General clinical aspects of muscle disease

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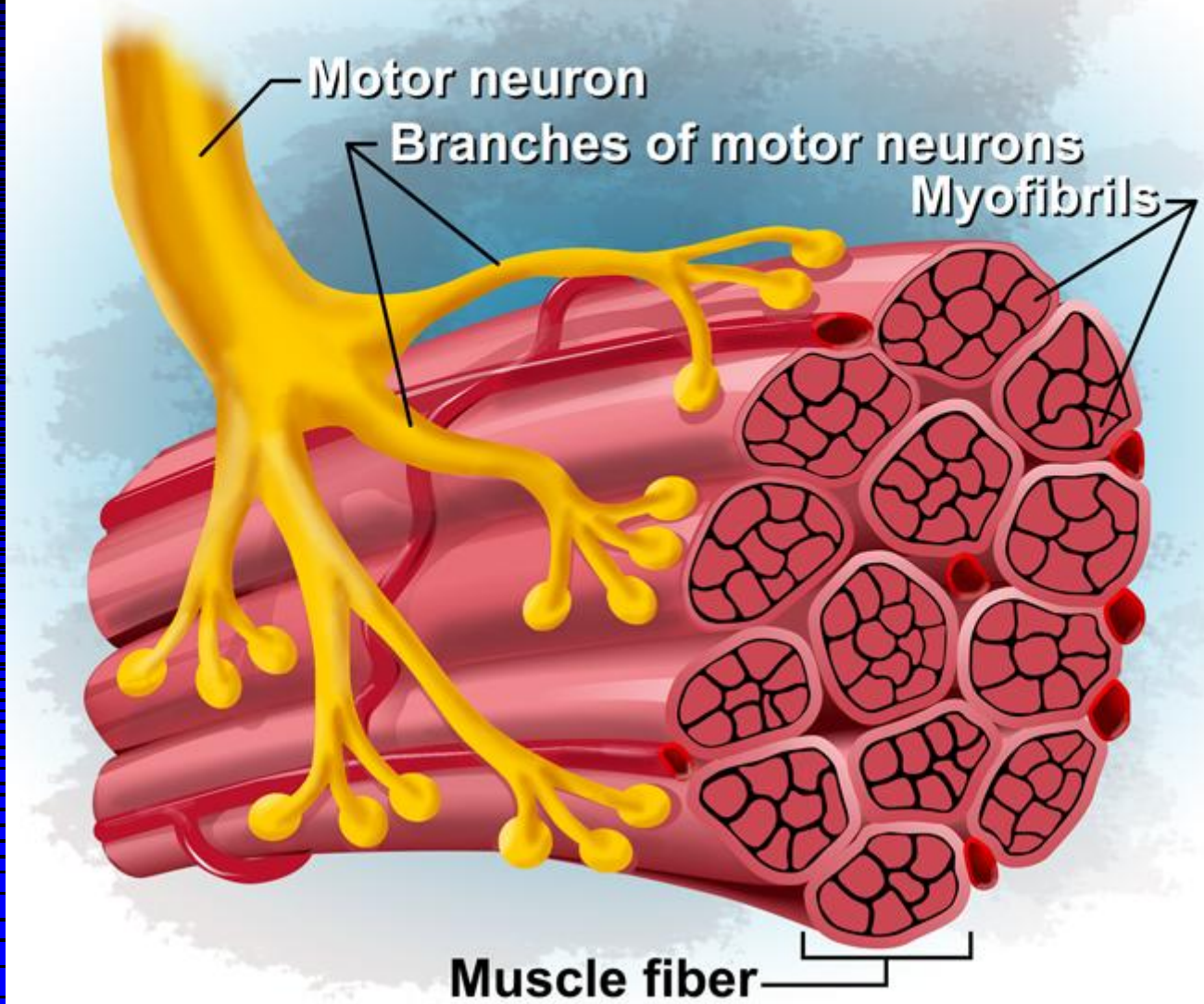
The Motor Unit



General clinical aspects of muscle disease

- Neuromuscular junction disorders
- Muscle fibre disorders

What the adult generalist will see

- Myasthenia gravis
- Myotonic dystrophy
- Myositis
- (Mitochondrial disorders)
- Facioscapulohumeral muscular dystrophy (FSH)

What the adult generalist might worry about

- Metabolic myopathy
- Fatigue syndromes
- Muscle pain syndromes

Symptoms and Signs of muscle disease

- Symptoms = History
- Signs = Examination
- Mutually related

Symptoms and Signs of muscle disease

- Very limited
- Chronology

Symptoms

- Weakness
  - Pattern
  - Chronology
- Pain
- Cramps and contractures
- Fatigue
- Wasting or hypertrophy

Symptoms of weakness

- Facial
  - Often none
  - Eye closure in sleep
  - Balloons/whistle/smile
- Eyes
  - Diplopia
  - Ptosis
  - Head turning
- Neck
  - Lifting head off pillow
- Shoulder girdle
  - Activities above shoulder height
  - Grooming
- Pelvic girdle
  - Stairs/chairs/running
- Ventilatory muscles
  - Symptoms of hypoventilation

Weakness

- Progressive
  - Slowly
    - Many muscle diseases
  - Rapidly
    - Myositis
    - Rhabdomyolysis (e.g. metabolic myopathies, drugs)
    - Myasthenia

Weakness

- Variable
  - Myasthenia/myasthenic syndromes
- Episodic
  - Metabolic myopathies
  - Periodic paralysis

Pain

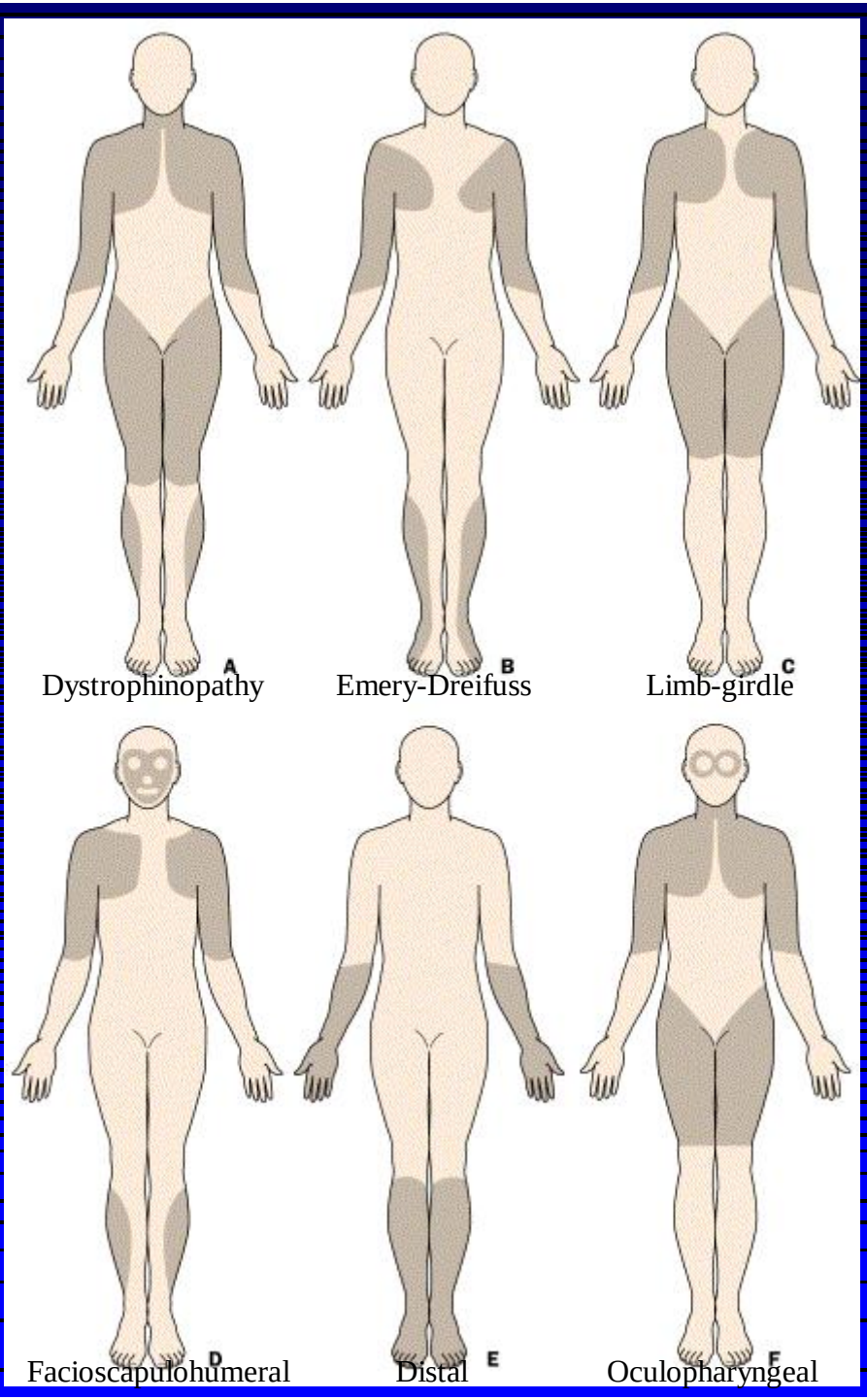
- At rest
- “Non-specific”
  - Musculoskeletal (e.g. FSH)
  - Low back pain (e.g. FSH)
  - Hip & knee
- On exercise
  - Metabolic myopathies
  - Dermatomyositis
- Cramps
  - = neurogenic

