MYOPATHIES

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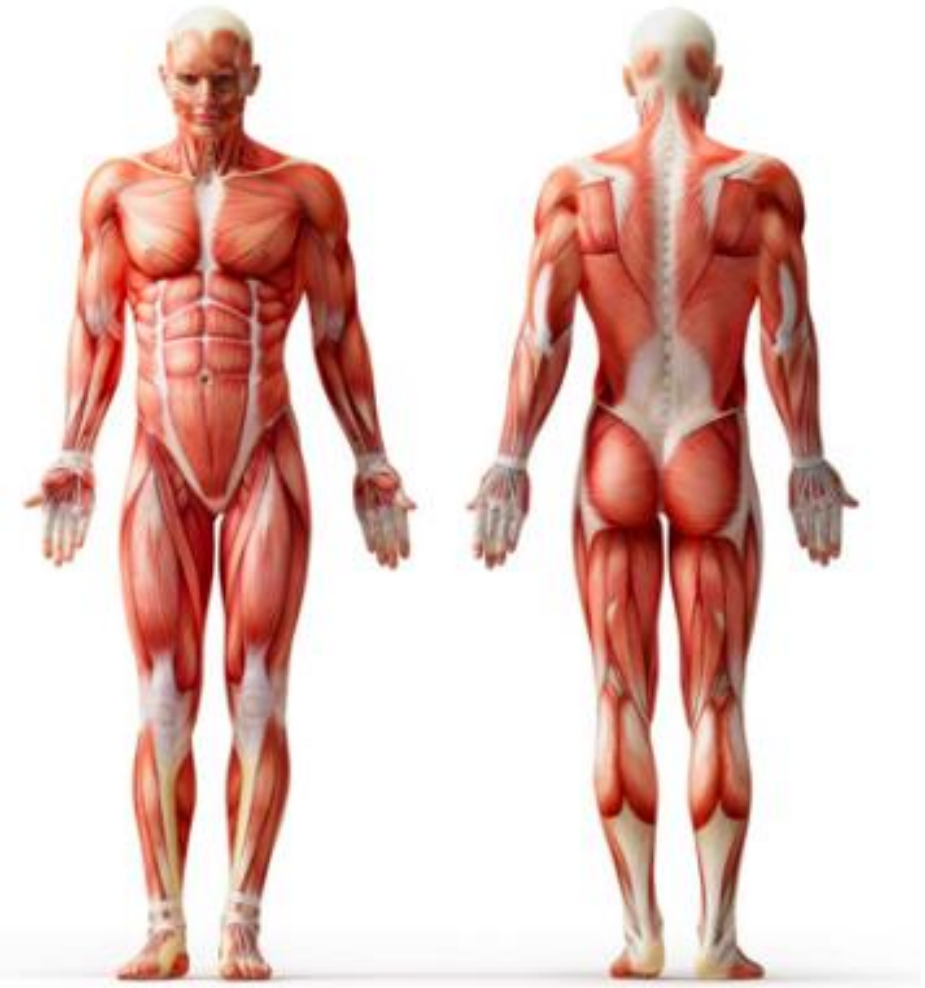
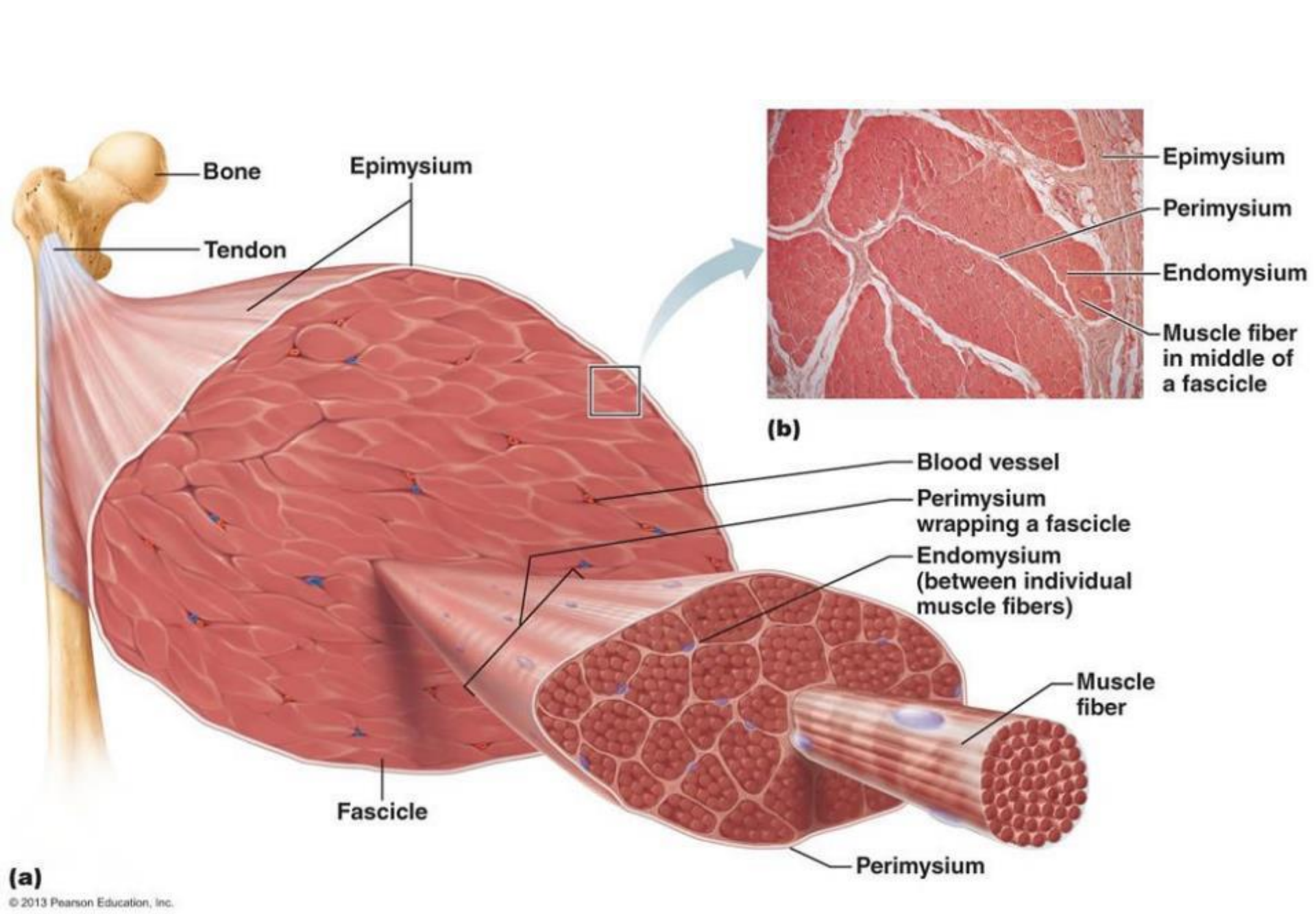
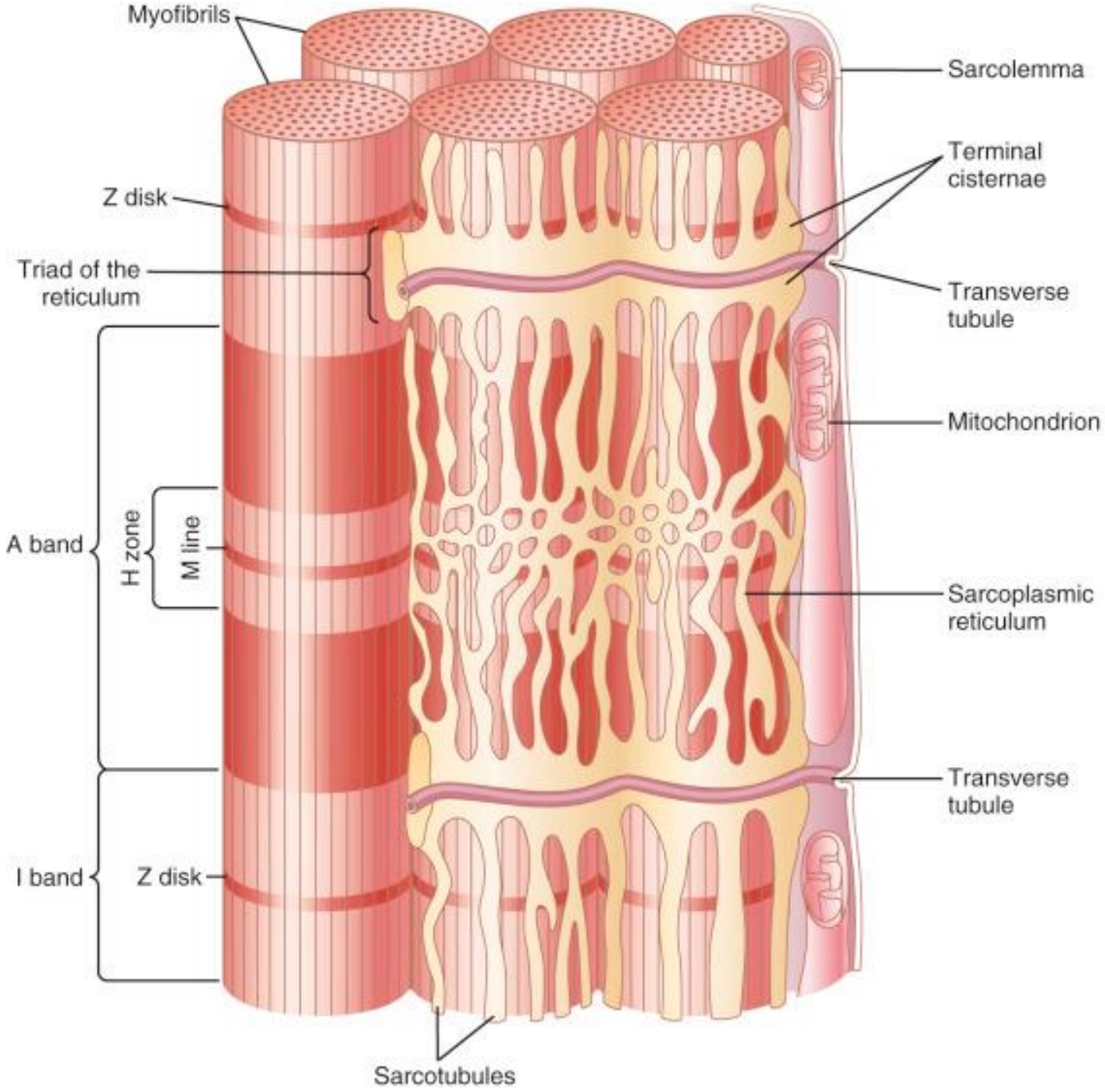
MYOPATHY

