# Neuromuscular Junction Studies

Arthur A Rodriquez MD, MS

# Myasthenia Gravis

- Autoimmune disorder caused by antibodies to the acetylcholine receptor
- Circulating Ab tests are not detectable in all patients
- Repetitive Nerve Stimulation (RNS) and single fiber electromyography (SFEMG) remain the most sensitive and reliable tests for Diagnosis and Management

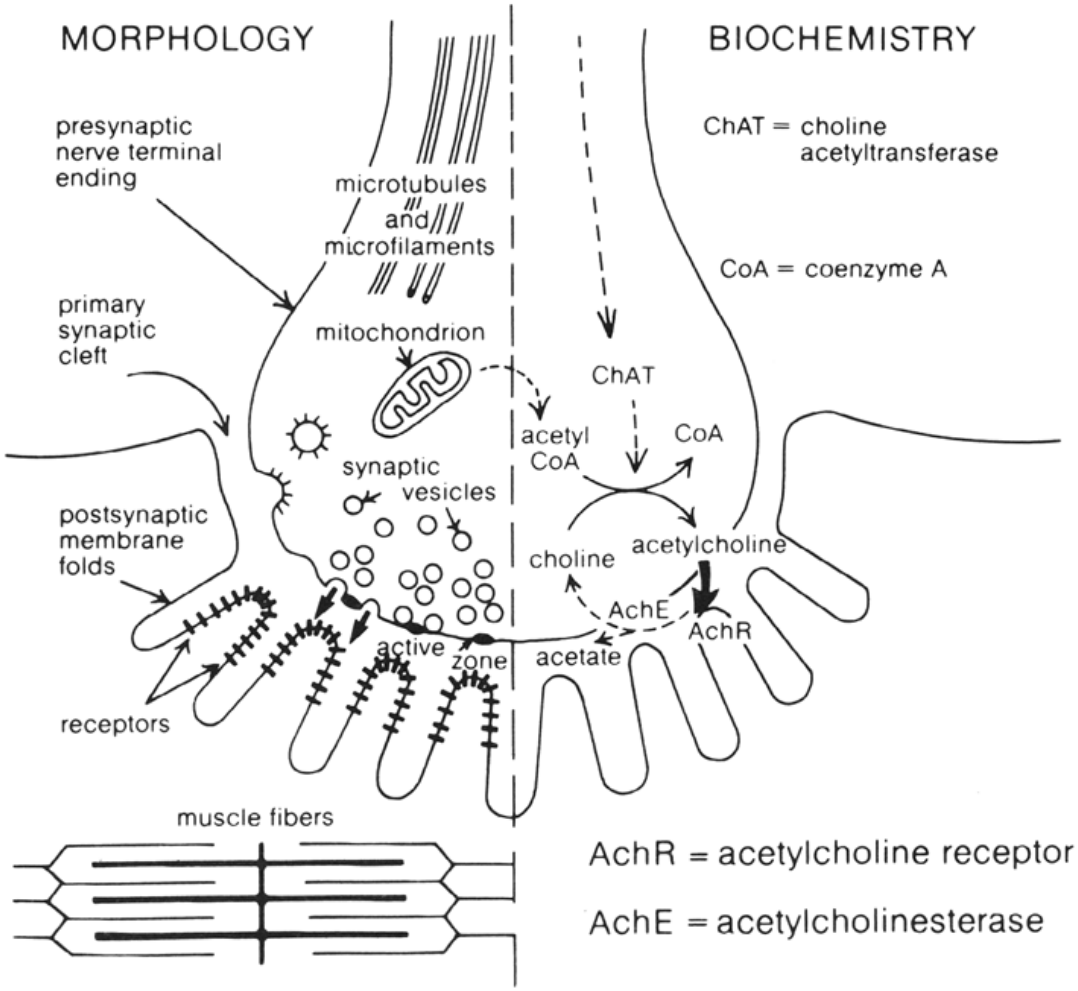
# Other Neuromuscular Disorders

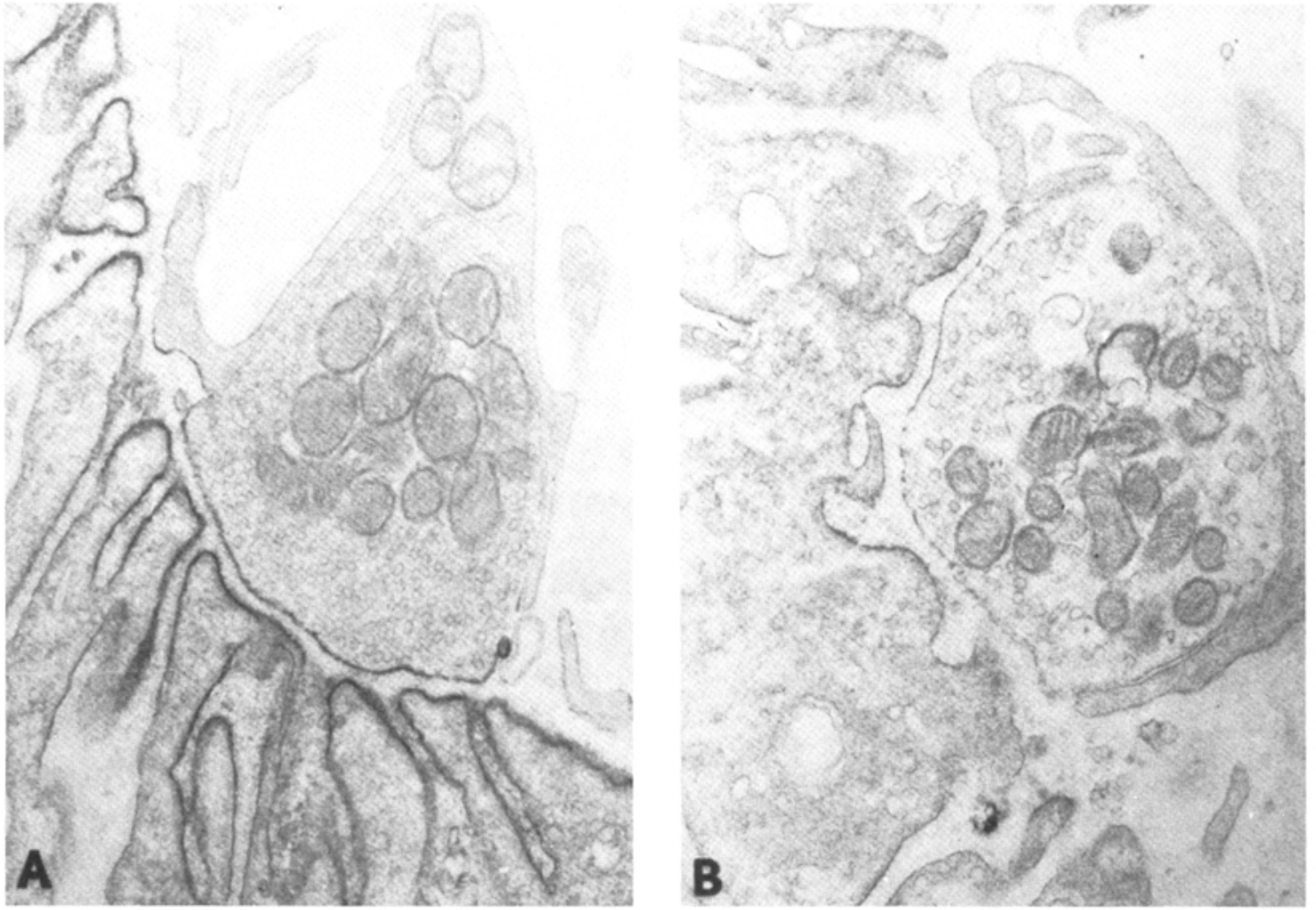
- Congenital myasthenia
- Neuromuscular disorders with prominent collateral sprouting
- Botulism
- Lambert-Eaton myasthenic syndrome
- Muscle Membrane disorders

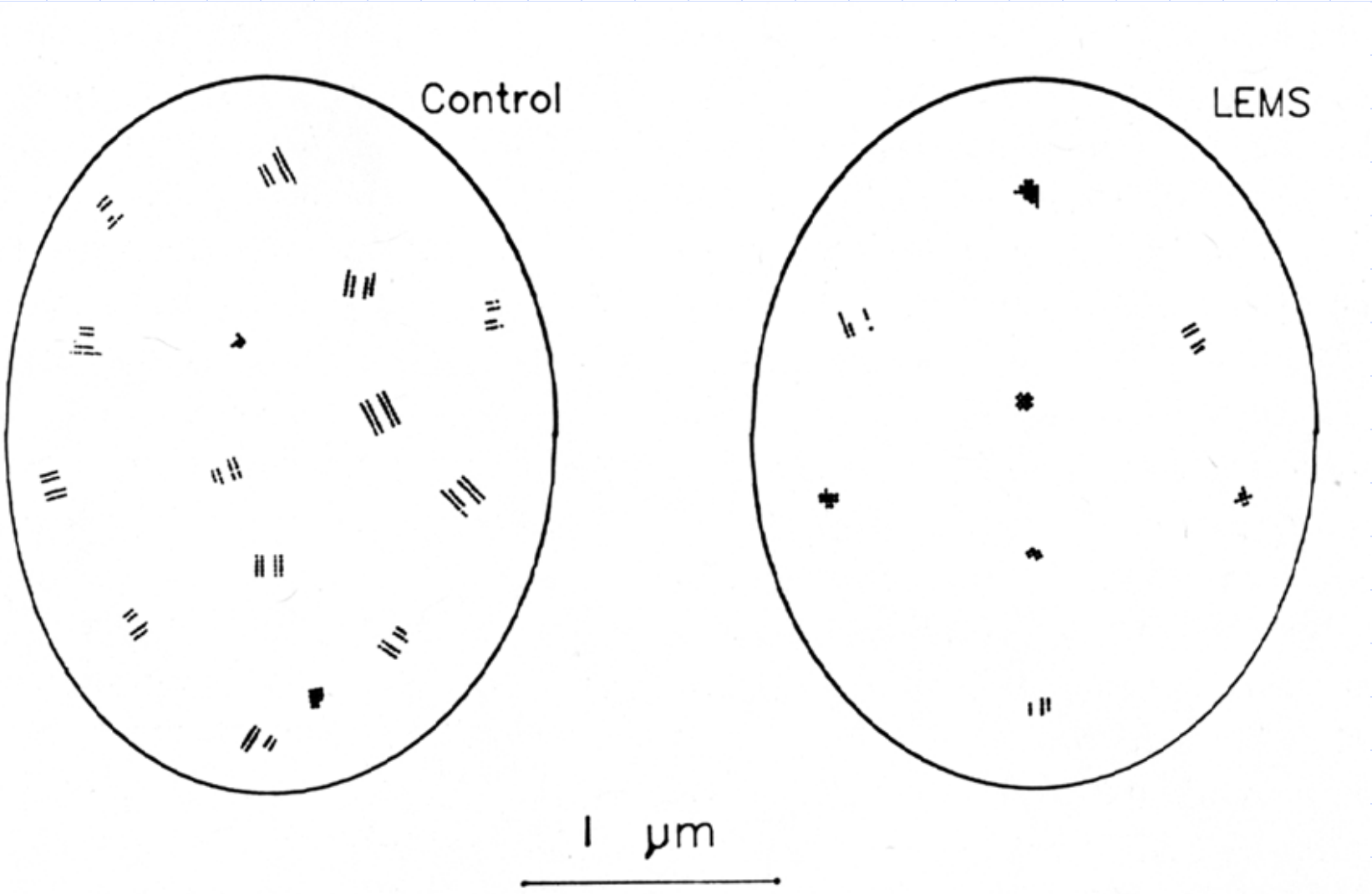
# Repetitive Nerve Stimulation

- We manipulate the amplitude of the end plate potential
- Neuromuscular junction blockade must occur in some neuromuscular junctions to identify abnormality
- It is unusual to obtain abnormal results if there is no clinical weakness in the muscle studied