Examination

- Atrophy/hypertrophy
- Pattern of weakness
- Reflexes and sensation
- Additional phenomenon
  - Myotonia
  - Rippling muscle

Alan Emery

Lancet 2002



Dystrophinopathy Emery-Dreifuss Limb-girdle

Facioscapulohumeral Distal Oculopharyngeal

Investigations

- Serum creatine kinase
- Electromyography
- Imaging
- DNA
- Specific biochemistry

Overview of muscle disorders

- Neuromuscular junction disorders
- Myopathies

Neuromuscular junction disorders

- Myasthenia gravis
- Lambert Eaton myasthenic syndrome
- Peripheral nerve hyperexcitability syndromes ("neuromyotonia")
- Congenital myasthenia

Myasthenia gravis

- Prevalence 1:10,000
- Antibody mediated
  - Anti-acetylcholine receptor
  - Anti-MuSK
  - Rare other antigens/unknown
  - Neonatal MG, response to therapy
- 75% ocular onset
- 10-20% remain ocular
- 10% thymoma (AChR positive)

MG
Cardinal features

- Fatiguability = variability

MG
Cardinal features

- Ocular
- Bulbar
- Neck
- Proximal limb
- Fingers

Lambert Eaton syndrome

- 50% cancer-associated (SCLC)
- Anti-voltage-gated calcium channel antibodies
- Ocular features rare
- Proximal weakness (lower limbs)
- Autonomic symptoms
- Reflexes

Peripheral nerve hyperexcitability

- Autoimmune
  - Anti-voltage gated potassium channel
  - Muscle twitching and cramping
  - +/- CNS involvement (Morvan)
- More common
  - Cramp/fasciculation syndrome (twitching toes)
  - Responds to “anti-convulsants)

Congenital myasthenia

- Pre-, synaptic, and post-synaptic syndromes
- Very rare
- Ocular onset common, but some limb -girdle
- Rare adult presentations
  - Slow-channel syndrome (neck + finger extensors) – autosomal dominant

Myopathies

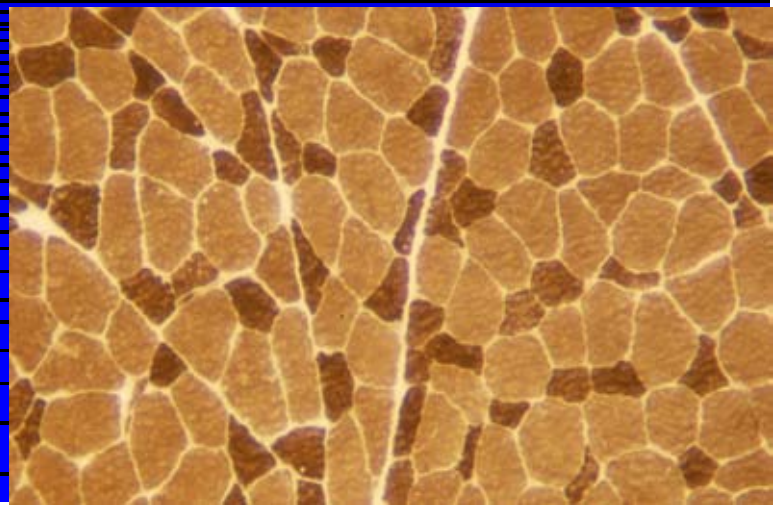
- Acquired
- Inherited

Acquired Myopathies

- Endocrinopathies
- Drug-induced
- Idiopathic inflammatory myopathies
- Metabolic myopathies
- Infection

Endocrinopathies

- Rarely the presenting feature
- Often present on examination
- Always recovers when the endocrinopathy does
- Serum CK often normal (except hypothyroidism)
- EMG – “myopathic”
- Biopsy – type 2 fibre atrophy



Drug-induced

- Asymptomatic hyperCKemia
- Myalgia
- Acute rhabdomyolysis
- Acute quadriplegic myopathy
- Chronic proximal myopathy
- Mitochondrial myopathy
- Dyskalemic myopathy
- Focal myopathies

Idiopathic inflammatory myopathies

- Polymyositis
- Dermatomyositis
- Inclusion body myositis (IBM)

Idiopathic inflammatory myopathies

- Polymyositis
  - Cell-mediated/cytotoxic
- Dermatomyositis
  - Humoral/antibody mediated

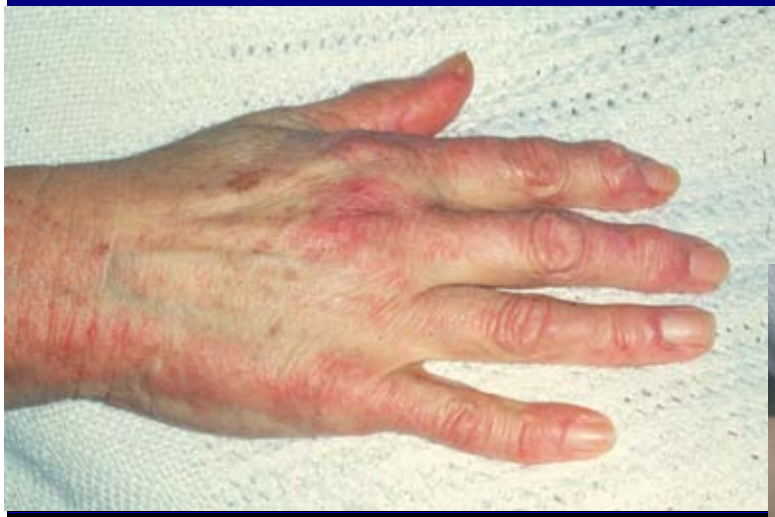
Myositis

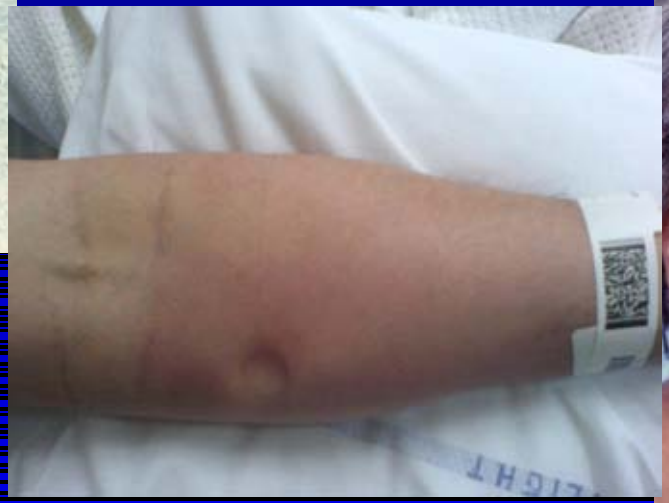
- “Pure” polymyositis rare
  - Frequently associated with CTD
- Dermatomyositis
  - Rash may be absent
  - Confusing overlap with “Anti-synthetase” syndrome