- *Myo-* muscle
- *Pathos* - suffering
- A disorder in which there is a primary functional or structural impairment of *skeletal muscle.*






Myofibrils
Sarcolemma
Terminal cisternae
Z disk
Triad of the reticulum
Transverse tubule
Mitochondrion
A band
H zone
M line
Sarcoplasmic reticulum
Transverse tubule
I band
Z disk
Sarcotubules

Muscle Fibers

- **Type 1, Slow twitch, red:**
  - Aerobic
  - Generating force over a more protracted interval.
  - Fatigue slowly
  - More dependent on a steady supply of oxygen
  - ++++ myoglobin → redder
    Contain more lipid and mitochondria than fast-twitch fibers

- **Type 2, Fast twitch, white:**
- Anerobic
- Generating large amounts of force quickly
- Contain more glycogen and myofibrillary ATPase
- Less myoglobin → white
- Fatigues easily

Symptoms of Myopathies

- **Limb muscle weakness and atrophy :**
  - *Proximal muscle weakness* is the cardinal symptoms of myopathy
  - E.g. difficulty combing hair, washing hair in shower, climbing stairs, squatting, waddling gait
  - Shoulder girdle → scapular winging

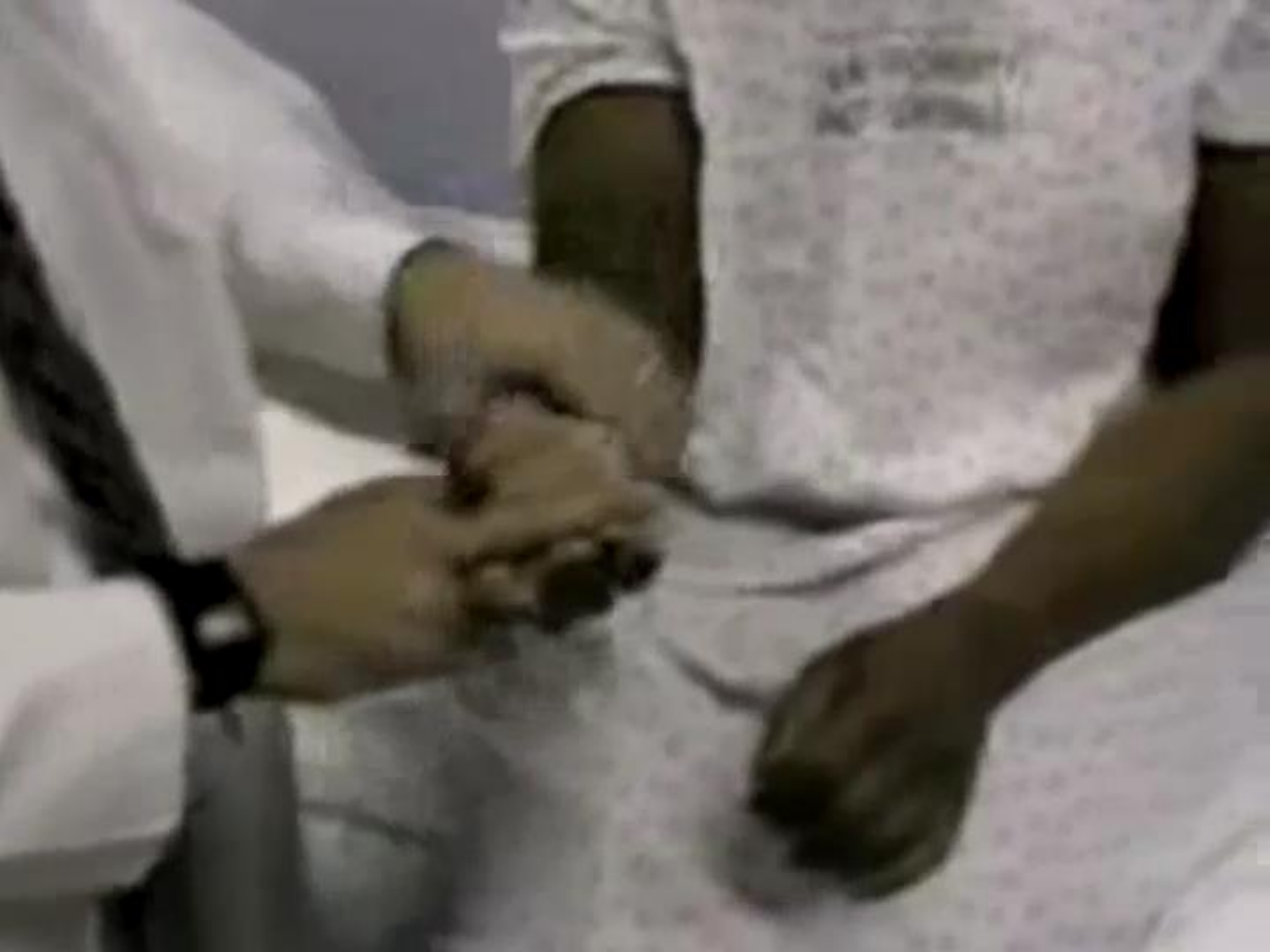
- **Other muscles:**
  - Eye muscles → ophthalmoplegia, ptosis
  - Facial weakness → “myopathic facies”, difficulty closing eyes, whistling, using straw,
  - Bulbar muscles → dysphagia, chocking, nasal speech,
  - Respiratory muscles → dyspnea, orthopnea,
  - Cardiomyopathy → heart failure, arrythmias

