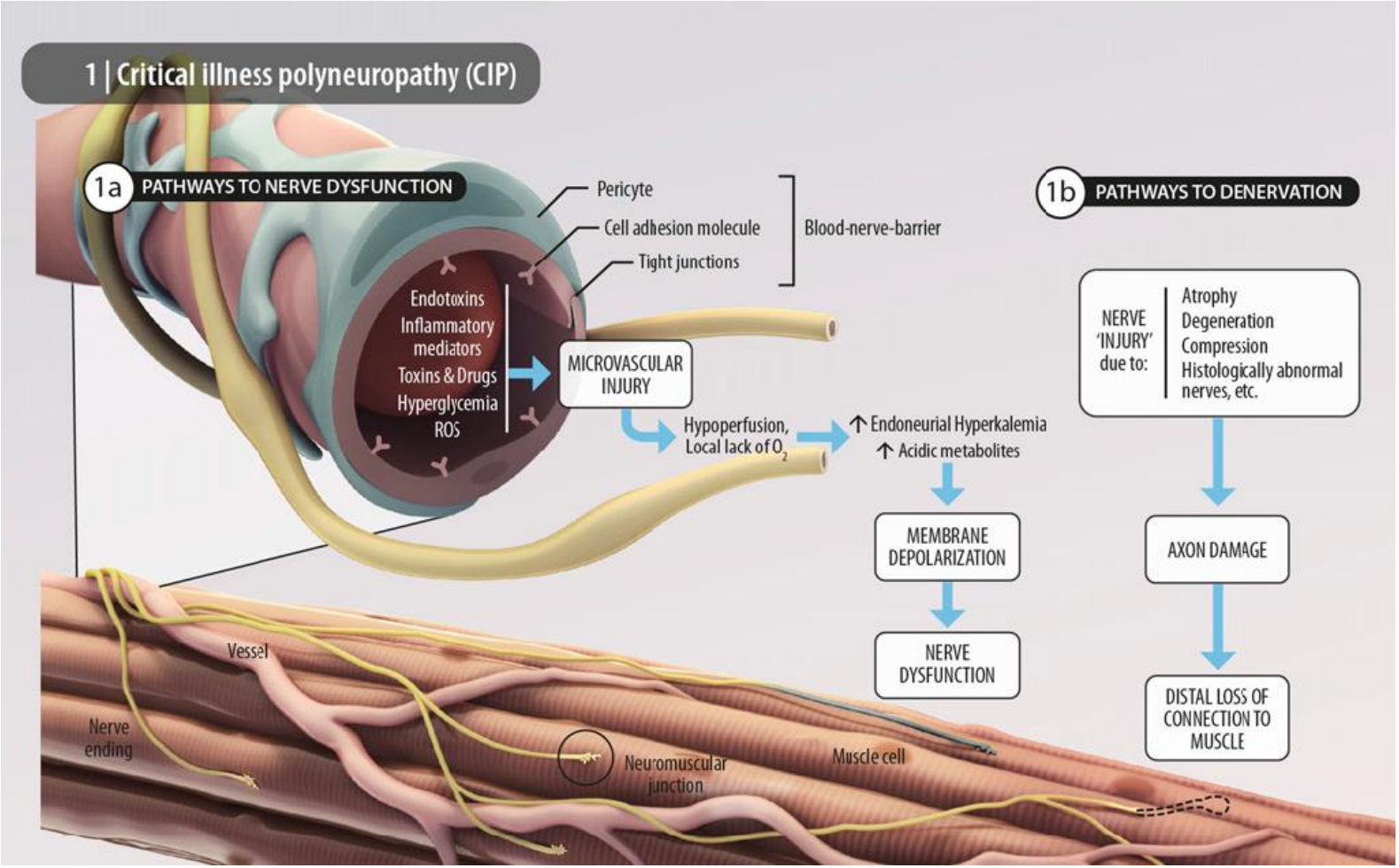
- Autopsy and surgical pathologic studies reveal (non-inflammatroy) acute degeneration of sensory and motor axons.

- Muscle histopathology in CIP reveals angulated atrophic fibers of both fiber types.



Semithin section using toluidine blue stain

Hypothesis of CIP



- No overarching mechanism has been identified to explain the occurrence of CIP.

Am J Respir Crit Care Med 2012;187:238-246

Critical Illness Myopathy

- Skeletal muscle dysfunction in the critically ill derives from a variable combination of decreased muscle mass and impaired contractility.

- Up to two-thirds of patients treated for status asthmaticus develop elevations in serum creatine kinase, and one-third have clinical features of myopathy.

- Risk factors included total corticosteroid dose and illness severity.

Diagnostic criteria for CIM

Panel 2: Diagnostic criteria for critical illness myopathy

1 The patient is critically ill (multiorgan dysfunction and failures)
2 Limb weakness or difficulty weaning patient from ventilator after non-neuromuscular causes such as heart and lung disease have been excluded
3 CMAP amplitudes less than 80% of the lower limit of normal in two or more nerves without conduction block
4 Sensory nerve action potential amplitudes more than 80% of the lower limit of normal
5 Needle electromyography with short duration, low-amplitude motor unit potentials with early or normal full recruitment, with or without fibrillation potentials in conscious and collaborative patients; or increased CMAP duration or reduced muscle membrane excitability on direct muscle stimulation in non-collaborative patients
6 Absence of a decremental response on repetitive nerve stimulation
7 Muscle histopathological findings of primary myopathy (eg, myosin loss or muscle necrosis)

Definite diagnosis of critical illness myopathy is established if all seven criteria are fulfilled. Probable diagnosis of critical illness myopathy is established if criteria 1 and 3–6 are fulfilled. Diagnosis of intensive care unit-acquired weakness is established if only criteria 1 and 2 are fulfilled. CMAP=compound muscle action potential. Modified from Lacomis and colleagues,[4] by permission of John Wiley & Sons.

Lancet Neurol 2005; 10:931–941.

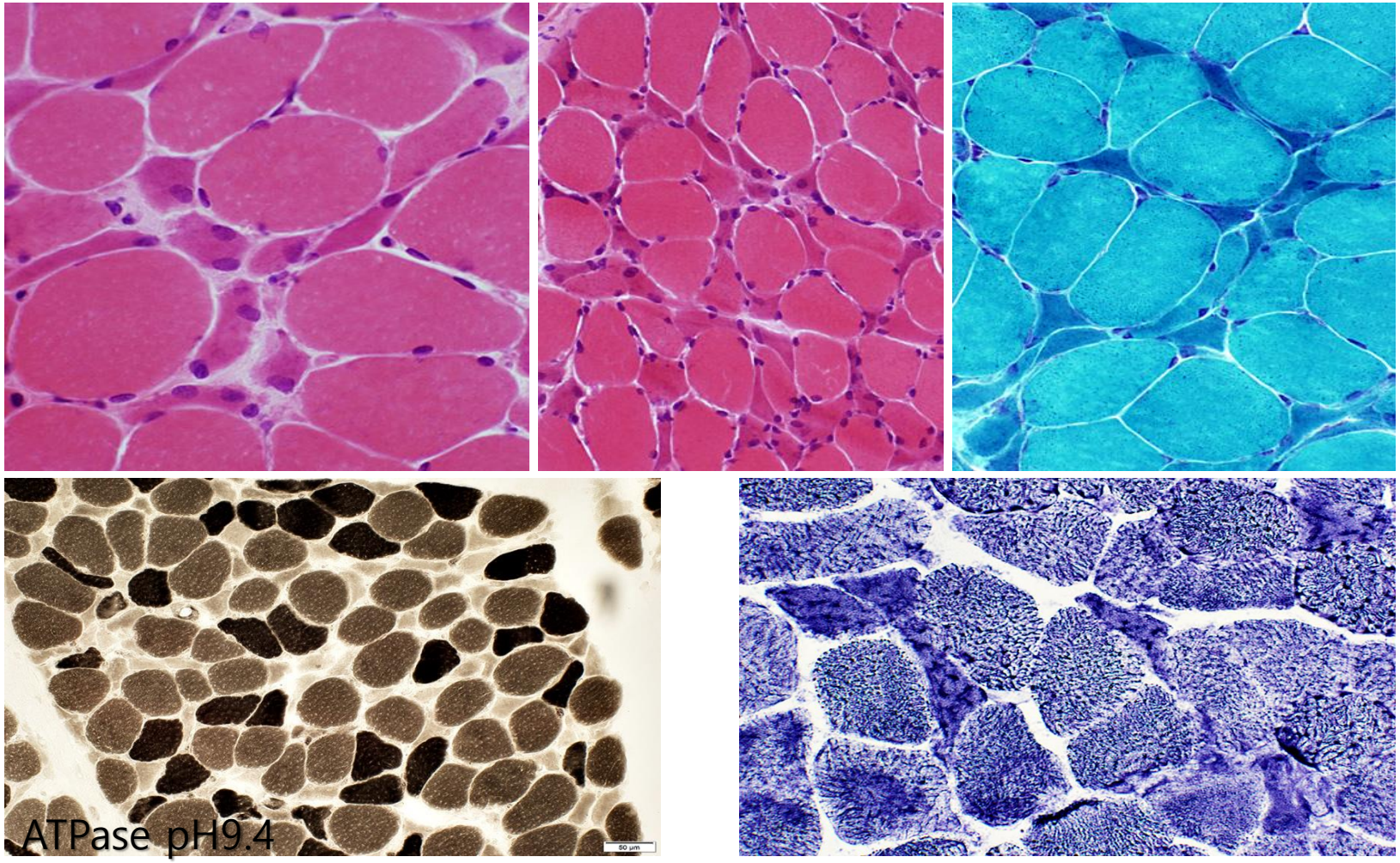
Table 3. Diagnostic criteria of critical illness myopathy*

1. SNAP amplitudes >80% of the lower limit of normal;
2. Needle EMG with short-duration, low-amplitude MUPs with early or normal full recruitment, with or without fibrillation potentials;
3. Absence of a decremental response on repetitive nerve stimulation; and
4. Muscle histopathologic findings of myopathy with myosin loss.
5. CMAP amplitudes <80% of the lower limit of normal in two or more nerves without conduction block;
6. Elevated serum creatine kinase (CK); and
7. Demonstration of muscle inexcitability.

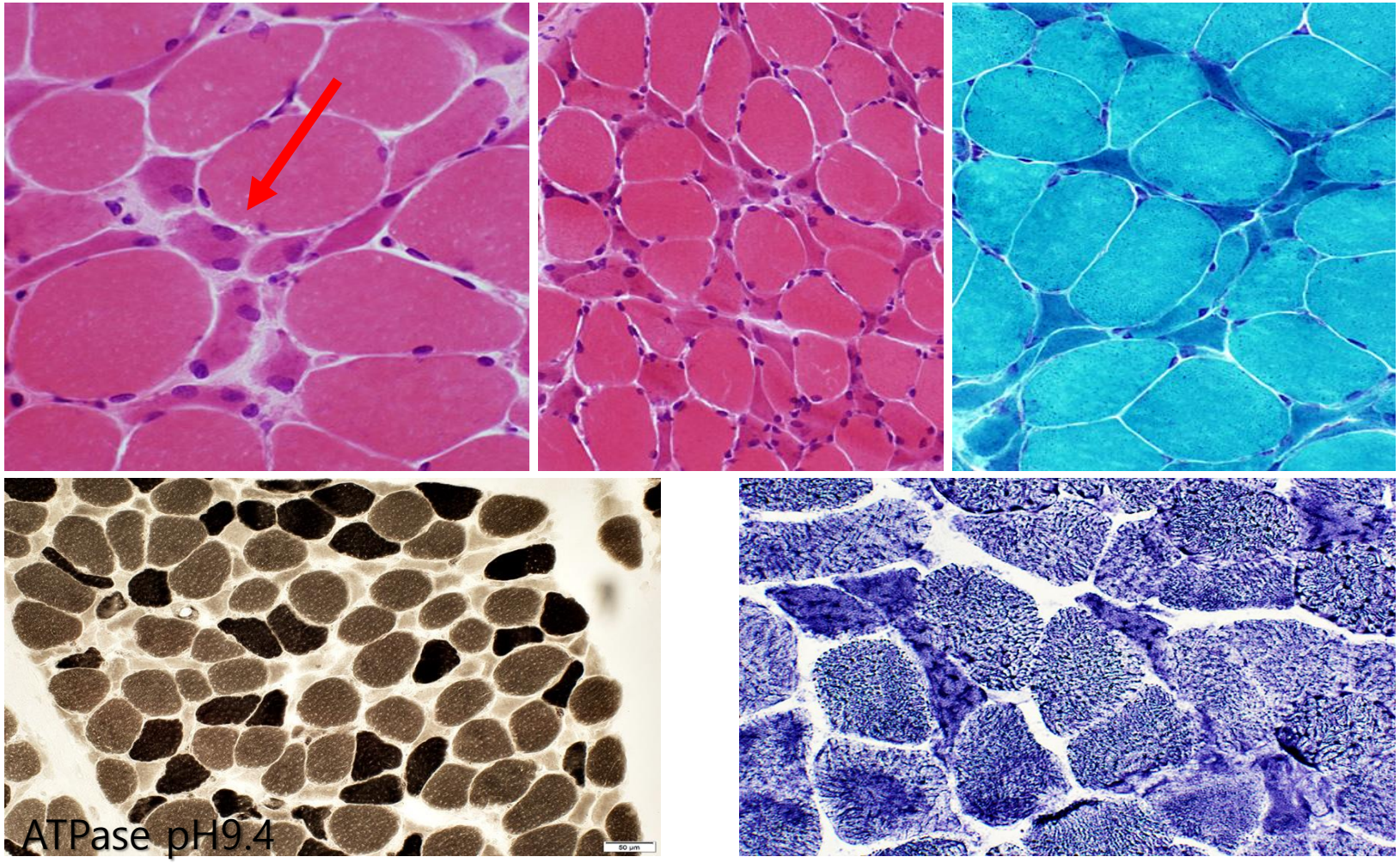
**For a definite diagnosis of critical illness myopathy, patients should have all of the first five features.*