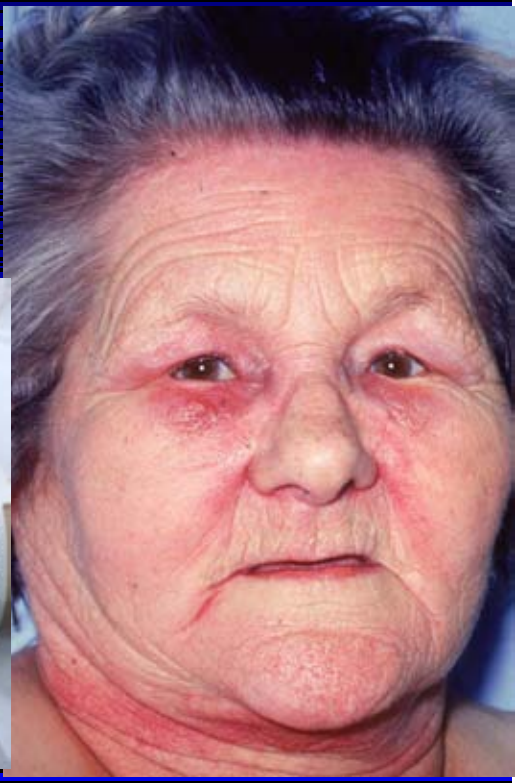
Clinical features of Myositis

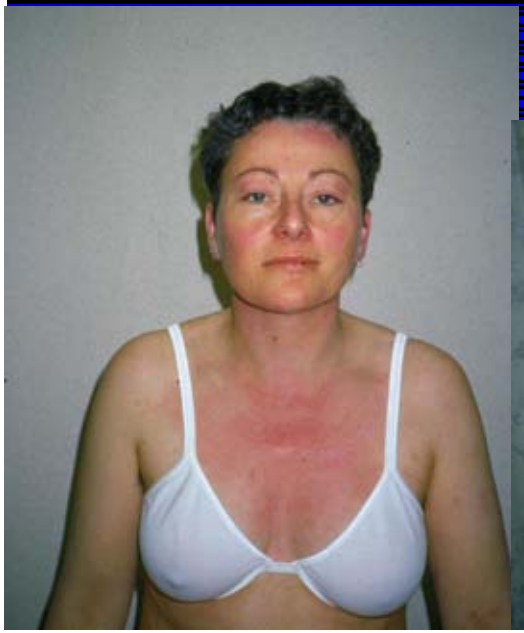
- Proximal weakness
  - Acute/subacute in DM
  - Chronic in PM
- Skin involvement in DM
- Elevated CK
- Myopathic/"irritable" EMG