# NEUROMUSCULAR JUNCTION

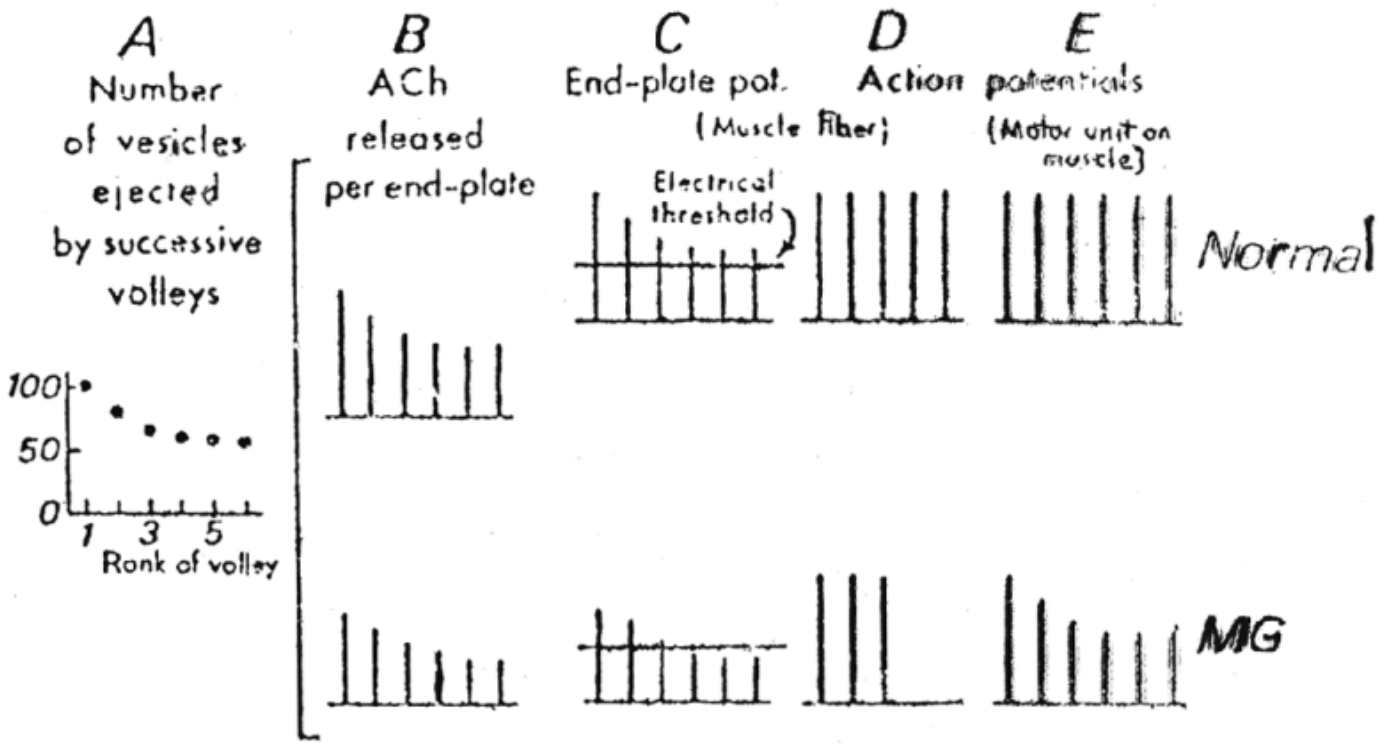



A
B

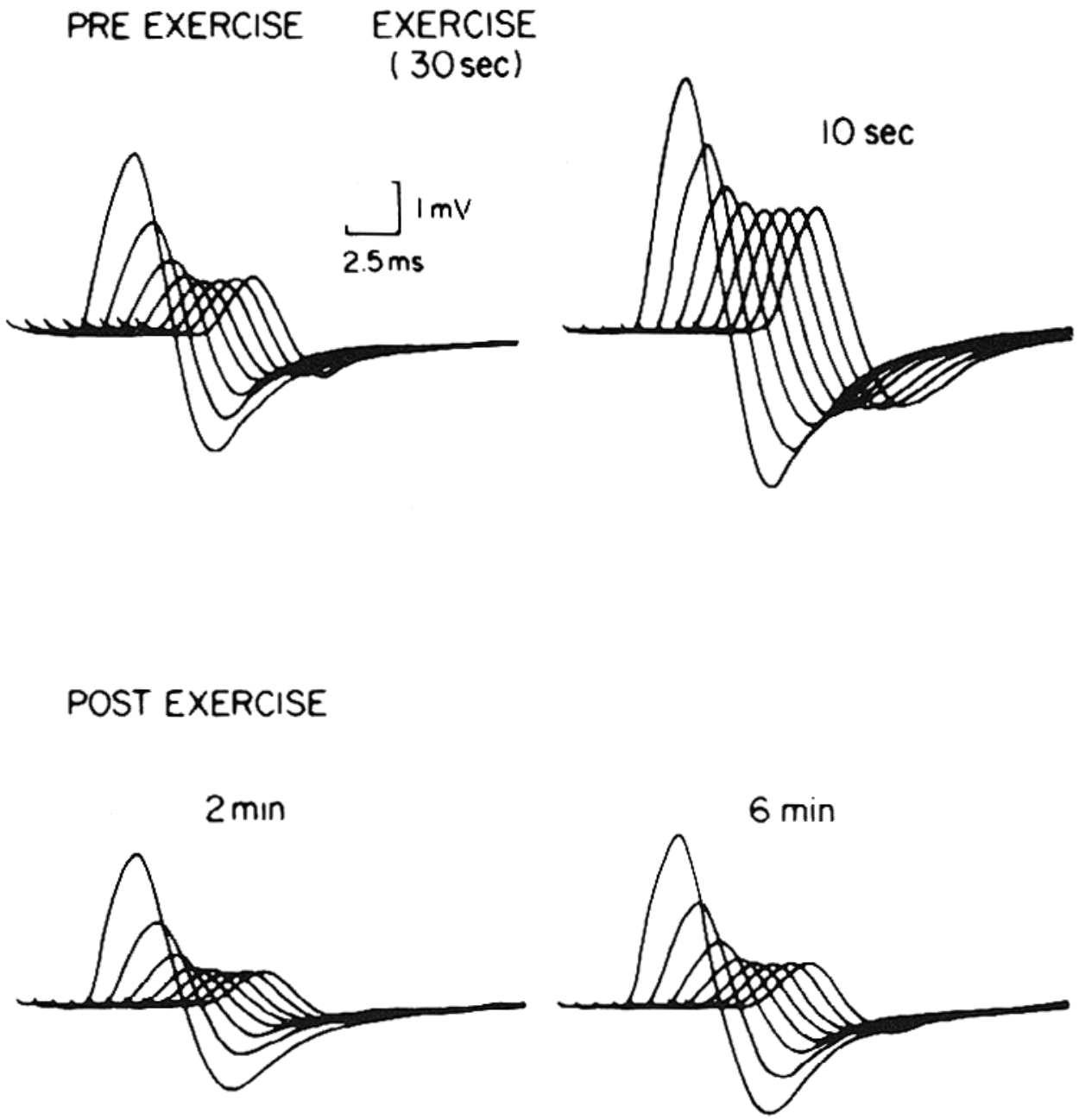

Control
LEMS
1 µm

# Repetitive Nerve Testing

- The neuromuscular junction physiology at low rates of stimulation
- We manipulate the amount of acetyl-choline released
- Changes in acetylcholine levels then result in changes in the end plate potential



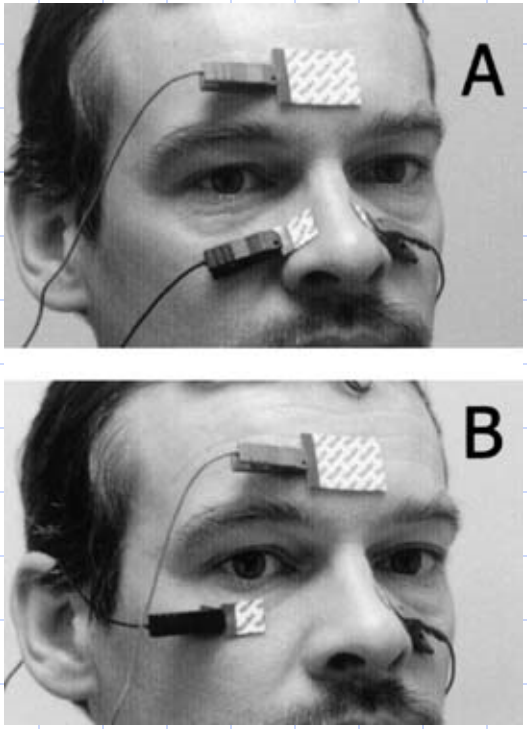

From Desmedt, 1973


PRE EXERCISE
EXERCISE
( 30 sec)
1 mV
2.5 ms
10 sec
POST EXERCISE
2 min
6 min

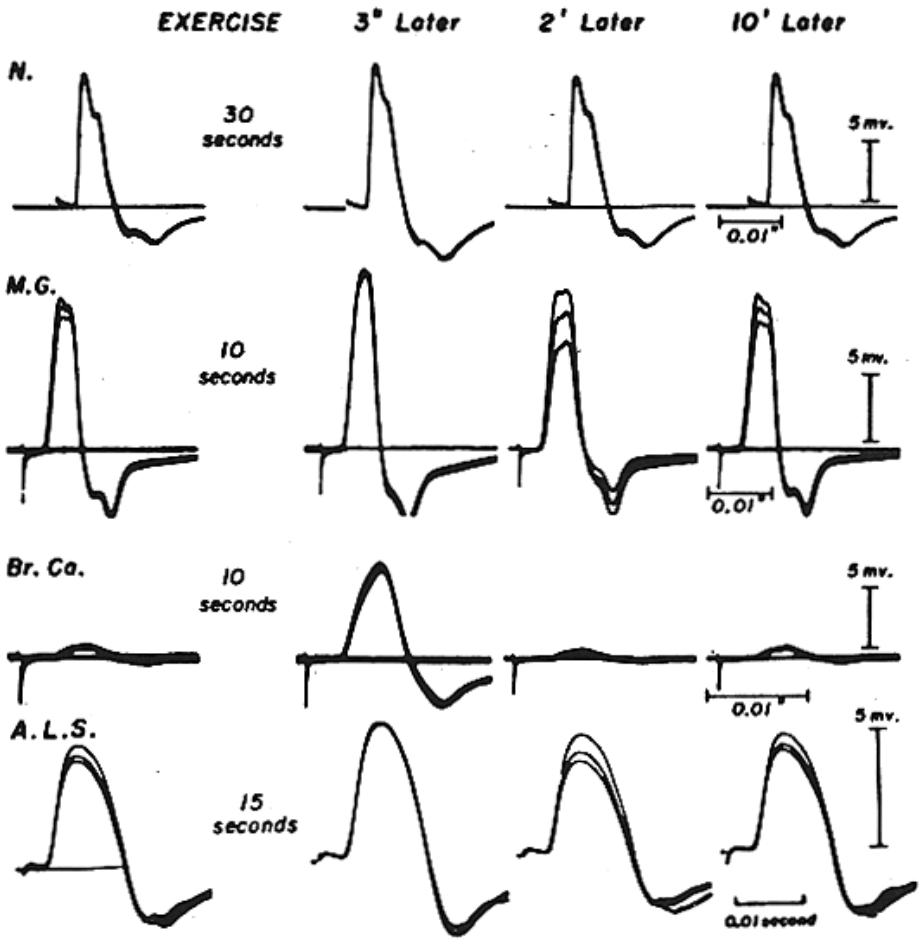
# Technical Considerations

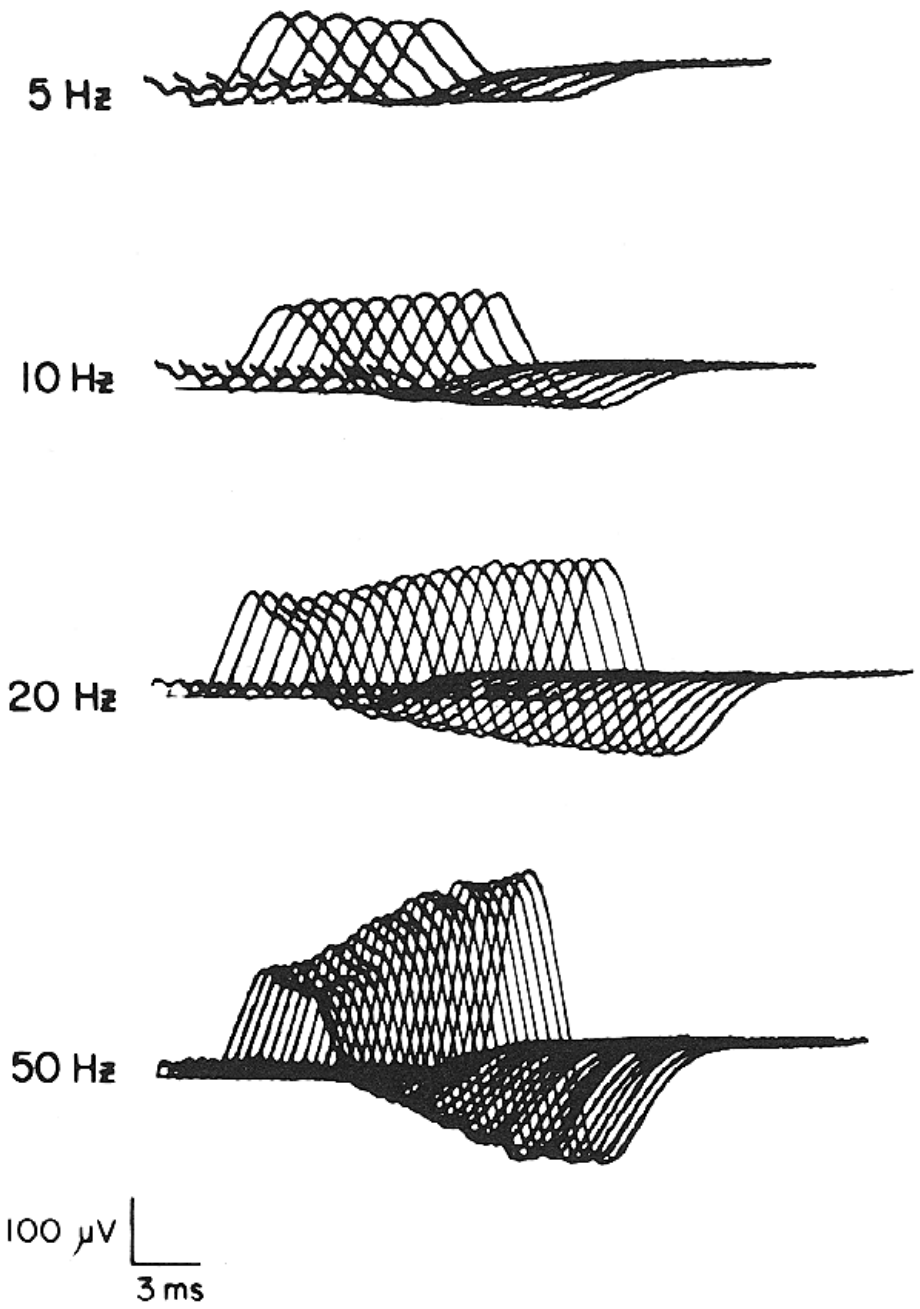
- Warm limb muscles to 34 Deg
- Immobilize both recording and stimulation sites
- Supramaximal stimulation
- Choose two proximal and one distal muscle (APB, SCM, and Nasalis are common-test weak muscles)
- If a decrement is found, repeat the test after five minutes