Muscle Nerve 2005;32:140-163

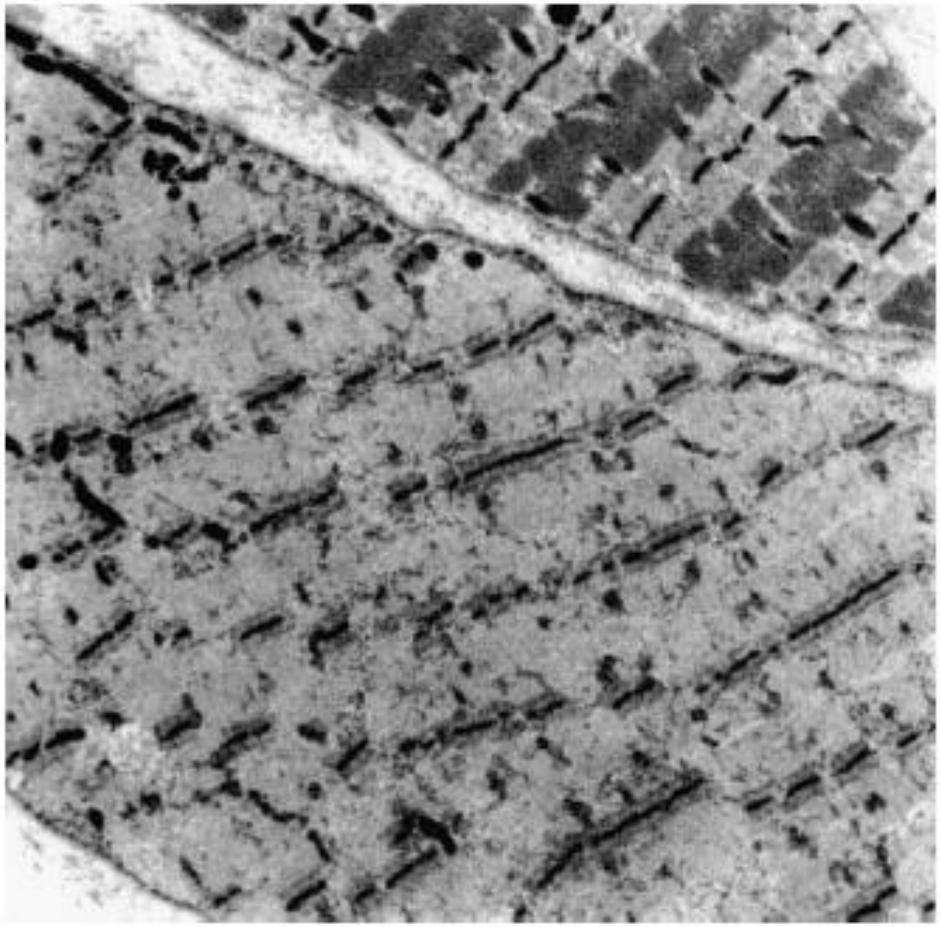
Pathology of CIM



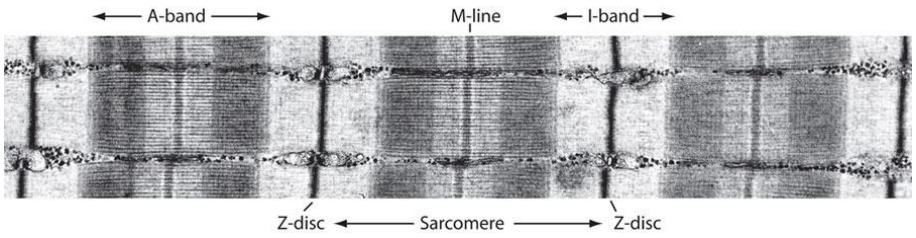
Pathology of CIM

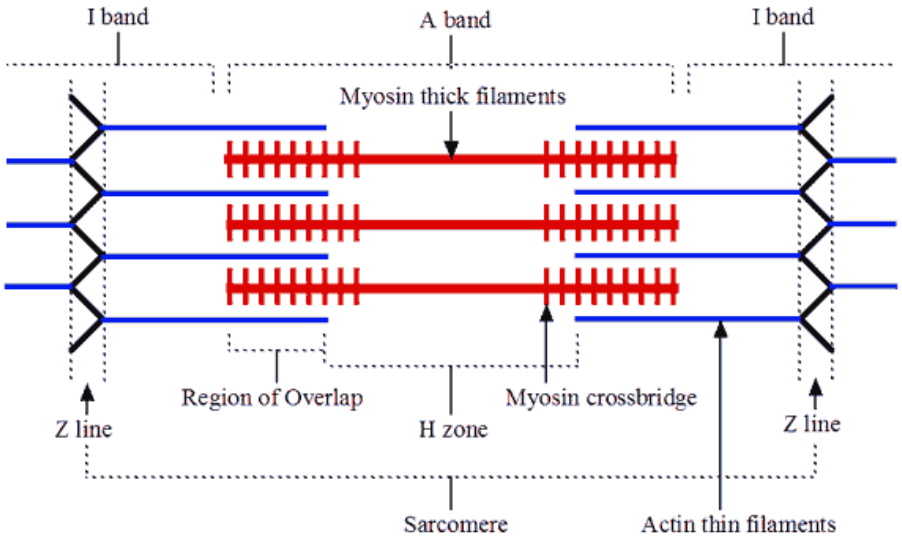


Ultrastructure of CIM

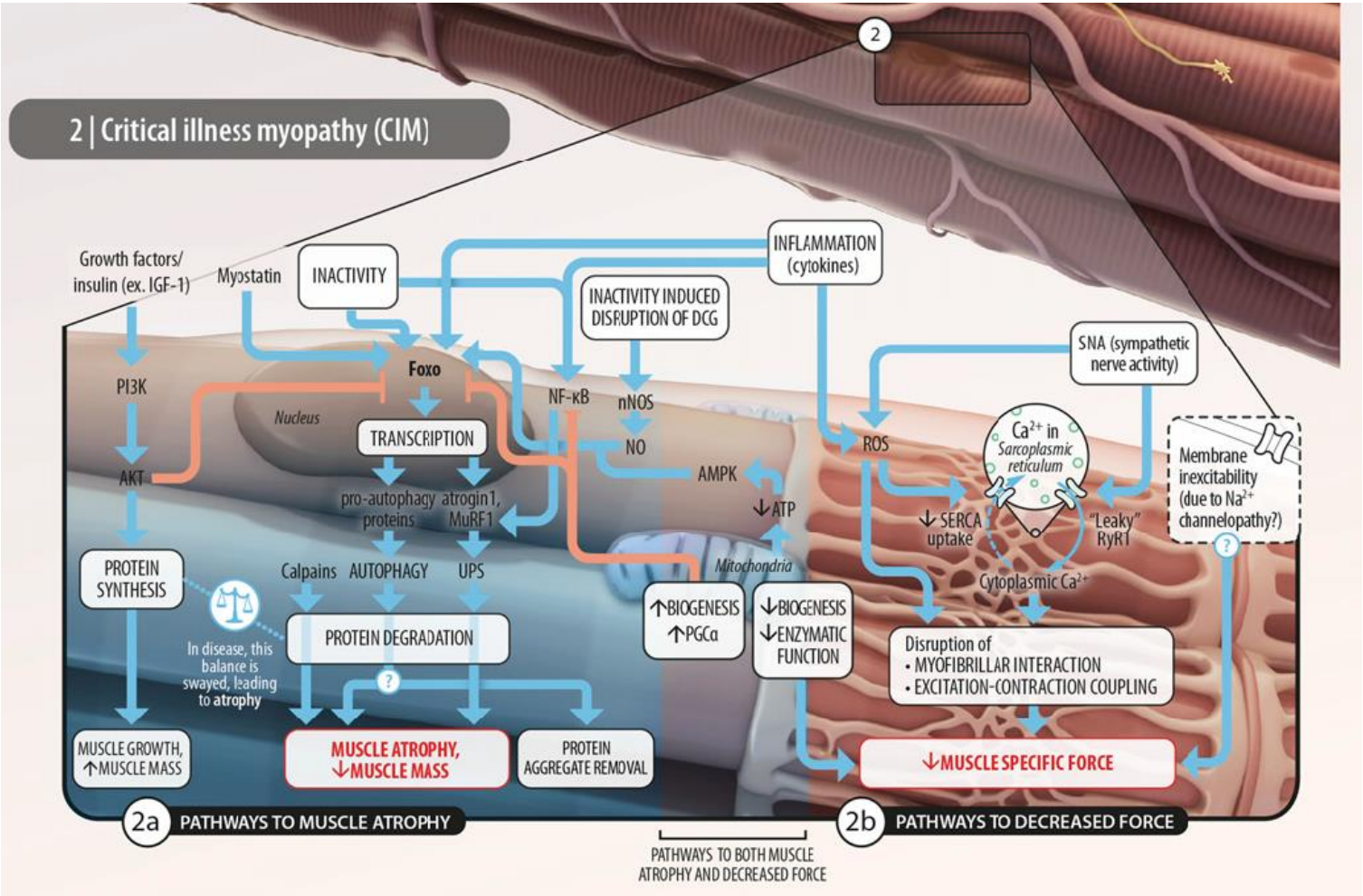


Muscle pathology of CIM patient





Hypothesis of CIM

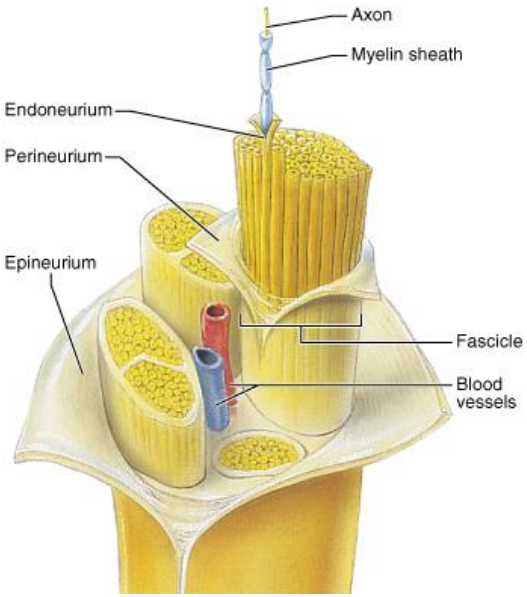


- Numerous cellular signaling networks participate in the development of CIM.

Am J Respir Crit Care Med 2012;187:238-246

Electrodiagnostic studies

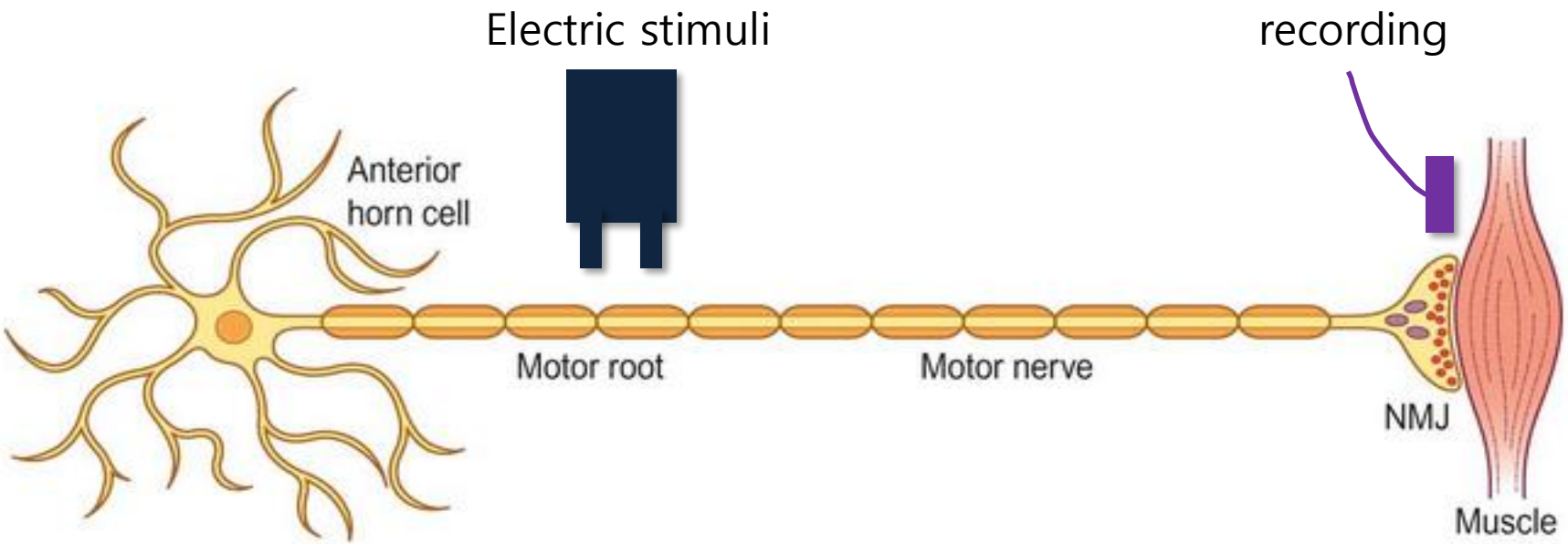
Peripheral nerve



- Myelin: increase the speed at which impulses propagate along the *myelinated* fiber. myelination helps prevent the electrical current from leaving the axon.