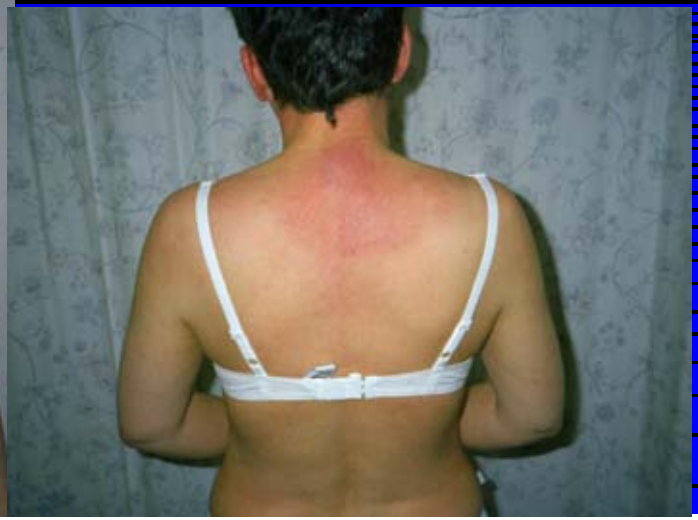
Dermatomyositis

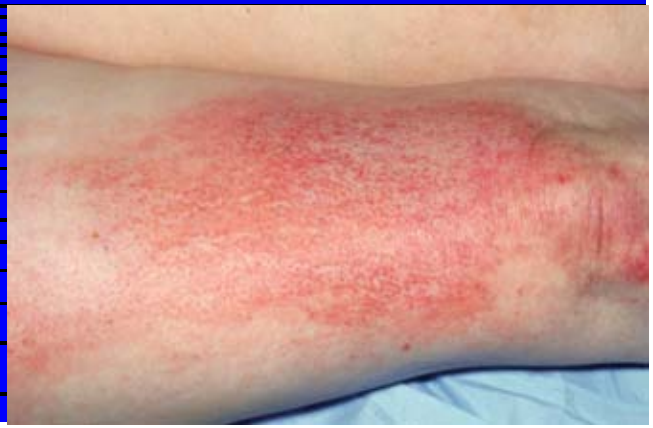












Cancer and Myositis

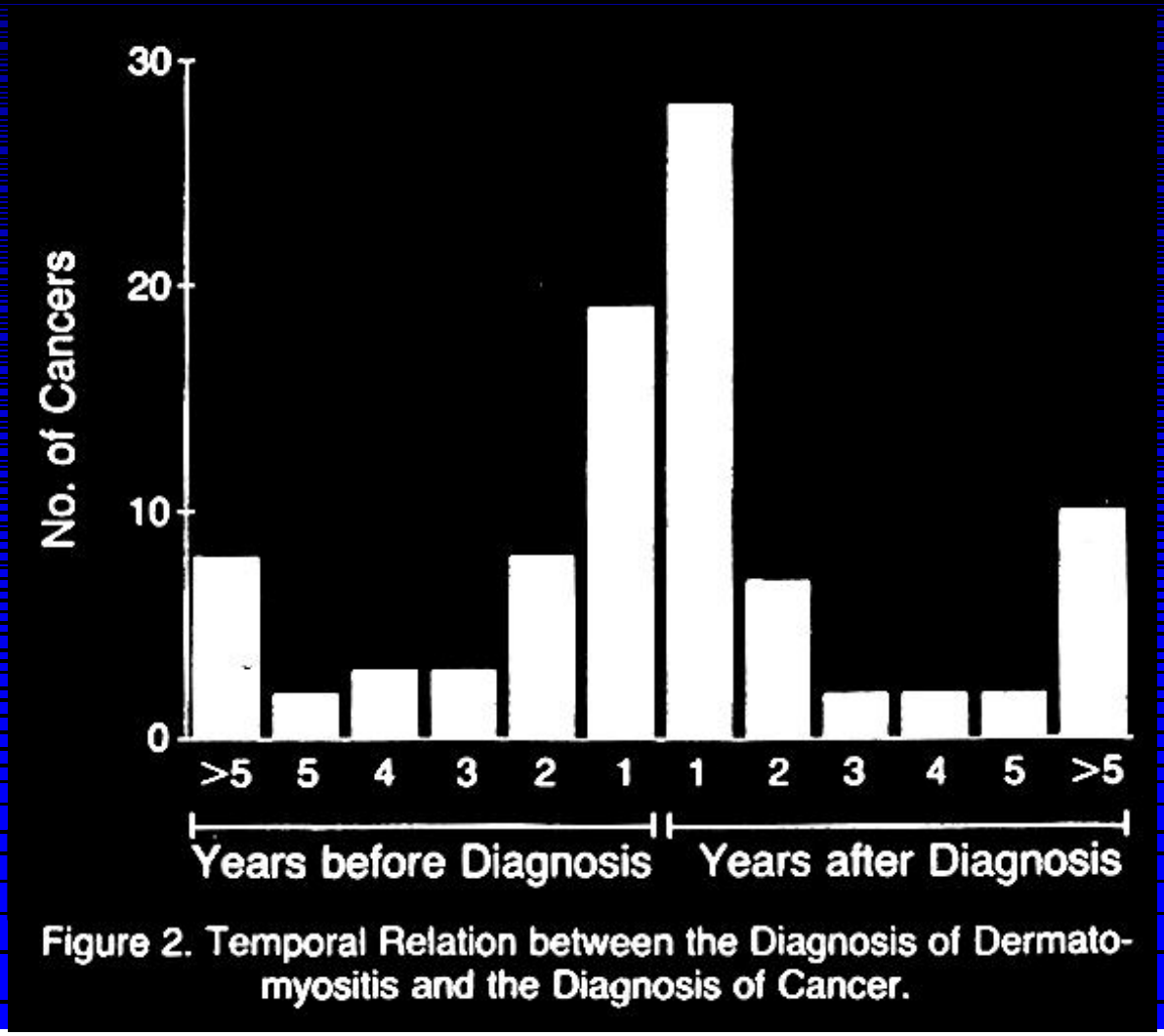


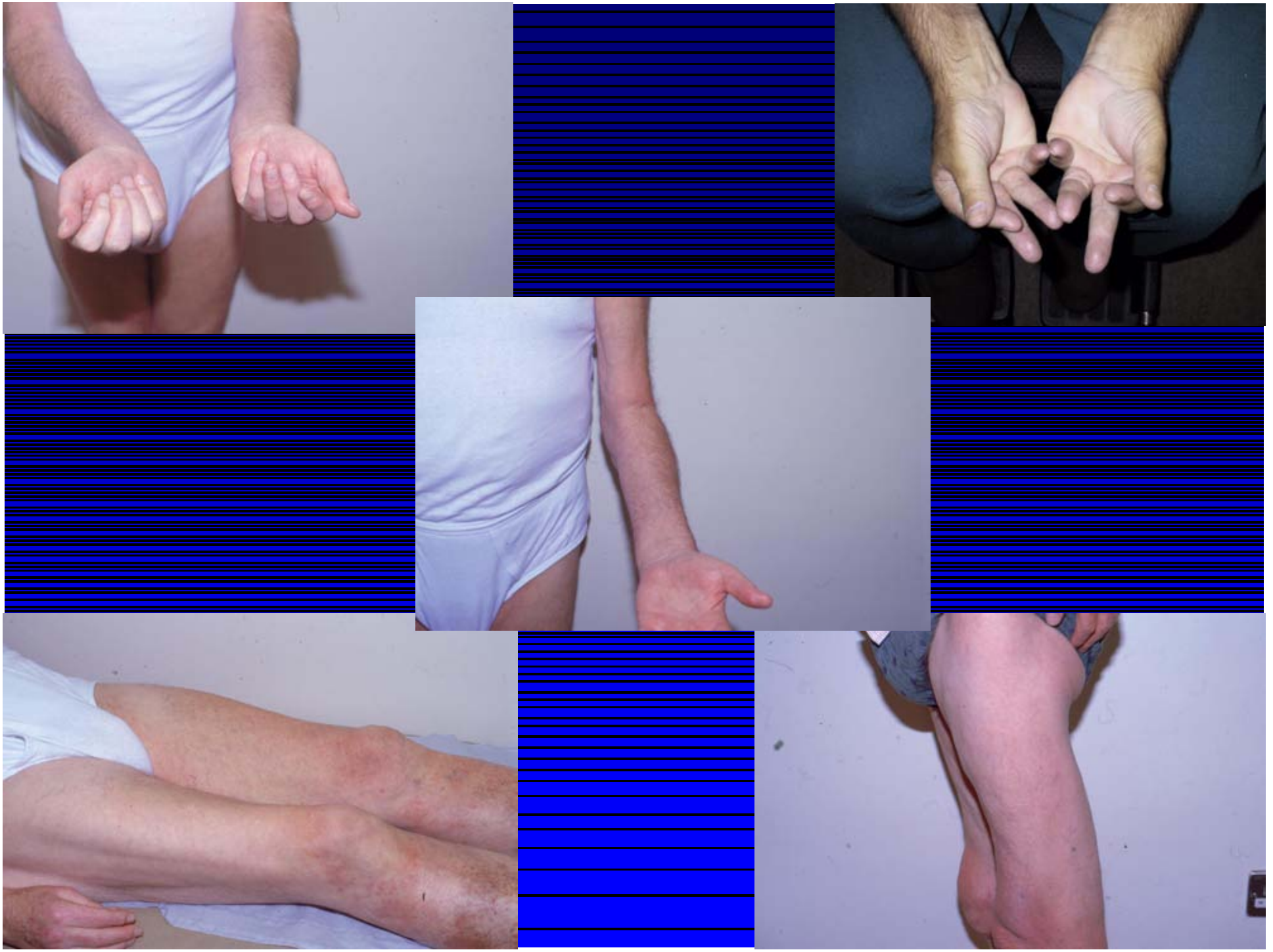
Figure 2. Temporal Relation between the Diagnosis of Dermatomyositis and the Diagnosis of Cancer.

Inclusion body myositis

- Commonest myopathy in the >50 yrs
- Males > females
- Aetiology uncertain
  - Some features of cell-mediated autoimmunity
  - But responds poorly, if at all, to immunosuppression
- Characteristic clinical features

Inclusion body myositis

- Quadriceps weakness
- Finger flexion weakness (ankle)
- Dysphagia



Inherited Myopathies

- Muscular dystrophies
- Myotonic dystrophy
- Metabolic myopathies
- Channelopathies

Muscular Dystrophies

- Definition/nomenclature???
- Primary disorder of muscle
- Genetic
- Progressive
- Degenerative
- Malfunction of a protein essential for normal muscle function

Classification

- X-linked
  - Duchenne DMD
  - Becker BMD
  - Emery-Dreifuss XREDMD

Classification

- Autosomal recessive
  - Limb-girdle — LGMD 2
  - Emery-Dreifuss — AREDMD
- Autosomal dominant
  - Limb-girdle — LGMD 1
  - Facioscapulohumeral — FSH
  - Oculopharyngeal — OPMD
  - Emery-Dreifuss — ADEDMD

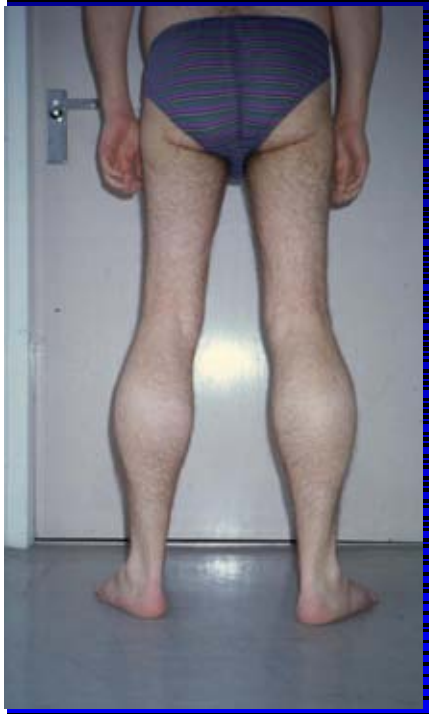
Muscular dystrophies
Main clinical characteristics

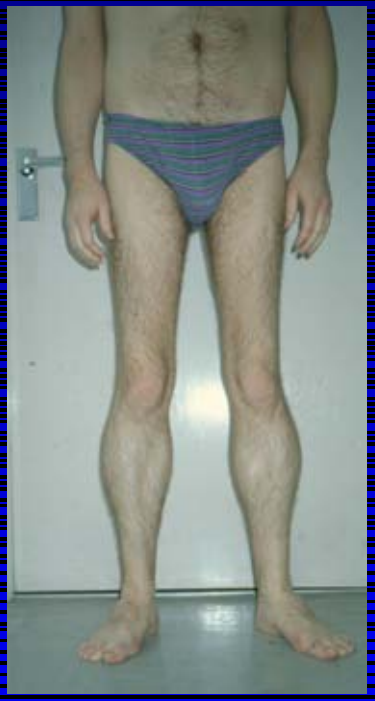
- Age of onset
- Distribution of weakness

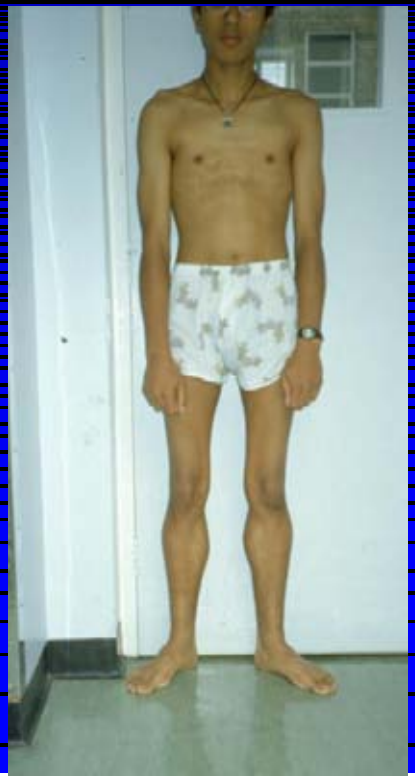
Muscular dystrophies
Main clinical characteristics

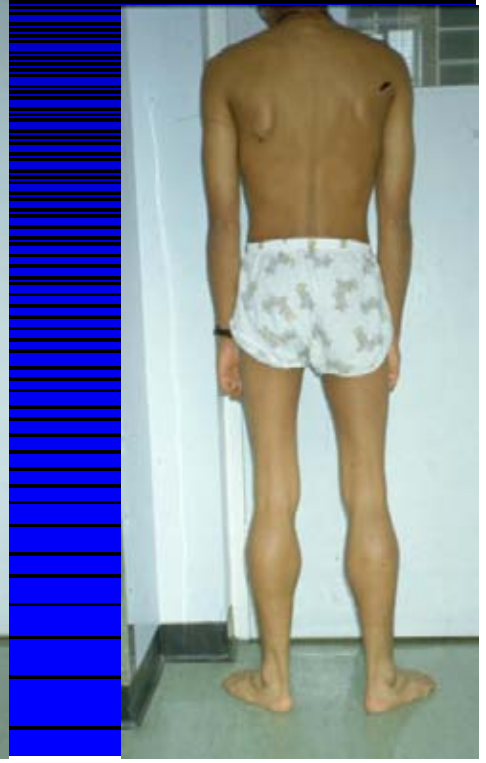
- Age of onset
- Distribution of weakness
  - Limb-girdle
    - Duchenne & Becker
  - Facioscapulohumeral
  - Oculopharyngeal