# Nasalis and Orbicularis Oculi

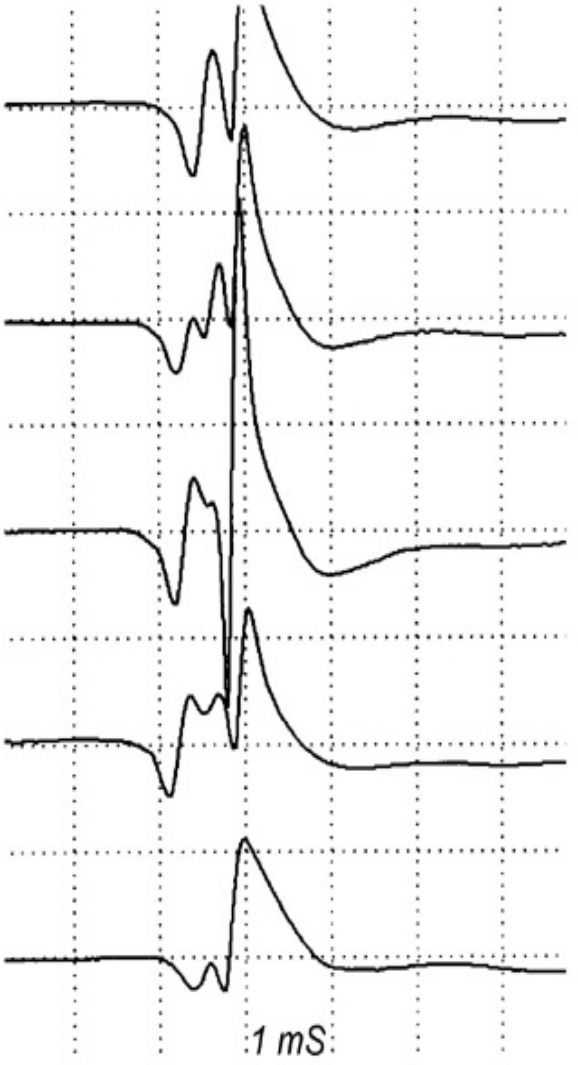


Electrodiagnostic Testing for Disorders of the Neuromuscular Junction
J. R. Daube, M.D., Rochester, Minnesota



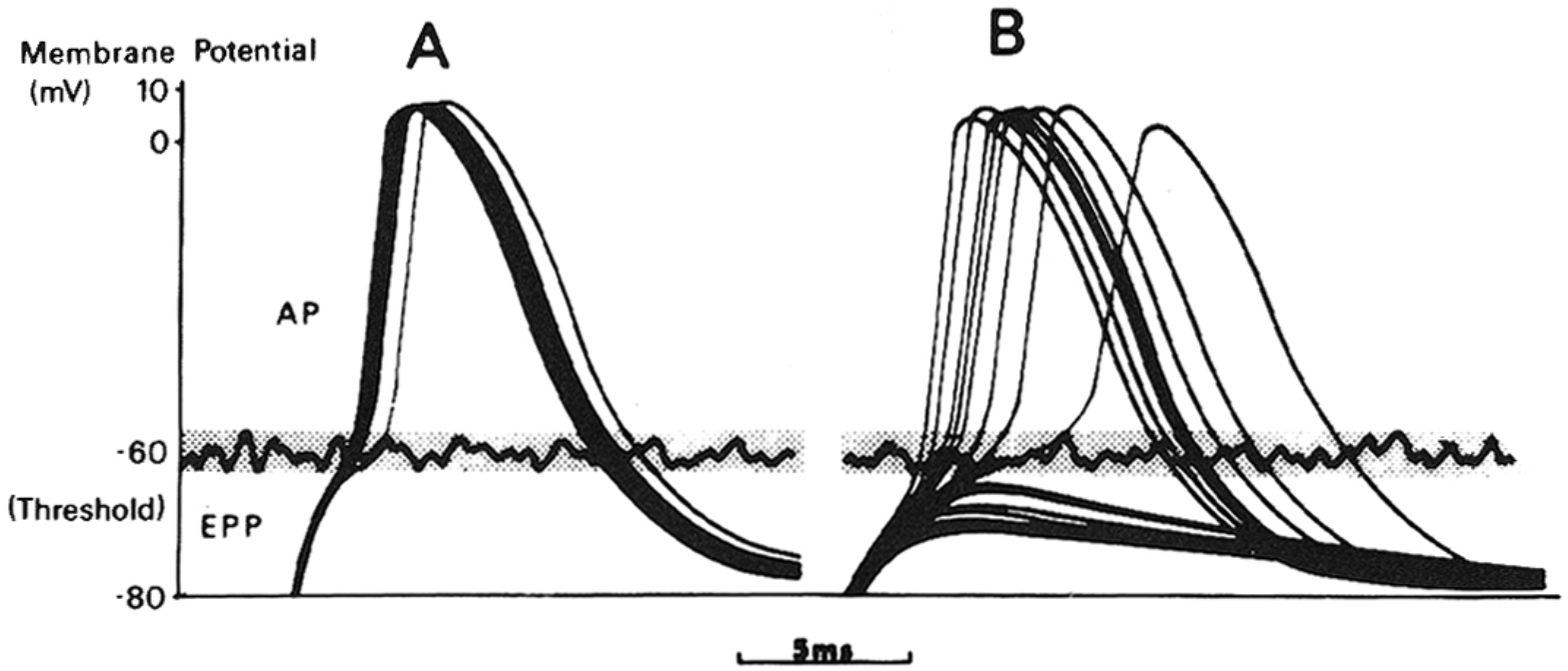

5 Hz
10 Hz
20 Hz
50 Hz
100 μV
3 ms

# Findings on Concentric Needle Electromyography - Jiggle



# Single Fiber Electromyography

We measure the rise time of the end plate potential during physiologic rates of activation


Membrane Potential
(mV)
10
0
-60
(Threshold)
-80
AP
EPP
A
B
5ms

# Technique

- Concentric needle with 25 u diameter recording surface 4 mm from the needle tip
- Trigger and delay line
- Filters 500hz-20kHz

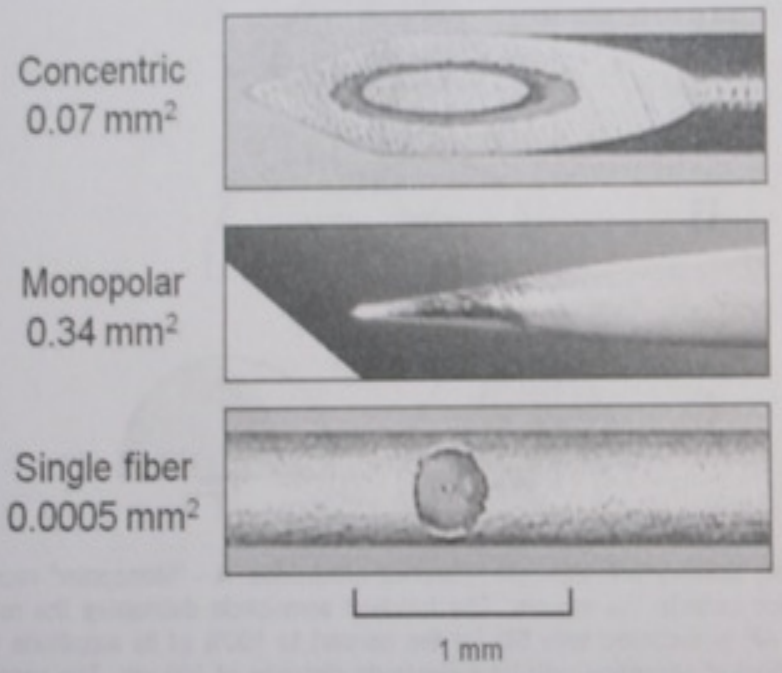
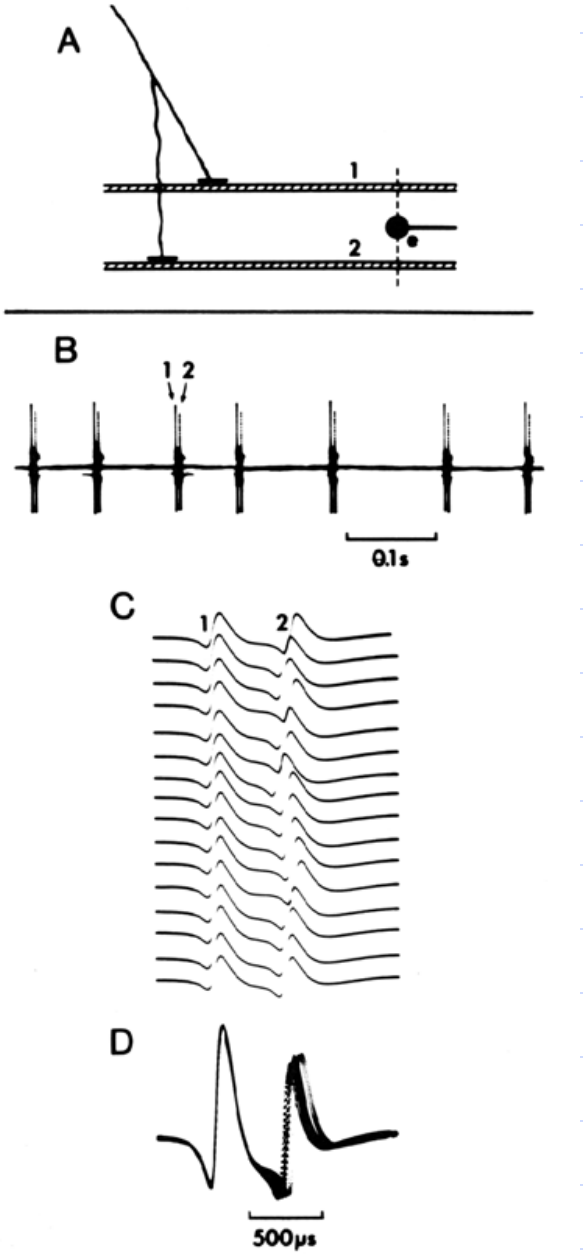



**Fig. 2.4.** Microphotographs of three types of EMG electrodes. (Figure courtesy S. Nandedkar)


A
1
2
B
1 2
0.1s
C
1
2
D
500μs

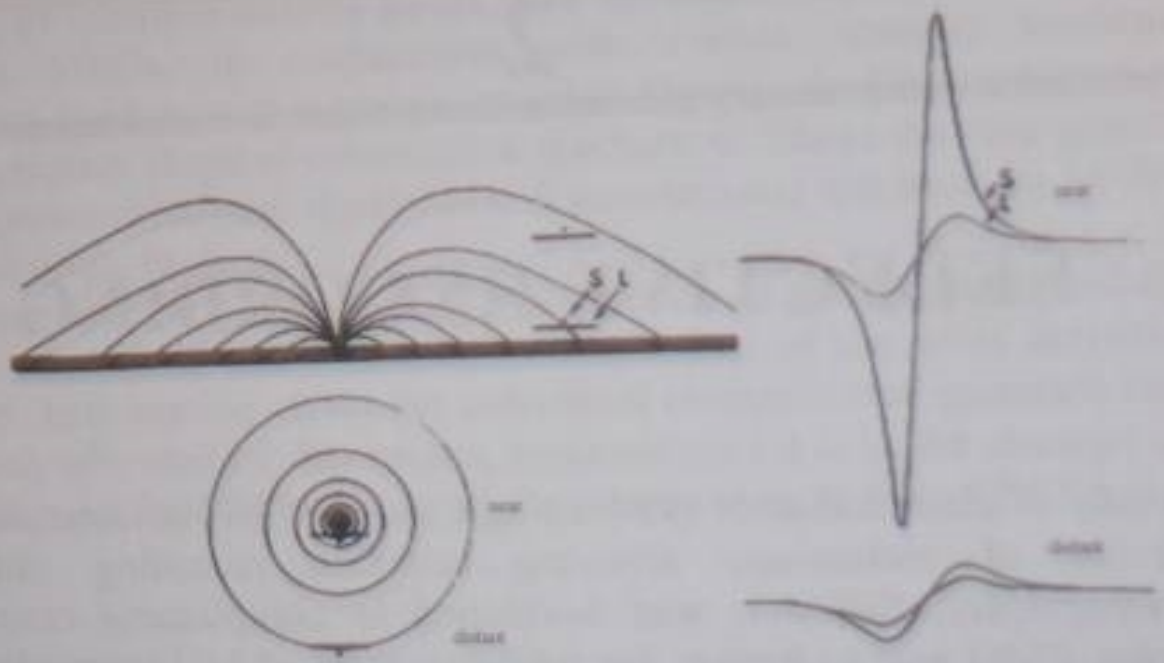


**Fig. 2.1.** The electrical field around a muscle fiber recorded with a small (S) and a large (L) electrode surface. The large electrode shunts the isopotential lines at short fiber - electrode distances, but less so at longer distances. Thus at a short distance the large electrode records a lower amplitude of the AP than the small electrode.