- Axon: conducts electrical impulses away from the neuron's cell body or soma

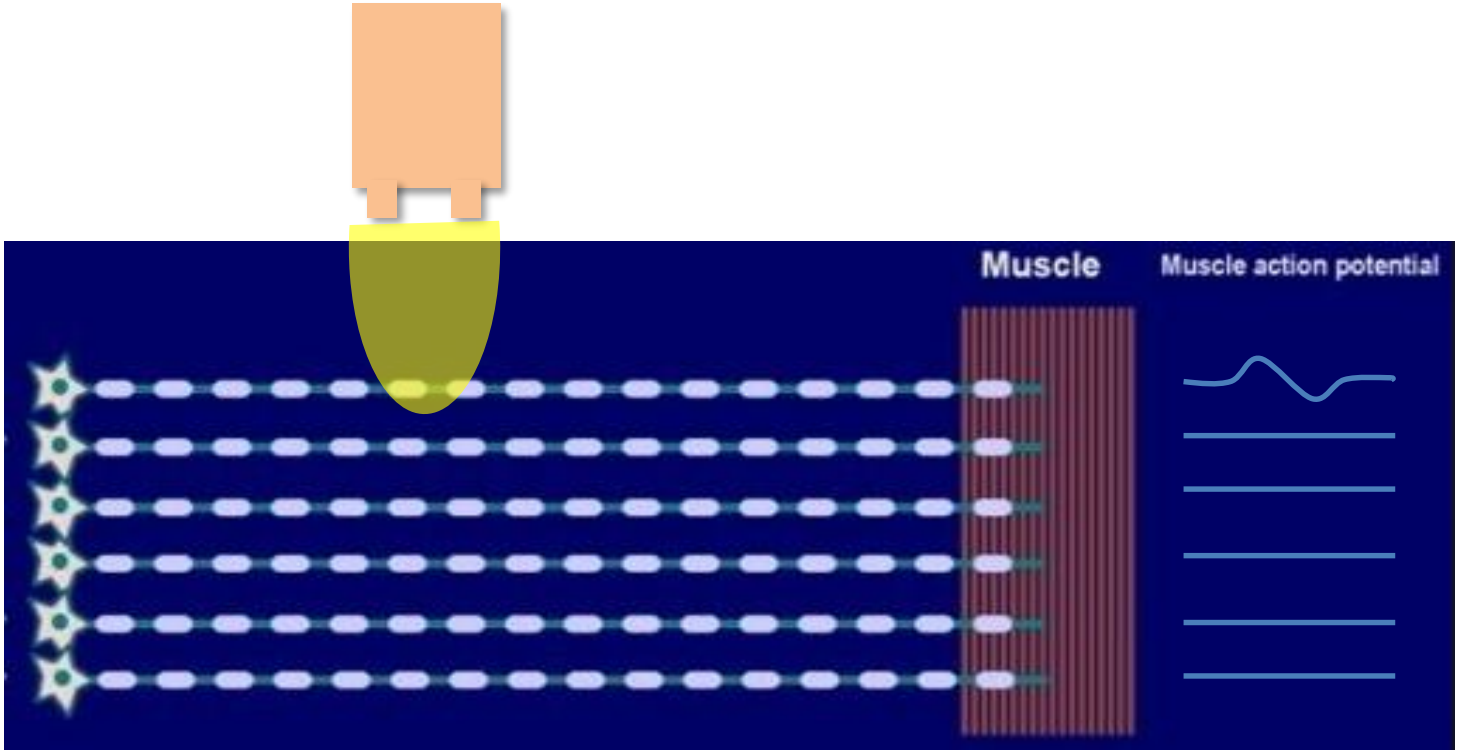
Nerve conduction study (1)



