Introduction to Neuromuscular Disorders: From ALS to ZasP

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Disclosures

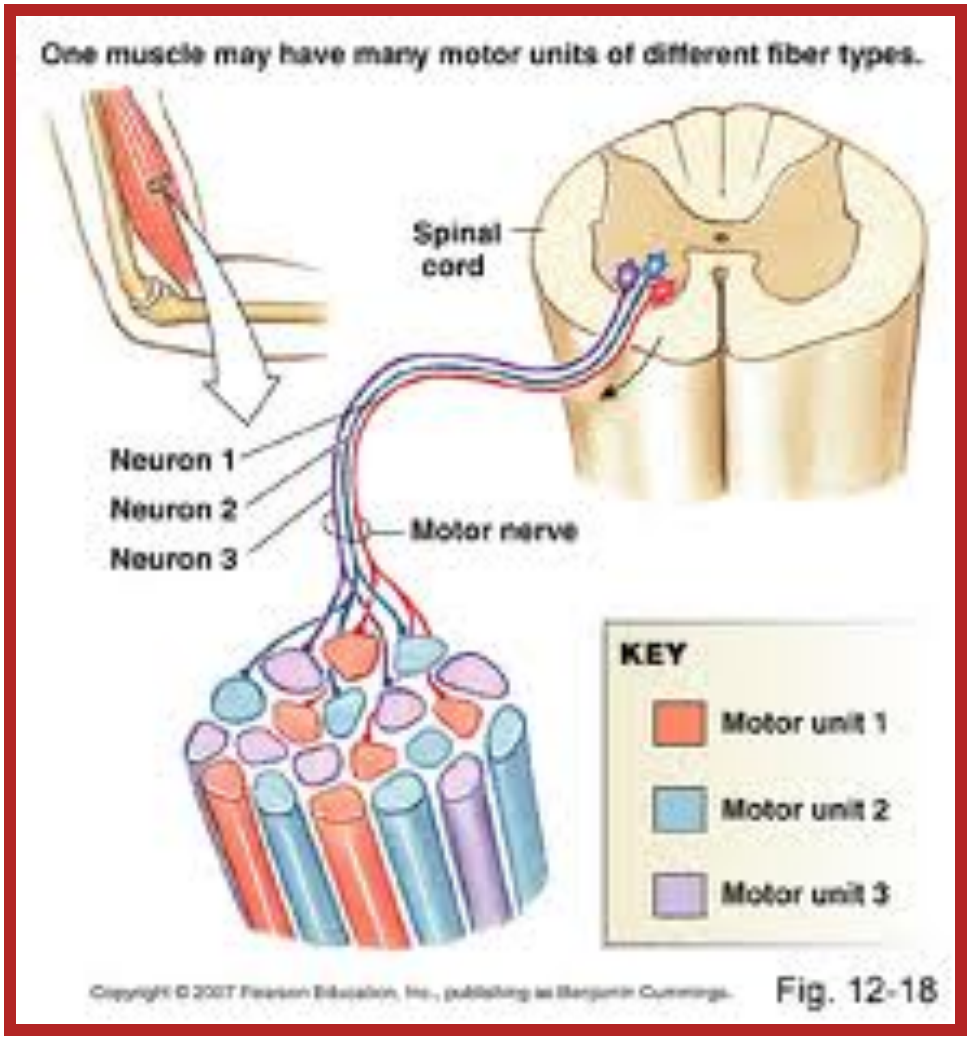
- Receive medication from Abbott Labs for clinical trial of VPA in SMA
- Received support from Alexion for a clinical trial of eculizumab in MG
- Will be discussing some off label uses of drugs and agents
- This is an impossible talk to give!!!
  - Will *not* be a comprehensive overview of all neuromuscular diseases

Objectives

- Definition and clinical limits of term “neuro-muscular disease” (NMDs)
- Classification and list of most important NMDs
- How does a clinician diagnose these patients?
  - Show and tell with pictures and videos
- BRIEF overview of several *relatively* common NMDs (all are “rare”; < 200,000 in U.S.)
  - Won’t discuss pathogenesis, treatment
    - Other lectures later in course

NM Disease
Definition

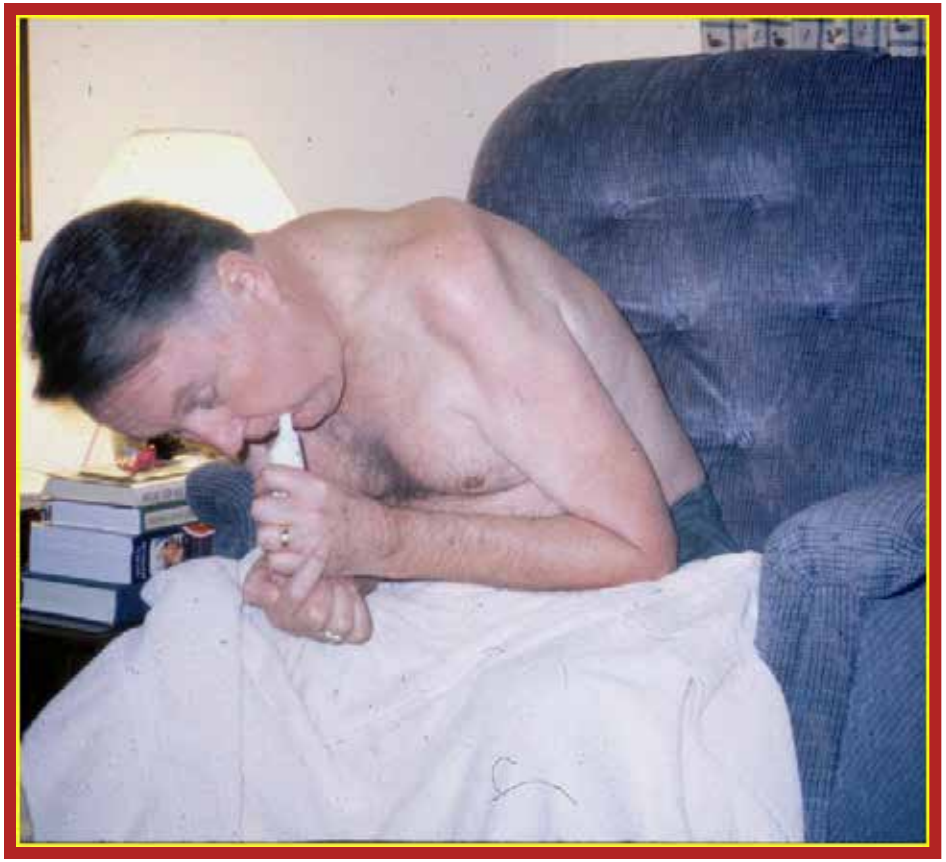
- Dx. of “motor unit”
- 4 main components
  - – Anterior horn cell
  - – Peripheral nerve
  - – NMJ --Muscle
- Seen by neurologists, some PMR, rheum
- Not brain, spinal cord
  - – “Rectum of neurology”



Motor Unit
Inspirational Aside

". to move things is all that mankind can do, for such the sole executant is muscle, whether in whispering a syllable or in felling a forest."

Charles Sherrington, 1924



Courtesy Joanne Lynn, Wendy King

Neuromuscular Diseases
Classification

- **Anterior horn cell disease**
  - Genetic: spinal muscular atrophy (SMA)
  - Acquired: amyotrophic lateral sclerosis (ALS)
- **Peripheral nerve**
  - Genetic: Charcot-Marie-Tooth dx. (CMT)
  - Acquired: Diabetic neuropathy (axonal)
    - Demyelinating Guillain-Barre syndrome (GBS); Chronic acquired demyelinating polyneuropathy (CIDP)

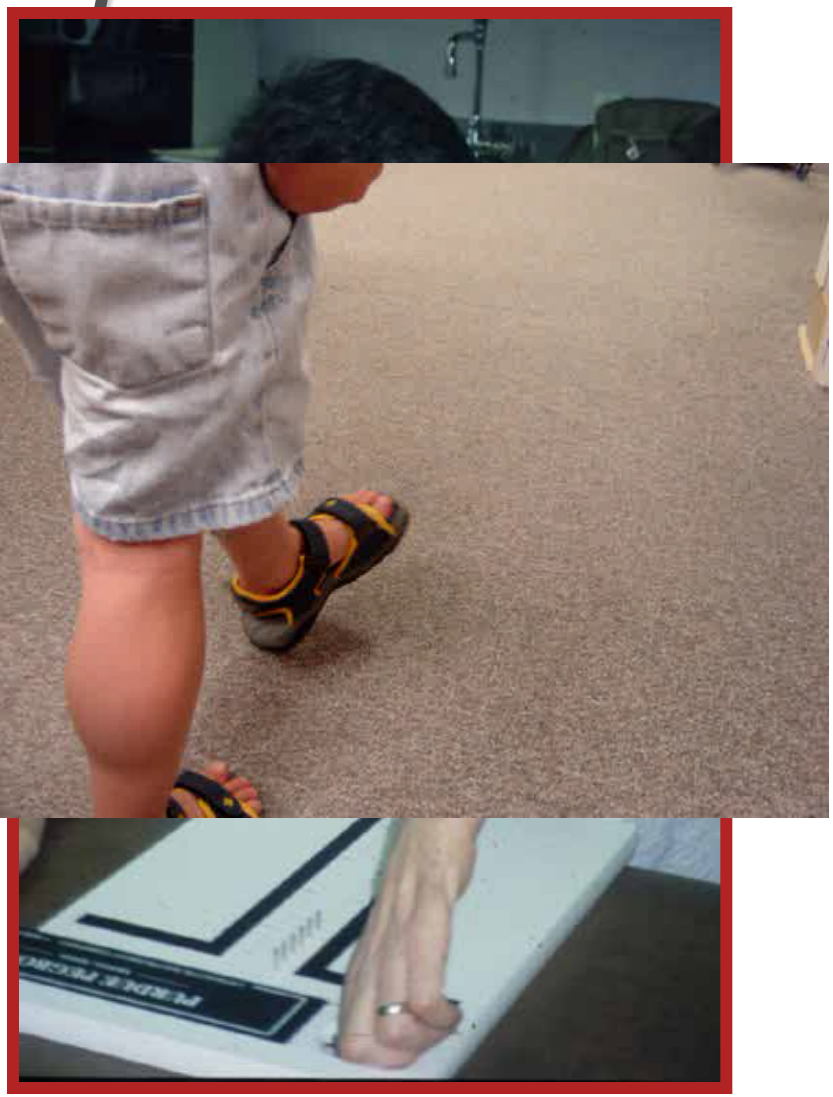
Neuromuscular Diseases
Classification/Approach

- **Neuromuscular junction**
  - Genetic: Cong. myasthenic syndromes (CMS)
  - Acquired: myasthenia gravis (MG) & Lambert-Eaton myasthenic syndrome (LEMS)
- **Muscle**
  - Genetic: Muscular dystrophies (e.g. DMD)
  - Acquired: idiopathic inflammatory myopathies
    - Polymyositis (PM); dermatomyositis (DM); inclusion body myositis (IBM)

Diseases of Motor Unit

Symptoms/Complaints

- WEAKNESS!!
- Functional difficulties
- Late milestones in kids
- Fatigue; dec. endurance
- Cramps/stiffness
- Muscle pain
- Hypertrophy/atrophy
- “Other” (heart, GI, resp.)