# Trigger and Delay Line

- Amplitude trigger displays the potential in the same location (delayed sweep places it in the center of the screen)
- Variations in the time required to initiate a SFAP for both muscle fiber discharges appear as variations of the non triggered potential

# Filters (500Hz-20kHz)

- Distant activity that would interfere with the recording has a low frequency content
- The goal is to measure the interpotential intervals from the rise times of the negative spike (high frequency content)

# Frequency Domain Plot

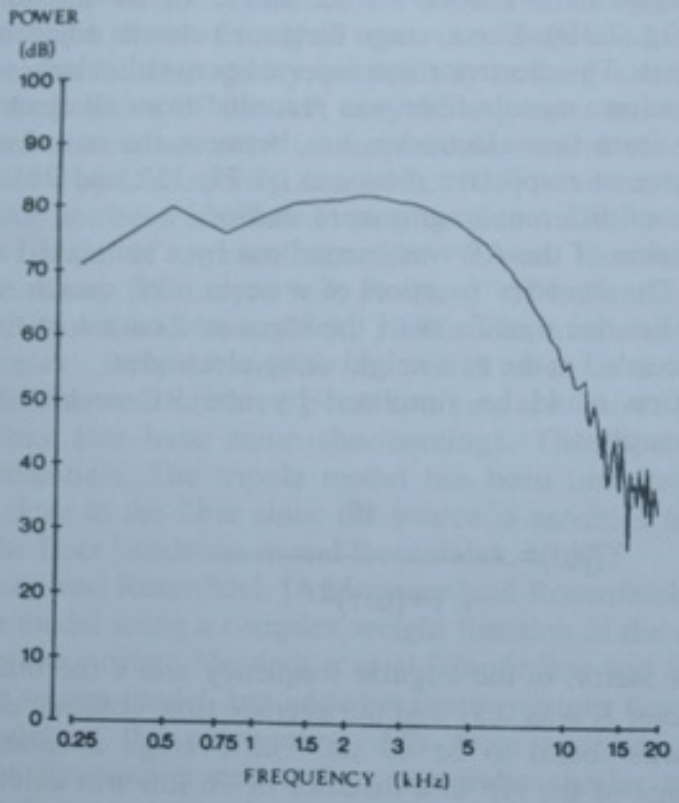


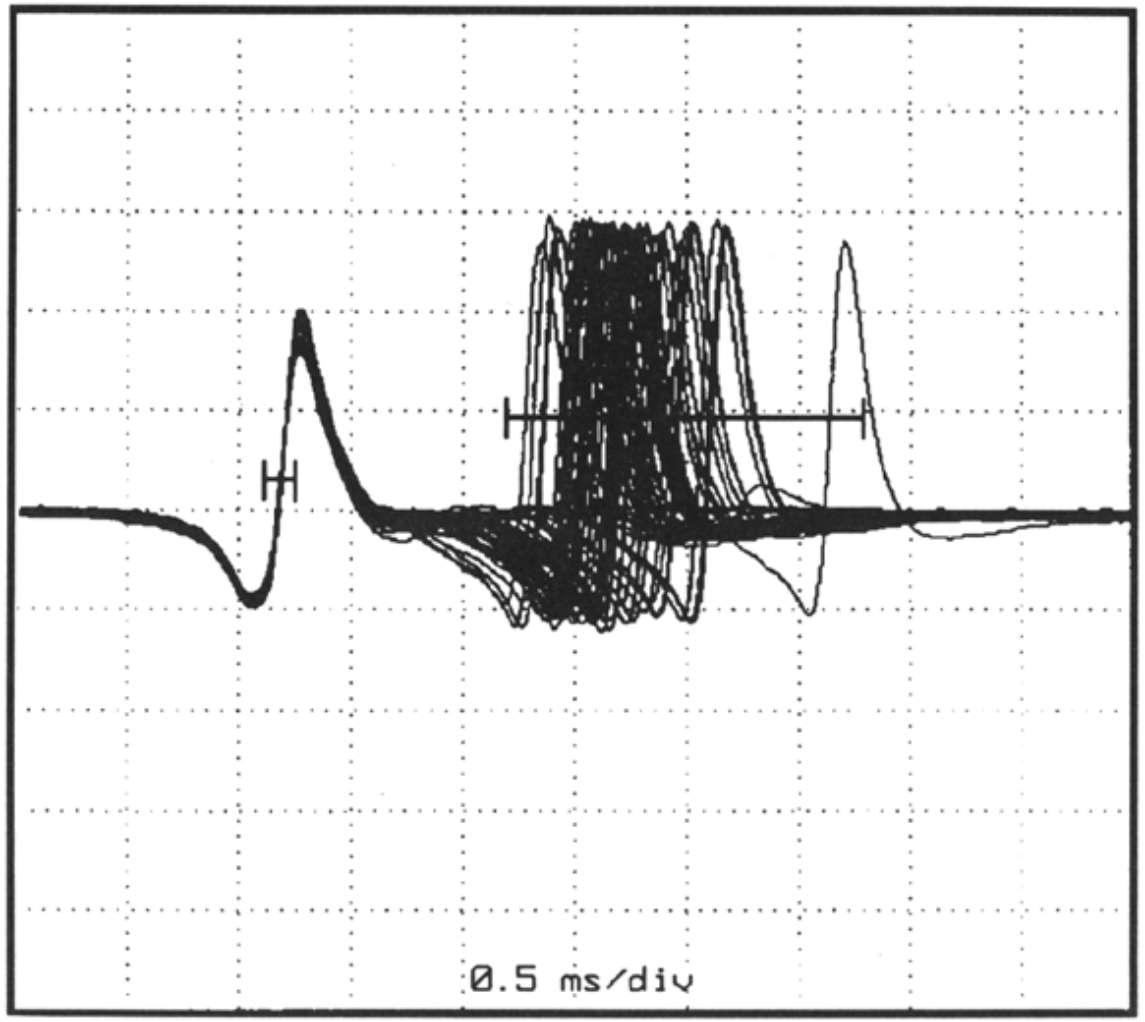

**Fig. 3.1.** Power spectrum of a single muscle fiber AP. Ordinate: Power spectrum normalized to a total mean square value. Abscissa: Frequency.

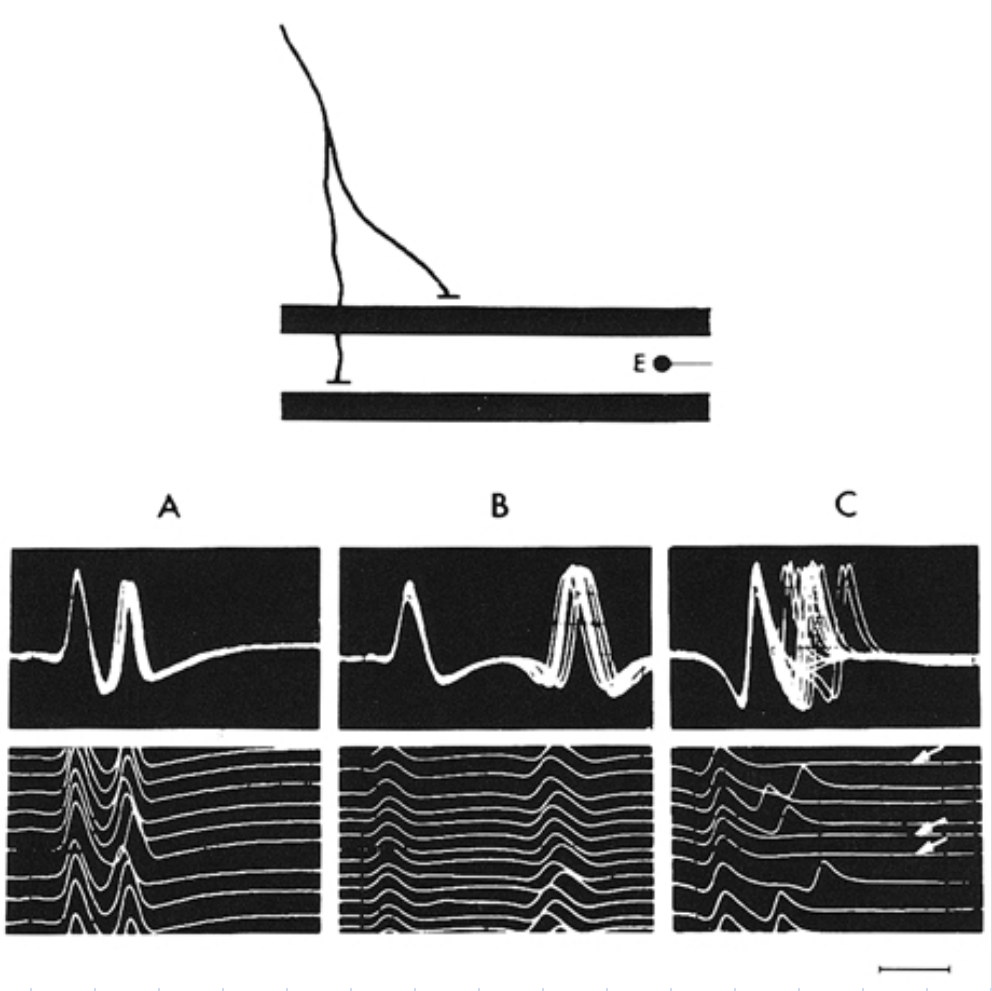
# Technique

- Slowly advance the electrode, “tuning in potentials to obtain an amplitude of 200uv and a rise time < 300usec
- Capture 100 discharges when 2 or more single fiber time locked discharges are obtained.
- Computer calculates the mean consecutive difference
- Determine the percentage of potential pairs with blocking by inspection

# Mean Consecutive Difference (MCD) A Measure of Jitter

- MCD = (IPI1-IPI2) +(IPI2-IPI3)+…(IPIn-1-IPIn)/n-1
- Normative values specific to each muscle and for each decade are published. The MCD is approximately 33usec.
- A study is abnormal if the mean jitter exceeds the upper limit or if more than 10% of pairs have increased jitter.