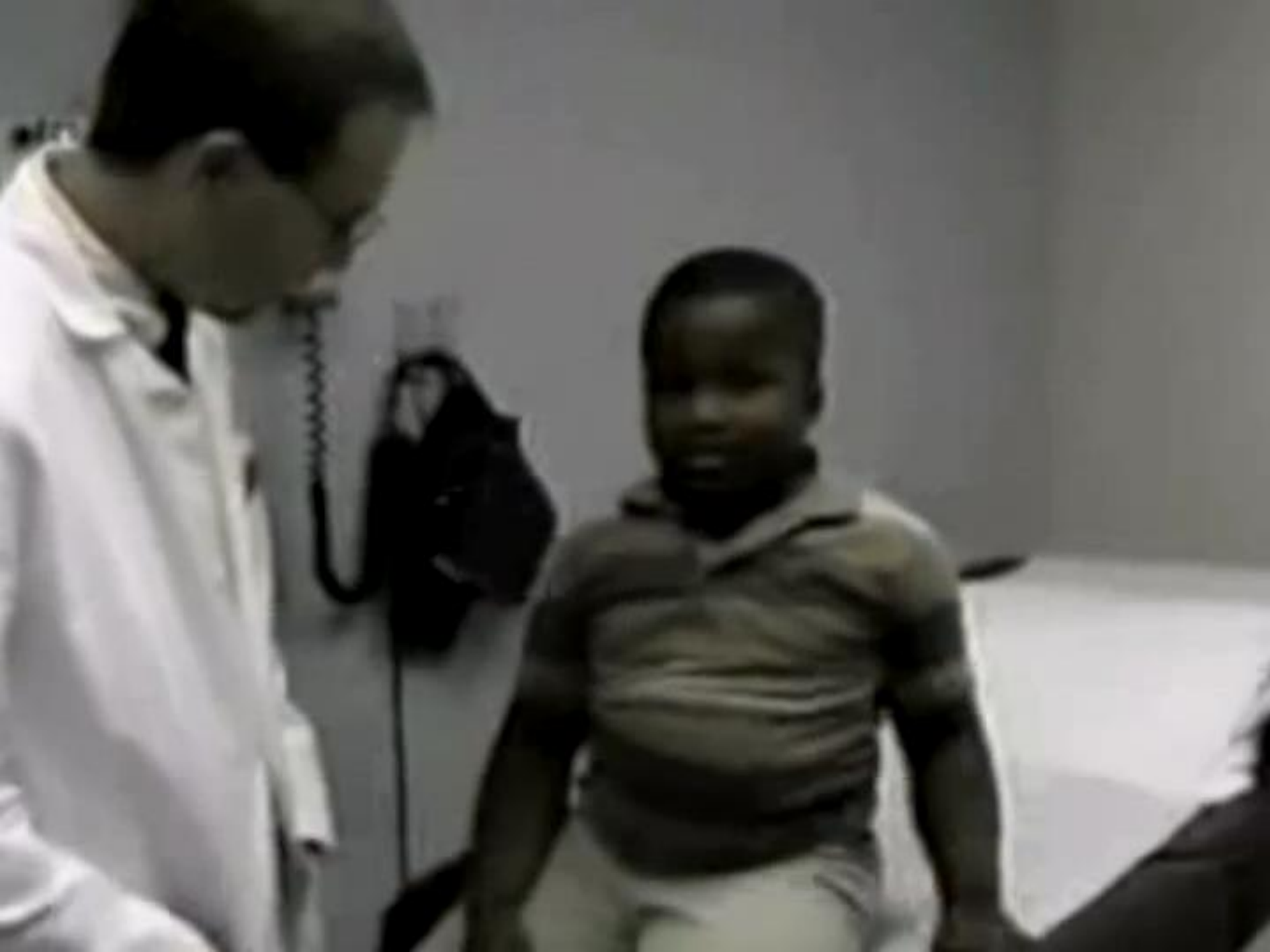
Symptoms of Myopathies

1. Exercise intolerance
   - Suggests a disorder of energy utilization. Short exercise (carb), long (lipid)
2. Cramps:
   - Involuntary contractions of muscle for seconds to minutes.
   - Most are benign (typically calves).
   - Not specific for muscle. Occur in motor neuron disease, chronic neuropathies, etc
   - Risk factors: old age, dehydration, prolonged sitting, diuretics, low Mg, hypoT4, DM
3. Myalgia: muscle pain
4. Myoglobinuria → dark urine
5. Myotonia

Myotonia

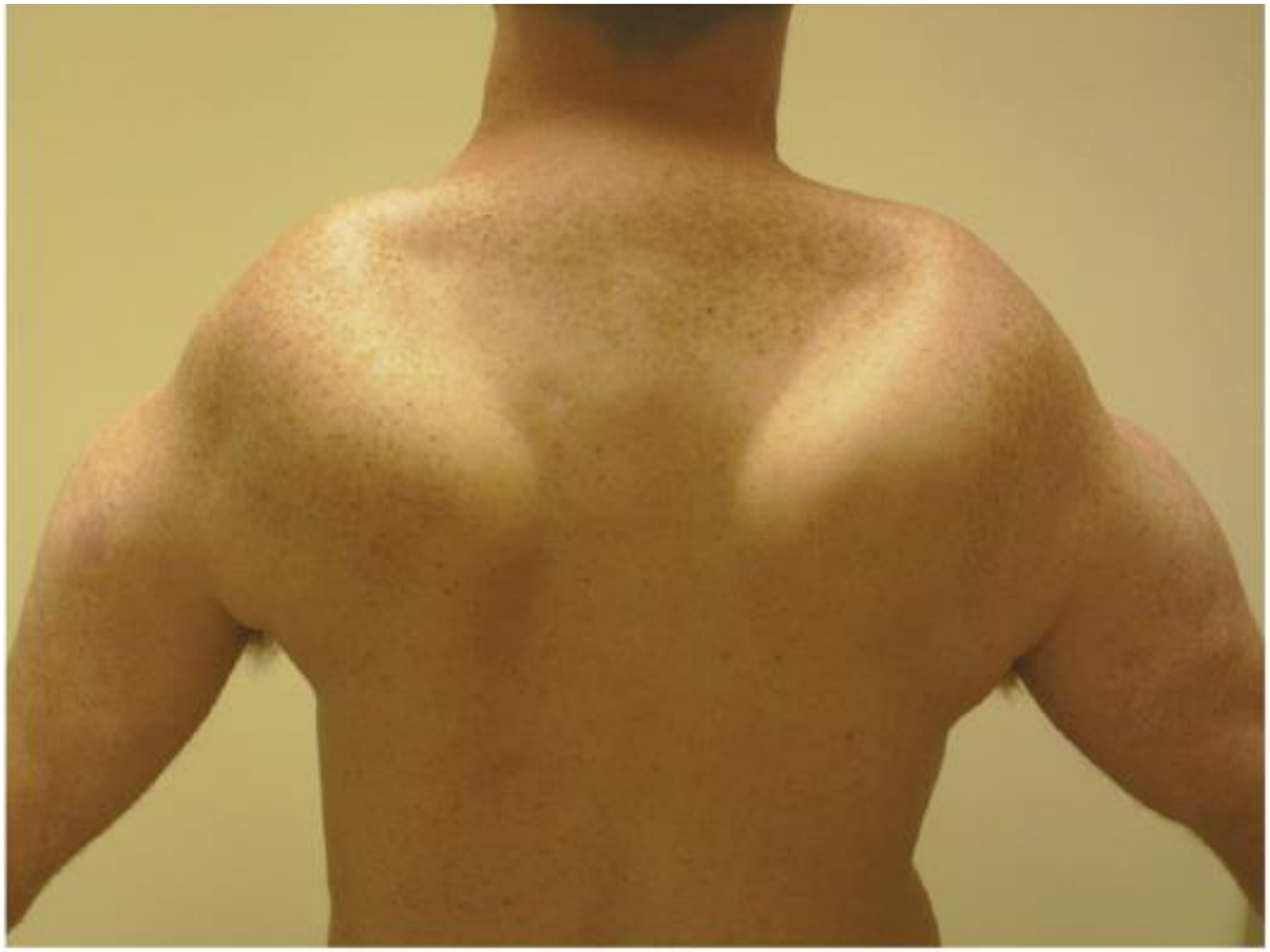
- Impaired relaxation after sustained voluntary contraction.
- Commonly involves intrinsic hand muscles and eyelids.
- Caused by repetitive depolarization of the muscle fibers
- Myotonia can be tested clinically :
  - Tapping the muscle (percussion myotonia)
  - Voluntary contractions of muscle groups (action myotonia)
    - Squeezing on examiner's fingers or shaking his hand or forceful closure of eyes