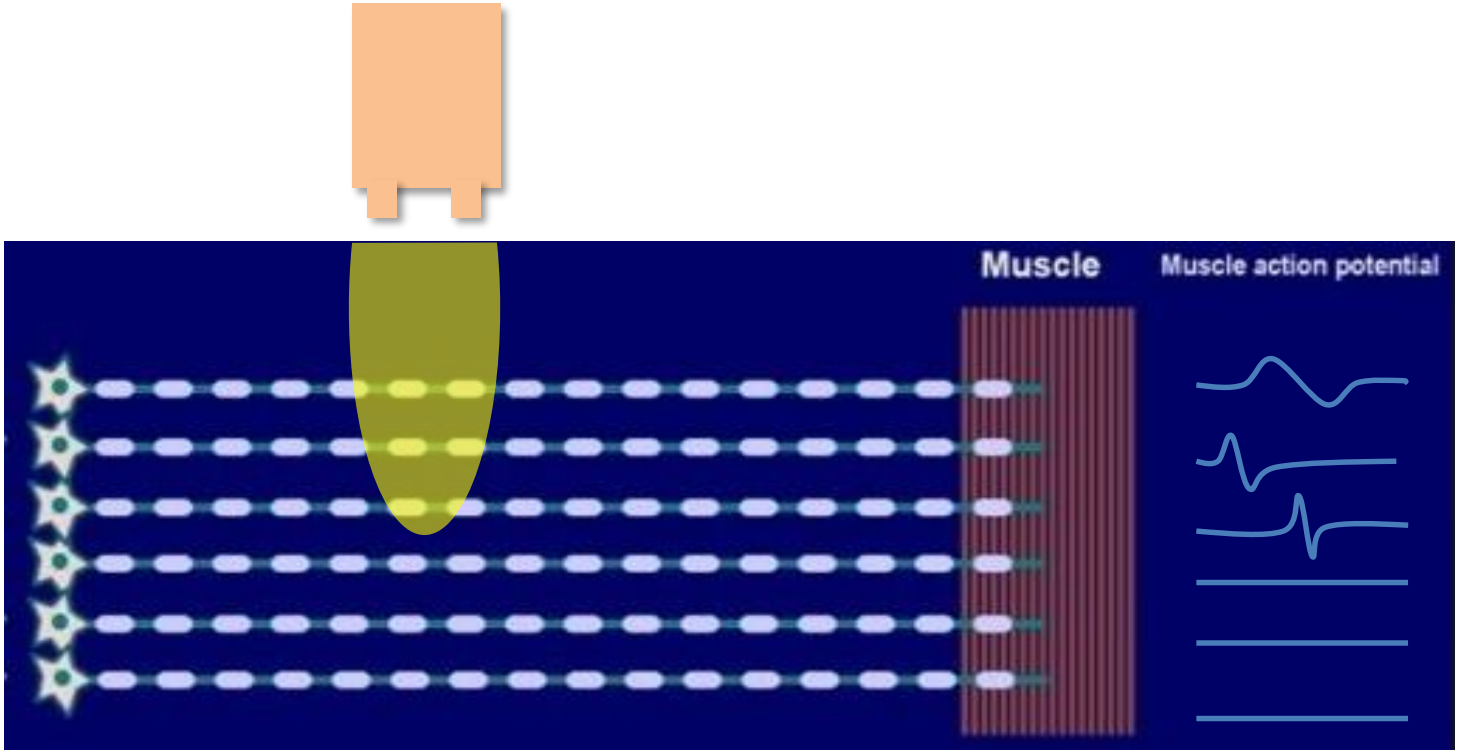
- Measurement

  : amplitude and velocity

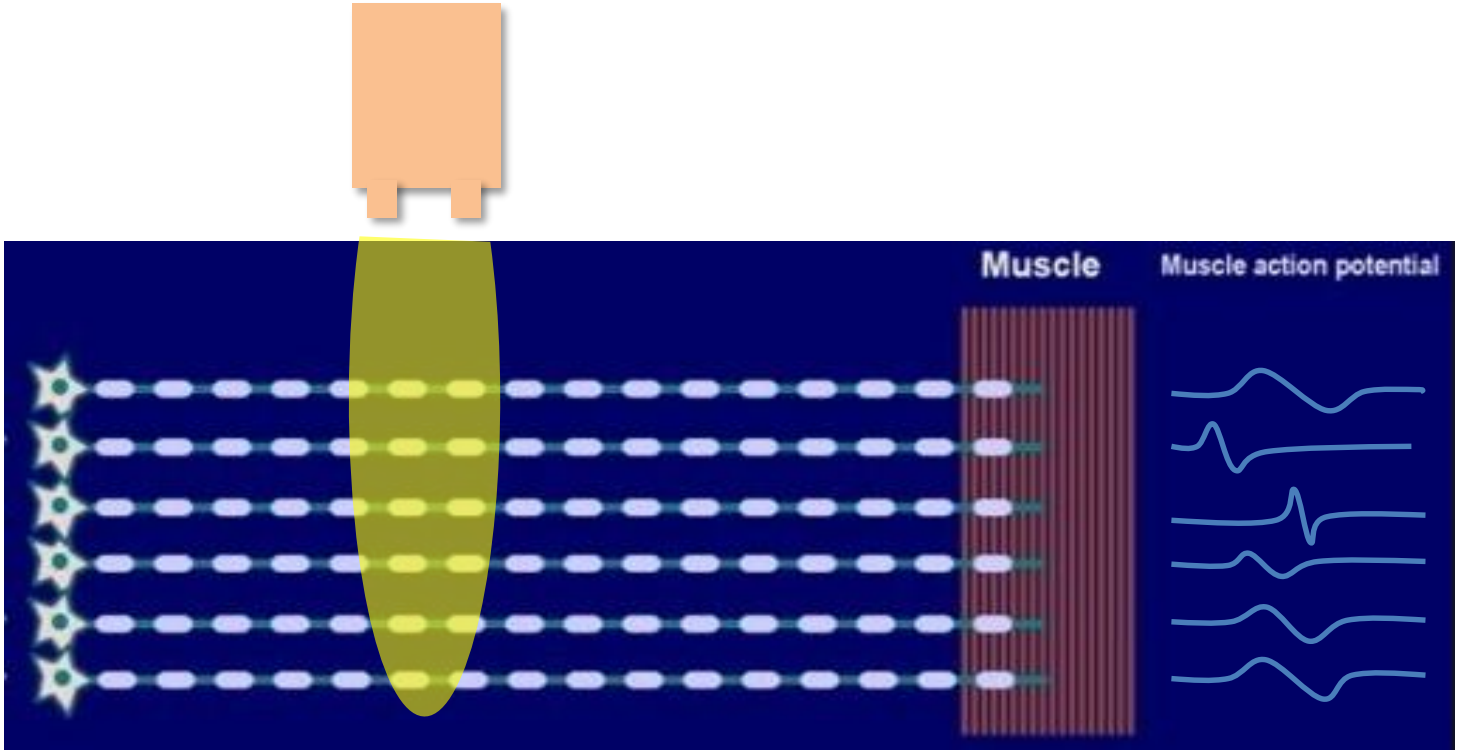
Nerve conduction study



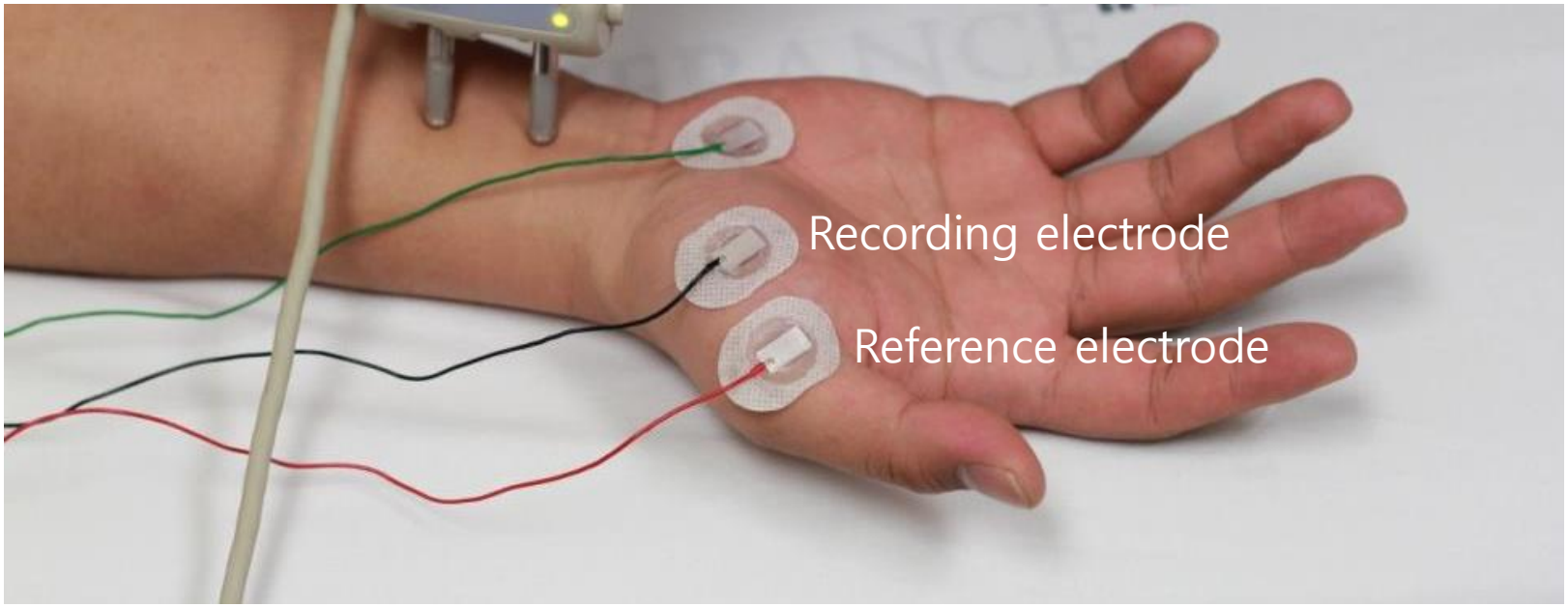
Nerve conduction study



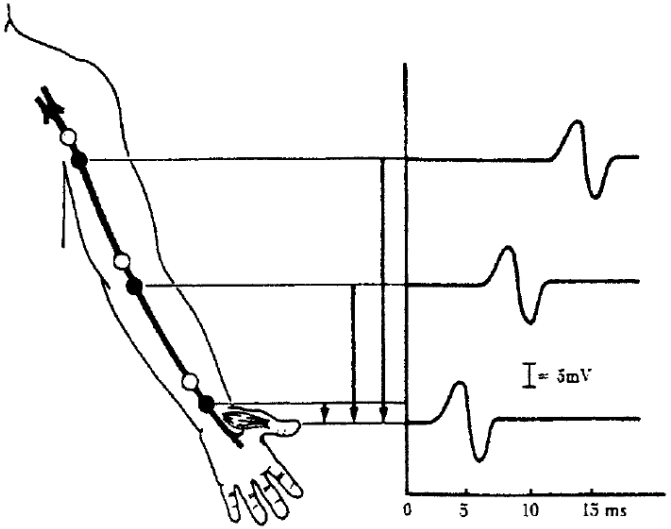
Nerve conduction study



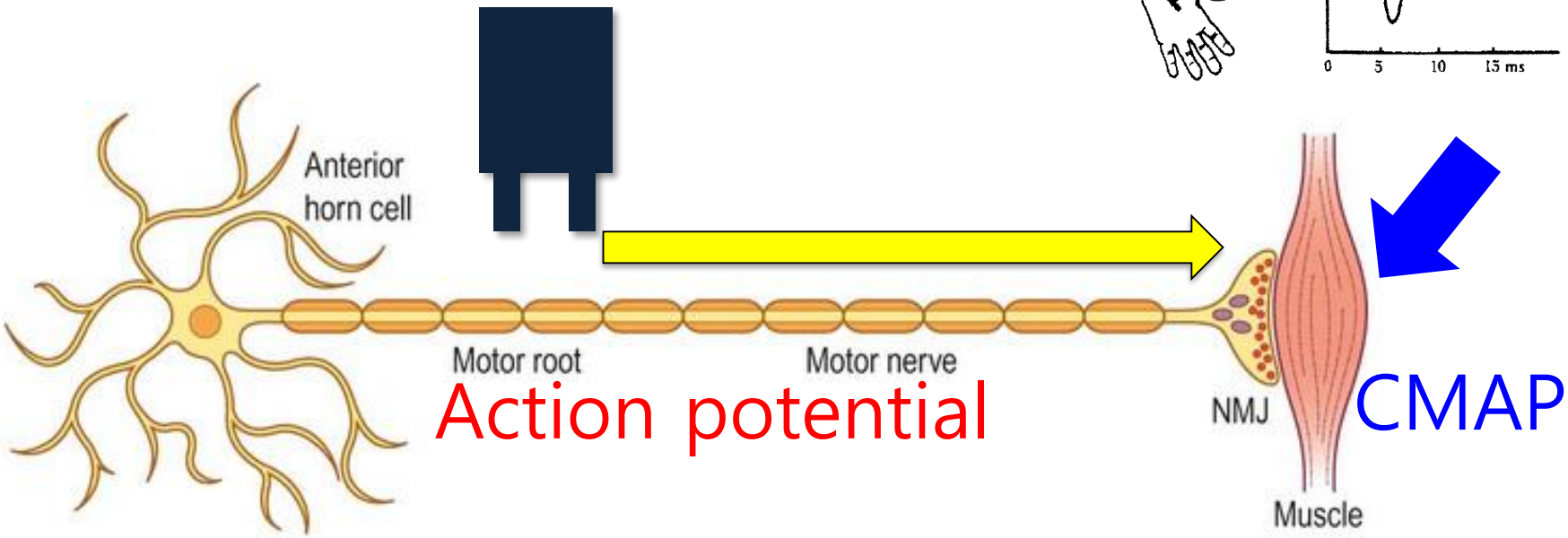
Motor nerve conduction study



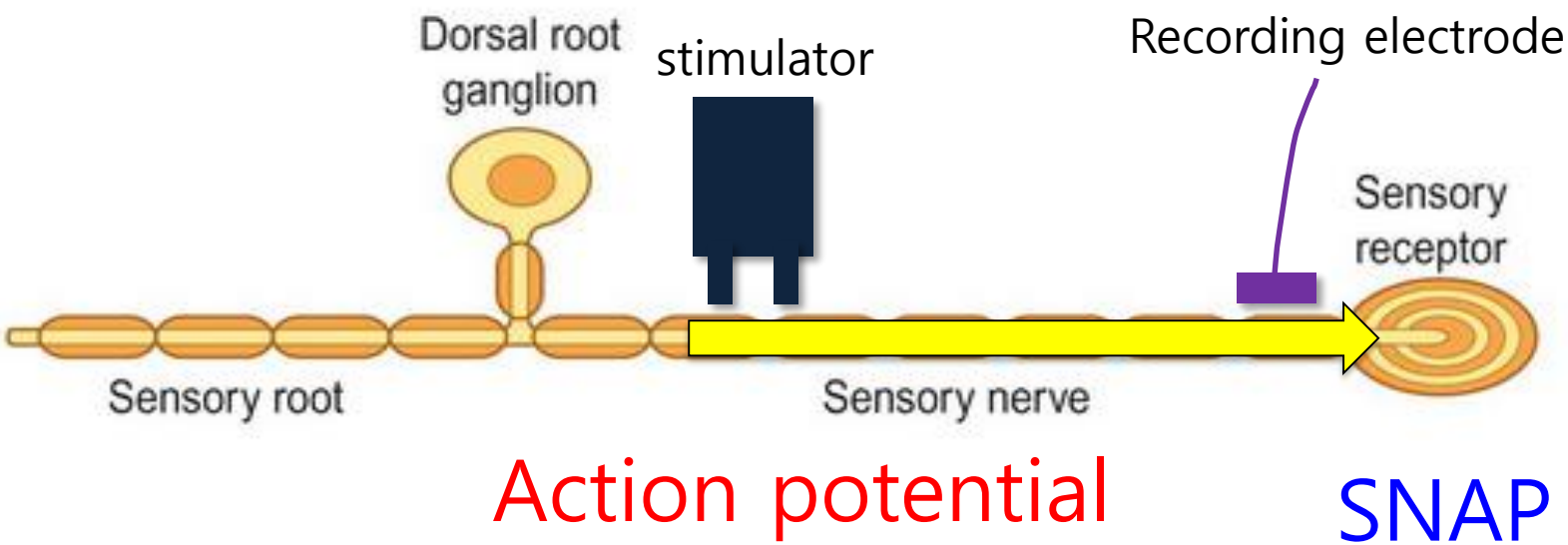
Motor nerve conduction study



Electric stimulator



Sensory nerve conduction study



Sensory nerve conduction study