0.5 ms/div


E
A
B
C

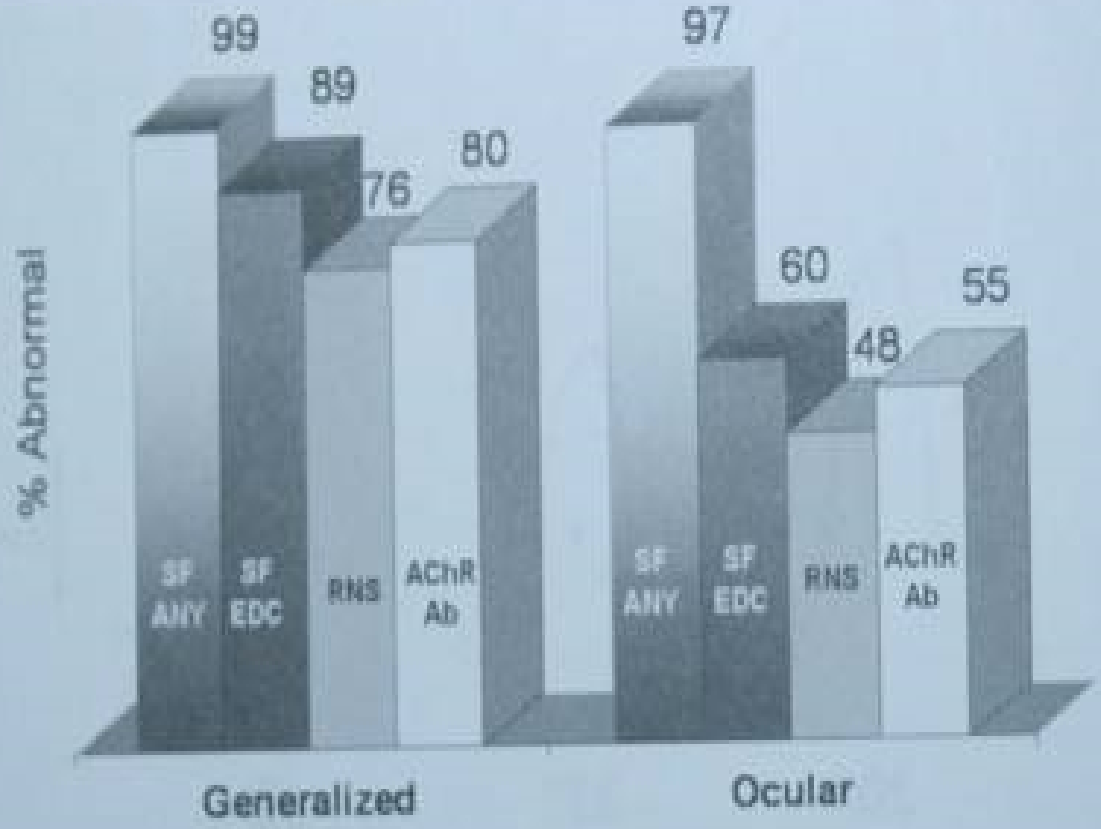
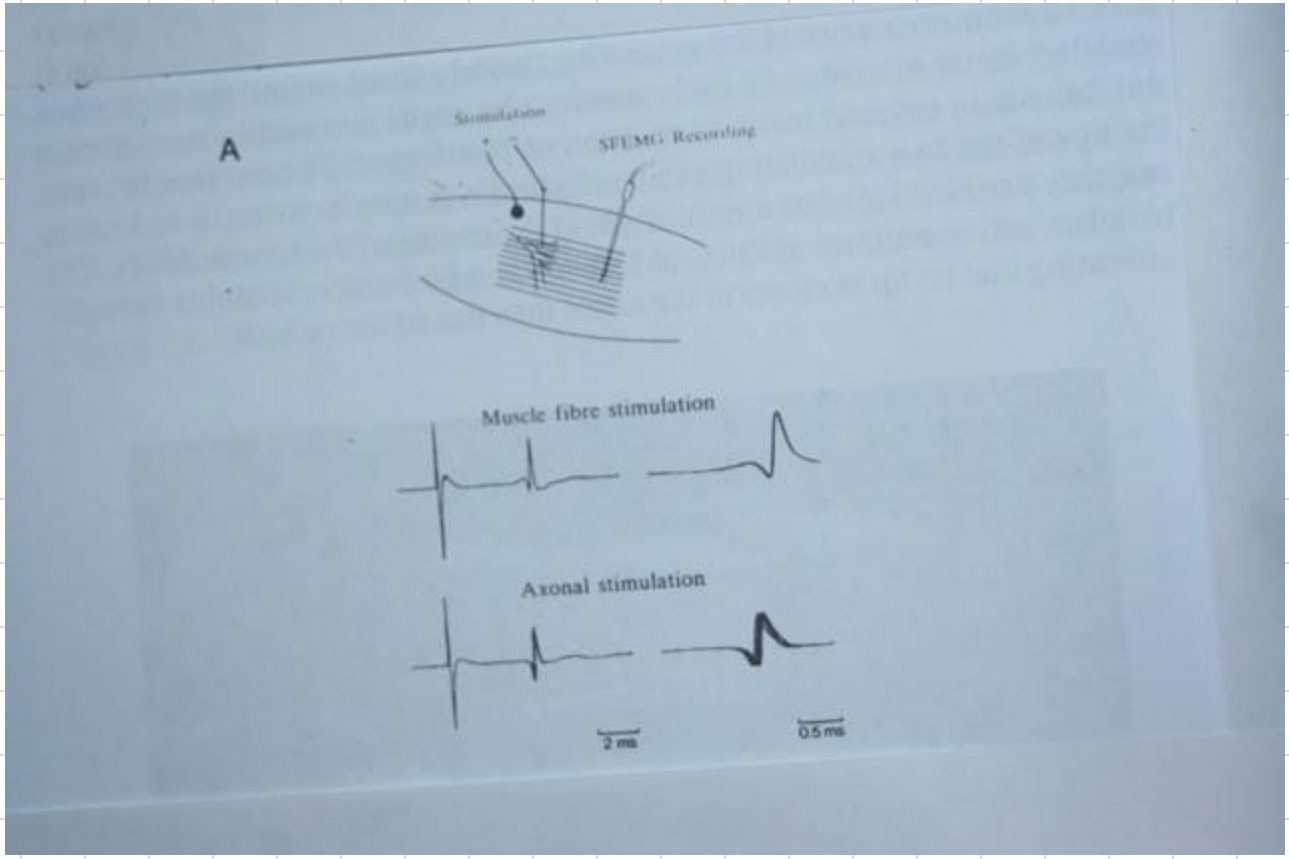


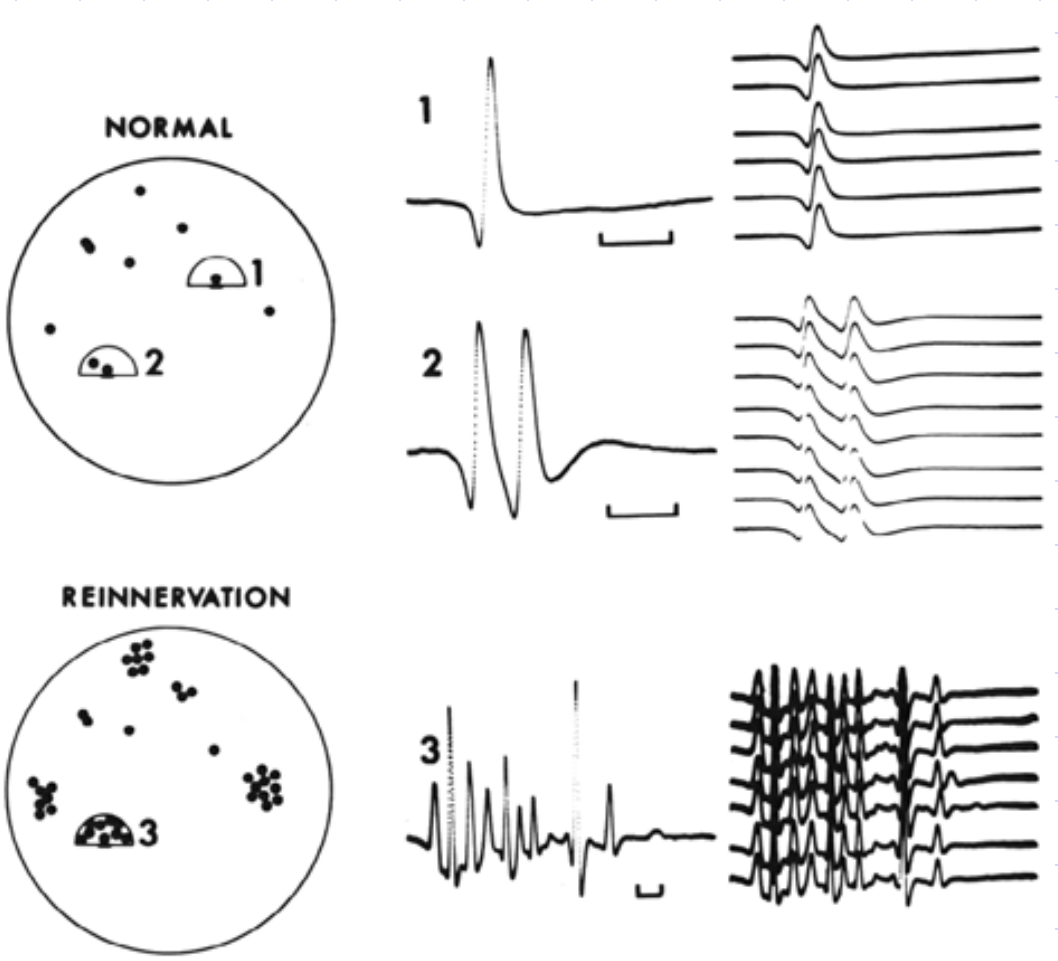

**Fig. 16.7.** Sensitivity of diagnostic tests in 844 patients with generalized or ocular MG, performed before thymectomy or immunosuppression. SFANY – increased jitter in any tested muscle; SFEDC – increased jitter in EDC; RNS – abnormal decrement in a hand or shoulder muscle; ARA – elevated AChR antibody level. (Sanders DB, Massey JM, Juel VC, Hobson-Webb L – unpublished)

# Stimulated Single Fiber EMG



# Fiber Density

- The mean of the number of time locked single fiber discharges recorded from twenty different sites or
- The mean of the number of muscle fibers belonging to one motor unit within the 350u recording area of the SFEMG electrode
- Approximately 1.4 –normal values are muscle specific