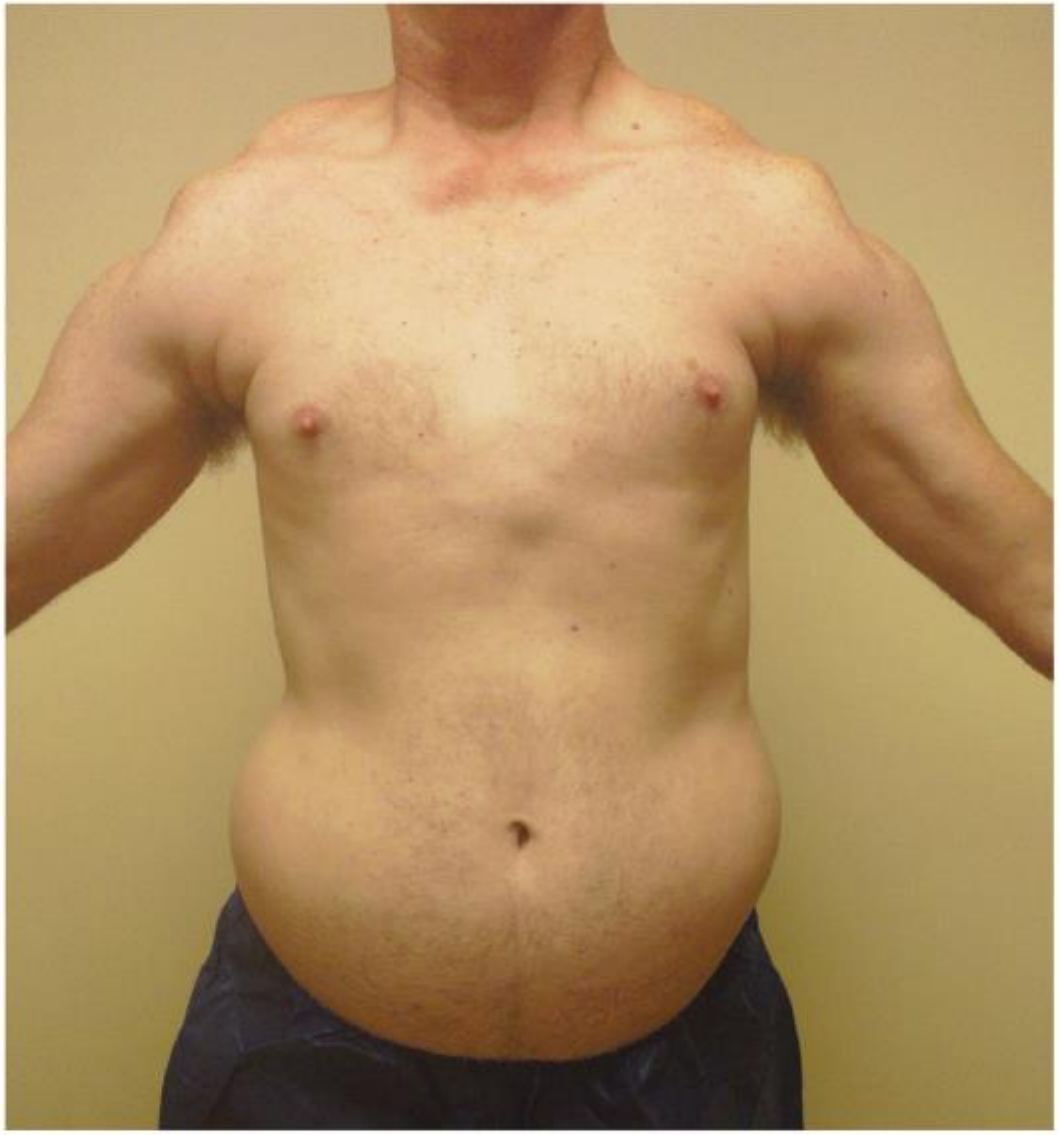


Examination

- General: wasting, myopathic facies, resp distress
- V/S: bradycardia, irregular heartbeat
- Memory abnormalities
- Specific pattern of weakness and atrophy (limb-girdle, scapulocperoneal, distal, facioscapulohumeral, ocular, etc)
- Cardiac; heart failure
- Respiratory: fibrosis



GURE 2-7 Man with facioscapulohumeral muscular dystrophy and bilateral scapular winging.



GURE 2-8 Prominent reversal of the anterior axillary folds, abdominal laxity, and the ''triple hump'' sign (protuberant deltoid muscle, acromioclavicular junction, and overriding scapula) in facioscapulohumeral muscular dystrophy.

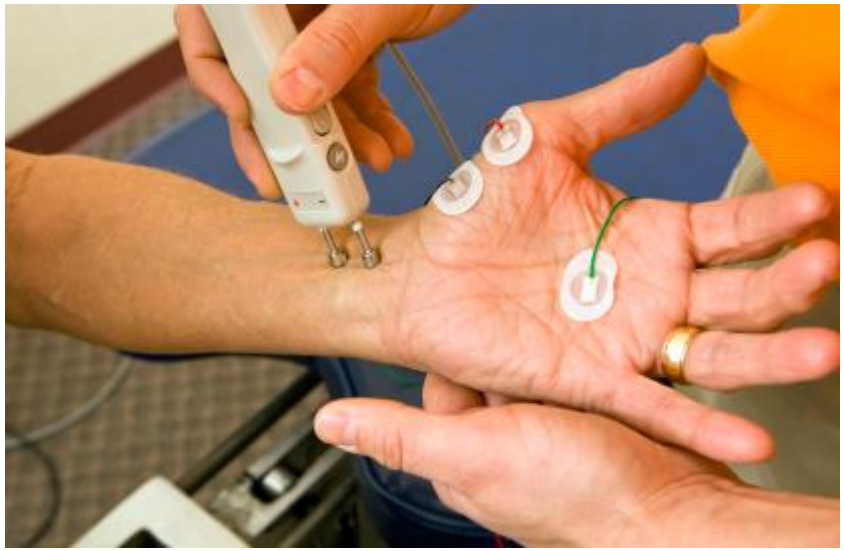
Lab Investigations

- Muscle enzymes:
- CK, aldolase, LDH and the aminotransferases
- ANA, ENA antibodies (anti-Ro/SSA, anti-La/SSB, anti-Sm, and anti-RNP)
- Myositis specific Ab (eg, anti-histidyl-t-RNA synthase [anti-Jo-1])
- Genetic testing

Serum Creatinine Kinase

- CK is an enzyme composed of muscle (M) and brain (B) monomers, resulting in MM, MB, and BB isoenzymes
- Serum CK reflects muscle membrane integrity and fluctuates with levels of activity
- Elevated creatine kinase may be seen with cardiac and skeletal muscle injury, including muscle, nerve, and motor neuron disorders affecting skeletal muscle.
- Strenuous exercise, intramuscular injections, or muscle trauma in the absence of generalized muscle disease

NCS



EMG

Investigations

- MRI:
  - Shows pattern of muscle involvement and features of inflammation
  - Can’t identify the exact etiology
- Muscle biopsy:
  - Essential for the diagnosis of inflammatory myopathies
- Genetic testing: for specific syndromes

Classification of Muscle Disorders

- Acquired:
  - **Inflammatory myopathies**: **dermatomyositis**, **polymyositis**, inclusion body
  - Drug-induced: **statin**, penicillamine, **steroids**, chloroquine,
  - Toxic: alcohol, cocaine, heroine,
  - Infectious: parasite, virus
  - Endocrine: steroid, **hypothyroidism**, hypoparathyroidism

- Hereditary:
  - **Muscular dystrophies**
    - Dystrophinopathies (Duchenne, Becker,)
    - Limb-girdle muscular dystrophies
    - **Myotonic dystrophies**
  - Congenital Myopathies
  - Channelopathies
  - Mitochondrial myopathies
  - Metabolic storage myopathies

Inflammatory Myopathies

- Dermatomyositis
- Polymyositis
- Inclusion body myositis
- Immune-mediated necrotizing myopathy

Polymyositis (PM) and Dermatomyositis (DM)

- Epidemiology:
  - The combined incidence is 2/100,000 annually
  - Female to male ratio of 2:1
  - Dermatomyositis affects children and adults
  - PM affects mainly adults
  - Can be part of an ***overlap syndrome****:* DM or PM is associated with another well-defined connective tissue disorder such as scleroderma, mixed CTD, Sjögren, SLE, or RA.