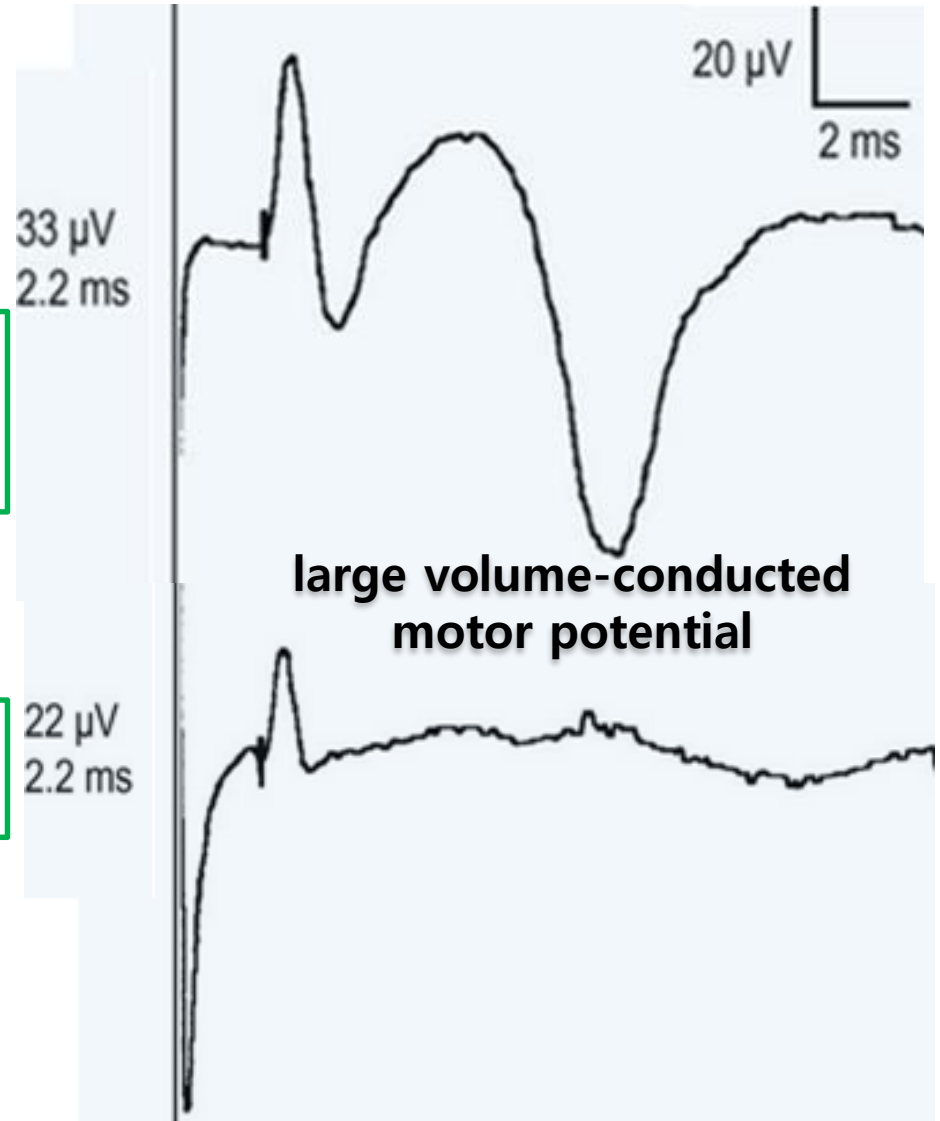
Antidromic recording

Larger amplitude
Less subjective to noise
Motor nerve : often stimulated

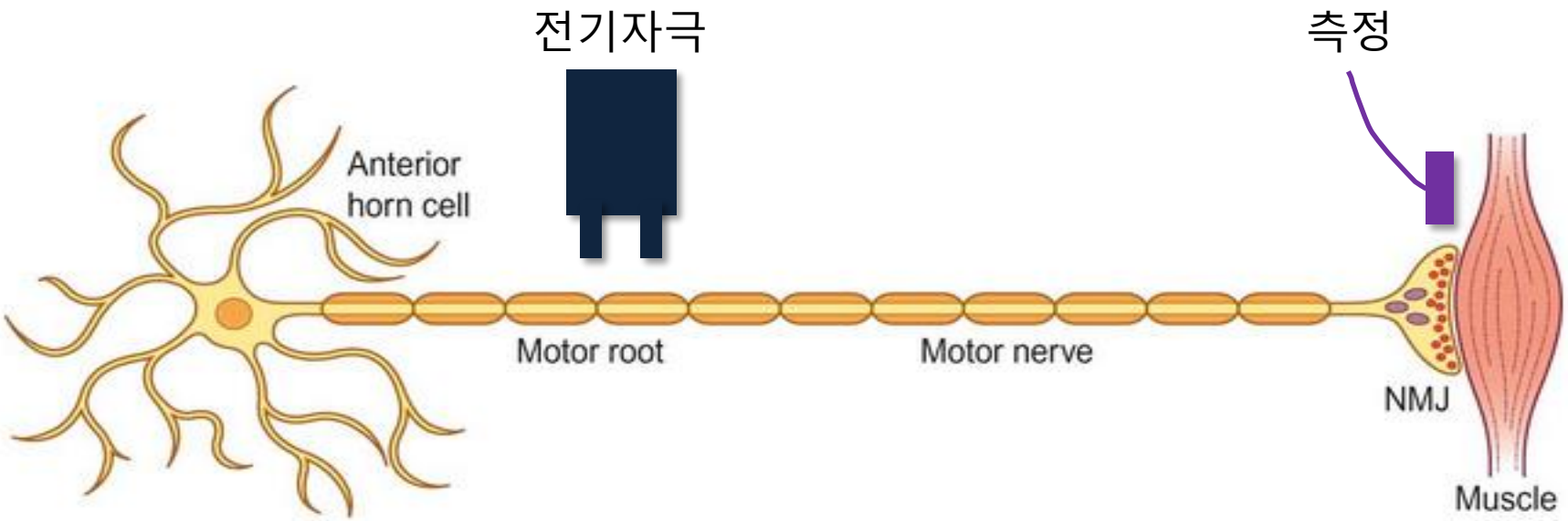
Orthodromic recording

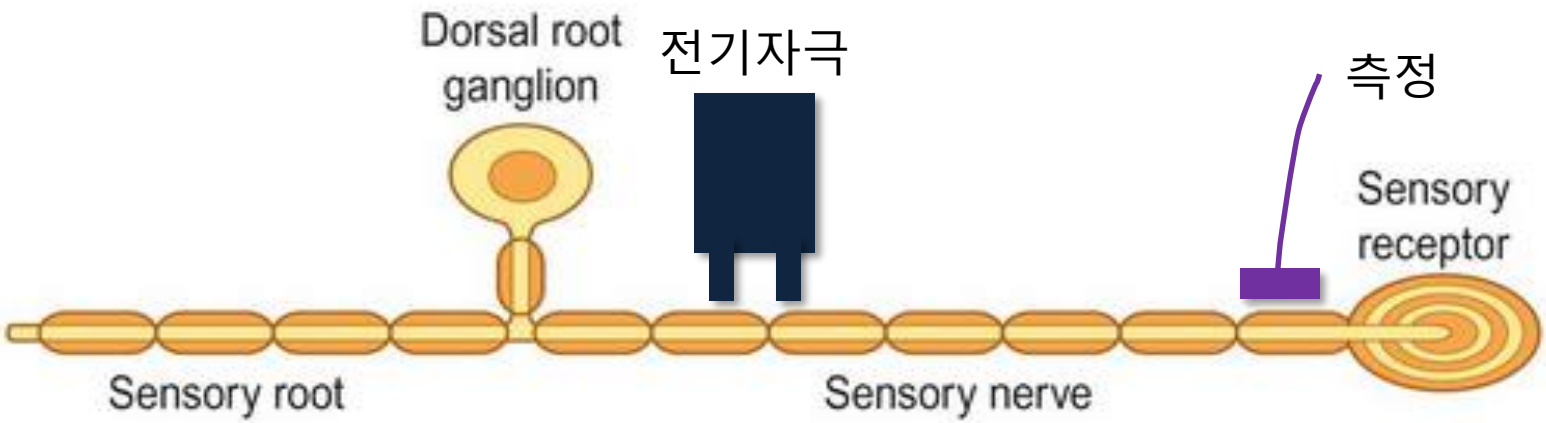
Smaller amplitude
Same onset latency

Latencies and conduction velocities are identical

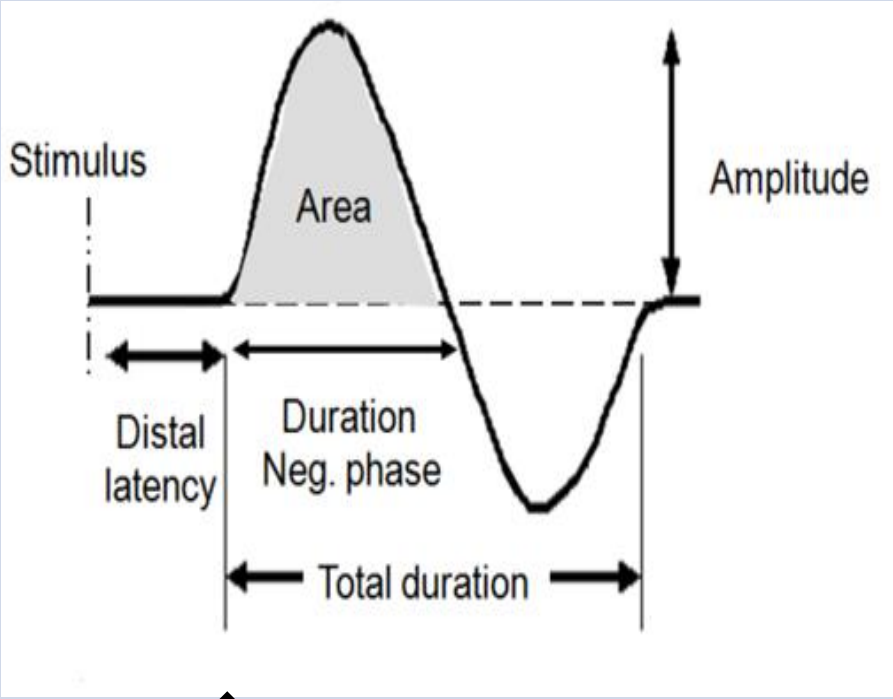
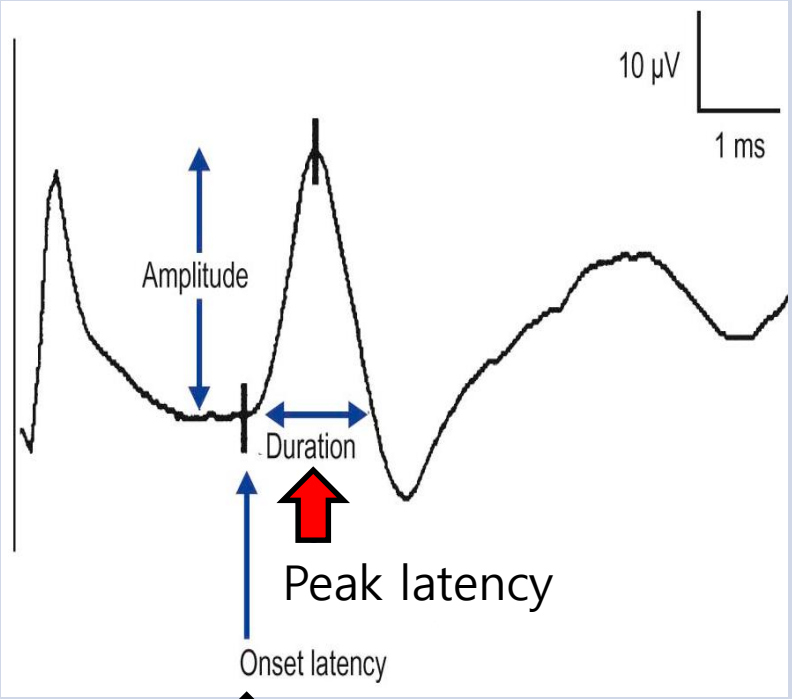


Nerve conduction study (2)

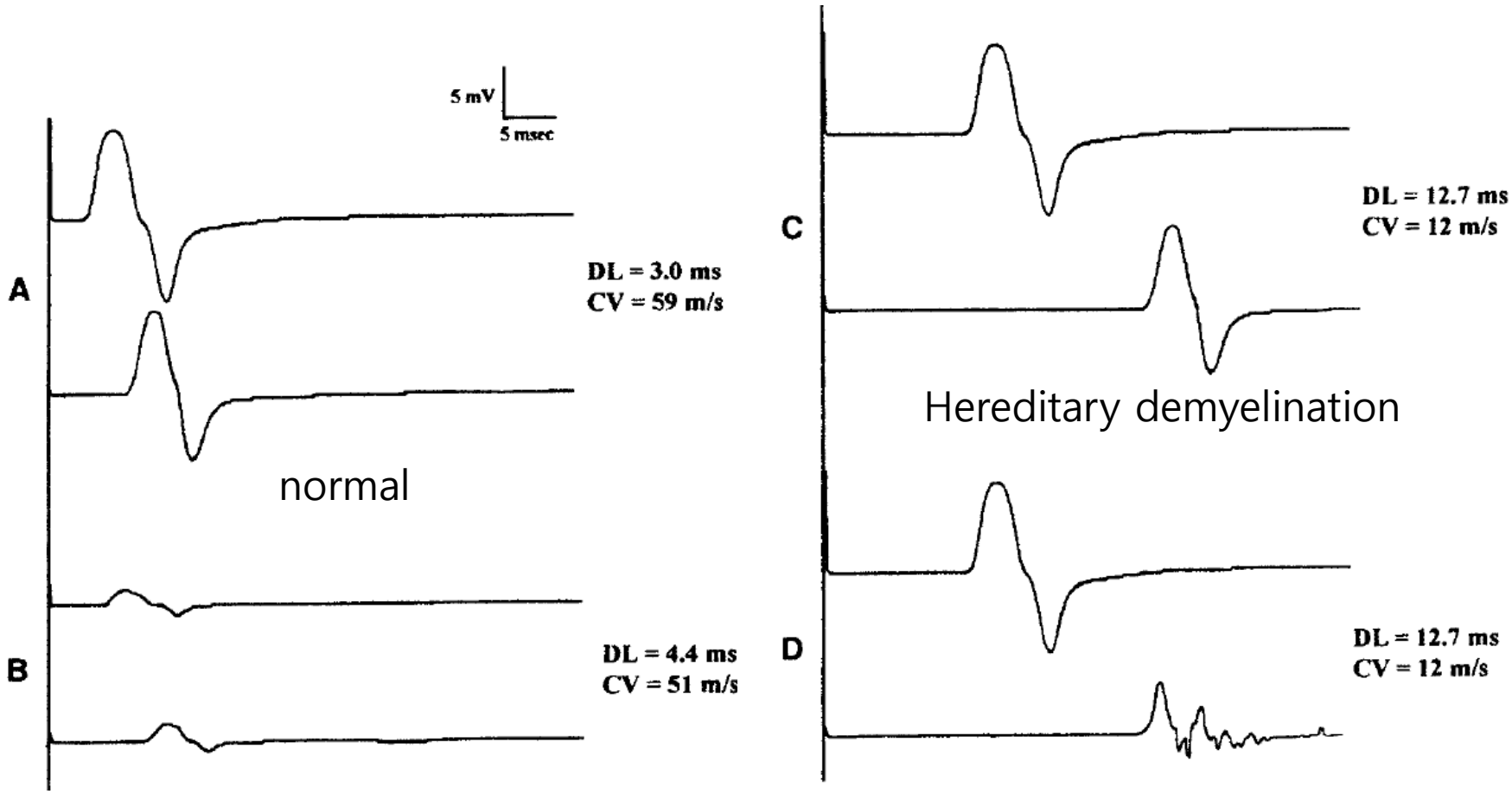




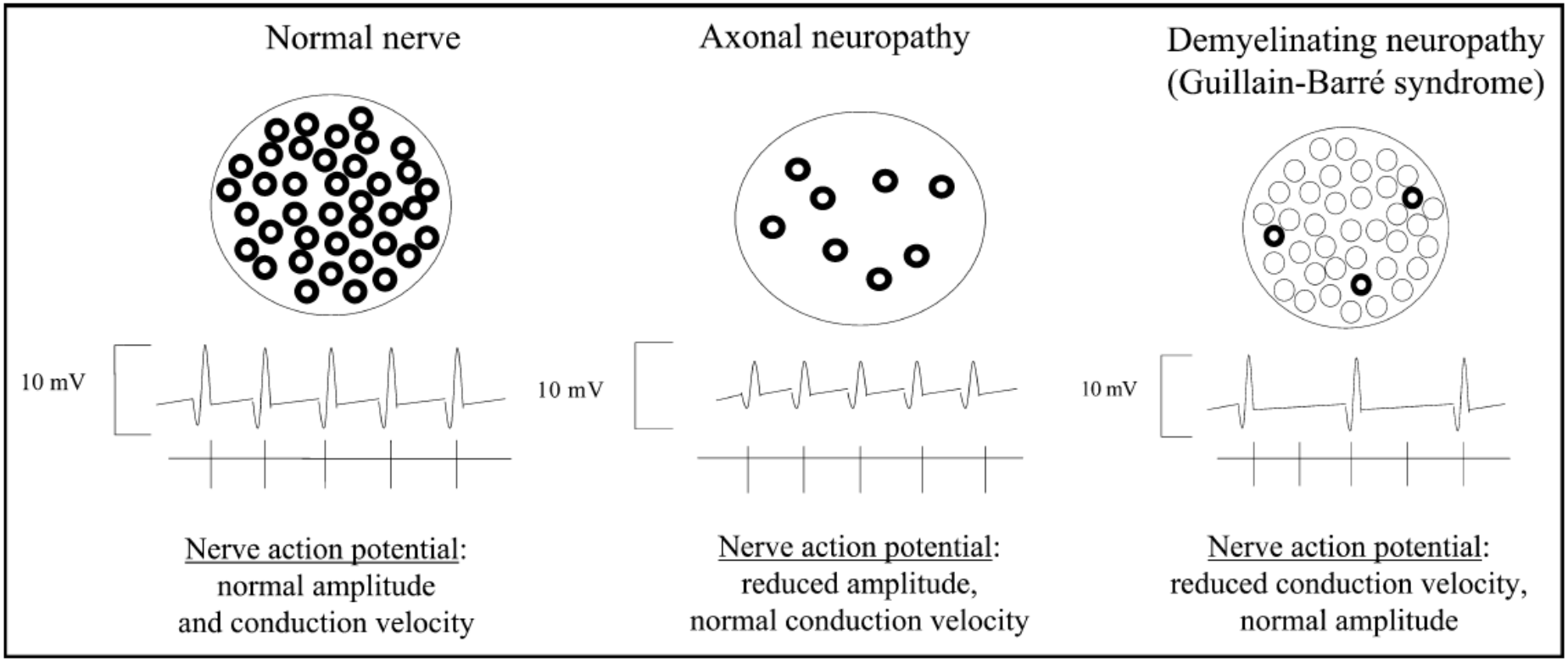
Nerve conduction study (3)