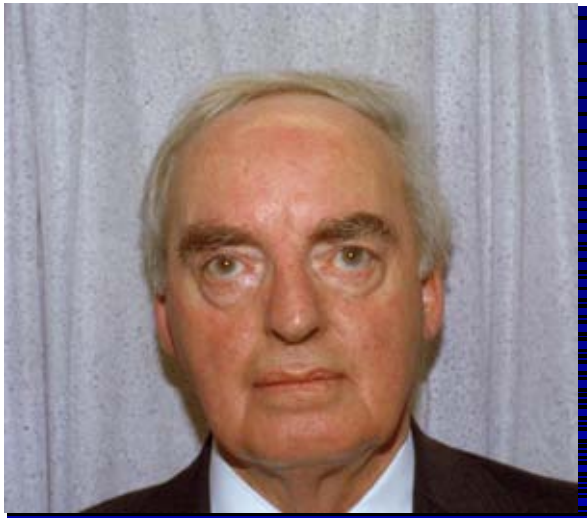
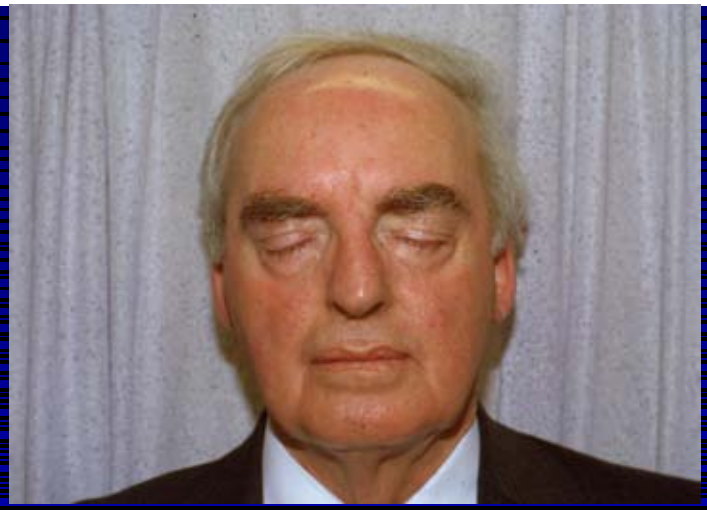
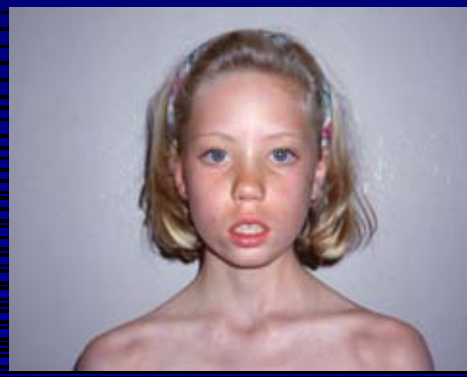
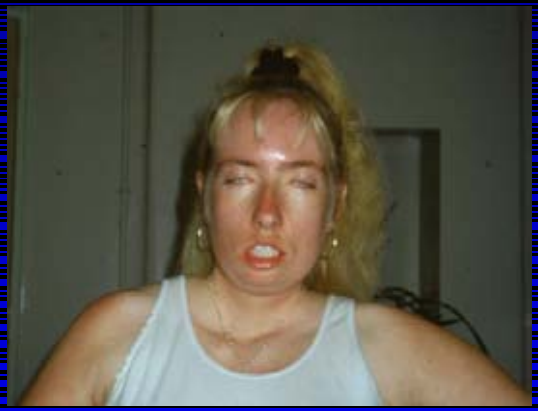
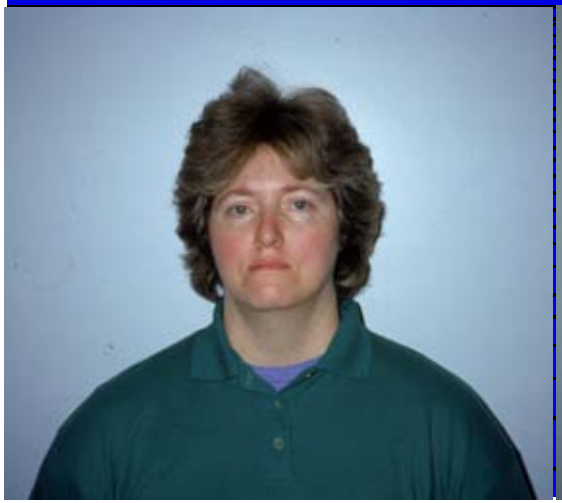
Becker MD