Polymyositis (PM)

- Presents in adults (> 20 years), women > men
- Acute or insidious (weeks-months).
- Symmetrical weakness.
- Proximal >distal muscles.
- Mild pain and muscle tenderness.
- Can have malaise, fever, and anorexia.
- Dysphagia
- Extraocular and facial muscles spared.
- Deep tendon reflexes are normal unless weakness is severe
- Associated with malignancy (less than DM)
- Cardiac myositis (arrythmia, heart failure)
- Polyarthritis in 45%, positive ANA in 40%

Dermatomyositis (DM)

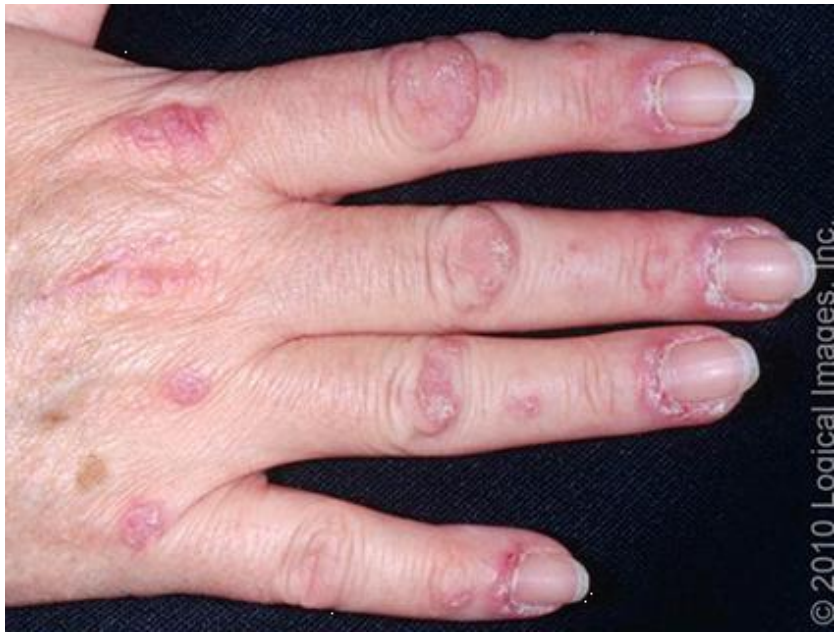
- A form of small vessel vasculitis.
- Any age.
- F> M.
- Weakness: acutely (over several weeks) or insidiously (over months)
- Proximal >distal, legs>arms.
- Difficulties swallowing, chewing, and speaking occur (1/3).

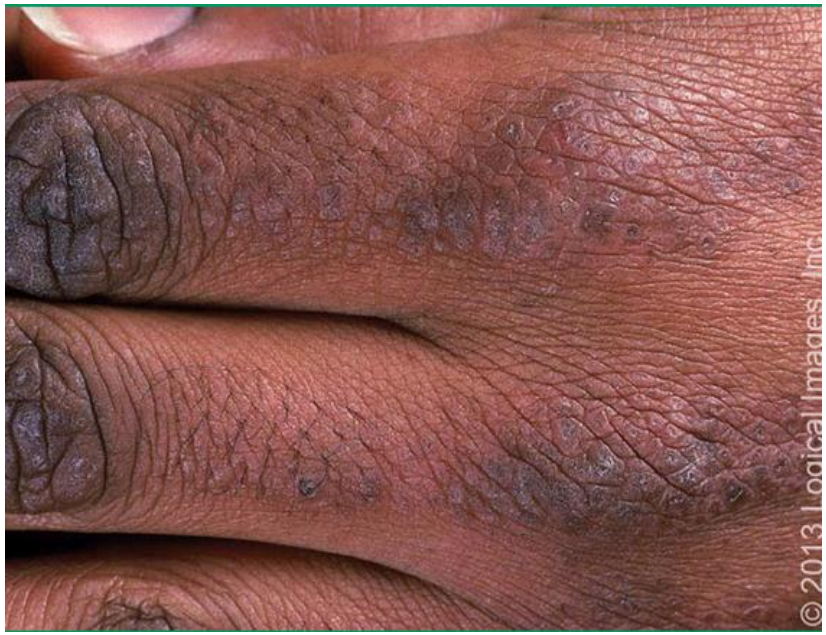
Dermatomyositis (DM)

Gottron's Papules

Pathognomonic for dermatomyositis

Violaceous scaly papules overlying the joints on the dorsal hand.

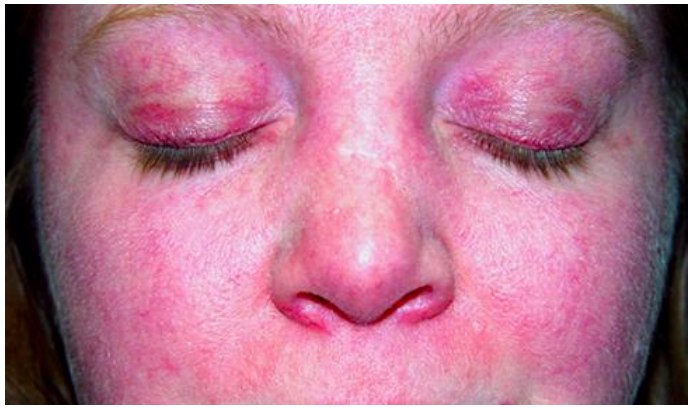


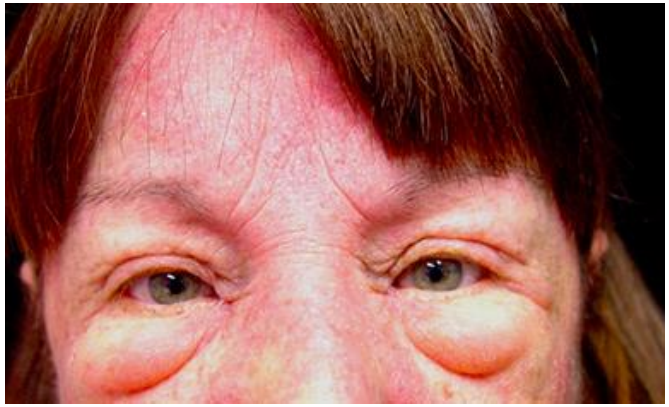


Dermatomyositis (DM)

Helitrope Rash

- Pathognomonic for dermatomyositis
- Violaceous eruption on the upper eyelids, sometimes associated with periorbital edema