Motor NCS	Sensory NCS
	
Onset latency	Onset latency
Amplitude: mV	Amplitude: uV

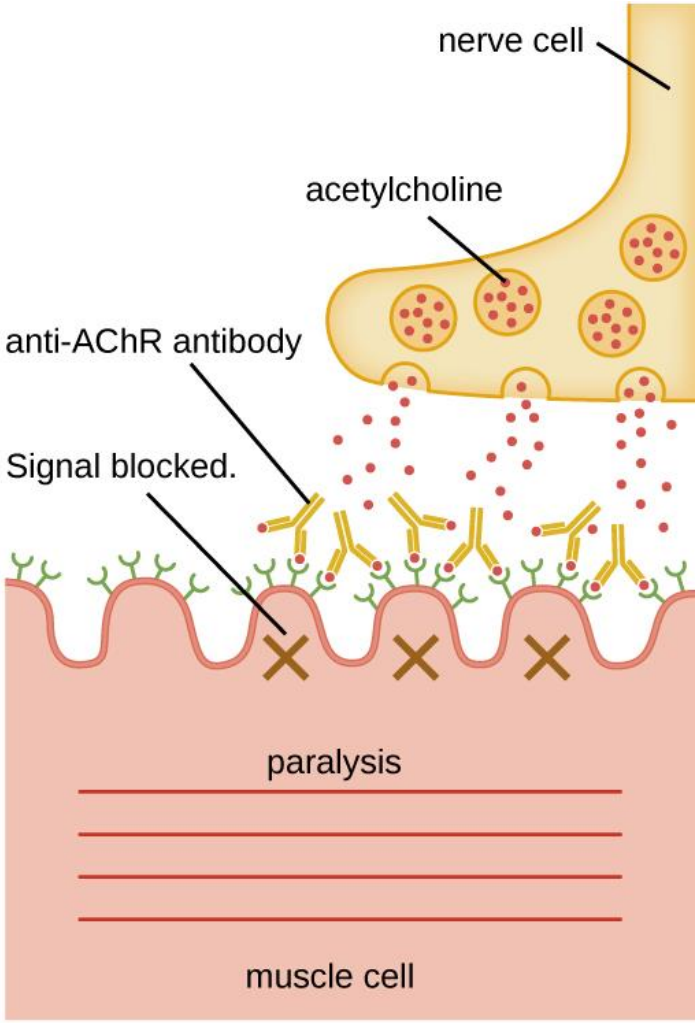
Motor nerve conduction study

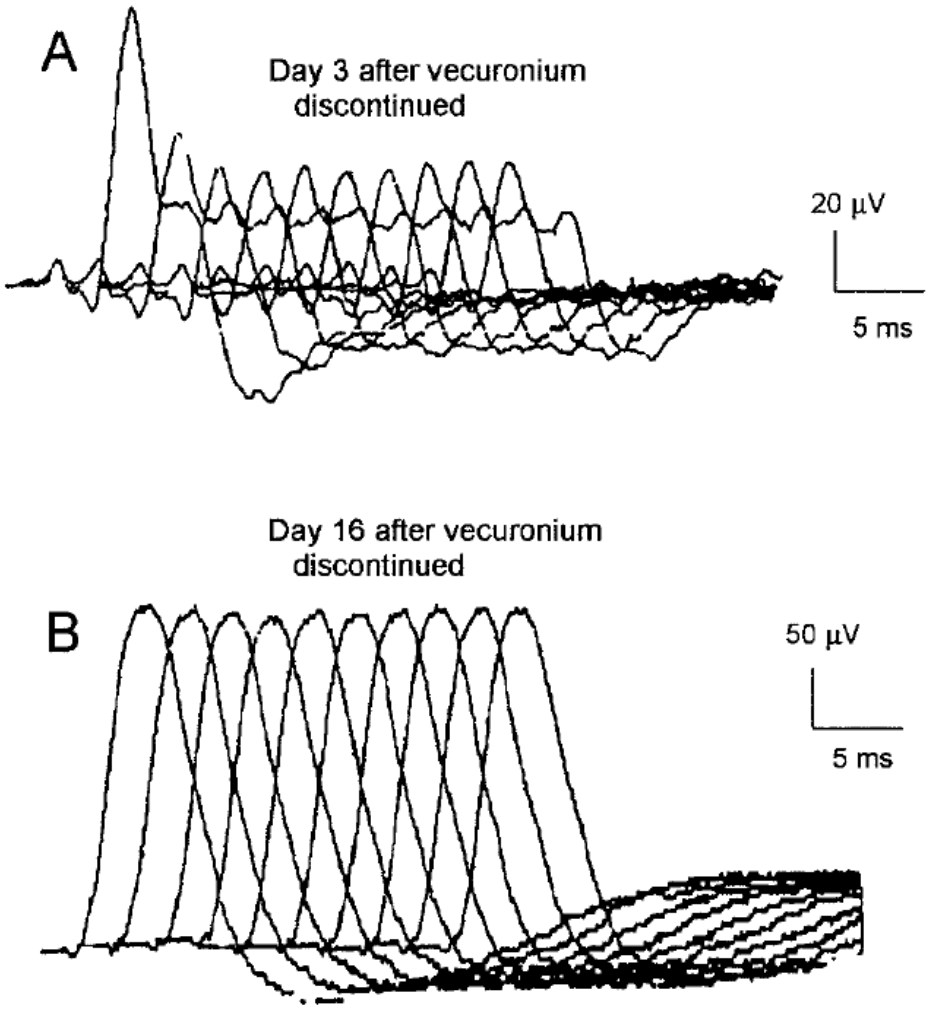


Motor NCV

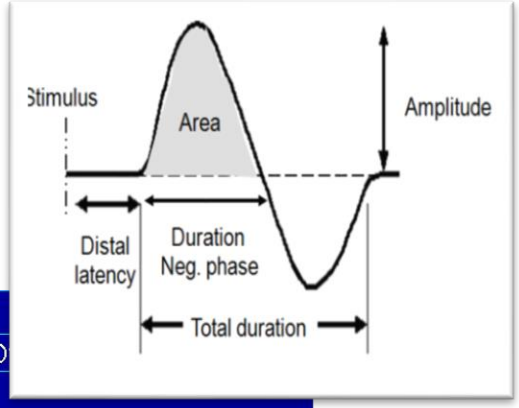

Normal nerve
Axonal neuropathy
Demyelinating neuropathy
(Guillain-Barré syndrome)
10 mV
10 mV
10 mV
Nerve action potential:
normal amplitude
and conduction velocity
Nerve action potential:
reduced amplitude,
normal conduction velocity
Nerve action potential:
reduced conduction velocity,
normal amplitude

Repetitive nerve stimulation





Motor NCV in ICU



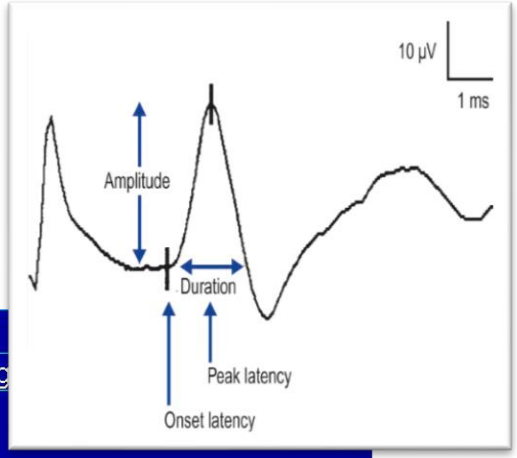
Switch: N-R
Stimulator: 1
Rate: 1 Hz
Level: 39.2 mA
0.1 ms
Single
5 ms
Step: 1
Average: O
A1 A2 A3 A4 A5
Recording Site: ADM

Stimulus Site	Lat1 ms	Dur ms	Amp mV	Area mVms
A1: Wrist	2.5	15.4	2.9	13.2
A2: Below elbow				
A3: Above elbow				
A4: Axilla				
A5: Erb's Point				

Segment	Dist mm	Diff ms	CV m/s
ADM-Wrist		2.5	
Wrist-Below elbow			
Below elbow-Above elbow			
Above elbow-Axilla			
Axilla-Erb's Point			

A1
A2
A3
A4
A5
39.2mA
5 mV
5 mV
5 mV
5 mV
5 mV
5 mV
500 ms
Amp 1: 2-10kHz
New Nerve Other Side MNC F-Waves SNC ANS Rep Stim MUNE CVD
20.0

Sensory NCV in ICU



Switch: N-R
Stimulator: 1
Rate: 1 Hz
Level: 19.6 mA
0.1 ms
Single
1 ms
Step: 1
Averag
A1 A2 A3
Recording Site:

Stimulus Site	Lat1 ms	Lat2 ms	Amp uV
A1: F-W			
A2: W-E			
A3: E-A			

Segment	Dist mm	Diff ms	CV m/s
R1-F-W			
R1-W-E			
R1-E-A			

A1
20 uV
A2
20 uV
A3
20 uV
100 uV
500 ms
Amp 1: 20-2kHz
New Nerve Other Side MNC F-Waves SNC ANS Rep Stim MUNE CVD
20.0

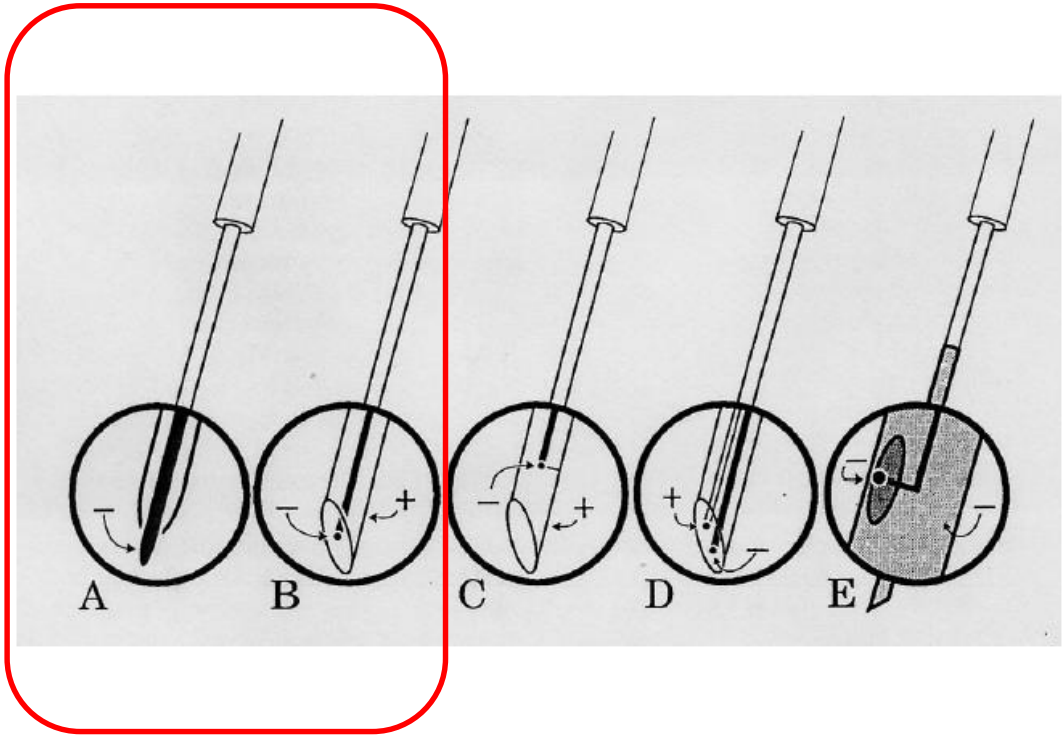
Interpretation

- Decreased motor NCV
  => Inflammatory neuropathy

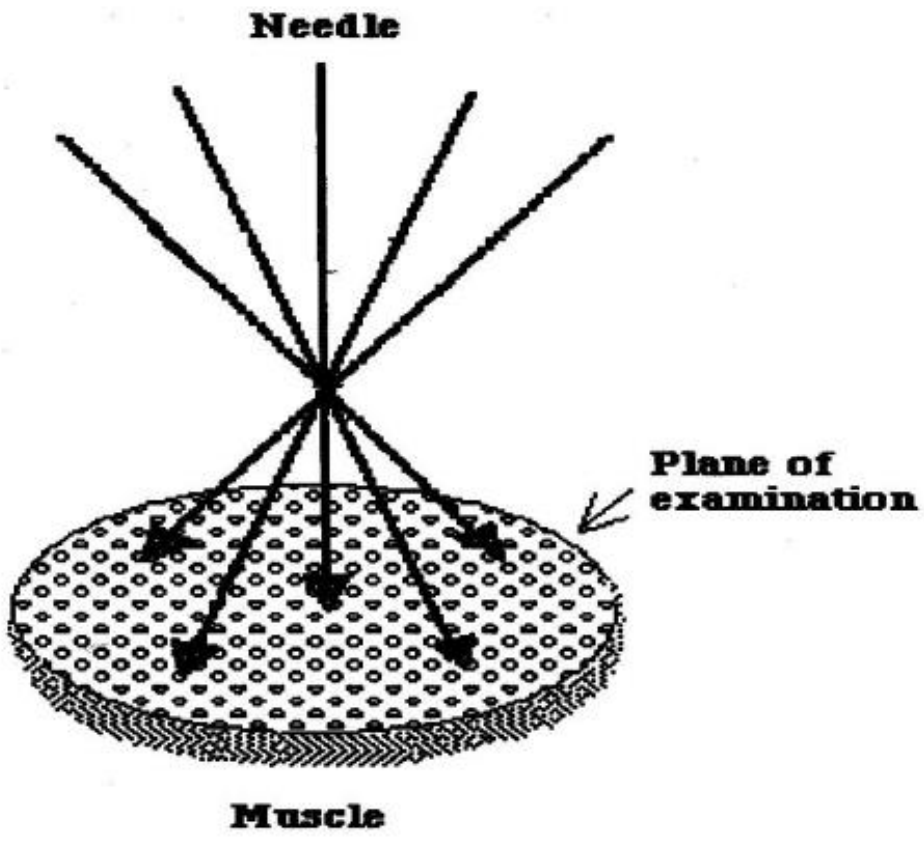
- Decreased CMAP
  1. Peripheral neuropathy
     => Critical illness neuropathy,
     Diabetic polyneuropathy,
     alcoholic neuropathy, and etc.
  2. Myopathy
  3. Muscle atrophy
  4. Radiculopathy