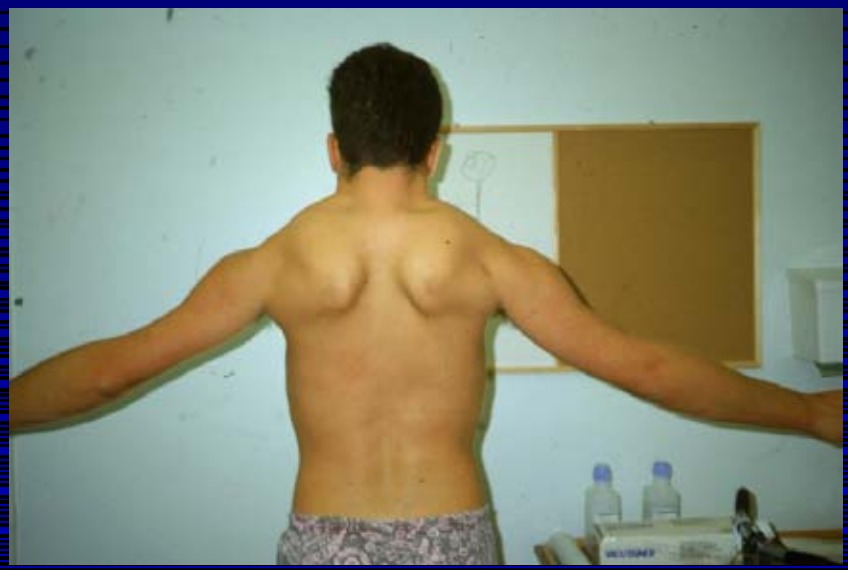


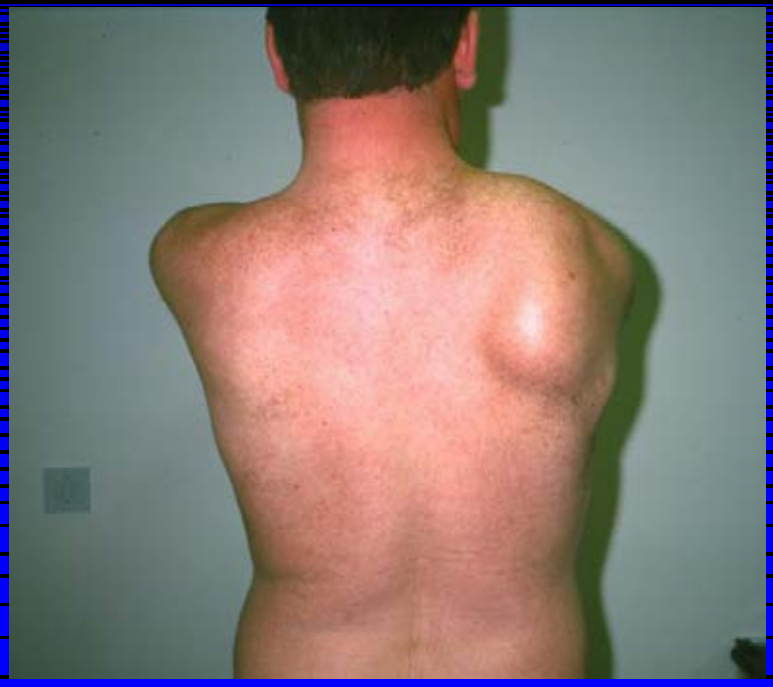


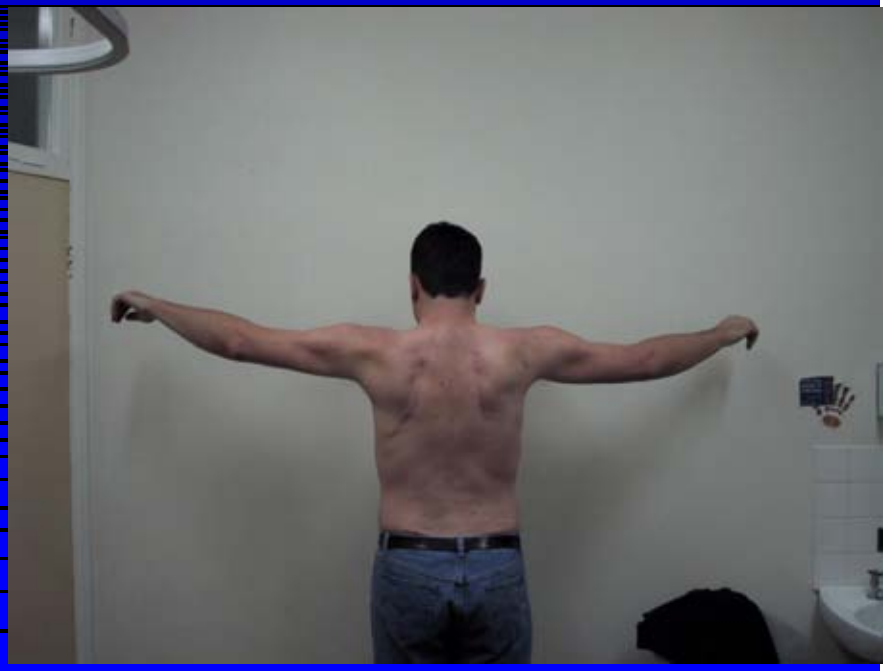










Myotonic Dystrophy Type 1

- Unstable trinucleotide repeat in DMPK
- Disorder of mRNA metabolism
- Aberrant/altered splicing of other genes
  - CLCN1 Myotonia
  - Insulin receptor IR

Myotonic Dystrophy Type 1

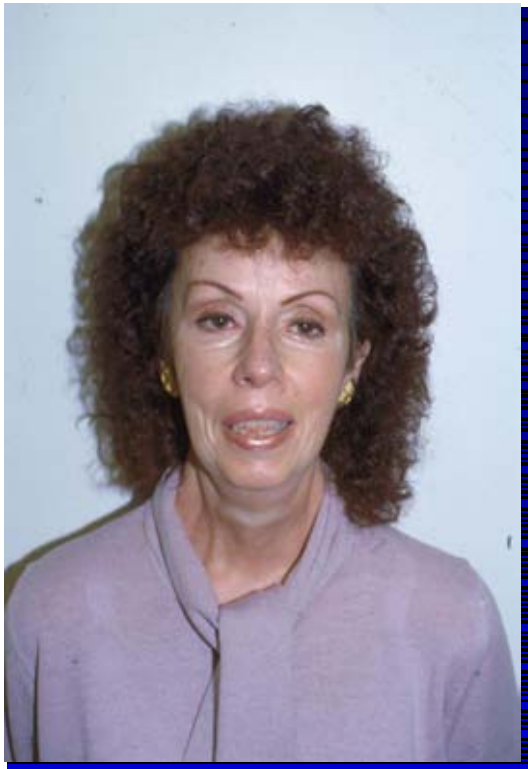
- Autosomal dominant
- Anticipation
- Multisystem disorder
  - Skeletal muscle
  - Smooth muscle
  - Brain
  - Heart
  - Lens
  - Endocrine system

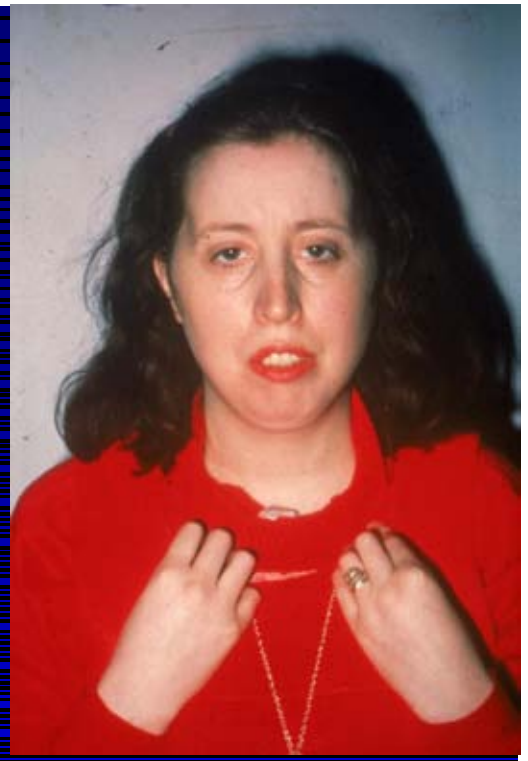
Myotonic Dystrophy Type 1

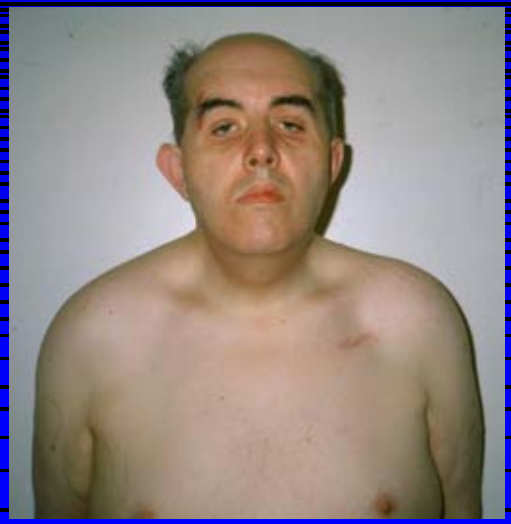
- Congenital
- Childhood-onset
- Classical adult
- Late-onset, asymptomatic

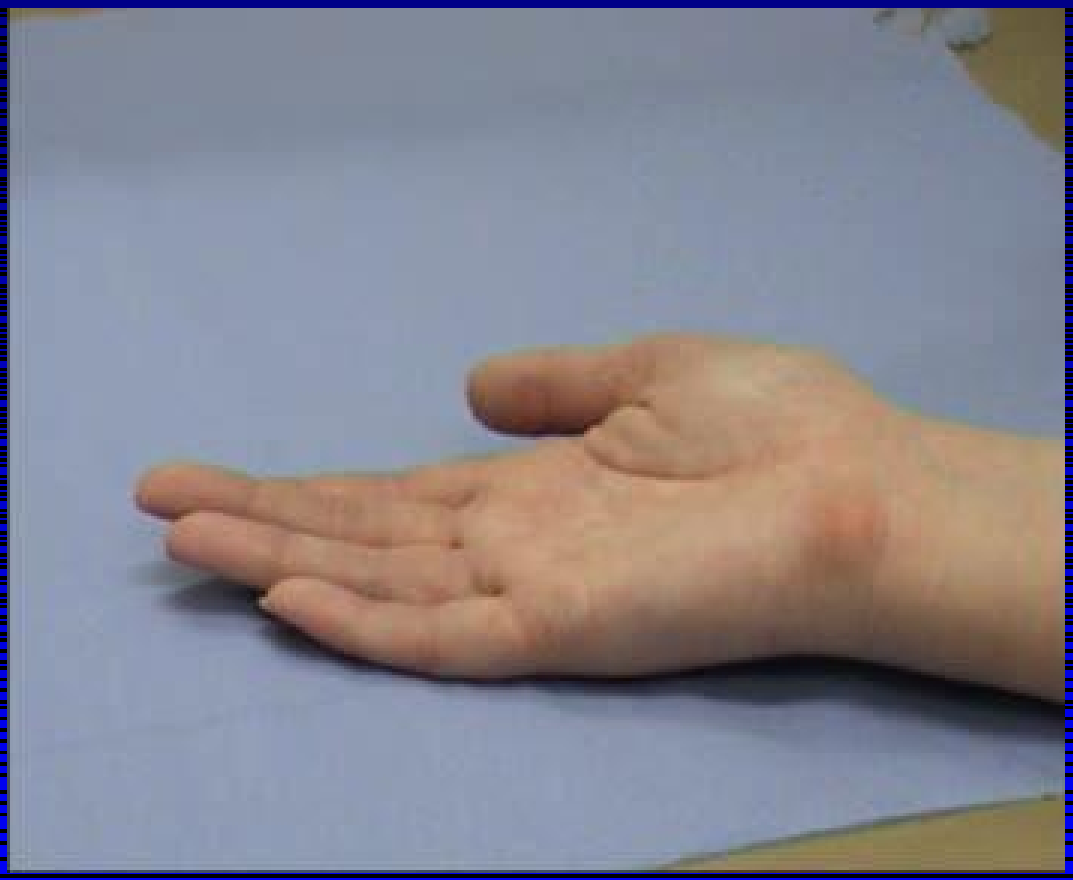
Adult form

- Onset in adolescence/early adult life
- Weakness
  - Facial
  - Neck
  - Distal limb
- Myotonia
- CNS involvement
  - Excessive daytime sleepiness
- Cardiac conduction problems