NORMAL
1
2
1
2
REINNERVATION
3
3

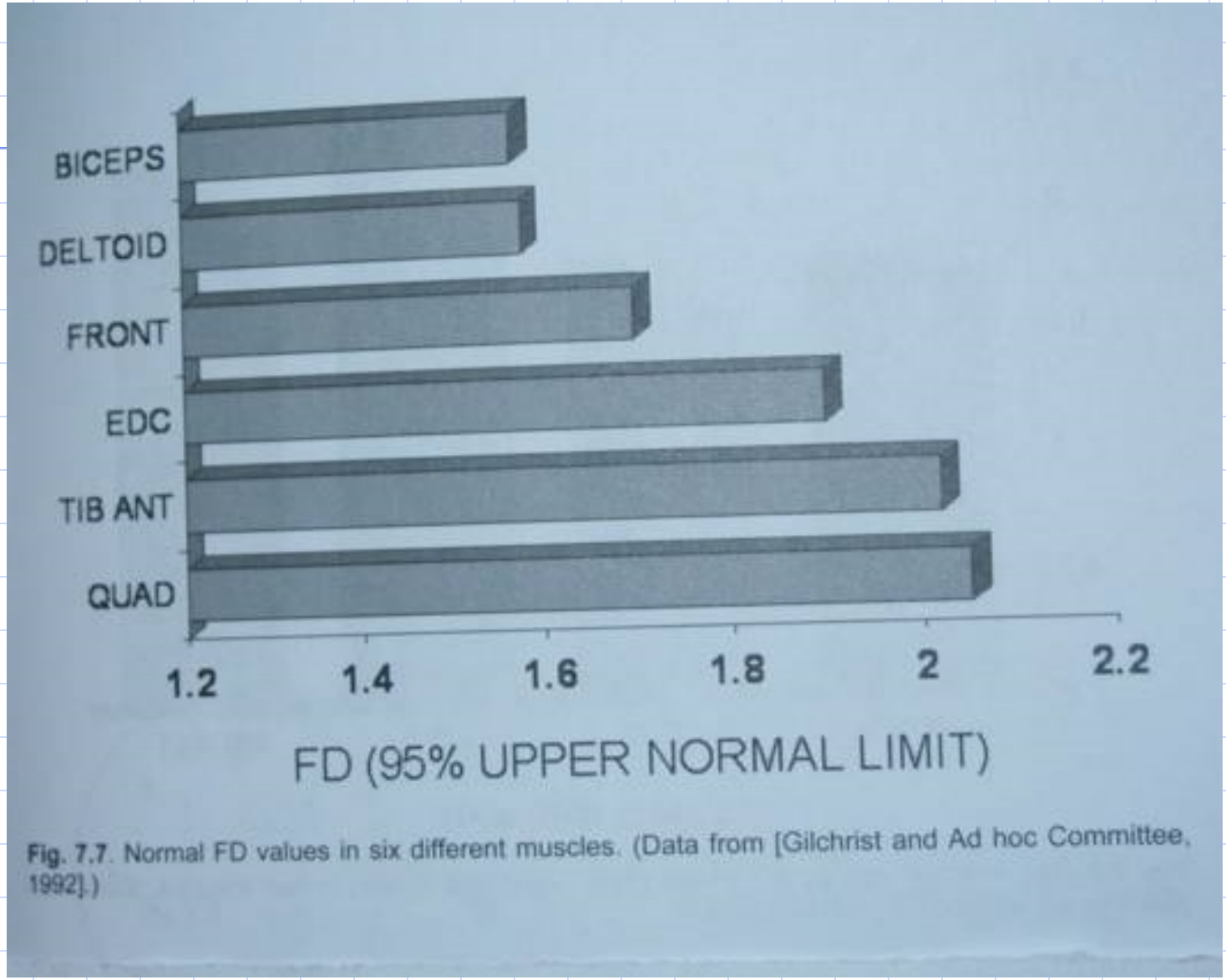



**Fig. 7.7**. Normal FD values in six different muscles. (Data from [Gilchrist and Ad hoc Committee, 1992].)

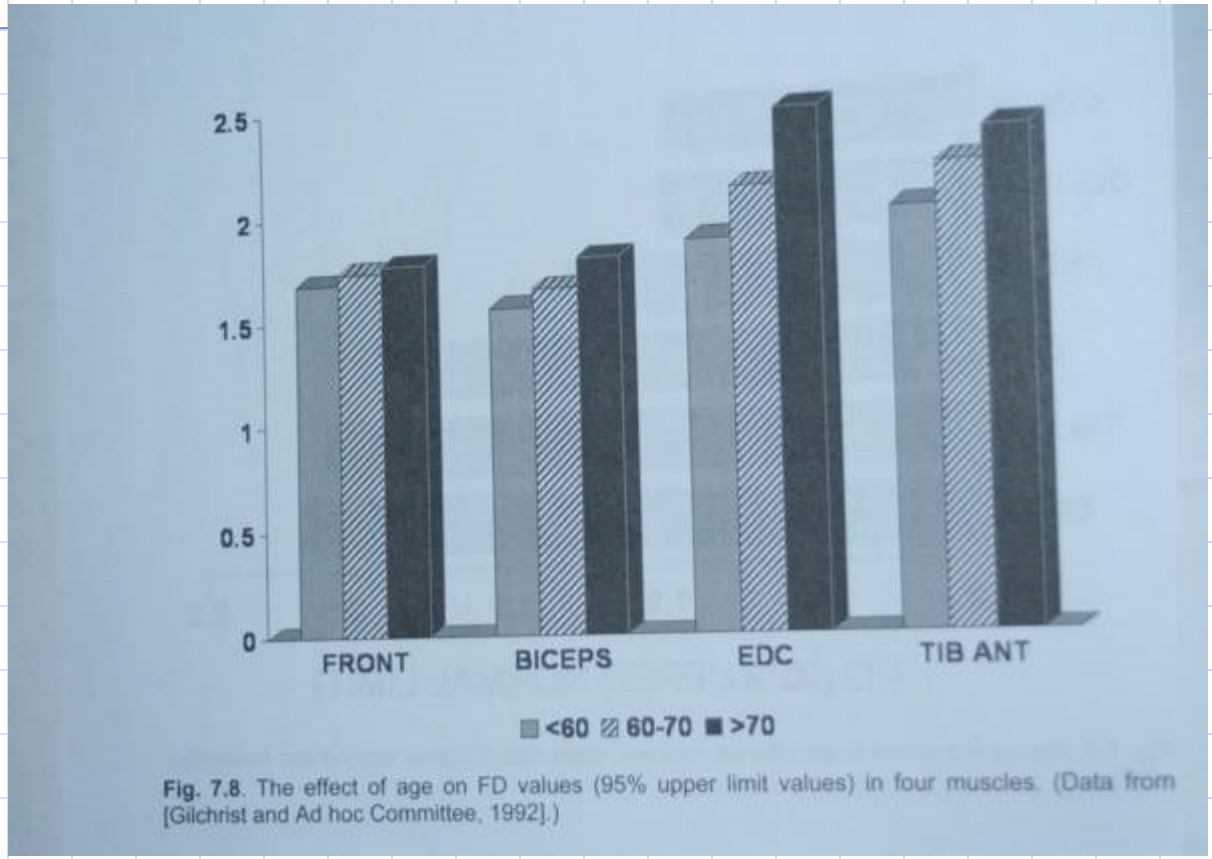



**Fig. 7.8**. The effect of age on FD values (95% upper limit values) in four muscles. (Data from [Gilchrist and Ad hoc Committee, 1992].)

# Fiber Density vs Jitter

- Ongoing reinnervation >FD >Jitter
- Inactive reinnervation >FD <Jitter
- Myasthenia Gravis <FD >Jitter

Repetitive stimulation requires changes in the:

Muscle fiber action potential amplitude.
MUAP amplitude at different rates of stimulation
MUAP amplitude from blocking of entire motor units
MUAP amplitude from blocking of individual muscle fibers
EPP amplitude

# Myopathies

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# Myopathy - Symptoms

- Proximal Weakness
  - arising from chair, stair climbing
  - brushing hair
  - lifting head off pillow
  - Episodic weakness
- Fatigue
- Atrophy
- Muscle Pain

# Myopathy History

- Other Medical History
  - connective tissue disease, cancer
- Family History
- Toxic Exposure
- Statin Therapy

# Myopathies - Signs

- Strength
  - proximal weakness mostly (distal weakness helps with the specific diagnosis)
  - scapular winging
  - neck, spine weakness (“dropped head”)
- Gait
  - Gower’s Sign
  - excessive lordosis
  - genu recurvatum
  - Trendelenburg sign

# Myopathies - Signs

- Myotonic Dystrophy
  - facial weakness, frontal balding, temporalis muscle wasting
  - percussion myotonia
- Dermatomyositis
  - Rash
  - Lung disease

# Myopathies - Signs

- What should not be seen in pure myopathies?
- Sensation -usually normal
- Reflexes - usually preserved early on
- Fasciculations - not seen

# Myopathies - Laboratory Tests

- Serum Creatine Kinase
  - upper normal varies from 200 - 500
  - depends upon lab, gender, race
  - can see up to ~1000 in denervating diseases
  - over 1000 suggests muscle disease
- AST, LDH, aldolase can also be elevated
  - less sensitive than CK
  - also elevated in liver disease

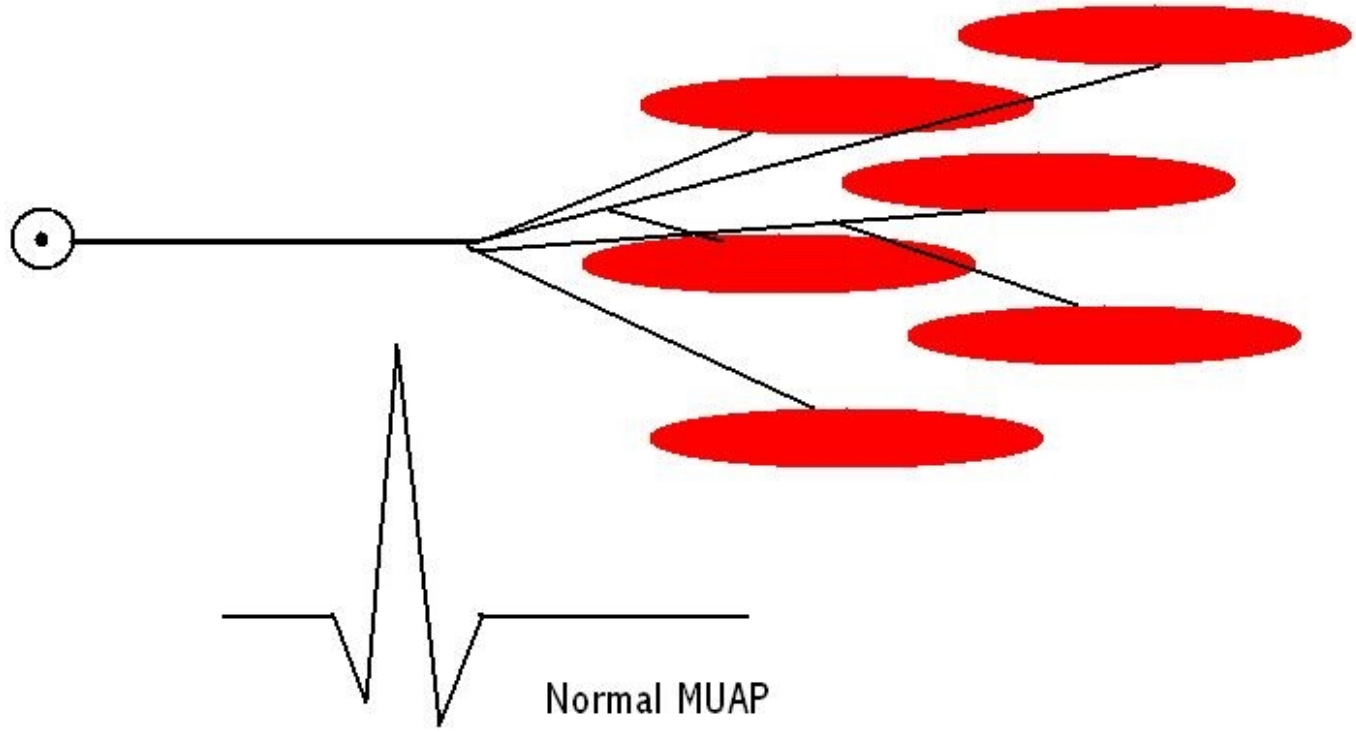
# Electrodiagnostic Approach to Myopathies

- Sensory Nerve Conduction
  - should be normal
  - if abnormal, consider other disease process
- Motor Nerve Conduction
  - velocity should be near normal
    - if not, consider peripheral nerve disease
  - amplitude can be reduced in myopathies
    - but also in axonal neuropathies, NMJ disease

# Electrodiagnostic Approach to Myopathies

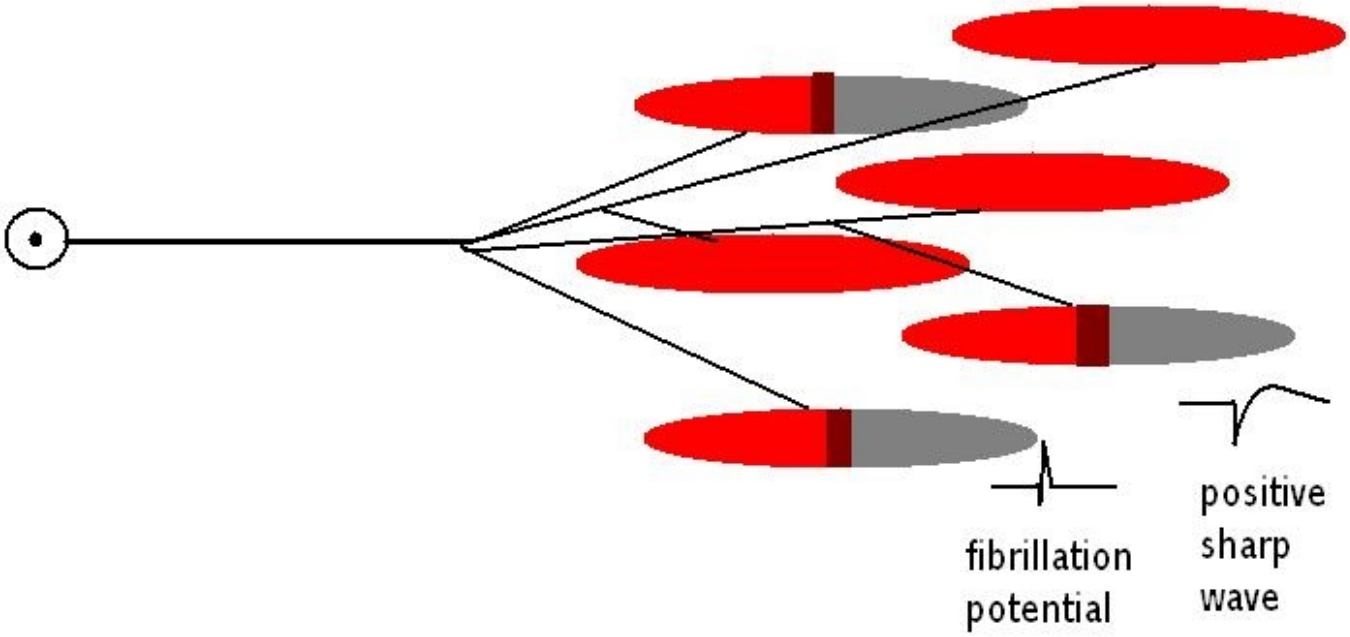
- If NMJ disorder is suspected, then do repetitive stimulation studies.
  - Usually normal in myopathies
  - Some myotonic conditions do have a decrement