Electromyography

A. Monopolar
B. Standard concentric
C. Single fiber
D. Bipolar
E. Macroelectrode



Electromyography



Electromyography

- Insertional activity and spontaneous activity
  - Muscle at rest
- MUAP morphology analysis
  - One MUAPs
- Recruitment
  - Minimal to moderate contraction
- Interference pattern
  - Maximal contraction

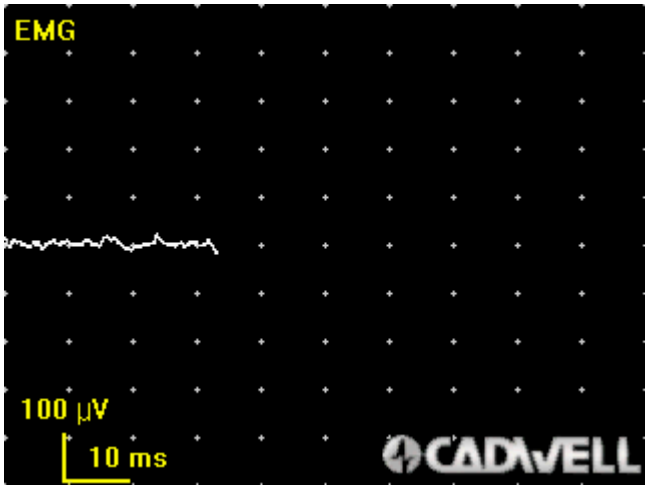
MUAP analysis

Normal finding

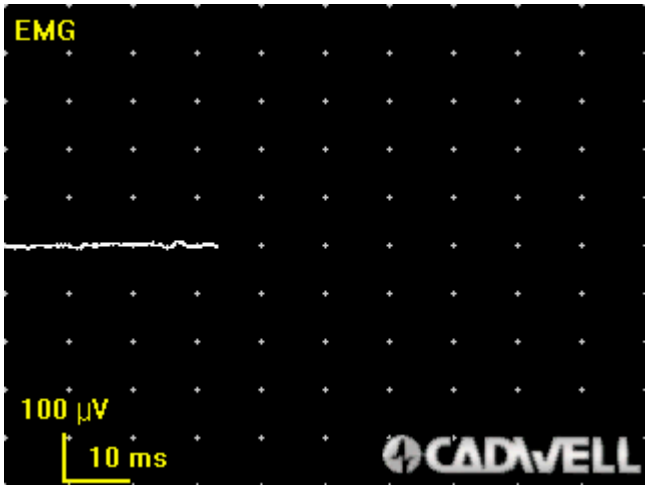
- **Insertional activity**
  - Usually lasts 300ms or less

- **Normal spontaneous activities**
  - Initial negative activities with irregular firing pattern

Endplate noise



Endplate spike

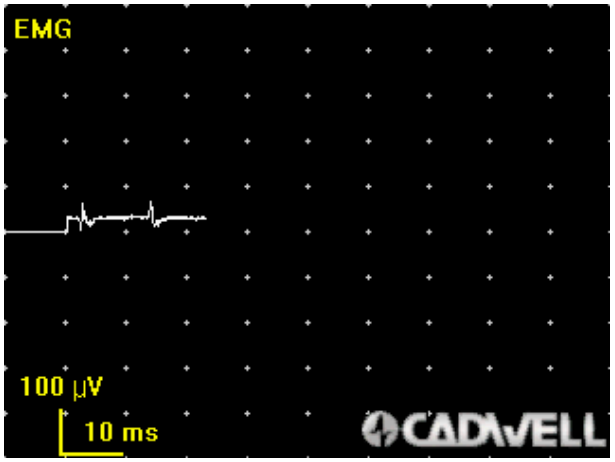


Spontaneous activity

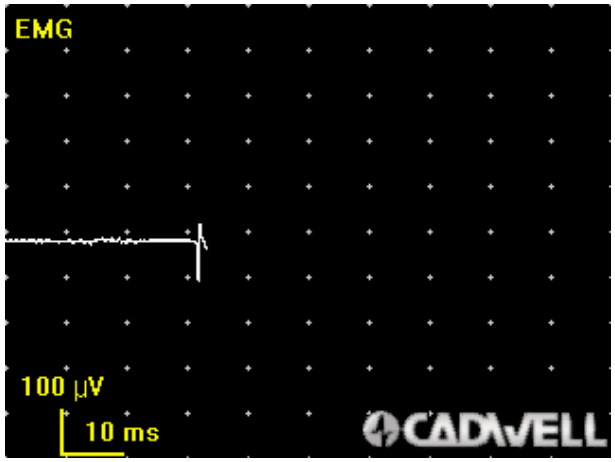
- **Abnormal spontaneous activity**
  - Initial positive activities with regular firing pattern

Muscle generator	Neural generator
- Fibrillation potentials	- Fasciculation
- Positive sharp wave	- Myokymic discharge
- Myotonic discharges	- Cramps
- Complex repetitive discharge	- Neuromyotonia