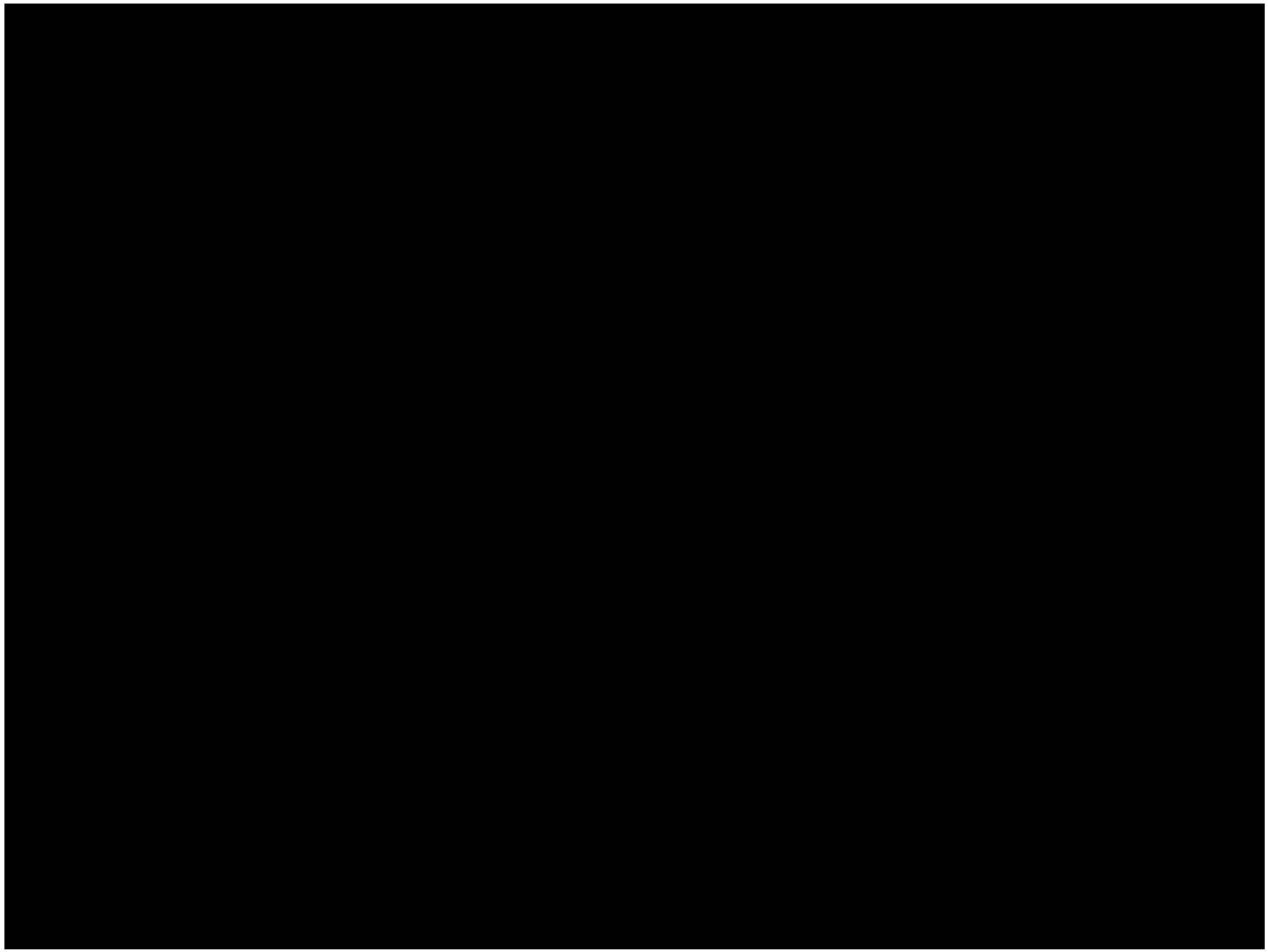


Neuromuscular Disease

Case Presentation

- 48 yo OSU prof - slow healing after ankle fx.
- ? distal weakness and stiffness
- Foot drop, clumsy in high school; trouble getting around
- Referred by orthopedic surgeon; why won't he heal?

Case Presentation



Neuromuscular Disease
Diagnostic Approach

- History & physical examination – PRIMO!
  - Duration, type, distribution of weakness
- Electrophysiologic studies (NCV, EMG)
- Laboratory (i.e. blood tests)
  - Serum tests (esp creatine kinase or CK)
  - Genetic testing (IF appropriate & available)
- Muscle/nerve biopsy
- Specialty tests (eg. forearm exercise test)

Electrodiagnostic Studies

- Answers *specific* ? raised by history & examination
- Localizes problem in the motor unit!
- Three components
  - NCV (shocks!)
  - Needle EMG
  - Repetitive stimulation for NMJ problem
- Special studies

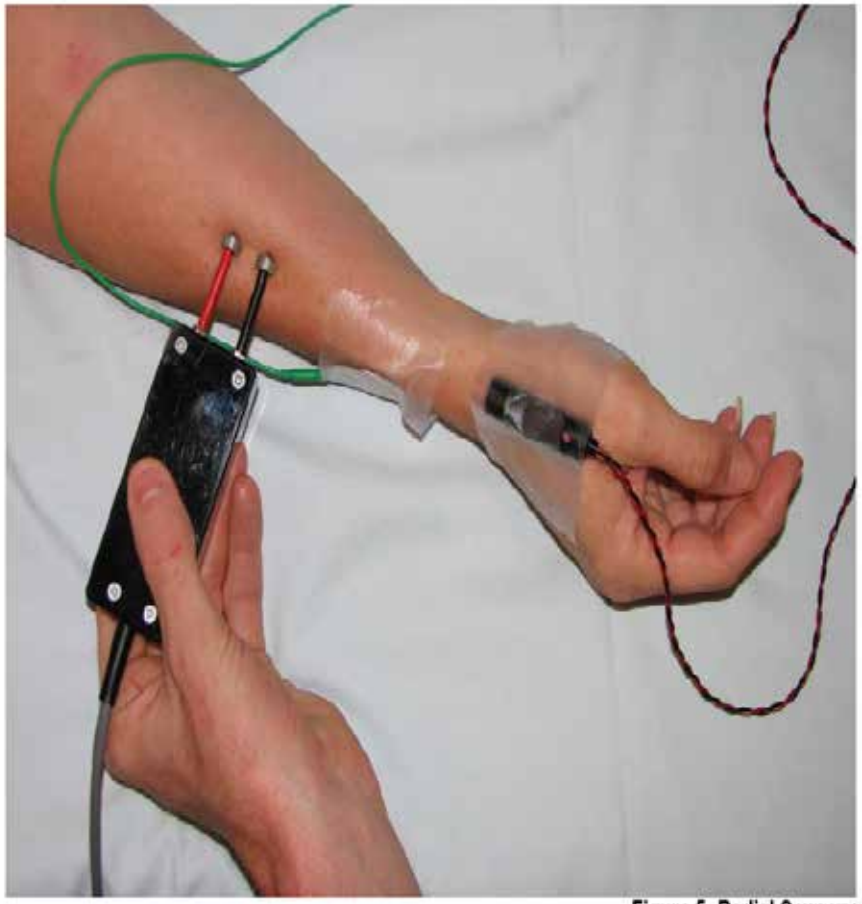
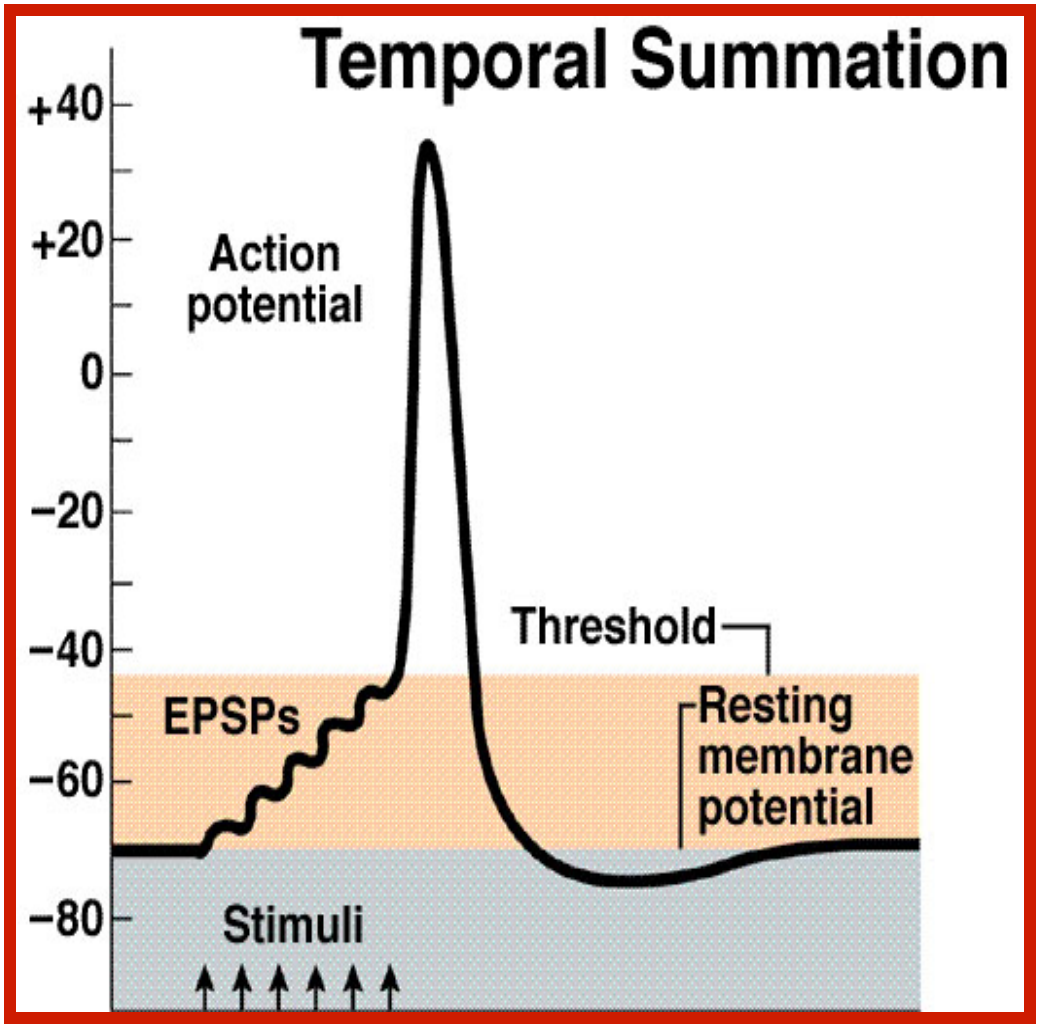


Figure 5- Radial Sensory

Neurodiagnostic studies

- NCVs measure summation of APs
  - generated by axons in the nerve (sensory nerve amplitude)
  - generated by axons and muscle fibers (motor nerves)
- Axonal disease will decrease amplitude of response



Nerve Conduction Studies

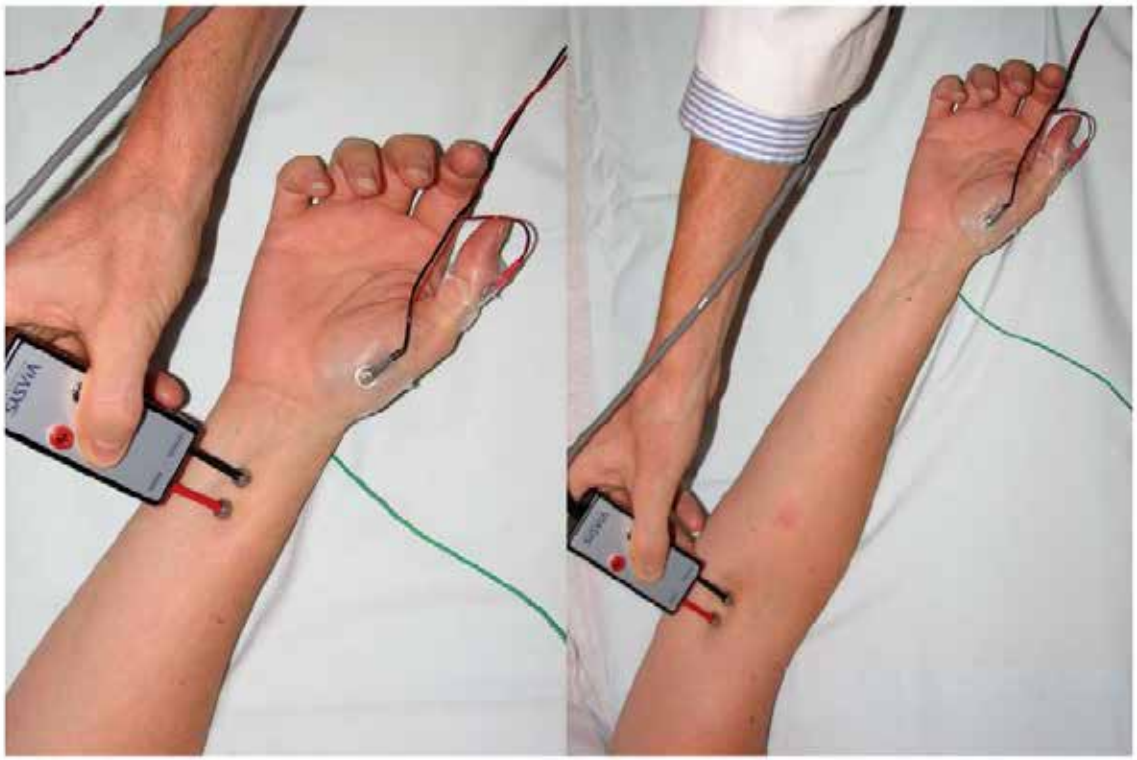


Figure 12- Median Motor, Wrist

Figure 12- Median Motor, Elbow

- Velocity depends upon intact myelin
- Dx. affecting myelin will change latencies, velocities