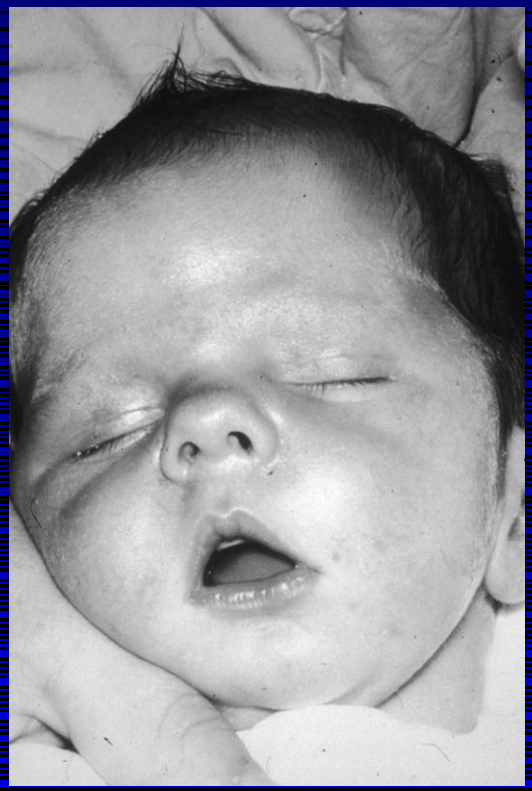


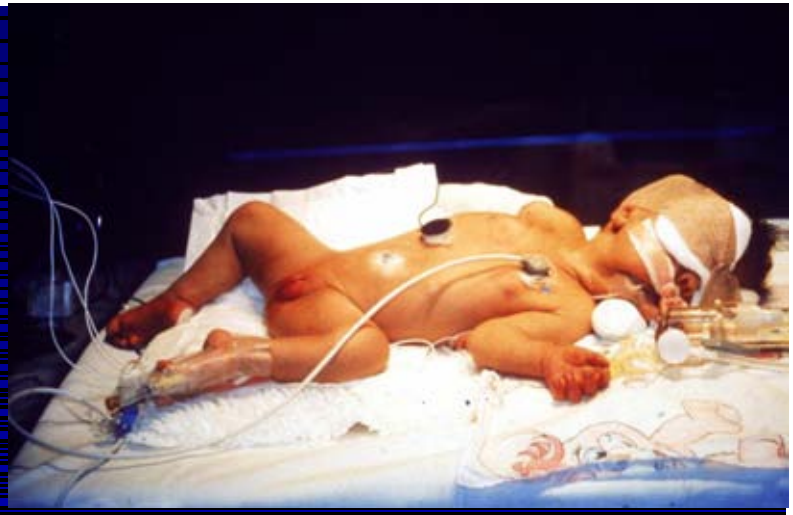


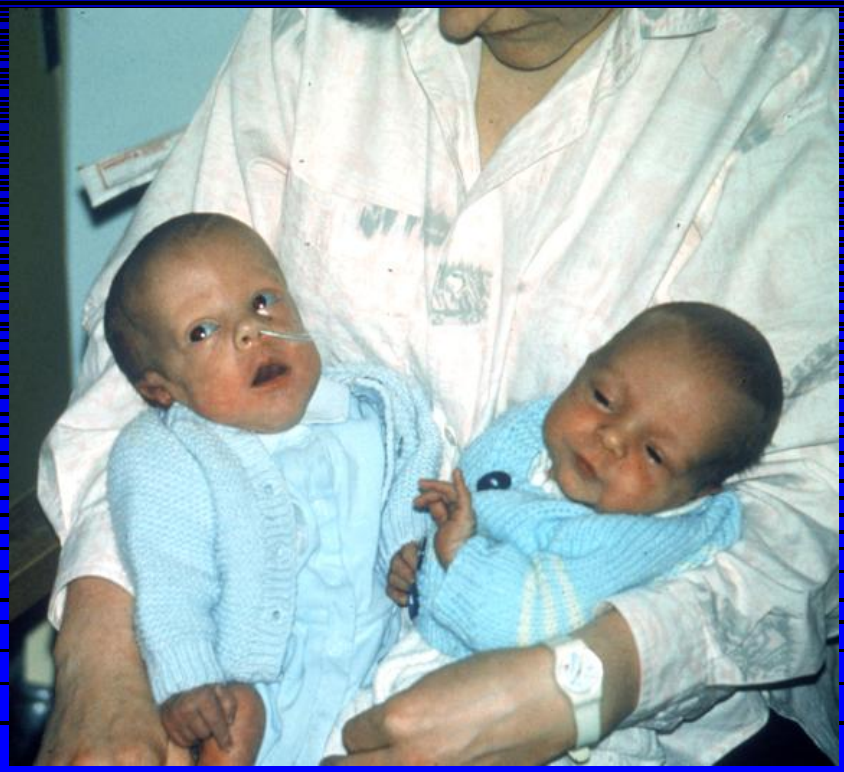


Congenital myotonic dystrophy

- Floppy baby
- Feeding and respiratory difficulties

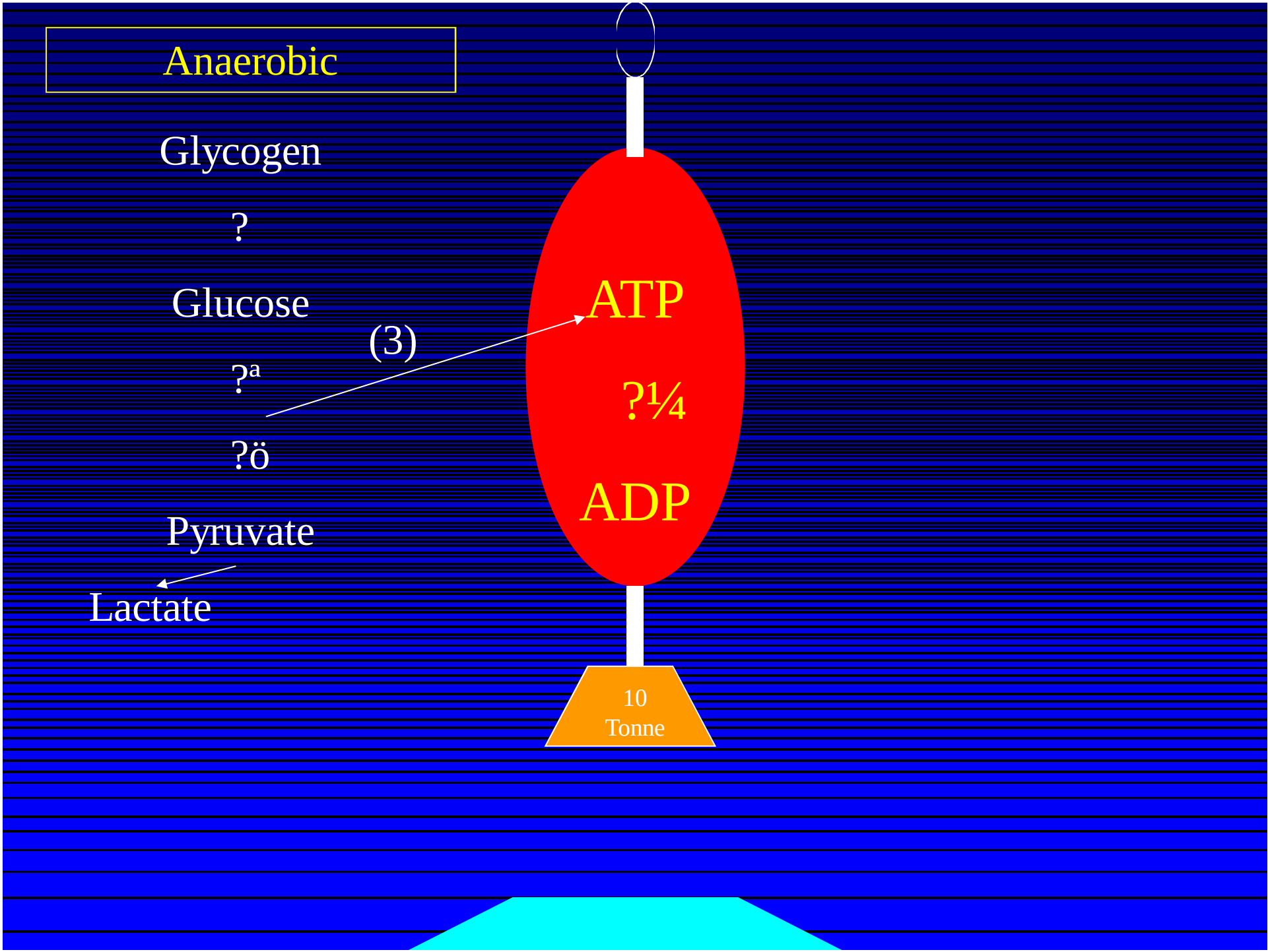






Metabolic myopathies

- Disordered carbohydrate metabolism
- Disordered lipid metabolism
- Mitochondrial disorders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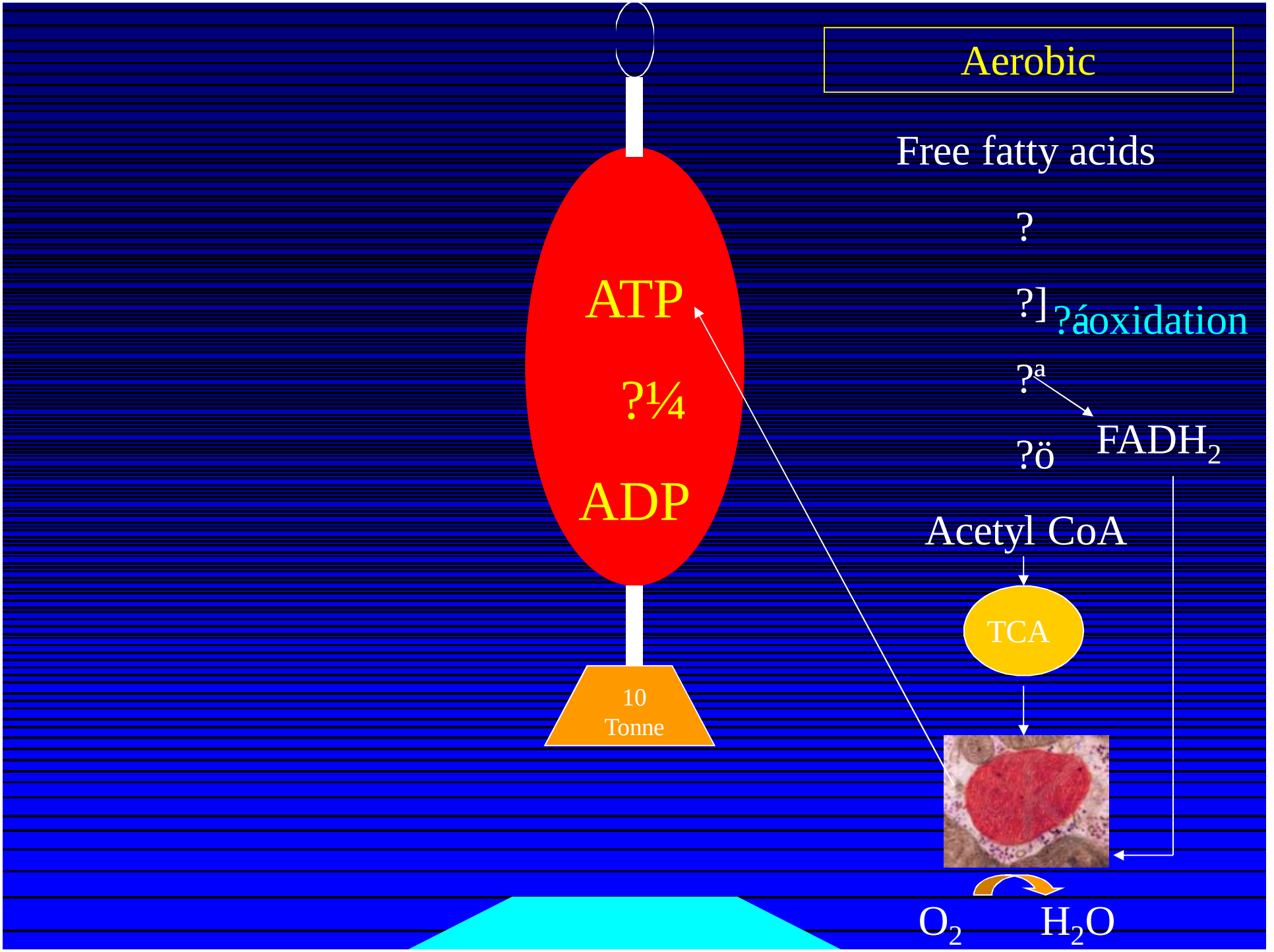
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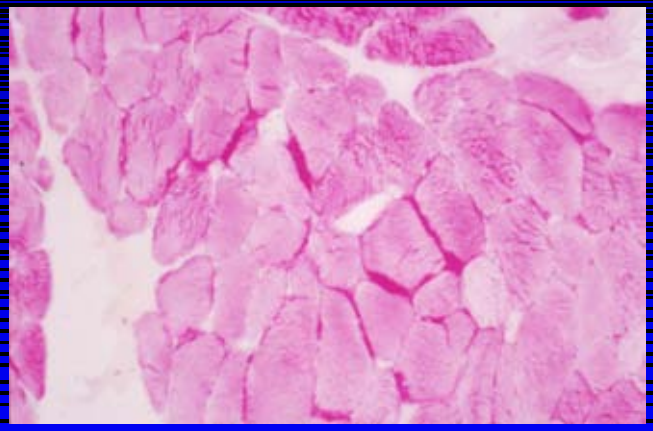
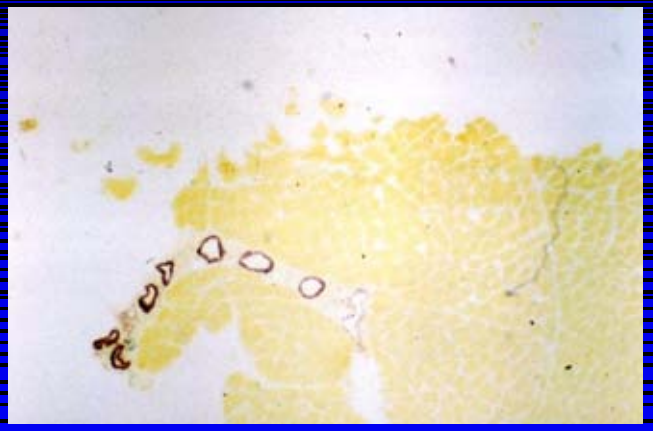
Fatigue in Metabolic Myopathies
Early

- Glycogenoses
  - Myophosphorylase deficiency (McArdle's)



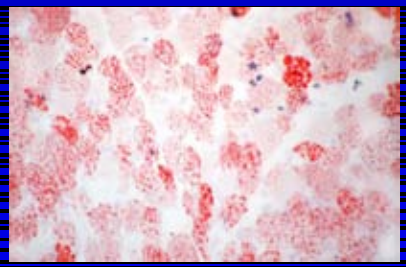


  - Phosphofructokinase deficiency
  - Other glycogenoses

Fatigue in Metabolic Myopathies

Late

- Disorders of fatty acid transport
  - Carnitine palmitoyltransferase deficiency



- Disorders of fatty acid ?-oxidation
  - Very long-chain acyl CoA dehydrogenase deficiency

(Exacerbated by fasting)

An exception

- Acid maltase deficiency
  - Lysosomal enzyme
  - Not related to energetics

Acid maltase deficiency
Pompe

- Neonatal onset
- Adult onset
  - Limb-girdle syndrome
  - Diaphragmatic involvement

Channelopathies

- Periodic paralysis
  - Sodium (hyperkalemic PP)
  - Calcium (hypokalemic)
- Malignant hyperthermia
- Myotonia congenita

Myotonia congenita

- Autosomal dominant (Thomsen) or recessive (Becker)
- CLCN1
- Myotonia without permanent weakness

Muscle pain/fatigue syndromes

- Pain on exercise suggestive of metabolic myopathy – timing crucial
- Resting muscle pain rarely due to muscle disease
- If examination, sCK and EMG normal muscle biopsy not helpful

Management issues

- Immunosuppression
- Respiratory
  - NIV
  - Cough-assist
- Cardiac
  - Pacemaker
  - ICD
- Symptomatic
  - Anticonvulsants
  - Anti-myotonic
  - Modafinil
  - Diuretics

Conclusions

- History, history, history
- Examination
  - Pattern of weakness
- Short differential diagnosis
  - Selective investigation

(Tea break)