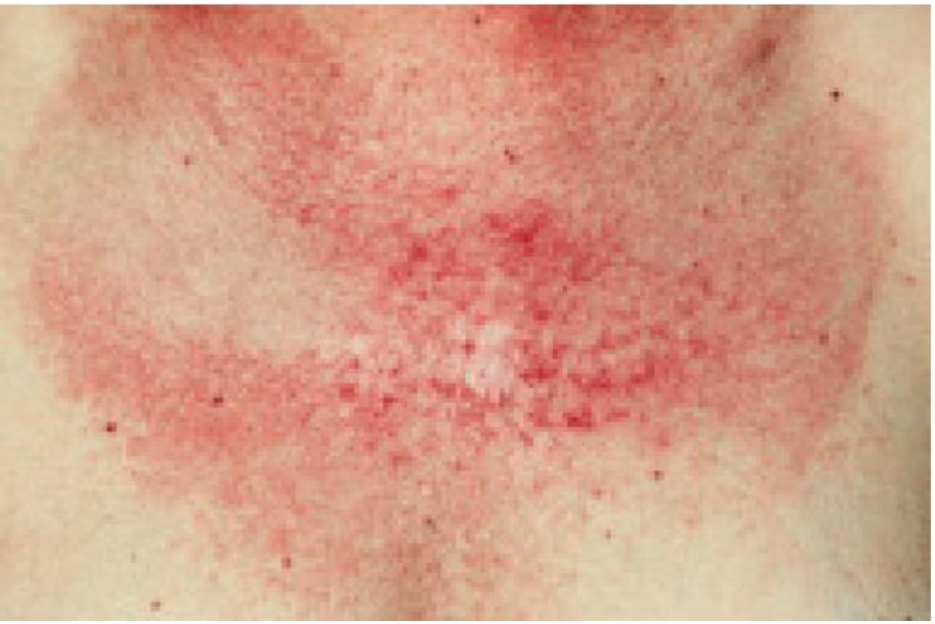


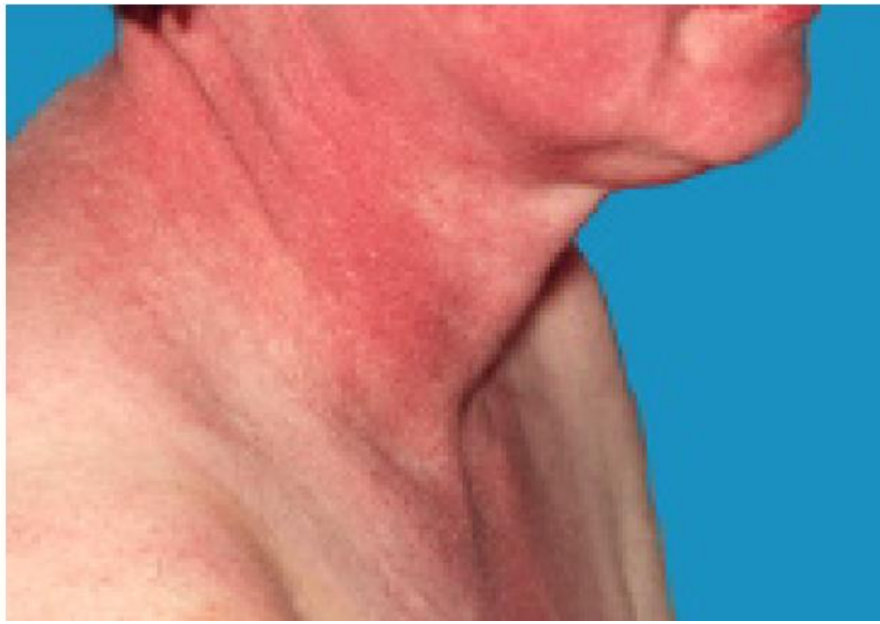


Dermatomyositis (DM)

Shawl sign

- Erythematous rash covering the upper arms and shoulders or a V-shaped rash affecting sun-exposed surfaces on the upper chest.





Dermatomyositis

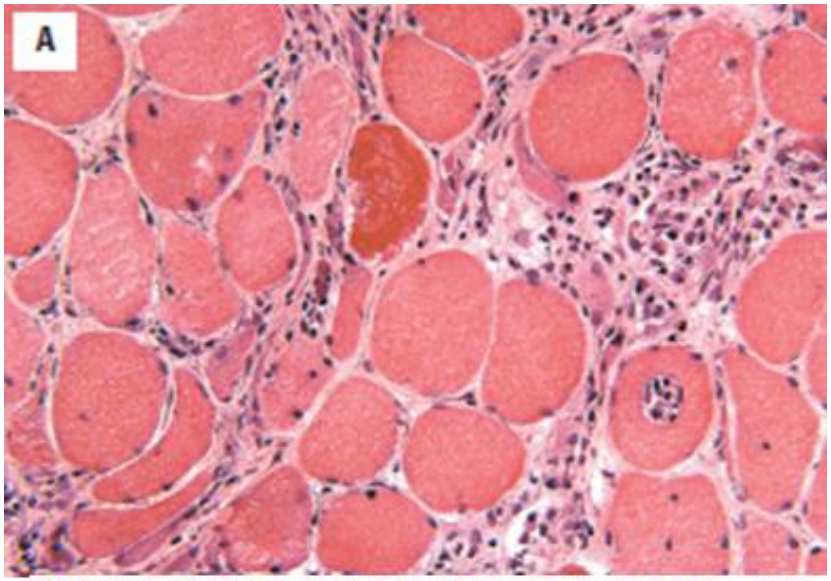
- Non-Skeletal Manifestations :
  - Cardiomyopathy.
  - Dysphagia and delayed gastric emptying.
  - Respiratory muscle weakness
- Autoimmunity:
  - Interstitial lung disease (usually anti-Jo-1).
  - Raynaud's
  - Polyarthritis
  - ANA can be positive
  - Anti–synthetase antibodies (commonest anti-Jo-1, also anti-PL-7, anti-PL-12, etc).
  - Myositis-specific antibodies: *Anti–Mi-2, anti-MDA5 (CADM-140), anti p155/140 or anti-MAS*
- Malignancy:
  - Increased risk of cancer in adults (up to 40% of adults with).
  - Breast, ovarian, lung, pancreatic, NHL, stomach, colorectal or melanoma

Diagnosis of PM & DM

- **Blood tests:**
  - In PM, **CK** should always be **elevated** (>fivefold),
  - In DM, **CK** can be elevated or normal.
  - Elevated levels of other enzymes such aldolase, AST, and ALT
  - Autoantibodies, ANA (80%), anti-Jo1 (20%), anti SRP (5%), anti-Mi-2 (5-35%)
  - Overlap antibodies : anti-PM/Scl, anti-Ro, anti-La, anti-U1 snRNP (SLE, systemic scleroderma, RA or mixed CTD), anti-U2 snRNP (scleroderma)

- **EMG**: myopathic pattern
- **Muscle MRI**: edema, inflammation, fibrosis, calcification or fatty replacement of muscle tissue.
- **Muscle biopsy** is indicated to confirm diagnosis.

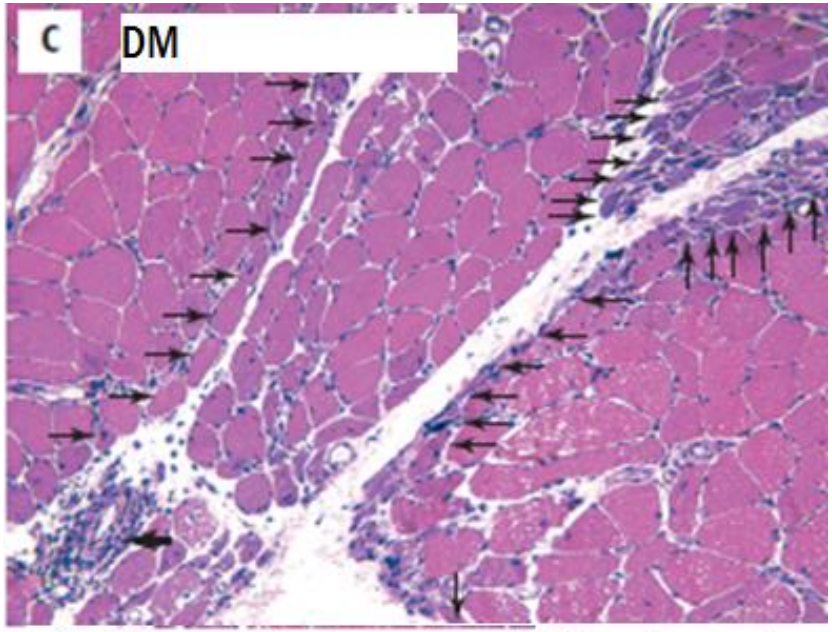
Polymyositis Pathology



Polymyositis. Endomysial lymphocytic inflammation with invasion of muscle fibers

- Inflammatory cells (CD8+ T cells) invading non-necrotic, healthy muscle fibers.
- Invaded muscle fibers express MHC-1
- No perifascicular atrophy.
- No immunoglobulin deposition
- No complement deposition.

Dermatomyositis Pathology



1. Inflammation in perimysial blood vessels
2. Perifascicular atrophy

- Perifascicular atrophy:
  - Pathognomonic.
  - Sublethal myofiber stress and ischemia at the interface of the muscle fascicle and the perimysium.
- Inflammation:
  - Perivascular in blood vessels in the perimysium
  - CD4+ plasmacytoid dendritic cells.
  - - Complement activation (MAC) and deposition on capillaries.