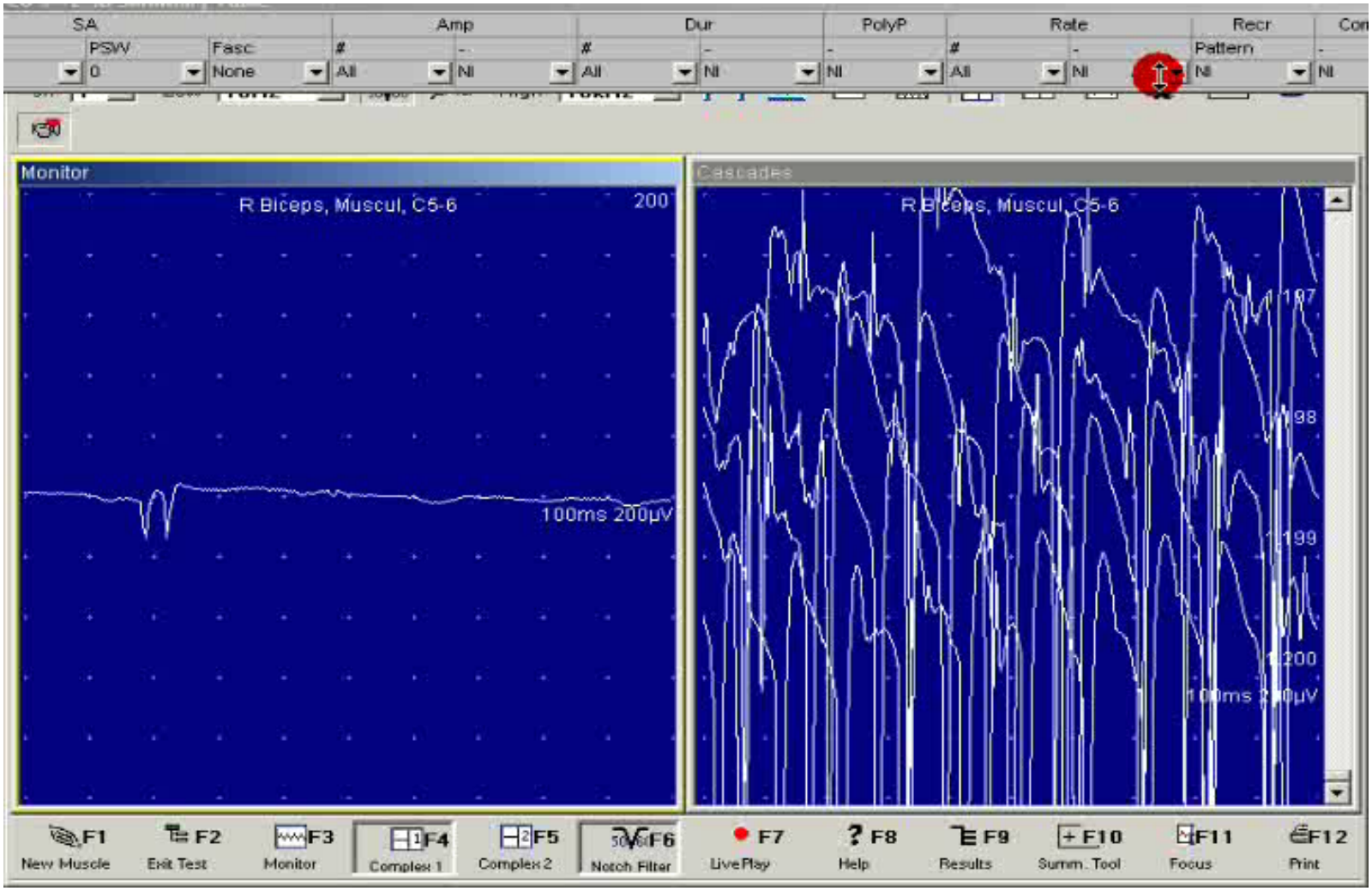
Electromyography

- Activated muscle generates motor unit potentials (MUPs)
  - Neurogenic or myopathic dx. cause changes in MUP amplitude, duration, firing rate, and recruitment that allows classification

EMG FINDINGS

	LESION / EMG Steps	NORMAL	NEUROGENIC LESION		MYOGENIC LESION		
			Lower Motor	Upper Motor	Myopathy	Myotonia	Polymyositis
1	Insertional Activity	Normal	Increased	Normal	Normal	Myotonic Discharge	Increased
2	Spontaneous Activity	—	Fibrillation, Positive Wave	—	—	—	Fibrillation, Positive Wave
3	Motor Unit Potential	0.5-1.0 mv, 5-10 msec	Large Unit, Limited Recruitment	Normal	Small Unit, Early Recruitment	Myotonic Discharge	Small Unit, Early Recruitment
4	Interference Pattern	Full	Reduced, Fast Firing Rate	Reduced, Slow Firing Rate	Full, Low Amplitude	Full, Low Amplitude	Full, Low Amplitude

EMG of Case



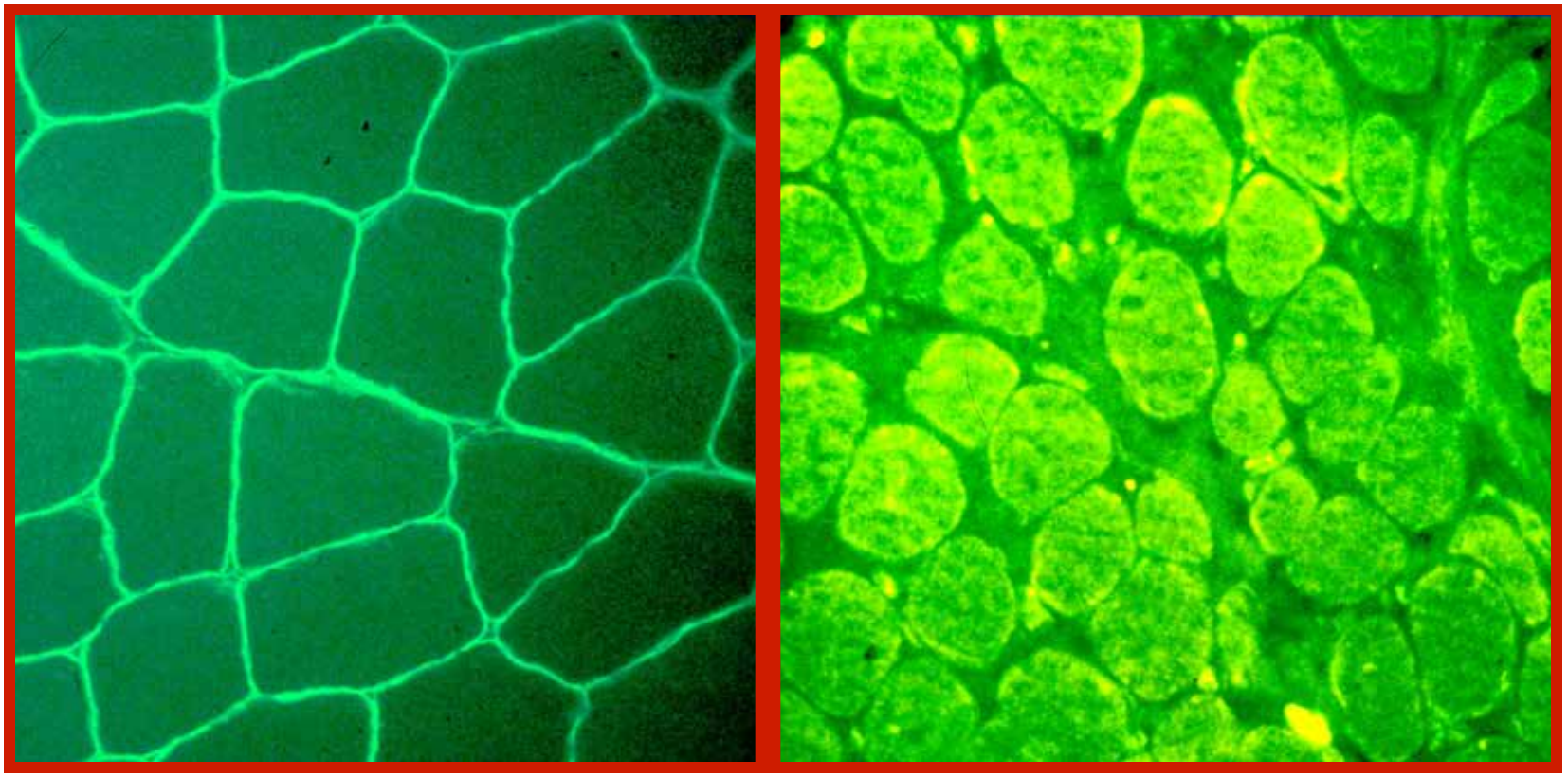
- Genetic testing positive for repeat of myotonic dystrophy type 1 (DM1)

Muscle & Nerve Biopsy

- Indications reduced ~50% with genetic testing
  - Still indispensable in many patients (IBM)
- Often does *not* give SPECIFIC diagnosis
- No benefit in patients with isolated myalgia!

Muscle Biopsy

Immunostaining



Normal **Patient**

Genetic testing confirmed Duchenne dystrophy

Neuromuscular Diseases
Classification/Approach

- **Anterior horn cell disease**
  - **Genetic: spinal muscular atrophy (SMA)**
  - **Acquired: amyotrophic lateral sclerosis (ALS)**
- Peripheral nerve
  - Genetic: Charcot-Marie-Tooth dx. (CMT)
  - Acquired: diabetic polyneuropathy (axonal)
    - Demyelinating Guillain-Barre syndrome (GBS); Chronic acquired demyelinating polyneuropathy (CIDP)

Spinal Muscular Atrophy
Background

- Many types; 5q SMN related most common
  - Autosomal recessive proximal MND
- Affects 1 in 6-8,000 live births
  - Most common fatal genetic disease of infants
  - Carrier frequency ~1:40; 7 million US carriers
- Affects all ages; leading cause of morbidity and mortality **(adults)**
- Major focus of clinical and basic research at OSU (Burghes, Kaspar, Kolb, Beattie labs)

SMA Type 1
Acute Werdnig-Hoffman

- Dec. fetal movement
- Onset < 6 mos.
- Hypotonia, weakness; legs > arms; **never sit!**
  - Poor head control
- Bulbar muscle weakness
  - Weak suck, swallow
- Tongue fascics in 50%
- Bell-shaped chest Respiratory distress
  - **Death < 2 years**