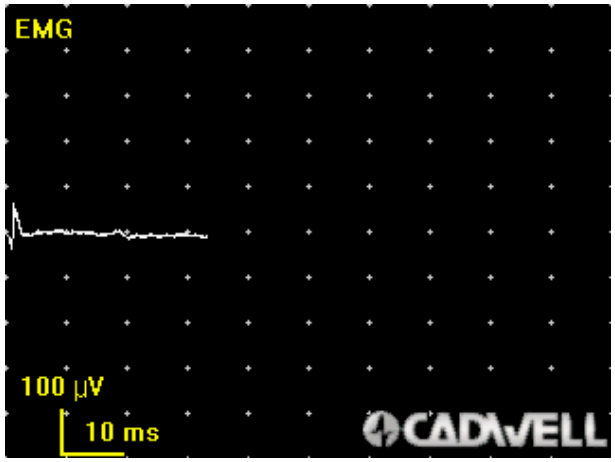
Positive sharp waves



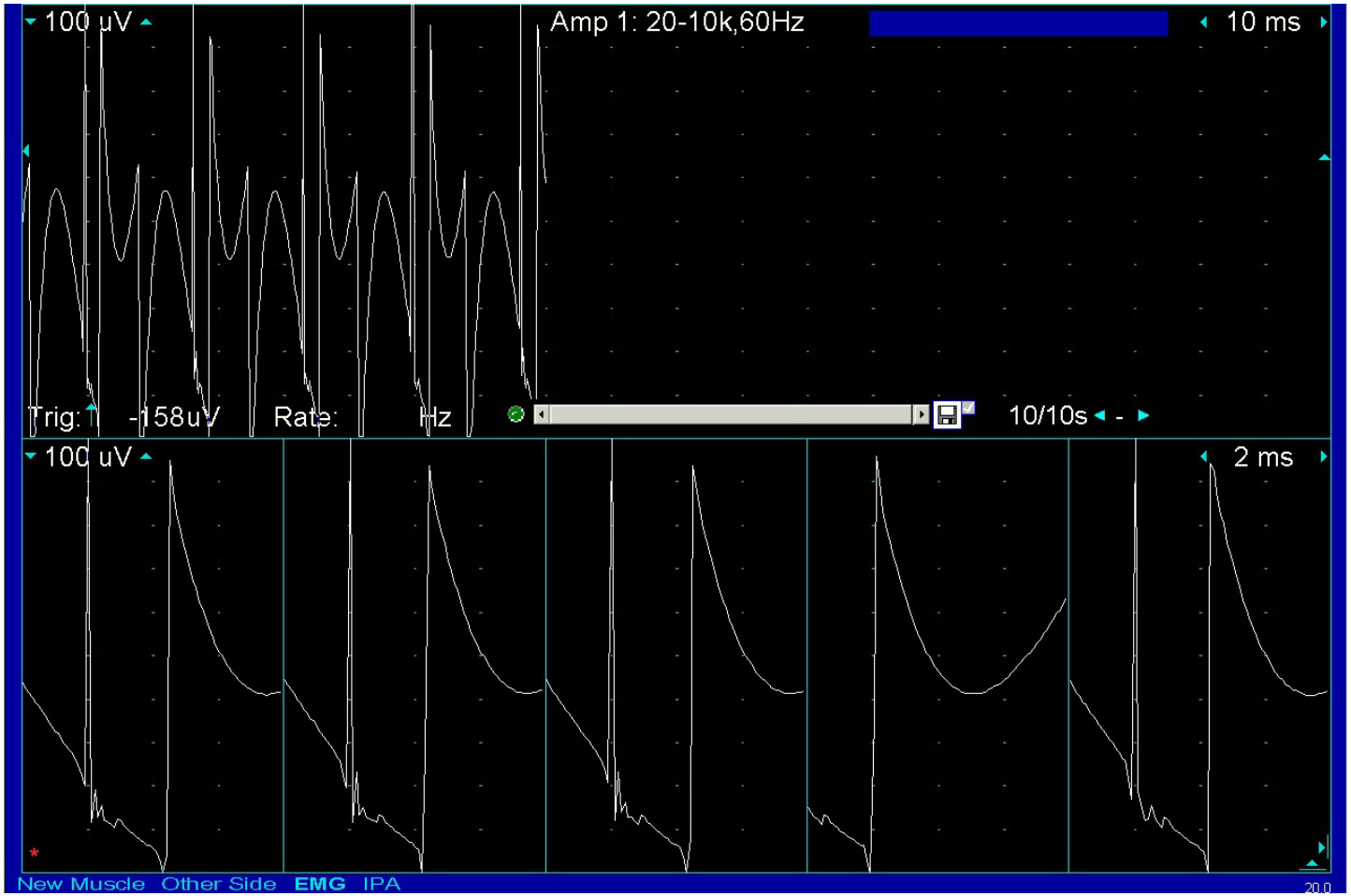
Fibrillation potentials



Myotonic discharges

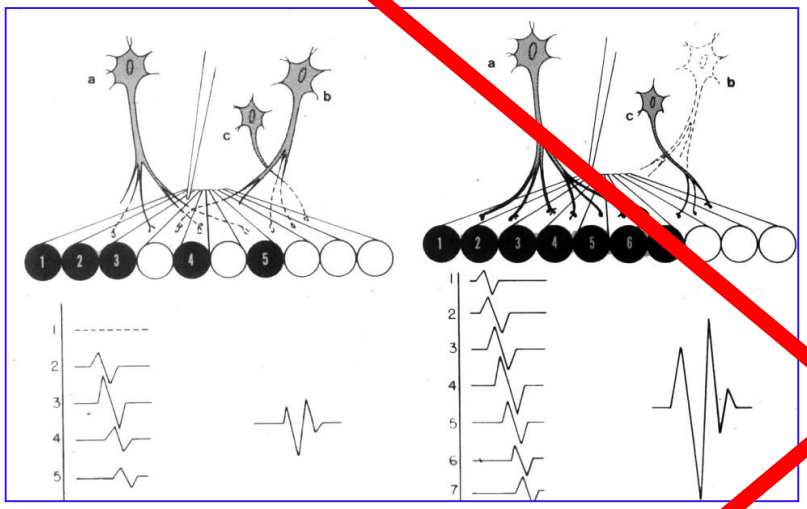


Spontaneous activities in ICU

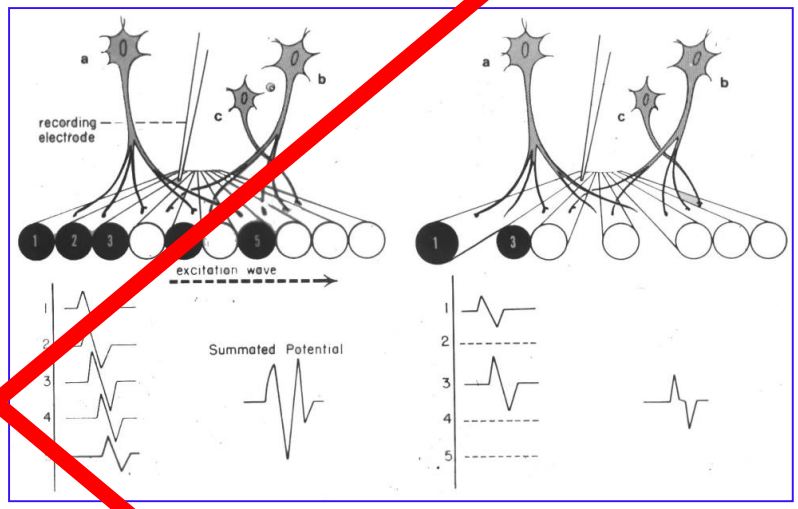


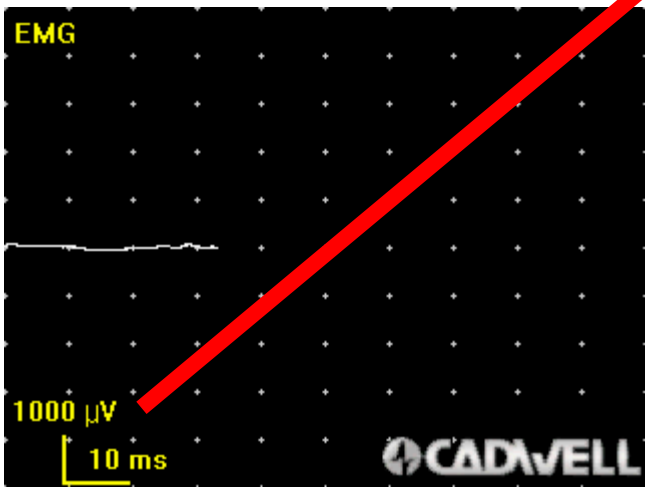
MUAPs analysis

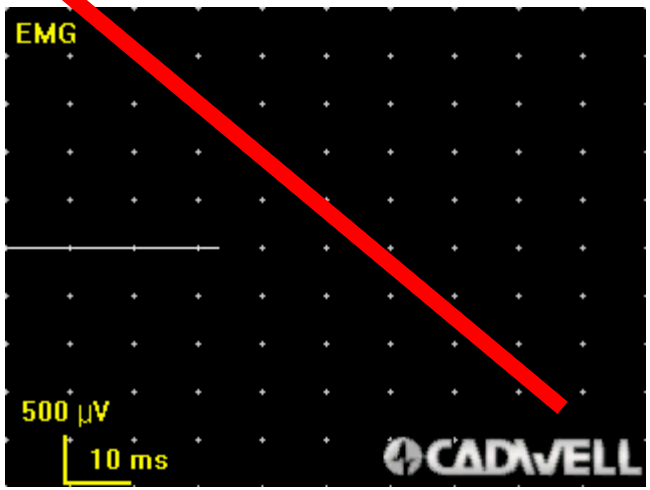
Chronic neurogenic process



Myogenic process



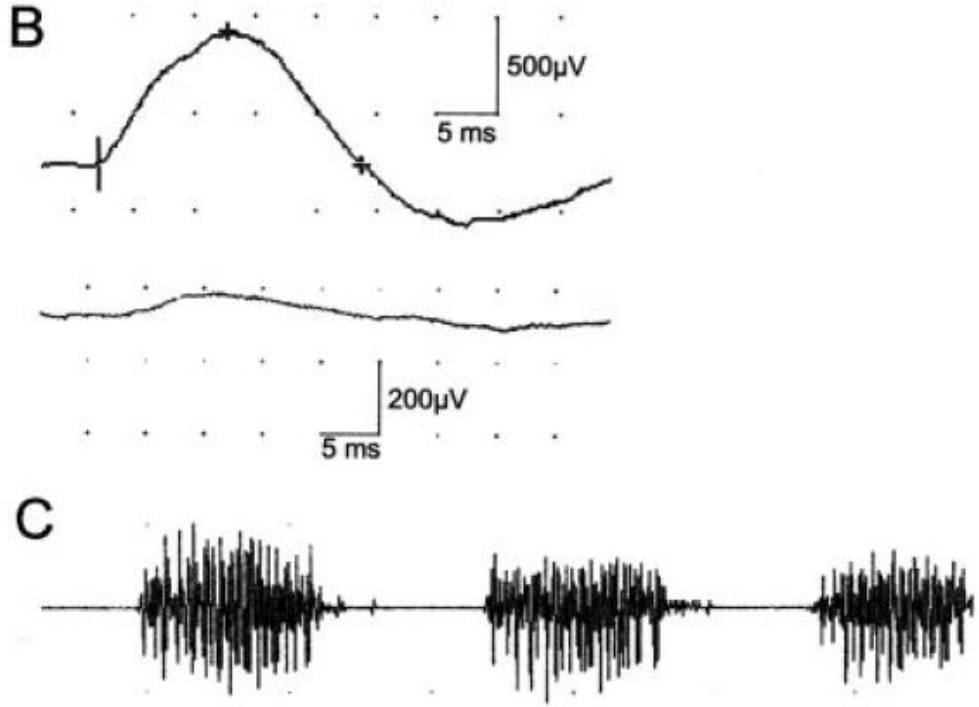


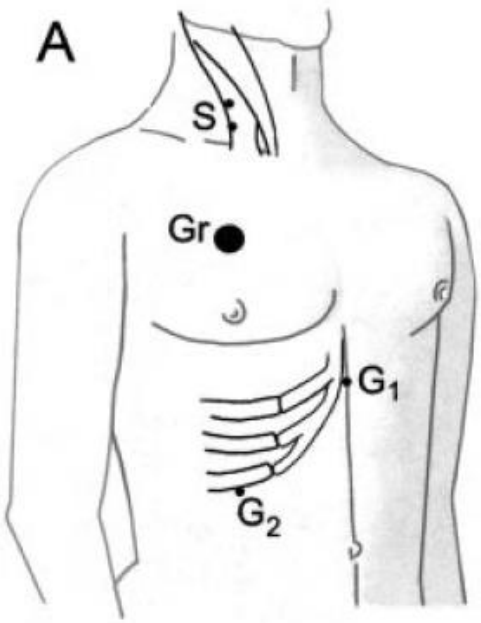


Time factors after nerve injury

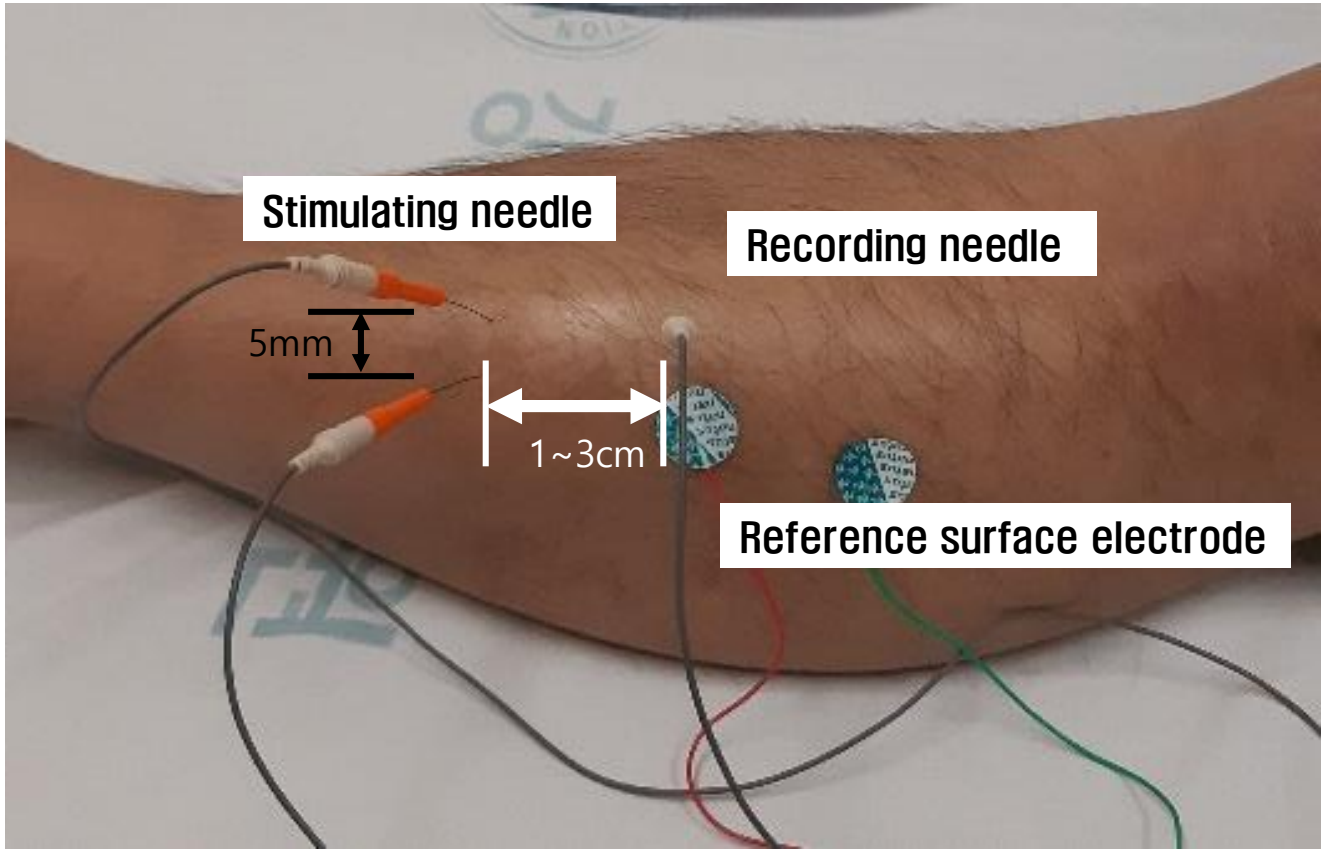
	Immediate	Hyperacute	Acute	Subacute	Subacute -chronic	Chronic
		<4 days	1wk~ 3-6wks	3-6wks~ 2-3mons	2-3mons~ many mons/yrs	>several mons/yrs
Clinical findings	Abnl	Abnl	Abnl	Abnl	Abnl	Nl/abnl
NCS	Nl	Nl	Abnl	Abnl	Abnl	Nl/abnl
MUAP recruitment	↓	↓	↓	↓	↓	↓/nl
Spontaneous activity	Nl	Nl	Nl	Abnl	Abnl	Nl
MUAP morphology	Nl	Nl	Nl	Nl	reinnervated	reinnervated

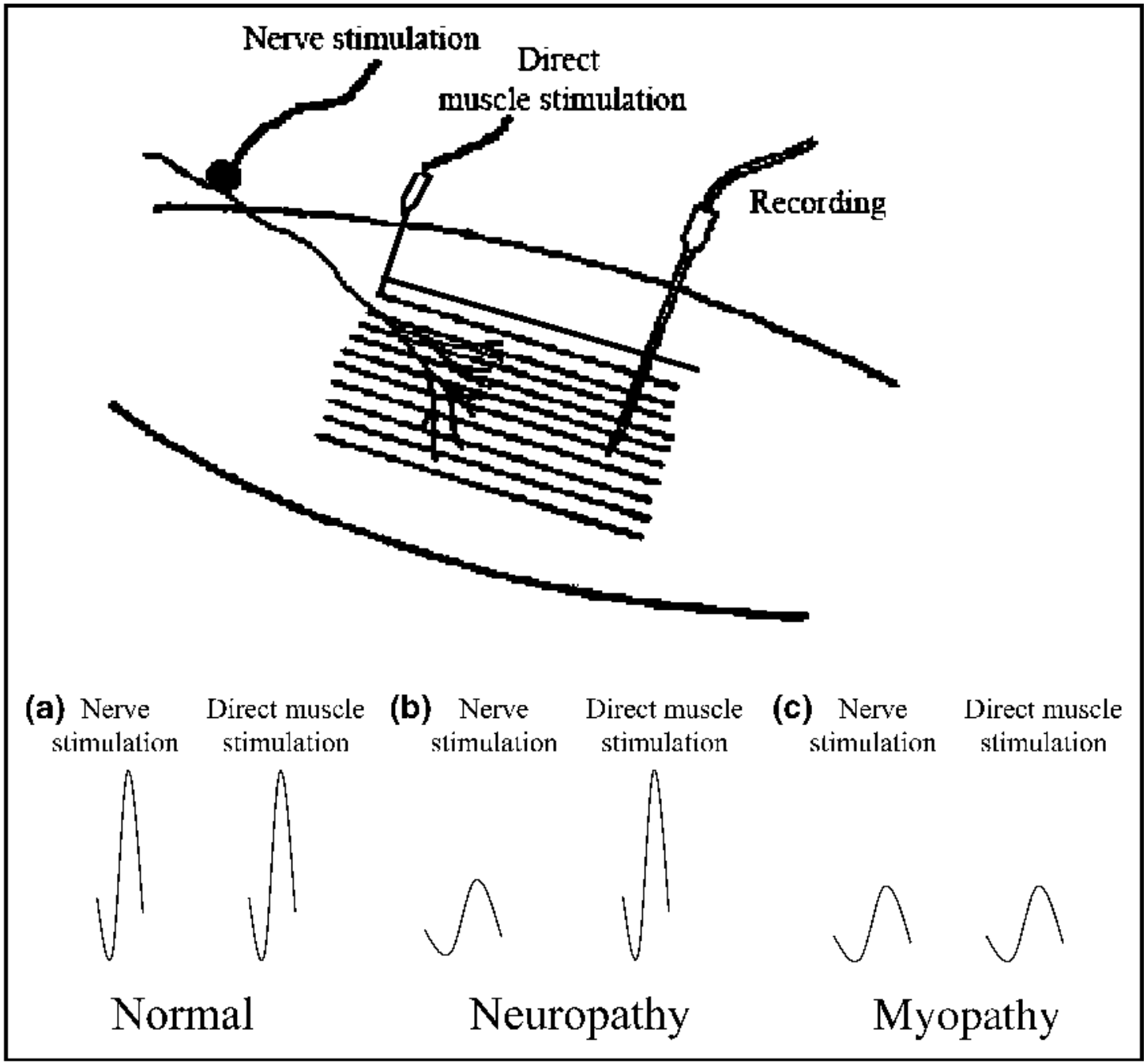
Phrenic nerve evaluation





Direct muscle stimulation




Nerve stimulation
Direct
muscle stimulation
Recording
(a) Nerve stimulation
Direct muscle stimulation
(b) Nerve stimulation
Direct muscle stimulation
(c) Nerve stimulation
Direct muscle stimulation
Normal
Neuropathy
Myopathy

Summary

- Clinical features
  - Critical illness neuropathy: axonal neuropathy
  - Critical illness myopathy: type II fiber atrophy

- Electrodiagnostic features
  - Difficulty in diagnostric evaluation of ICU-acquired neuromyopathy
    - 60Hz artifact
    - Edema
    - Severe weakness
    - Poor voluntary effort
  - Direct muscle stimulation is a alternative tool for differential diagnosis of CIP and CIM.

In Alhambra palace