Management of PM & DM

- Cancer screening.
- Evaluate coexisting autoimmune disorders , ANA,
- Exclude cardiac and pulmonary involvement
- Corticosteroids:
  - Some require high dose for long time.
  - Risk of opportunistic infections (PCP), osteoporosis, cataract, weight gait, etc
  - Monitor blood glucose, serum potassium levels, BP, and eyes
- Steroid-sparing therapy:
  - Methotrexate, azathioprine, mycophenonlate, etc
- Physical therapy
- Occupational therapy

Inclusion Body Myositis (IBM)

- Adult men> 50 y.
- Proximal lower extremity weakness is usually the first sign
- Chronic slowly progressive symmetric myopathy
- **Wrist and Fingers flexors**, hip flexors, quadriceps muscles
- Mild facial weakness
- Esophageal dysmotility and dysphagia
- **Endomysial inflammation** and **rimmed vacuoles.**
- Definitive diagnostic feature is **filamentous inclusions** and vacuoles 90%
- Anti-cN1A (NT5C1A) antibodies
- Poor response to immunotherapy

STATIN-INDUCED MYOPATHY

- Statins inhibit HMG-CoA reductase, rate-limiting enzyme of cholesterol biosynthesis.
- Can cause
  - Mild statin-associated myalgia or cramps (20%)
  - Myopathic weakness (up to 11%)
  - Severe myotoxicity or rhabdomyolysis, rare
  - Rarely, statins can cause an ***Immune-Mediated Necrotizing Myopathy*** *with* ***very high CK*** *and* ***antibodies to*** **Anti-HMG CoA-reductase**

- In most cases, both mild and severe side effects are self-limiting
- Discontinuation of the statin → resolution of symptoms

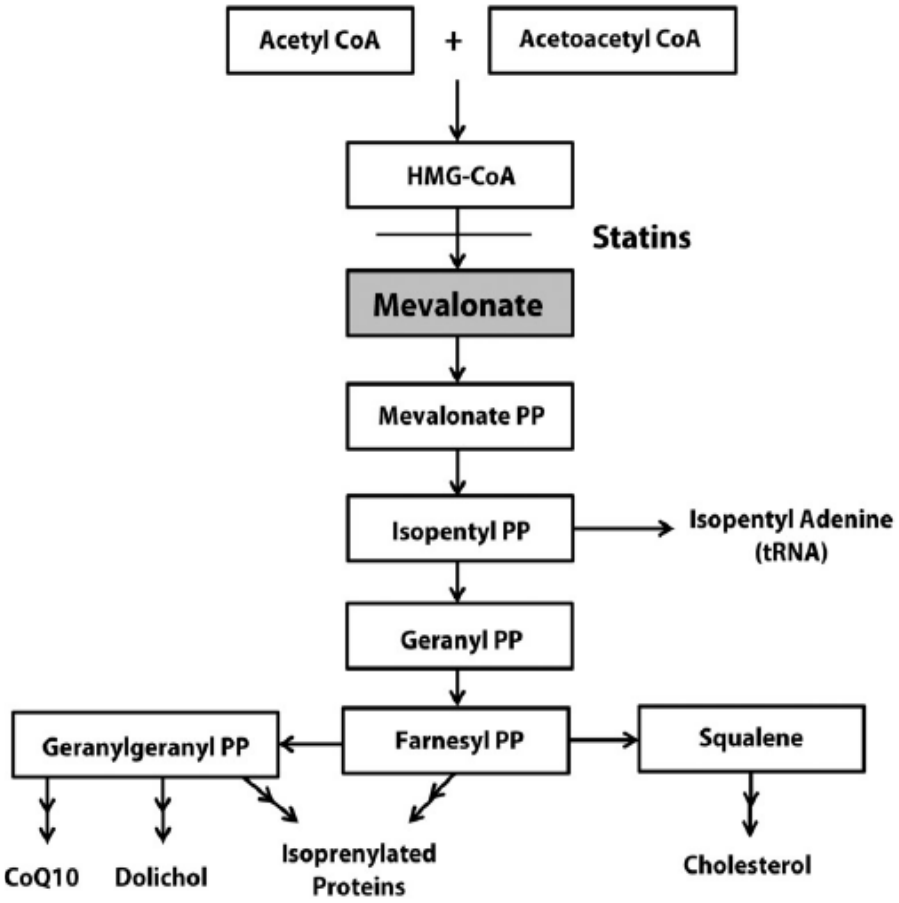
STATIN-INDUCED MYOPATHY

- Risk factors
  1. Older age
  2. Hypothyroidism
  3. Obesity
  4. Type of statin: Fluvastatin and Pravastatin are more myotoxic than to rosuvastatin
  5. Dose of statin.
  6. Preexisting liver disease → reduce metabolism of statin
  7. Liver enzyme inhibitors → increase levels of statins
  8. Genetic susceptibility: SLCO1B1 gene.

STATIN-INDUCED MYOPATHY

- Mechanism
  - ↓Mevalonate → ↓ farnesyl pyrophosphate and geranylgeranyl pyrophosphate → ↓ protein prenylation
  - Reduced prenylation of proteins causes:

1. impaired ubiquinone synthesis → mitochondrial dysfunction.
2. Impairment GTPases that promote cell survival →cell death.
3. Impairment of the process of N-glycosylation → defective proteins → muscle cells damage.



Steroid Myopathy

- Chronic exposure to high-dose oral steroids .
- May occur after just a few weeks of treatment.
- Unknown mechanism.
- ?diminished protein synthesis, increased protein degradation, alterations in carbohydrate metabolism, mitochondrial alterations, and reduced sarcolemmal excitability
- Women > men.
- Progressive proximal muscle weakness (worse in LE) .
- Normal CK levels.
- EMG: normal or myopathic.
- Biopsy: type 2 fiber atrophy and lipid accumulation in type 1 fibers.

Classification of Muscle Disorders

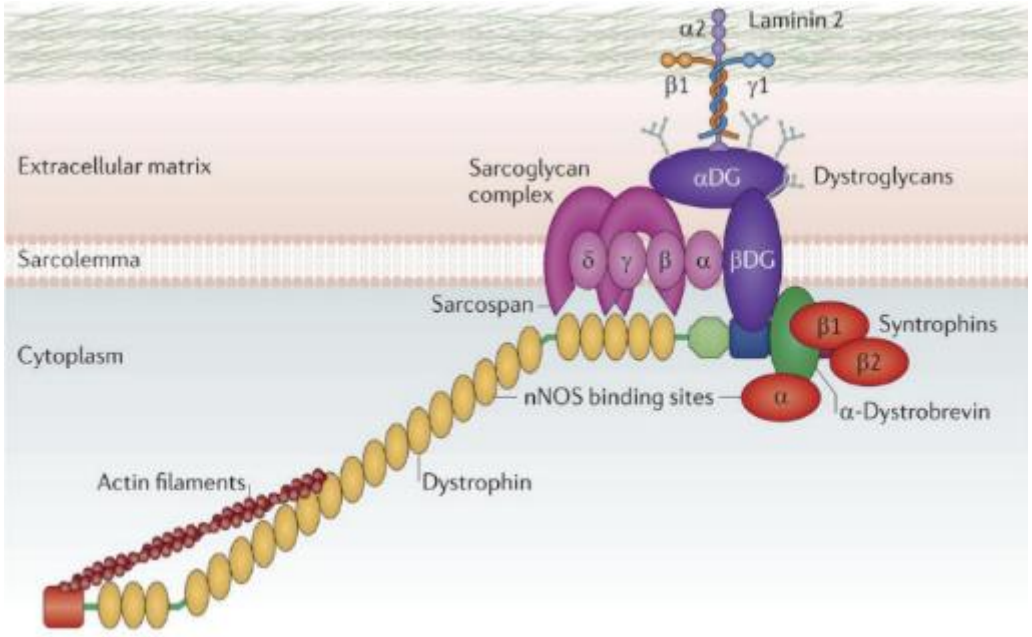
- Acquired:
  - **Inflammatory myopathies**: **dermatomyositis**, **polymyositis**, inclusion body
  - Drug-induced: **statin**, penicillamine, **steroids**, chloroquine,
  - Toxic: alcohol, cocaine, heroine,
  - Infectious: parasite, virus
  - Endocrine: steroid, **hypothyroidism**, hypoparathyroidism