SMA Classification

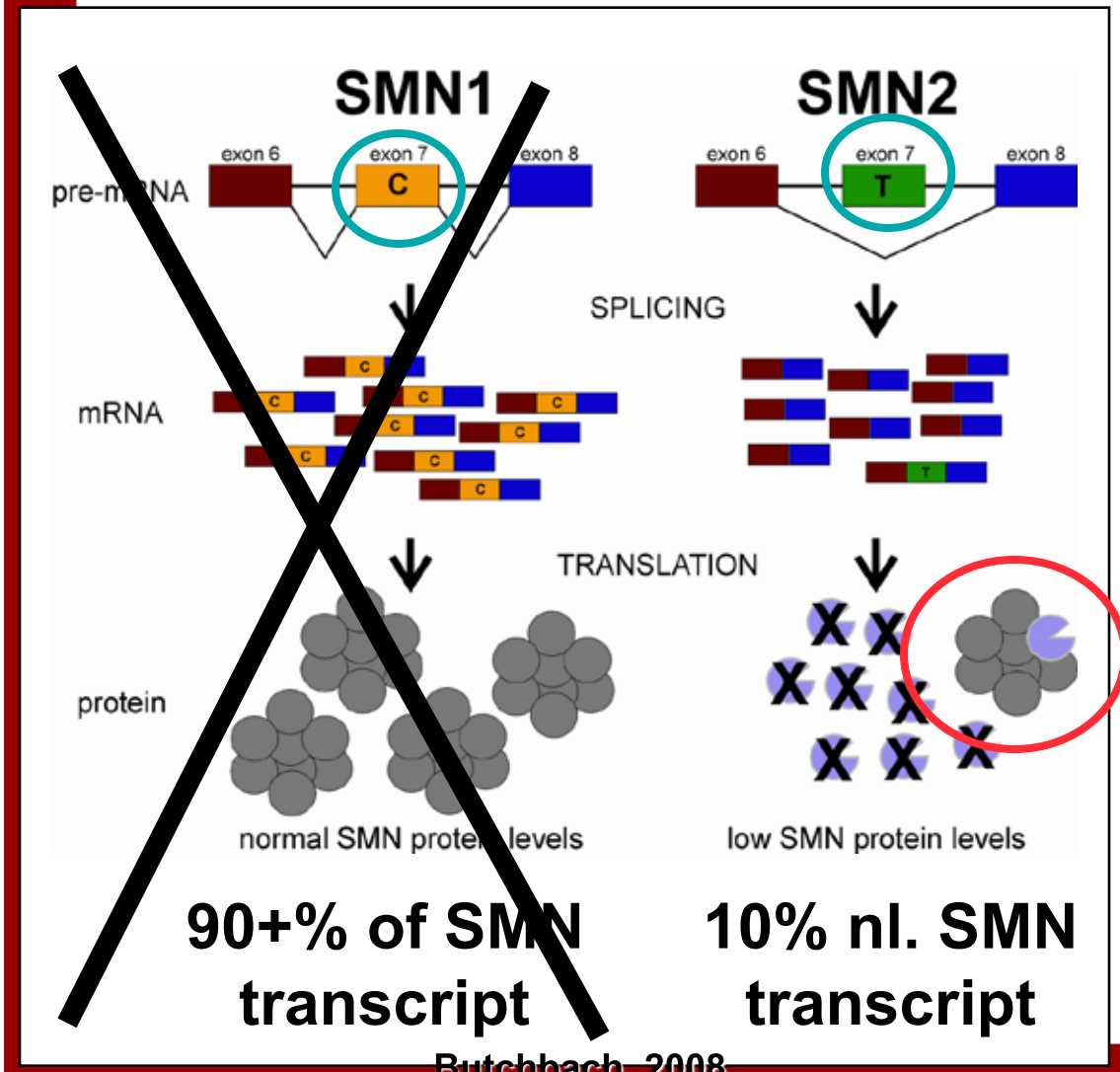
Updated 1991 Classification

Type	Onset	Function	Death	%
0	Prenatal	Resp support	<1 mo.	<1%
1	0 - 6 mos.	Never sit	<2 yrs.	60
2	< 18 mos.	Never stand	>2 yrs.	20
3	> 18 mos.	Stand alone	Adult	25
3a	< 3 years	Stand alone	Adult	
3b	> 3 years	Stand alone	Adult	
4	>21 years	Stand alone	Adult	5

SMA 3

SMN Gene Region

Results



Butchbach, 2008

- No SMN1 in SMA pts.
- 1 or more copies SMN2
- 90% SMN2 lacks exon 7
- Truncated, unstable, rapidly degraded, low level protein

BUT

- 10% is full length SMN
- *Partially* compensates
- Phenotype variability relates to SMN2 copy #

SMA Updated Classification

Type	Onset	Function	Death	SMN2 #
0	Prenatal	Resp support	<1 mo.	1
1	0 - 6 mos.	Never sit	<2 yrs.	2
2	< 18 mos.	Never stand	>2 yrs.	3,4
3	> 18 mos.	Stand alone	Adult	
3a	< 3 years	Stand alone	Adult	3,4
3b	> 3 years	Stand alone	Adult	4
4	>21 years	Stand alone	Adult	4-8

Molecular genetics validated the clinical classification!!

Hypothesis: If low SMN causes MN loss & inc. SMN2 is protective

- Inc. SMN2 expression → **Drugs to promote exon 7 inclusion, stabilize SMN2 inc. SMN2 product**

OR

- Converting SMN2 to SMN1
  --Promote exon 7 inclusion → **Antisense oligonucleotides**

OR

- Replacing SMN1 gene → **Viral mediated gene Transfer (Kaspar et al, 2010)**

may "rescue" MNs, prevent MN loss, allow reinnervation

Proximal SMA
Genetic Classification

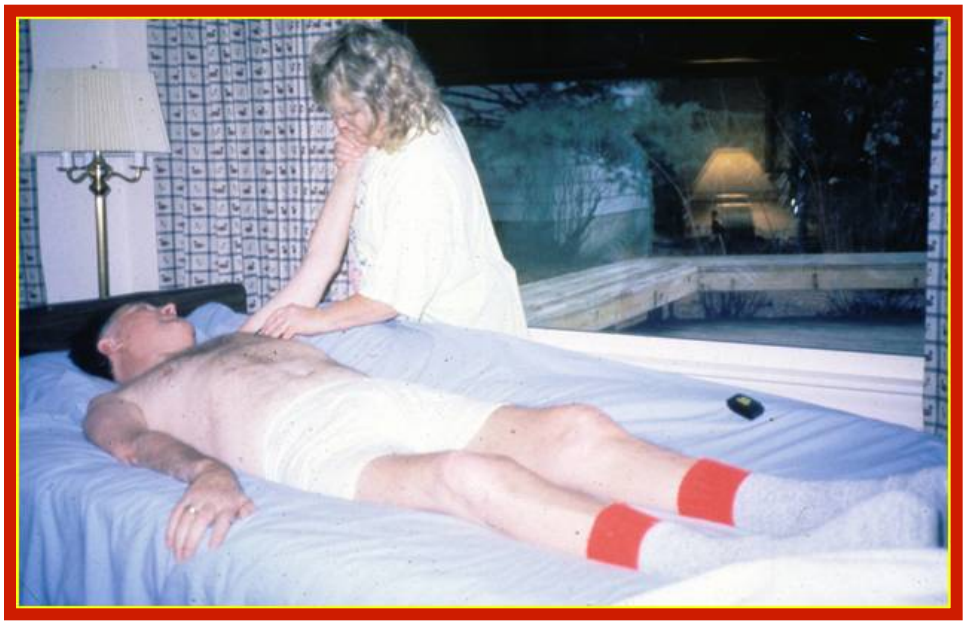
Autosomal dominant	*Locus*	*Gene*
Chronic proximal SMA (child)	?	?
Chronic proximal SMA (adult)	20q13.3	*VAPB*
Benign cong. with contractures	?	
Congenital with leg weakness*	12q23 +	?
Scapuloperoneal syndromes	12q24 +	?
Bulbo-SMA with gynecomastia	?	?
SMALD (lower ext. predom.)	14q32	?
X-linked		
Bulbo-SMA (Kennedy's dx.)	Xq12	*Androgen Rec.*
Infantile SMA with arthrogryposis	Xp11	*UBE1*

* same locus as distal HMN2
+ other loci identified

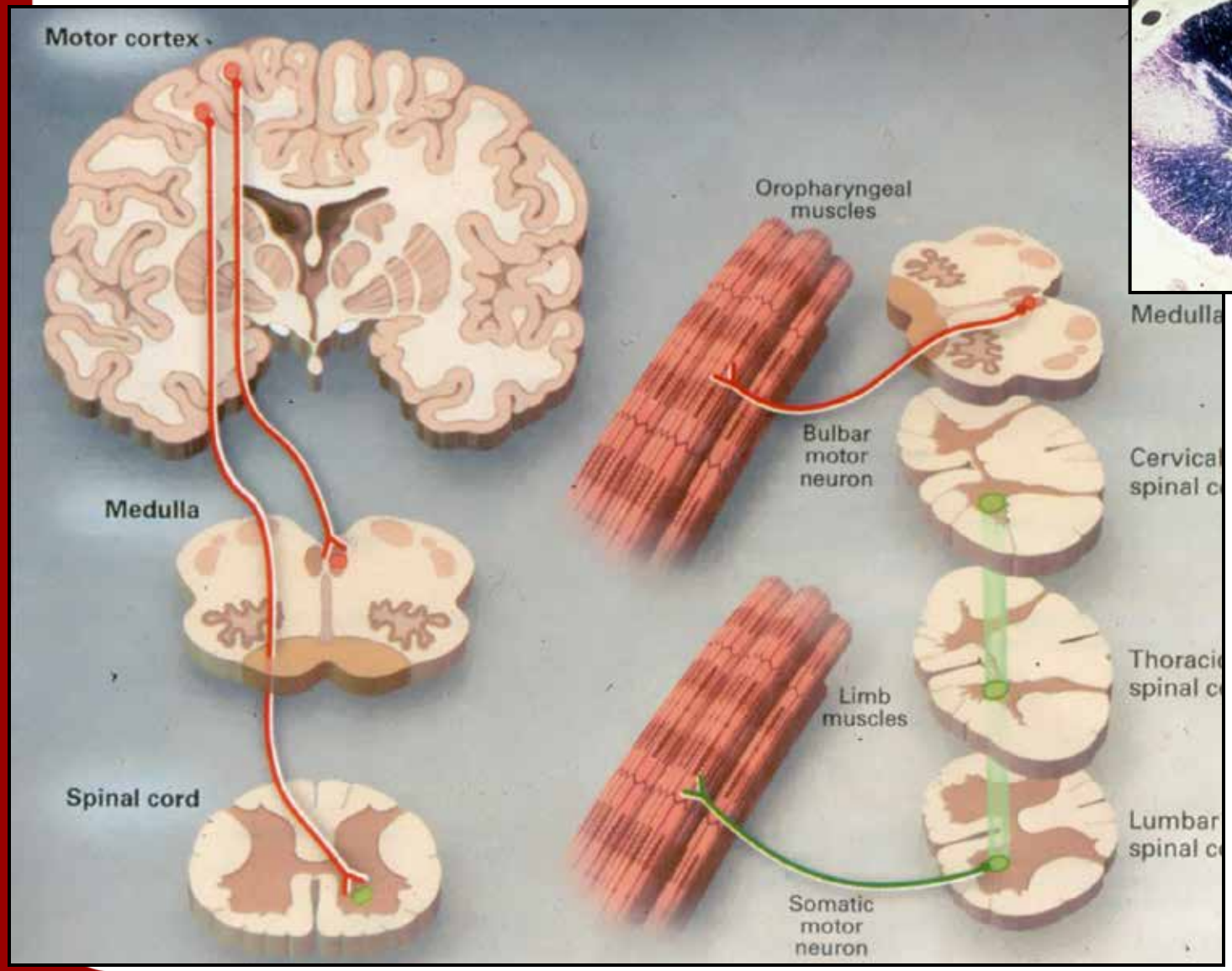
Amyotrophic Lateral Sclerosis

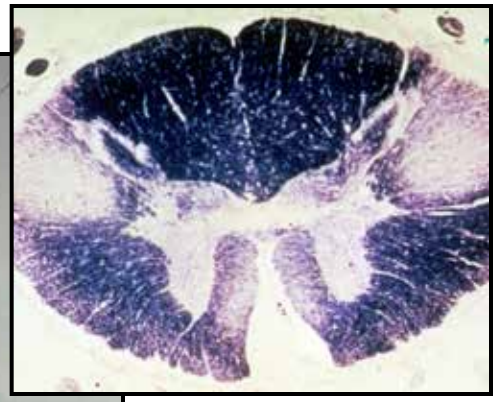
Lou Gehrig's Disease

- Affects ~2/100,000/yr
- Peaks > age 50 group
- Weakness progresses to complete paralysis
- Sensation, autonomics spared
- 50-60% die in 3-4 yrs.
  - 90+% in 5 yrs.
- ? pathogenesis
- Untreatable (riluzole?)