# Normal MUAP



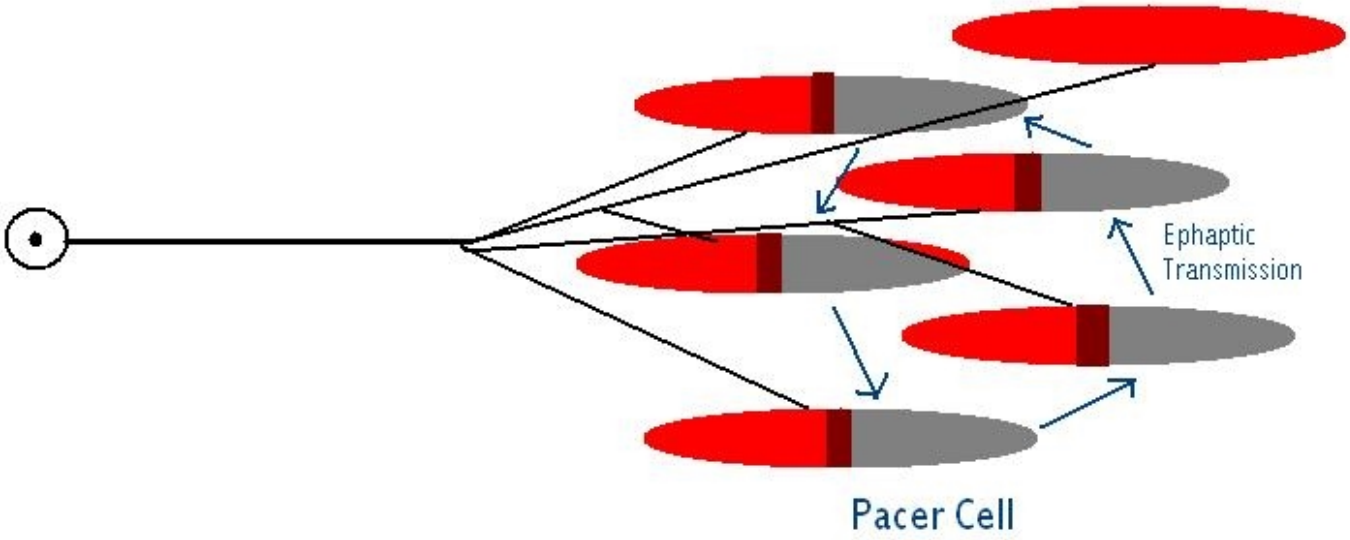
# At Rest

# Myopathies - Spontaneous Activity

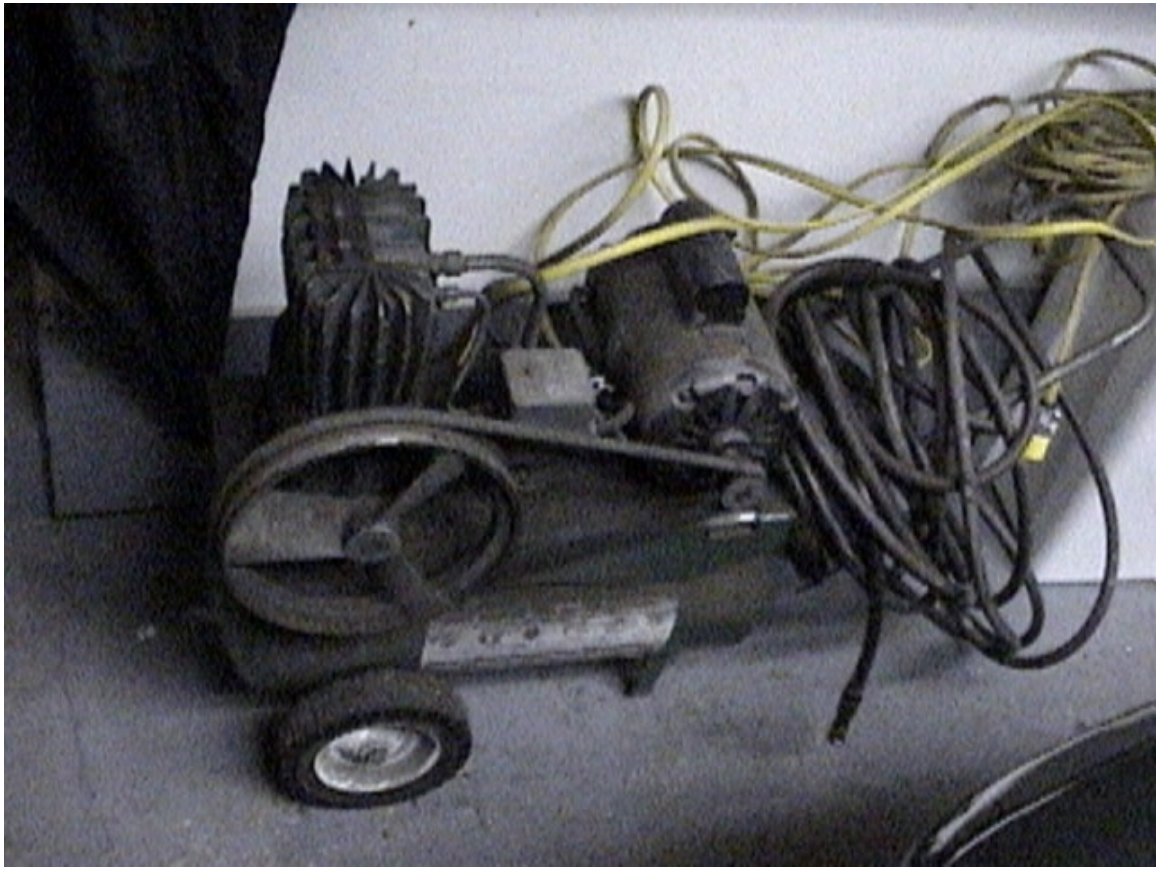


# Fibrillation Potentials

# Complex Repetitive Discharge



# Complex Repetitive Discharges



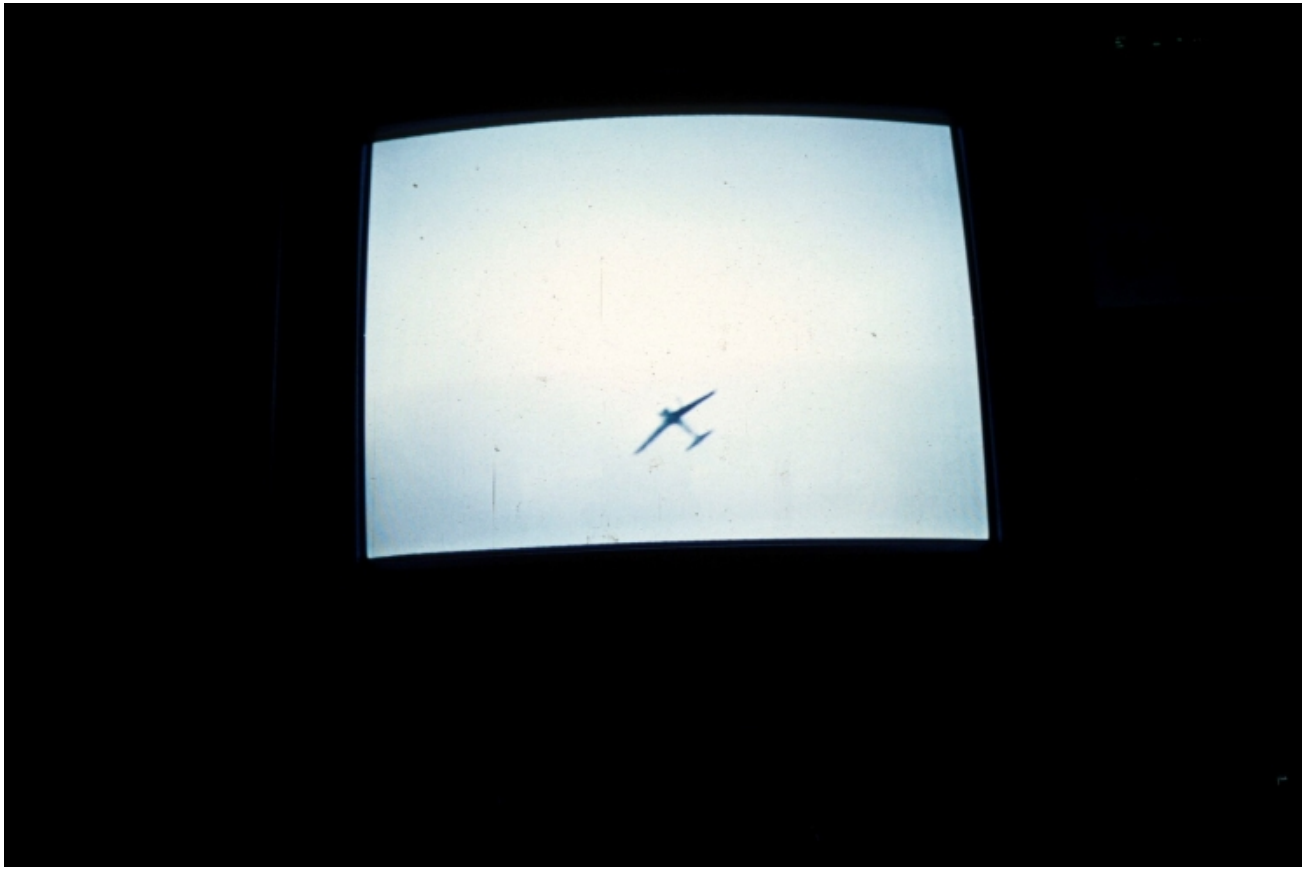
# Complex Repetitive Discharge

- Seen in chronic myopathies or neuropathies
- Due to ephaptic transmission between muscle fibers.  Pacer cell.
- Similar to cardiac re-entry phenomenon
- Constant discharge, sudden on - off
- Sounds like machinery

# Myopathies - Other Spontaneous Activity

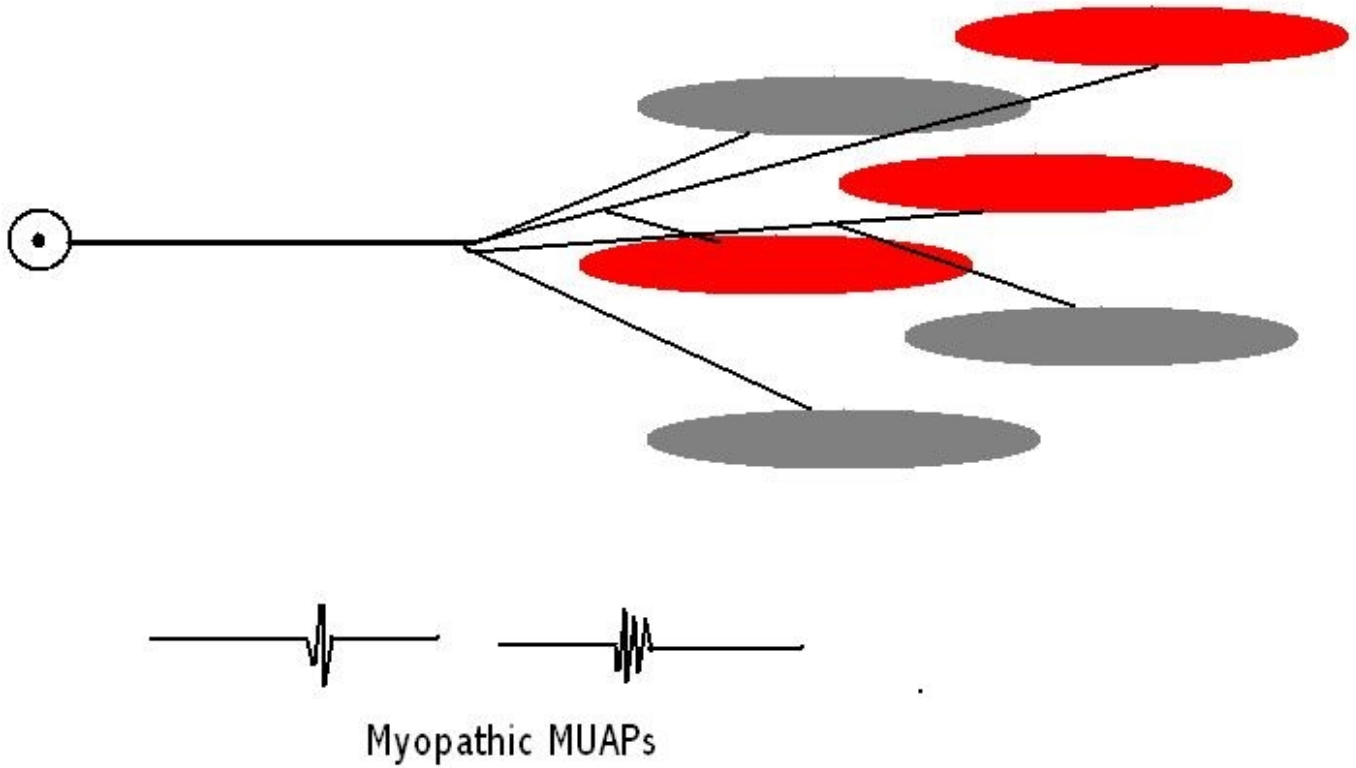
- Myotonia
  - originate from single muscle fibers
  - look like fibrillations or positive sharp waves
  - due to abnormal Cl conductance
  - wax and wane in frequency and amplitude
  - sound like dive bomber or revving motorcycle

# Myotonia in Action
# Tora Tora Tora

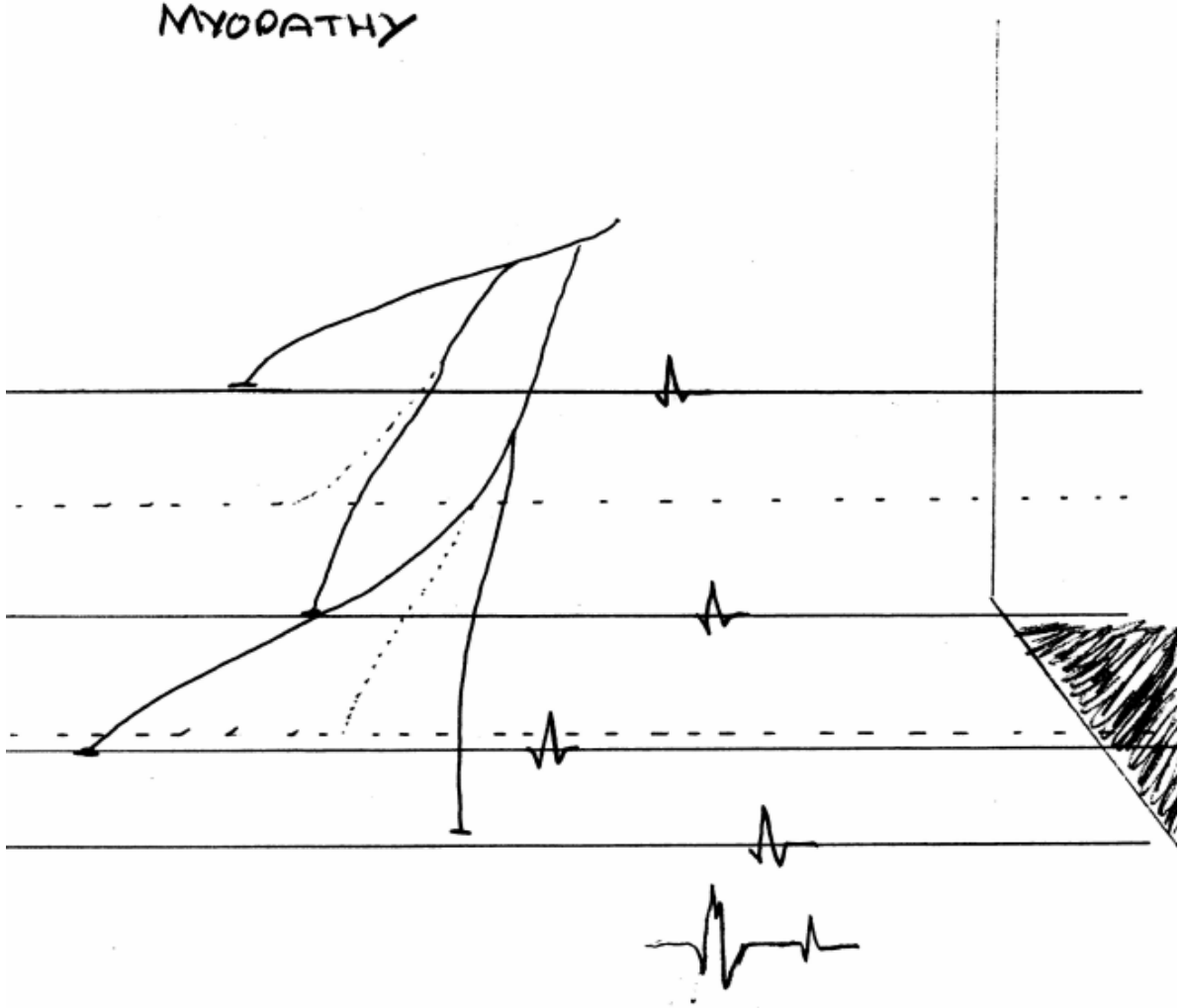


# Myotonia

# Myopathic MUAPs



MYOPATHY



DURATION – FEWER FIBERS CONTRIBUTE

SPIKE – ABSENT FIBERS (2 IN THIS EXAMPLE)