- Hereditary:
  - **Muscular dystrophies**
    - **Dystrophinopathies (Duchenne (DMD), Becker,)**
    - **Limb-girdle muscular dystrophies (LGMD)**
    - **Myotonic dystrophies (MD)**
  - **Congenital Myopathies**
  - Channelopathies
  - Mitochondrial myopathies
  - Metabolic storage myopathies

MUSCULAR DYSTROPHIES (MD)

MUSCULAR DYSTROPHIES (MD)

- Inherited myopathies
- Caused by mutation in genes important in maintaining the **structure** of muscle fibers
- Progressive degeneration of the muscles with connective tissue replacing muscle fibers
- Variable age at onset
- Systemic involvement



MD

1. **Dystrophinopathies:**
    1. Duchenne muscular dystrophy (DMD)
    2. Beker muscular dystrophy
2. **Myotonic dystrophy (MD)**
3. Limb girdle muscular dystrophies (LGMD)
4. Facioscapulohumeral MD (FSHD)
5. Oculopharyngeal MD (OPMD)
6. Emery-Dreifuss muscular dystrophy
7. Barths syndrome

DYSTROPHINOPATHIES

- X linked recessive disorders (manifest in males)
- Duchenne & Becker (DMD, BMD)
- Mutation in the **dystrophin gene** → absent or reduced Dystrophin protein → loss of mechanical reinforcement to the sarcolemma and instability of the glycoprotein complex
- Degeneration of muscle fibers, resulting in muscle weakness.

DMD

SYSTEMIC INVOVEMENT:

1. Cardiomyopathy: dilated cardiomyopathy and arrhythmias
2. Malignant Hyperthermia like reactions with rhabdomyolysis
3. Intestinal pseudo-obstruction
4. CNS involvement: Mental retardation, learning disabilities

INVESTIGATIONS:

1. CK is markedly elevated early in the disease
2. Electromyography: myopathic potentials
3. Muscle biopsy: necrosis, replacement with connective tissue and fibrosis, variation in muscle fiber size, absent dystrophin
4. Genetic testing

DMD

- Management:
  - Screening and treatment of cardiac, respiratory, gastrointestinal, and orthopedic complications.
  - Screening for osteoporosis plus calcium and vitamin D supplementation.
  - Physical therapy, occupational therapy and bracing
  - Avoidance of anesthesia and sedation if possible
  - **Glucocorticoids**:
    - Mainstay of treatment
    - Stabilizes sarcolemma
    - Increases strength, muscle, and pulmonary functions
    - Reduces cardiomyopathy and lowers mortality
    - Has an anabolic action in contrast to its catabolic action on normal skeletal muscle in unaffected people.

Becker Muscular Dystrophy

- Older age at onset
- Less severe symptoms
- Loss of ambulation is usually in the 4th decade
- Muscle biopsy shows decreased staining patterns rather than complete absence of dystrophin

	Clinical Phenotype			Gene Information		
Condition	Typical Onset	Progression	Creatine Kinase Level	Allelism	Gene	Protein
Duchenne muscular dystrophy	Early childhood	Slow to moderate	100–200X	Becker muscular dystrophy	*DMD*	Dystrophin
Becker muscular dystrophy	Late childhood	Slow	10–15X	Duchenne muscular dystrophy	*DMD*	Dystrophin

- Acquired:
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  - Drug-induced: **statin**, penicillamine, **steroids**, chloroquine,
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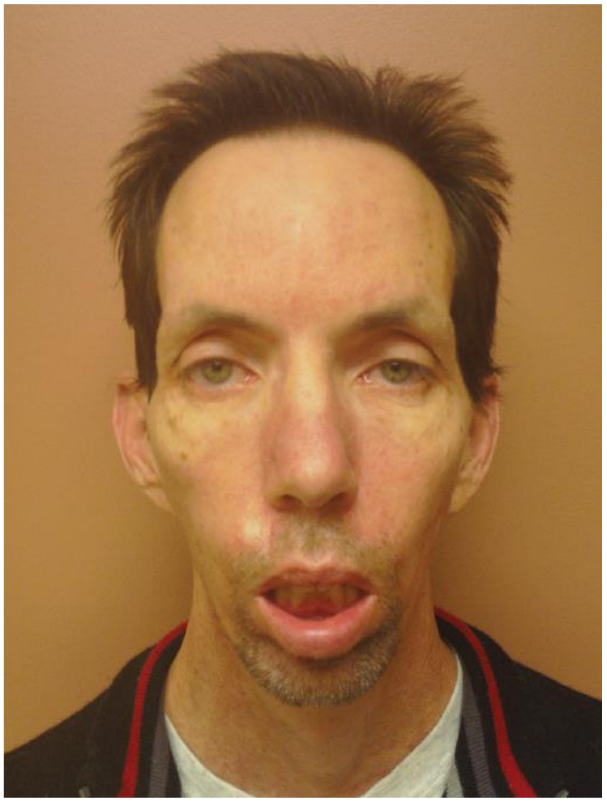
  - Mitochondrial myopathies
  - Metabolic storage myopathies

Myotonic Dystrophy (MD)

- A multisystem disorder
- The most prevalent inherited neuromuscular disease in adults
- Autosomal dominant
- Tandem repeats at DMPK gene (Anticipation phenomenon)
- Age of onset average is 29 years
- Myotonia
- Weakness of the forearms and peroneal muscles
- Ptosis and weakness of other facial muscles

MD

- Frontal bolding
- Cardiac: arrythmias, heart failure, sudden death
- Respiratory weakness: orthopnea,
- GIT dysmotility, constipation and diarrhea
- Cataract
- Endocrine abnormalities: NIDDM, hypoT4, male hypogonadism
- Low IQ



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    - **Limb-girdle muscular dystrophies (LGMD)**
    - **Myotonic dystrophy (MD)**
  - **Congenital Myopathies and Malignant Hyperthermia**
  - Channelopathies
  - Mitochondrial myopathies
  - Metabolic storage myopathies

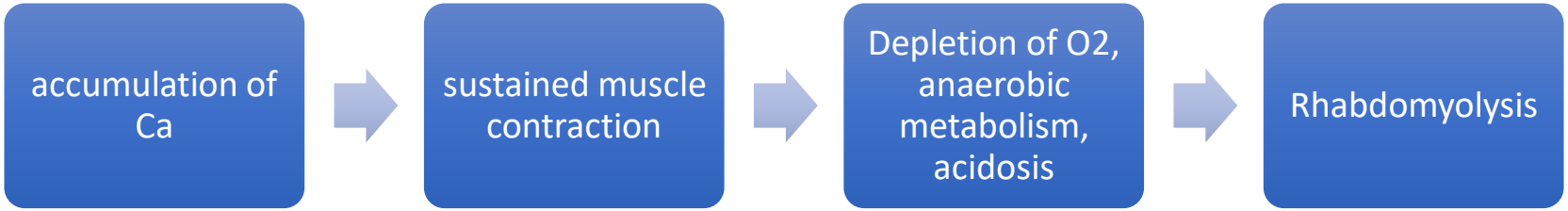
CONGENITAL MYOPATHIES

- Prenatally, decreased fetal movements
- Postnatally: Hypotonia, poor respiratory effort, difficulty feeding, reduced muscle bulk and weakness
- First year and beyond: delayed milestones, failure to thrive, recurrent respiratory infections and flaccid speech
- Include: *Central core disease, Multicore (minicore) disease, Nemaline myopathy, Myotubular (centronuclear) myopathy, Myofibrillar (desmin related), Congenital fiber type disproportion*
- Some are associated with **malignant hyperthermia**
- Slow or non progressive course
- No treatment

Malignant Hyperthermia (MH)

- Hypermetabolic reaction to volatile anesthetics and depolarizing neuromuscular blocking agents.
- Tachypnea, tachycardia, **rigidity**, acidosis, hyperkalemia, rhabdomyolysis, **high CK**, and **hyperthermia**.
- Associated with genetic muscle abnormalities causing calcium accumulation
- Associated with mutations of the ryanodine receptor (RYR1 gene), Na or Ca channels.
- Can be fatal
- Treatment:
  - **Remove** anesthetic agent.
  - Core **cooling**
  - **Dantrolene sodium**, an inhibitor of calcium release from the sarcoplasmic reticulum.

MH


accumulation of Ca
sustained muscle contraction
Depletion of O2, anaerobic metabolism, acidosis
Rhabdomyolysis

Conclusion

- Thank you