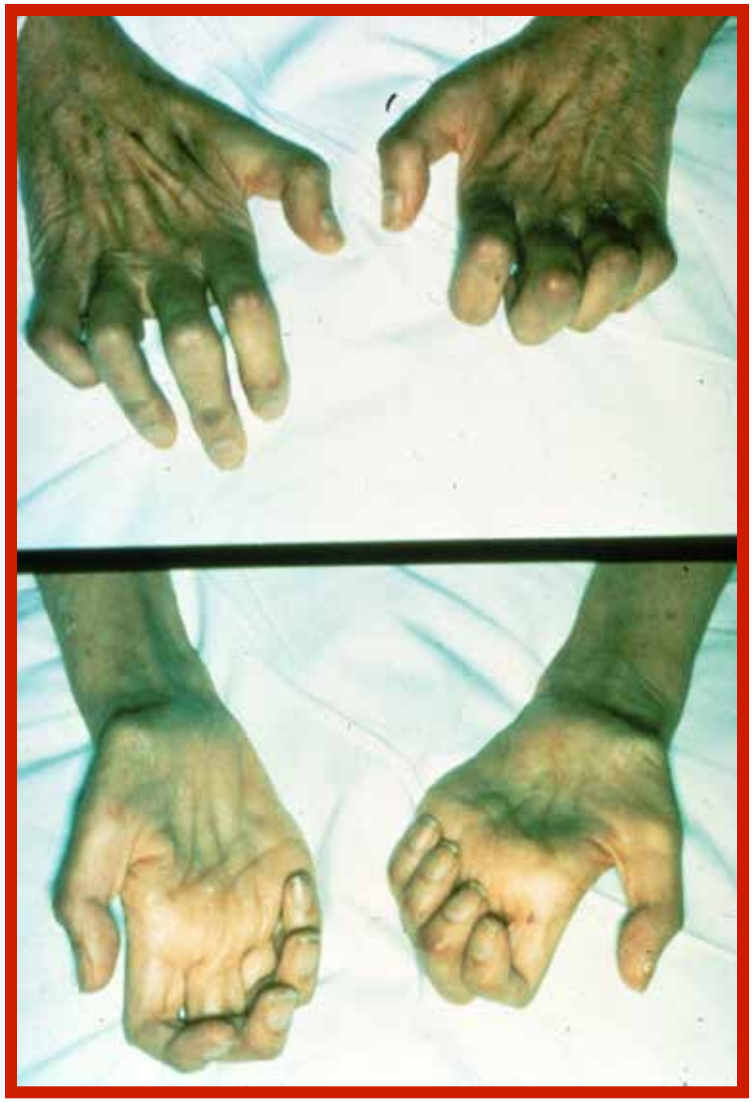
Anatomy of ALS





ALS Symptoms

- Lower motor nerves
  - Segmental weakness
  - Atrophy
  - Fasciculations
  - Muscle cramping
- Upper motor nerves
  - Stiffness
  - Spasticity
  - Hyperreflexia



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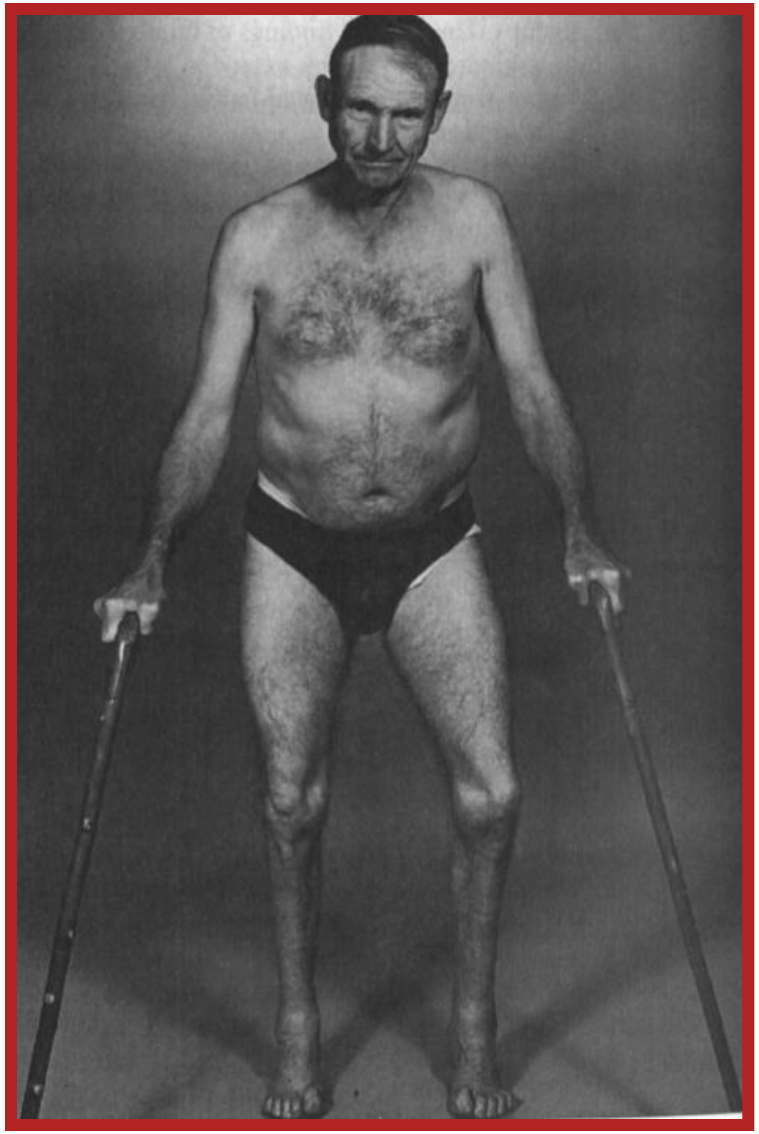
Charcot-Marie-Tooth Neuropathy



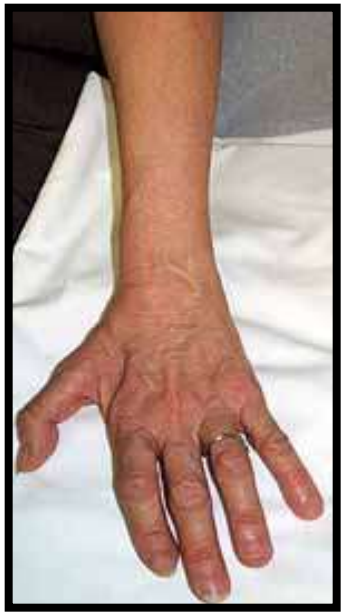
- GROUP of disorders
- Onset age variable even within families
  - Infancy to 70 years
  - Typically: 1st-3rd decade
- Length-dependent loss of sensation
- Distal weakness and atrophy, absent reflexes
- Foot deformities
  - Pes cavus, “champaigne bottle”

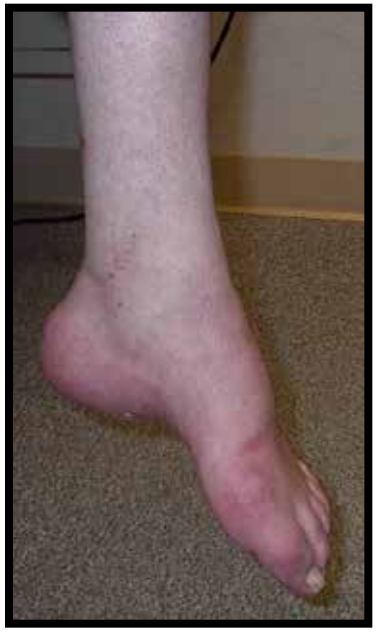
Charcot Marie Tooth

Symptoms

- Frequent tripping, falling
- Recurrent ankle injuries
- Slow running; difficulty with jumping
- Difficulty fitting shoes
- Gait disturbance (“walk like a duck”)
- “FLF”:funny-looking feet
- Leg cramps & pain
- Fatigue walking even short distances

CMT Genetics





- CMT1 demyelinating
  - NCV <30 m/sec
- CMT2 – axonal
  - NCV > 30 m/sec

CMT Syndrome	Gene	Locus	OMIM
AD Demyelinating			
CMT1A	*PMP22*	17p11	118220
CMT1B	*MPZ*	1q22	118200
CMT1C	*LITAF*	16p13	601098
CMT1D	*EGR2*	10q21	607678
CMT1E	*PMP22*	17p11	118300
CMT1F	*NEFL*	8p21	607734
AD Axonal			
CMT2A1	*KIF1B*	1p36	118210
CMT2A2	*MFN2*	1p36	609260
CMT2B	*RAB7*	3q13	600882
CMT2C	--	12q23	606071
CMT2D	*GARS*	7p15	601472
CMT2E	*NEFL*	8p21	607684
CMT2F	*HSP27*	7q11	606595
CMT2G	--	12q12	608591
CMT2I	*MPZ*	1q22	607677
CMT2J	*MPZ* (T124M)	1q22	607736
CMT2L	--	12q24	608673
AD Intermediate			
CMTDI A	--	10q24	606483
CMTDI B	*DNM2*	19p13	606482
CMTDI C	--	1p35	608323
CMTDI D	*MPZ* (D6Y)	1q22	607791

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- Muscle
  - Genetic: Muscular dystrophies (e.g. DMD)
  - Acquired: idiopathic inflammatory myopathies
    - Polymyositis (PM); dermatomyositis (DM); inclusion body myositis (IBM)

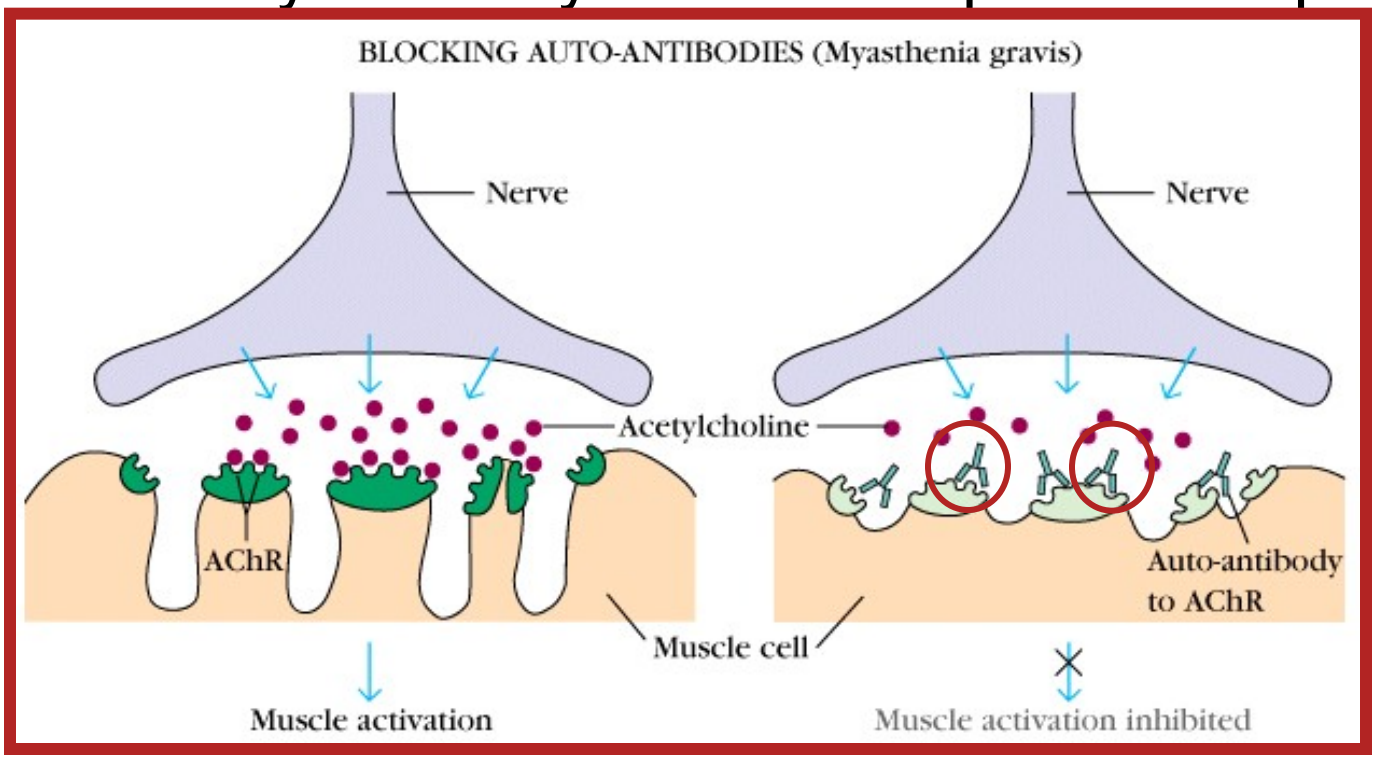
Myasthenia Gravis
Overview

- Autoimmune disease affects ~ 1:100,000
- Causes variable & fatigable weakness
  - Worsens with use
  - Eyes, bulbar muscles, face affected
- Proximal and symmetric limb weakness
- Can affect respiratory muscles & cause death

.