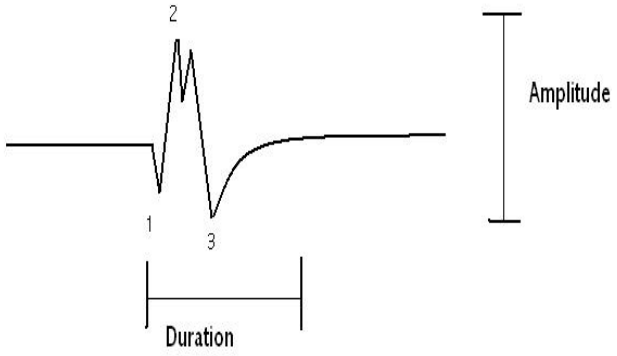
# Myopathic MUAPs

- Reduced Motor Unit Territory
  - fewer muscle fibers per motor unit
  - temporal dispersion along muscle fibers
  - less force per MUAP
- On EMG, one sees
  - small amplitude, short duration
  - polyphasic
  - early recruitment

# Recruitment: The Orderly Activation of Motor Units to Increase Muscle Tension

- Spatial
- Temporal

# Measuring MUAPs



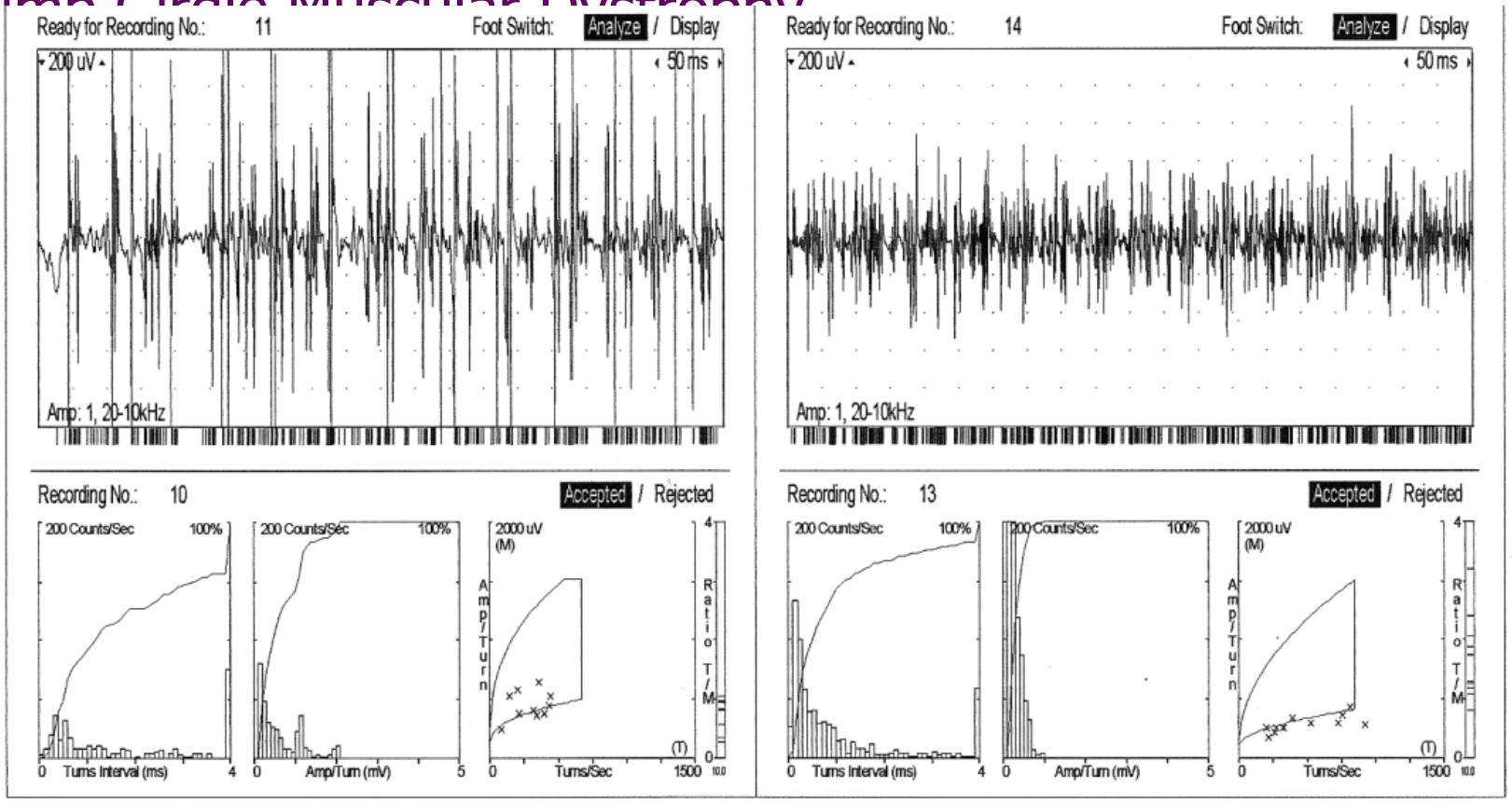

- Duration
  - most reliable
  - more difficult to measure
- Amplitude
  - easy to measure
  - depends upon needle position
- Phases
  - non specific

# Quantitative EMG

- Best way to measure duration
- Concentric Needle
- 2 Hz - 10 kHz filters
- 20 different average MUAPs
- exclude satellites
- get mean duration

# Interference Pattern Analysis

Limb Girdle Muscular Dystrophy




Vastus Medialis

Biceps brachii

# Specificity of EMG

- EMG can be diagnostic of myopathy but is rarely specific as to type of myopathy
  - exceptions exist, e.g. myotonia
- Specific diagnosis usually dependent upon combination of clinical presentation, lab data, biopsy, and EMG.

# Clues to the Specific Diagnosis

- Proximal vs Distal finding predominate
- Periscapular musclature findings
- Presence of myotonia
- Asymetric findings
- Cranial muscle involvement
- Presence of neurogenic MUAP changes
- Fibrillations

# Hereditary Myopathies

- Duchenne and Becker
  - normal motor and sensory NCS
  - fibs and psw's (Duchenne > Becker)
  - small MUAPs
  - early recruitment
  - proximal findings
  - some abnormalities in carriers, but not sufficient for reliable identification

# Hereditary Myopathies

- Limb Girdle Muscular Dystrophy
  - a number of distinct entities grouped together
  - normal motor and sensory NCS
  - fibs and psw's
  - mixture of small and normal MUAPs
  - +/- early recruitment

# Hereditary Myopathies

- Facioscapulohumeral Dystrophy
  - normal motor and sensory NCS
    - small amplitude CMAPs from atrophied muscles
  - fibs and psw's less prominent
  - small MUAPs
  - early recruitment
  - may initially present asymmetrically

# Hereditary Myopathies

- Myotonic Dystrophy
  - normal motor and sensory NCS
    - small amplitude CMAPs from atrophied muscles
    - decrements to repetitive stimulation
  - fibs and psw's (distal > proximal)
  - myotonia (distal > proximal)
  - small MUAPs (not in myotonia congenita)
  - early recruitment
  - may be associated with a polyneuropathy

# Hereditary Myopathies- Mitochondiral Myopathies

- A group of myopathies with both maternal mitochondrial or mendalian inheritance
- Often multi system disease
- Often ragged red fibers on trichrome stain
- Often with opthalmoplegia (confused with Myesthenia)
- EMG findings are usually minimal with early recruitment and short duration, low amplitude MUAP's

# Hereditary Myopathy- Myotubular Myopathy

- Infantile x linked severe form
- Juvenile autosomal recessive form
- Milder autosomal dominant
- EMG- polyphasic low amplitude MUAP,s fibs and pos sharp waves and CRD;s (the only congenital myopathies with spontaneous activity)
- Myotonic like discharges may suggest myotonic dystrophy

# Myofibrillar Myopathy

- Proximal and distal weakness
- Slow progression (onset may be after 40)
- May have peripheral neuropathy with mixed neuropathic and myopathic changes
- Autosomal dominant

# Inflammatory Myopathies

- Idiopathic
  - polymyositis, dermatomyositis, inclusion body myositis
- Infectious
  - HIV, Influenza, Hep B, Hep C, other viruses
- Bacterial (Strep, Staph, Yersinia)
- Fungal
- Parasites (Toxo, Trichinosis, Cestodes - tapeworms)

# Polymyositis - Dermatomyositis

- Symmetric Proximal > Distal Weakness, muscle pain
  - dysphagia, dyspnea, arrhythmias
- Increased CK, usually 5 - 50 fold increase
  - SGOT, SGPT, LDH, aldolase also increased
- Biopsy - endomysial inflammation, segmental necrosis
- Dermatomyositis (a vasculitis) - heliotrope rash

# Polymyositis - Dermatomyositis

- Needle EMG demonstrates
  - psw's and fibs, proximal > distal muscles
    - paraspinals most sensitive (thoracic good to test)
    - most patients have them
    - reflect severity of inflammation
    - reduced after steroids
  - CRDs
  - typical "myopathic" MUAPs, early recrt.
  - EMG one side, biopsy mod involved contralateral muscle

# Inclusion Body Myositis

- Usually >50y/o, M>F
- Weakness proximal = distal
  - finger and wrist flexors, knee extensors
  - may present asymetrically
- CK only mildly increased (<10 x normal)
- Less responsive to any treatment-a degenerative rather than immune disorder
- EMG similar to DM-PM but, less psw's & fibs, mixed large and small MUAPs.

# IBM Patients Mimicking ALS

- 9/70 IBM patients initially diagnosed with ALS in Columbia University series (Dabby R. et al., Archives of Neurol, 2001)
- Fasciculation potentials in 7 and long duration MUAPs seen in 8
- Quantitative motor unit analysis helped confirm myopathy in 4/5 patients restudied
- Exclude MMN (a form of CIDP)

# Critical Illness Myopathy

- Probably more common cause of ICU weakness than Critical Illness Polyneuropathy
- More likely in patients who receive steroids or non-depolarizing NMJ blockers
- Severe generalized weakness over several days
- Recovery occurs slowly over several months

# Critical Illness Myopathy

- Normal SNAPs (unless CIP co-exists)
- Small or absent CMAPs
- Diffuse fibs/psw's
- Short duration, small MUAPs expected
  - difficult to recruit
- Direct muscle and nerve stimulation both show small responses (research tool)

# Myopathy - Summary

- Important to complete thorough H&P
- Examine one side
- Do proximal and involved muscles
- Specific diagnosis depends upon clinical history, lab values, biopsy, genetic testing and EMG

# Summary

- Normal SNCV, Possibly small CMAP's in weak muscles, Normal RNS
- Early recruitment in weak muscles
- Short duration MUAP's when complex, polyphasic MUAP are excluded
- Fibs/PSW's most characteristic of inflamatory myopathies, inclusion body myositis, critical illness and a few metabolic and congenital myopathies (acid maltade def.).

# Summary

- Expect occasional larger amplitude, polyphasic MUAP's and occasional late components.
- Myotonic like discharges and myotonia in the inflammatory myopathies, myotonic dystrophy, myotubular myopathy, hyperkalemic periodic paralysis and chloroquine myopathy

# Summary

- Pattern of EMG changes may suggest the etiology (i.e. predominant involvement of deep forearm flexors in IBM)
- Sensory nerve conduction abnormalities uncommon but suggest a specific cause (e.g. IBM) or unrelated neuropathy
- Mixed neurogenic and myopathic changes on needle EMG also suggestive of IBM, and myofibrillar myopathies

# Question

- You find fibrillations in a patient in whom you are evaluating for possible myopathy. You start thinking that:
  a. This isn't a myopathy
  b. This is steroid myopathy
  c. This is polymyositis
  d. This is more likely a neuropathy

# Question

- In a patient with critical illness myopathy, motor nerve conductions would most likely show:

a. Marked slowing in CV
b. Prolonged distal latency
c. Reduced CMAP amplitude
d. Increased temporal dispersion