MG Therapy
Pathogenesis

- Caused by antibody to Ach receptor at endplate



  - Blocks receptor or accelerates degradation
  - Get less acetylcholine “bang for the buck” (fatigue)
  - Suggests treatment approach

MG Therapy

Time to Initial Response

THERAPY	TIME TO EFFECT
Pyridostigmine	10-15 minutes
Plasmapheresis	1-14 days
IVIG	1-4 weeks
Prednisone	2-8 weeks
Mycophenolate	2-6 months
Cyclosporine	2-6 months
Azathioprine	3-18 months
Thymectomy	Several mos to yrs ?
Rituximab	1-6 months

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- **Muscle**
  - **Genetic: Muscular dystrophies (e.g. DMD)**
  - Refers to genetic disorder associated with necrosis/degeneration/fibrosis on muscle biopsy

Classification of MD

Non-LGMD Autosomal Dominant Dystrophies

Dx.	Chrom.	Protein	Testing
DM-1	19q13.3	DMPK	Genetic
DM-2	3q21	ZNF9	Genetic
FSHD	4q35	?	Genetic
OPD	14q11.2-14	PABP2	Genetic

X-linked Recessive

Dx.	Chrom.	Protein	Testing
DMD/BMD	Xp21	Dystrophin	Genetic/IH
Emery-D	Xq28	Emerin	Genetic/IH

Classification of MD

LGMD

Autosomal Dominant LGMDs (LGMD1)

Dx.	Chrom.	Protein	Testing
1A	5q22.3-31.3	Myotilin	NA
1B@	1q11-21	Lamin A/C	Genetic
1C	3p25	Caveolin-3	IH
1D	6q23	?	NA
1E	7q	?	NA
1F	7q32.1	?	NA

Classification of LGMD

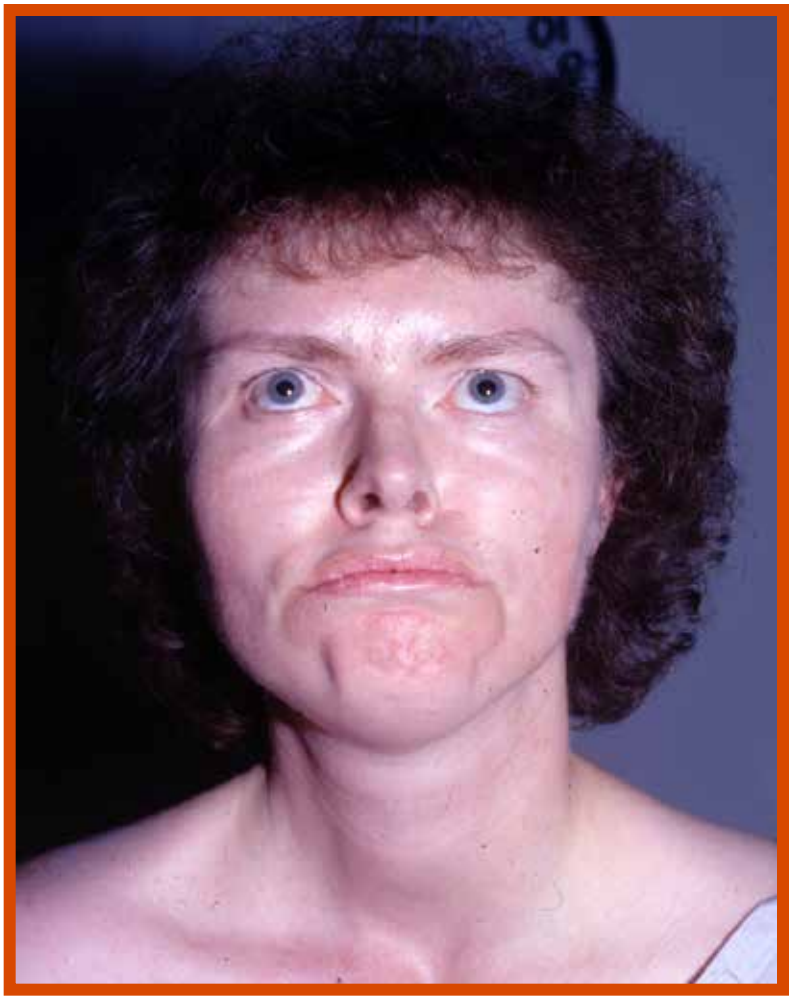
Autosomal Recessive LGMDs (LGMD2)

Dx.	Chrom.	Protein	Testing
2A	15q15.1-21.1	calpain 3	WB, genetic
2B@	2p13	dysferlin	IH, WB, gen
2C	13q12	γ-sarcoglycan	IH, genetic
2D	17q12-21.3	α-sarcoglycan	IH, genetic
2E	4q12	β-sarcoglycan	IH, genetic
2F	5q33-34	δ-sarcoglycan	IH, genetic
2G	17q11-12	telethonin	NA
2H	9q31-33	E3 ubiquitin ligase	NA
2I	19q13	FKRP protein	IH, genetic
2J	2q31	titin	

50% of LGMD cases still undiagnosable!

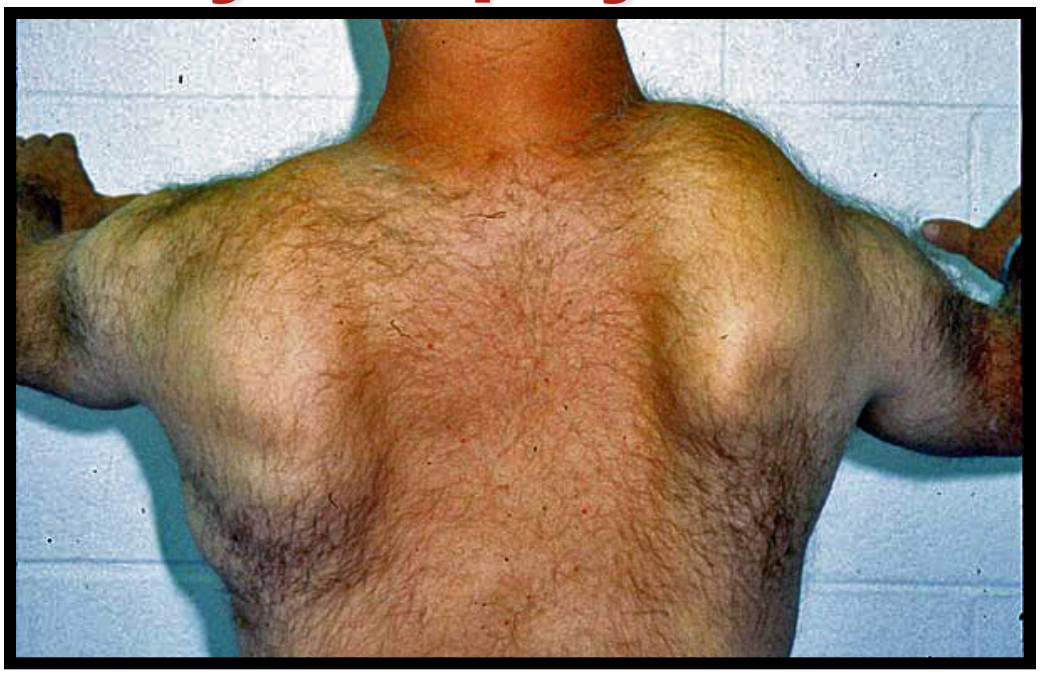
FSH Dystrophy

Overview



- Prevalence 1:20,000
- Autosomal dominant
  - 25% sporadic
- Sx. begin < age 20
  - 20% asymptomatic
- Severity variable
  - 20% need wchair
- Does not shorten life

FSH Dystrophy Genetics

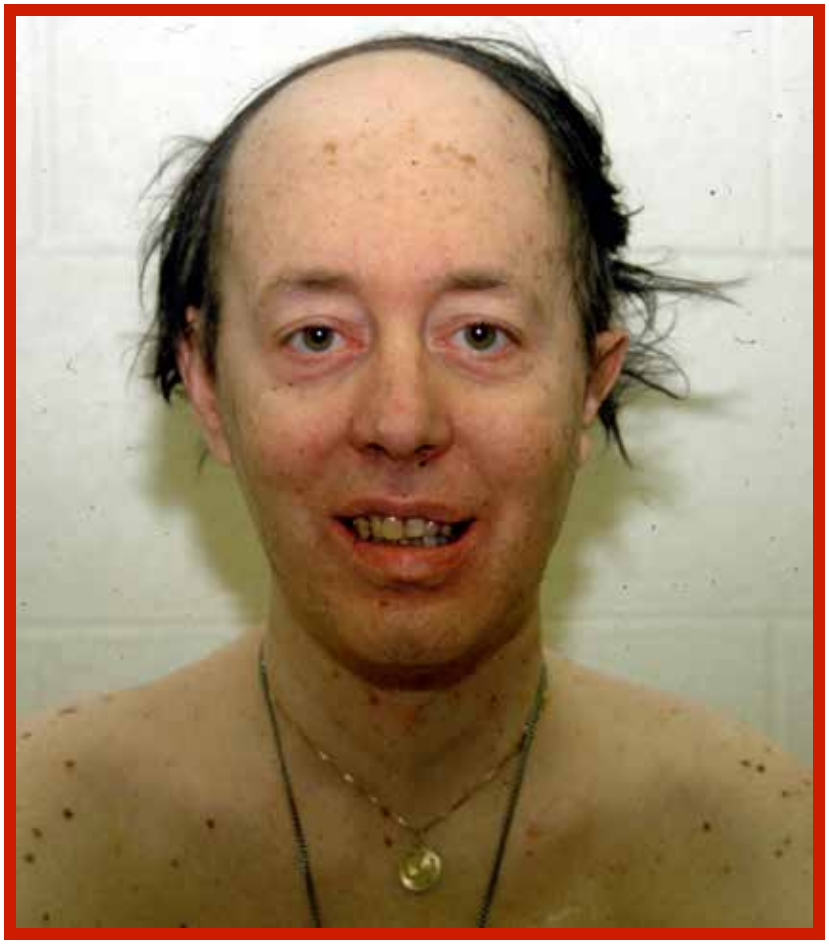


- Variable deletion in 3.3 kb repeat sequence D4Z4 at 4q35; “A” allele only
  - 95% -short fragment (normal is 38-300 kb
  - FSH < 35 kb; inverse correlation with severity
- Toxic gain of function of DUX4 transcript (Harper lab)

Myotonic Dystrophy

Overview

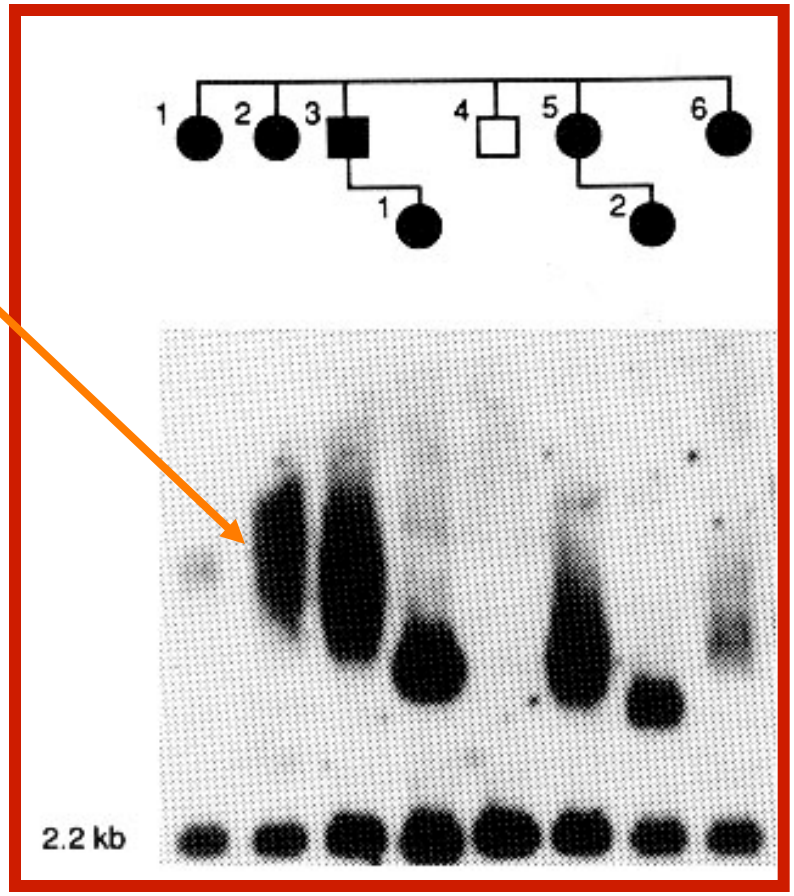
- Most common adult MD
  - 15 cases/100,000
- A.D. high penetrance
- Presents < age 50
- Variable severity & systemic involvement
- Myotonia by EMG!
- Multisystem disease
  - Heart, yes (cataracts), diabetes, TMJ, impotence



Myotonic Dystrophy

Genetics

- 19q13.3 expanded CTG repeat (nl < 35) in non-coding region of DMPK gene
  - Myotonin protein
- 98% of DM cases
- Repeat size correlates with severity
- Congenital form inherited from mother
  - Onset in infancy
  - Death in 25%



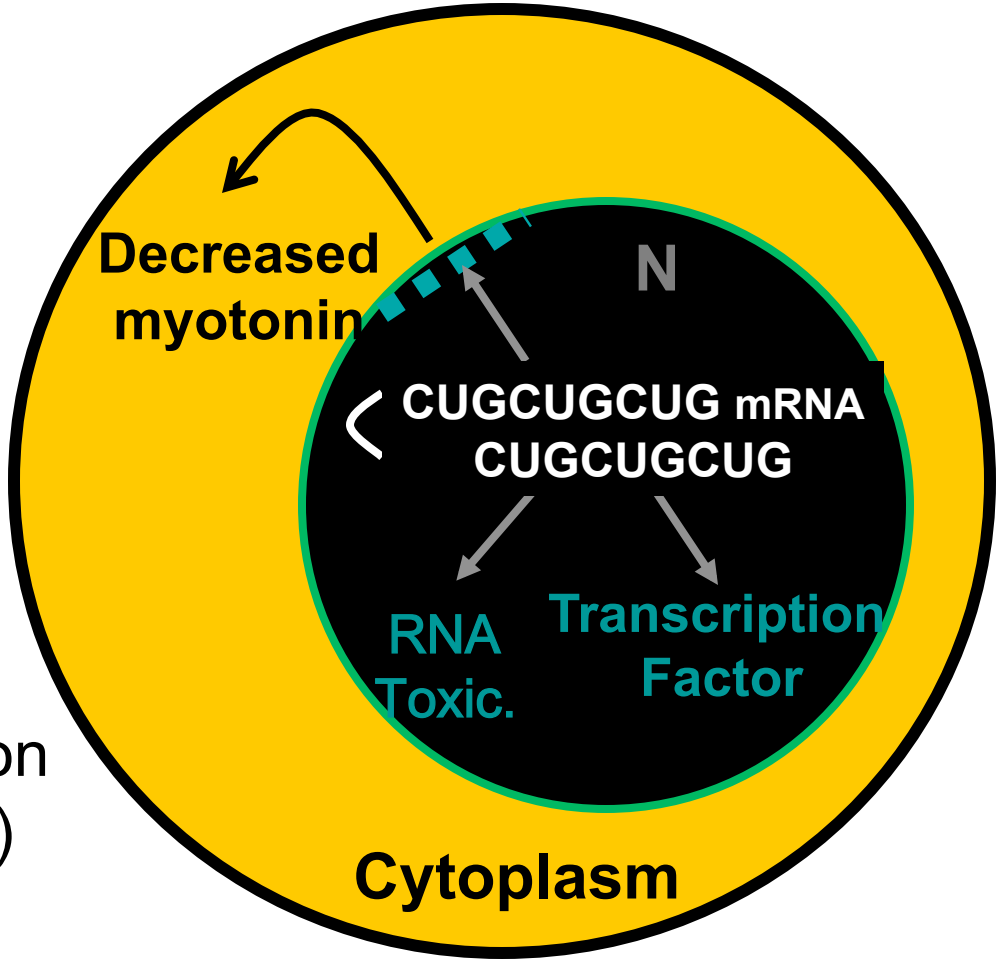
Prior et al, 1995

Myotonic Dystrophy
Genetics

- Repeat size correlates with disease severity
  - Classical disease 100 - 1000 repeats
  - Congenital often > 750
  - Minimal 50-150; “pre-symptomatic” 35-50
- Repeat unstable; true genetic anticipation
- DM2 locus at 3q21 in 2% (90% of PROMM)
  - CCTG repeat in ZNF9 gene (Liquori, 2001)
  - **Both DM tests available commercially**
- Other PROMM, DM3 not linked to either locus

Myotonic Dystrophy
Molecular Pathogenesis

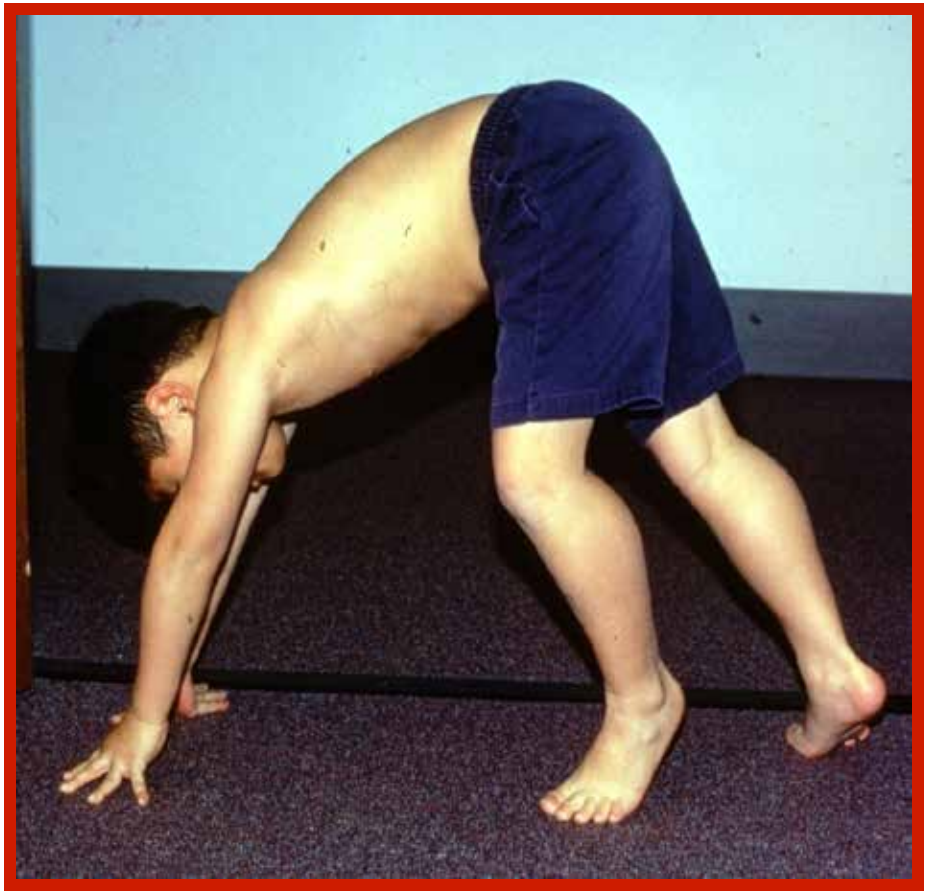
1. Decreased myotonin- (cardiac problems)
2. RNA toxicity– Myopathy, myotonia (dec. Cl^{-1} channels)
3. Binds to transcription factors muscleblind proteins
   Dec. protein expression (eg. SIX 5 – cataracts)



Duchenne Dystrophy

Overview

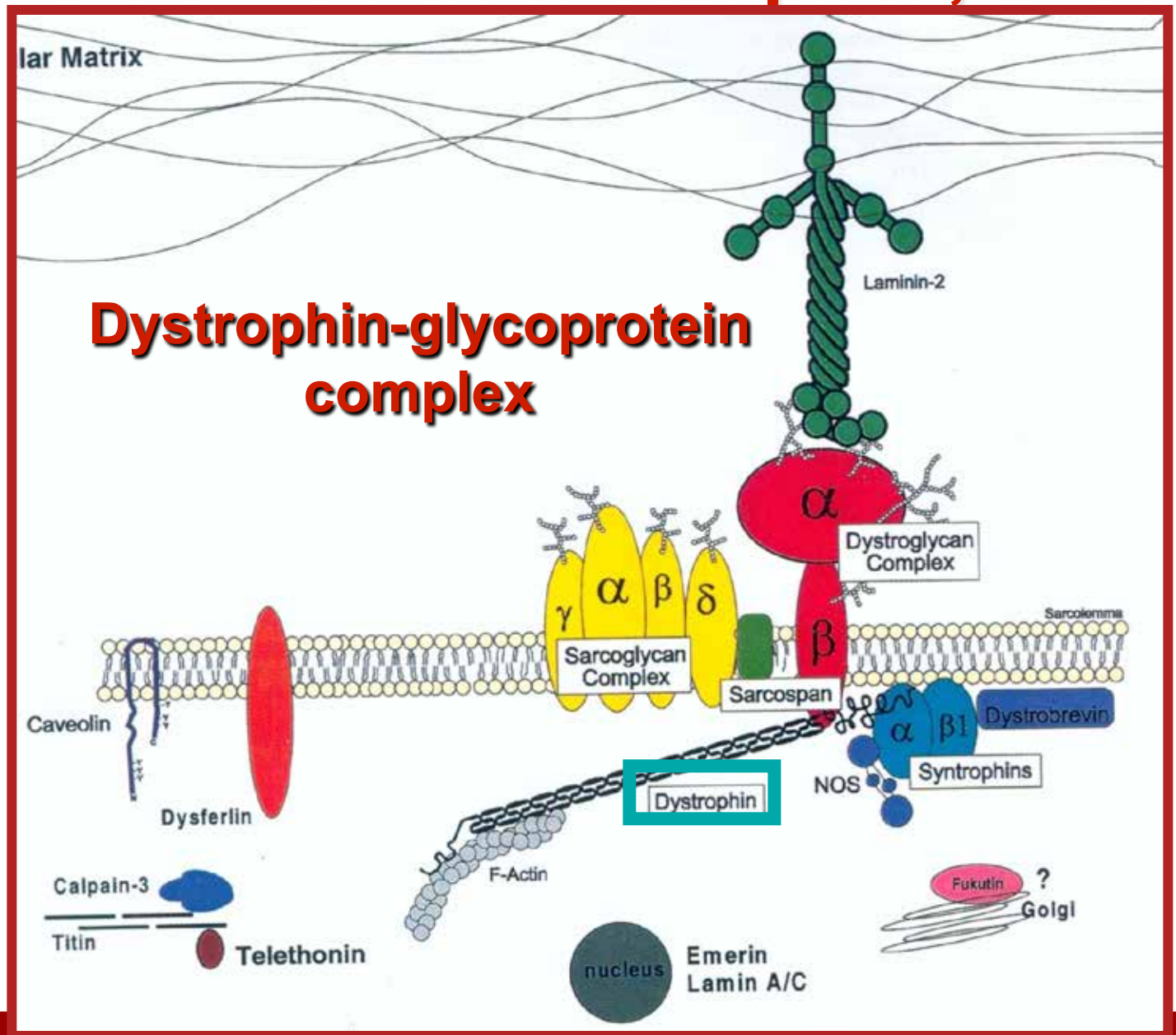
- Most common lethal XLR (1:3500 male births)
- Xp21 dystrophin gene mutation
  - New mut. in 1/3rd
- Usual onset 3-5 years
- Non-ambulatory ~age 12
- No rx: death ~age 20
  - Resp. compromise
  - Cardiomyopathy



Duchenne Dystrophy
Genetics

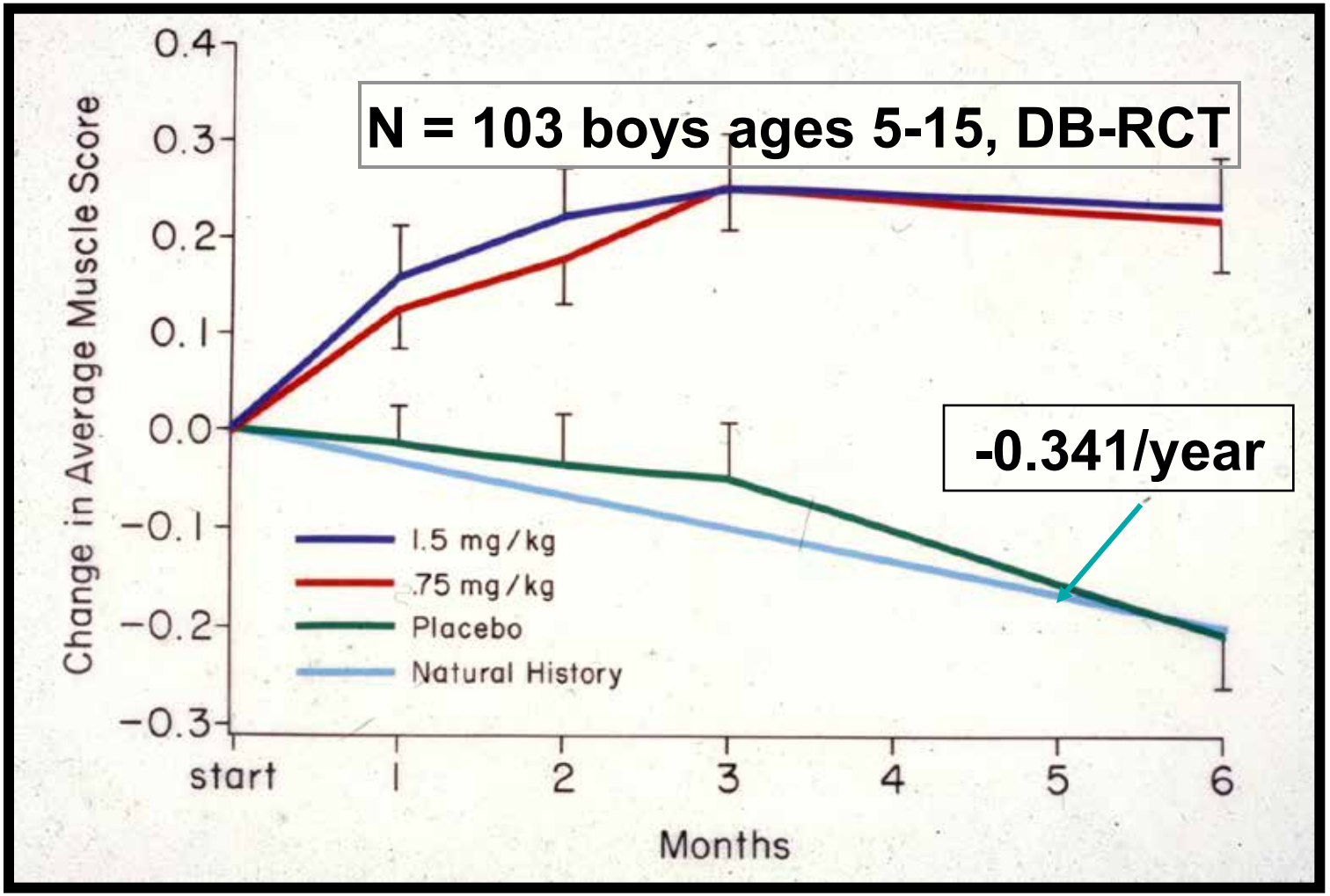
- Involves mutations in Xp21 dystrophin gene
- 70% mutations identified with traditional tests
  - 65% deletions; 5% duplications
- 20-25% point mutations detected
- Tests available commercially

DGC - Cohn & Campbell, 2000



Prednisone Therapy in DMD

Mendell et al (CIDD), NEJM, 1989



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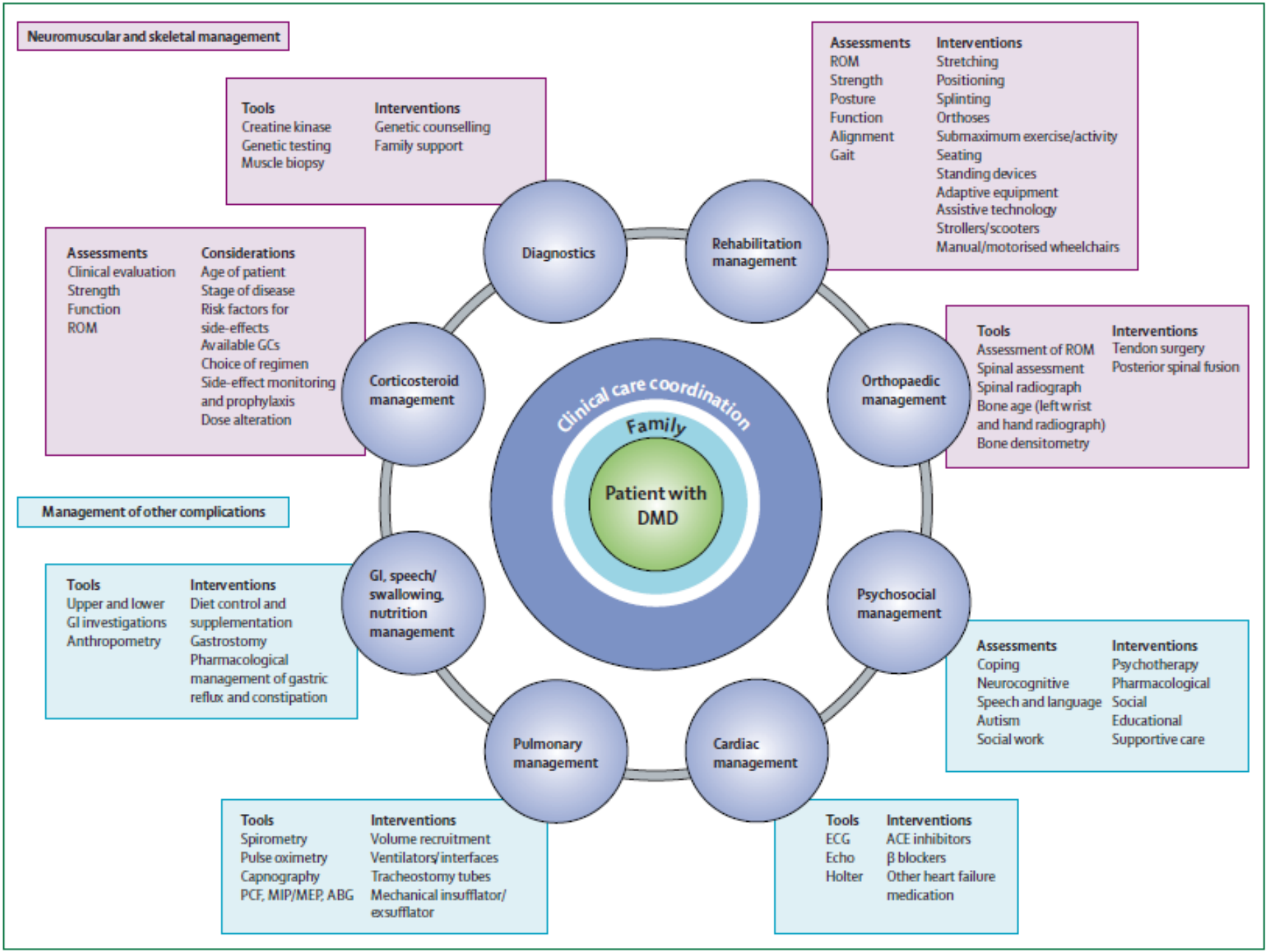
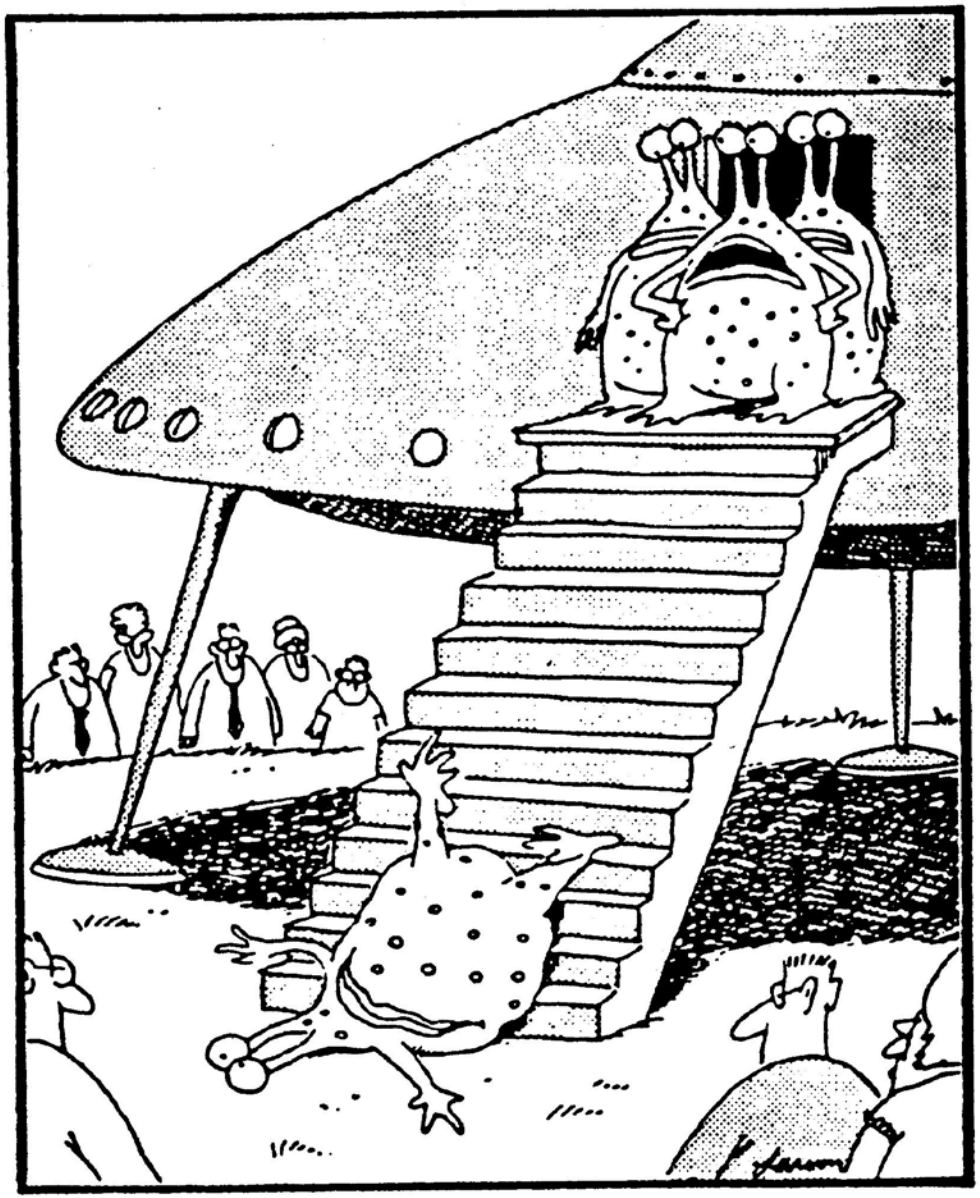

Neuromuscular and skeletal management
Tools
Creatine kinase
Genetic testing
Muscle biopsy
Interventions
Genetic counselling
Family support
Assessments
ROM
Strength
Posture
Function
Alignment
Gait
Interventions
Stretching
Positioning
Splinting
Orthoses
Submaximum exercise/activity
Seating
Standing devices
Adaptive equipment
Assistive technology
Strollers/scooters
Manual/motorised wheelchairs
Assessments
Clinical evaluation
Strength
Function
ROM
Considerations
Age of patient
Stage of disease
Risk factors for side-effects
Available GCs
Choice of regimen
Side-effect monitoring and prophylaxis
Dose alteration
Diagnostics
Rehabilitation management
Corticosteroid management
Orthopaedic management
Clinical care coordination
Family
Patient with DMD
Tools
Assessment of ROM
Spinal assessment
Spinal radiograph
Bone age (left wrist and hand radiograph)
Bone densitometry
Interventions
Tendon surgery
Posterior spinal fusion
Management of other complications
Tools
Upper and lower GI investigations
Anthropometry
Interventions
Diet control and supplementation
Gastrostomy
Pharmacological management of gastric reflux and constipation
GI, speech/ swallowing, nutrition management
Psychosocial management
Assessments
Coping
Neurocognitive
Speech and language
Autism
Social work
Interventions
Psychotherapy
Pharmacological
Social
Educational
Supportive care
Pulmonary management
Cardiac management
Tools
Spirometry
Pulse oximetry
Capnography
PCF, MIP/MEP, ABG
Interventions
Volume recruitment
Ventilators/interfaces
Tracheostomy tubes
Mechanical insufflator/ exsufflator
Tools
ECG
Echo
Holter
Interventions
ACE inhibitors
β blockers
Other heart failure medication

Final Word

- All are welcome to come to clinic
  - john.kissel@osumc.edu
- Pertinent references
  - Neuromuscular Disorders – Amato & Russell
  - Neuromuscular Home Page at Wash U.
    - http://neuromuscular.wustl.edu/
- Thanks to Wendy King, David Arnold, Victoria Lawson, Miriam Freimer, Joanne Lynn for slides!

Clinical NM Group

Including Barnacle Kolb



"Wonderful! Just wonderful!...So much for instilling them with a sense of awe"

Thank you for your attention!