DIFFERENTIAL DIAGNOSIS OF NEUROGENIC DISORDERS & MYOPATHIES

	NEUROPATHY	MYOPATHY
Weakness	distal	proximal
Sensory dysfunction	+	0
Loss of reflexes	early	late
Serum enzymes	+/-	+++
CSF protein	may be elevated	normal
Electromyography	neurogenic	myopathic

CLASSIFICATION OF PERIPHERAL NERVE DISEASES

Myelinopathy
- Acute inflammatory polyneuropathy (Guillain-Barré syndrome or GBS)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Charcot-Marie-Tooth, type 1 (CMT-1)

Axonopathy
- Wallerian degeneration (trauma, vasculitis etc.)
- Distal axonopathies (dying back neuropathies)

Neuronopathy
- Amyotrophic lateral sclerosis (ALS)

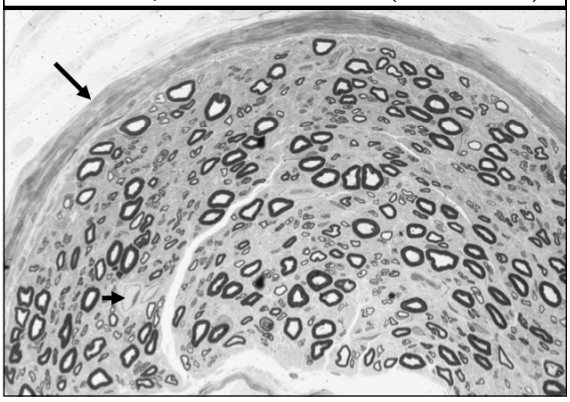
CLINICAL ROLE OF NERVE BIOPSY IS VERY LIMITED

- Identify the cause of a neuropathy (vasculitis, amyloidosis).
- Nerve conduction studies are more useful than nerve biopsy for distinguishing between a demyelinating neuropathy and an axonal disorder.

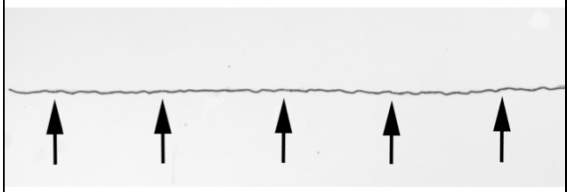
PATHOLOGICAL ANALYSIS OF SURAL NERVE BIOPSY

- ROUTINE HISTOLOGY
- SEMITHIN PLASTIC SECTIONS
- TEASED MYELINATED FIBERS
- ELECTRON MICROSCOPY

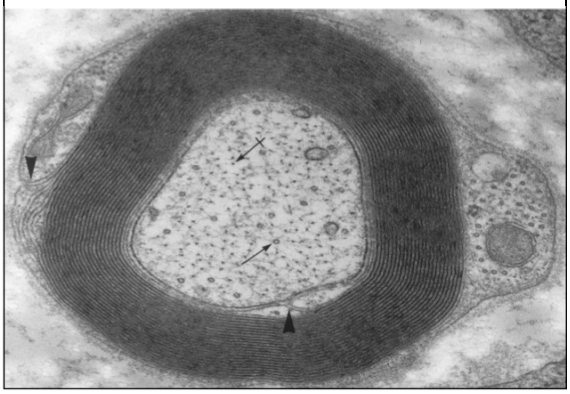
SURAL NERVE, SEMITHIN PLASTIC SECTION (TOLUIDINE BLUE)



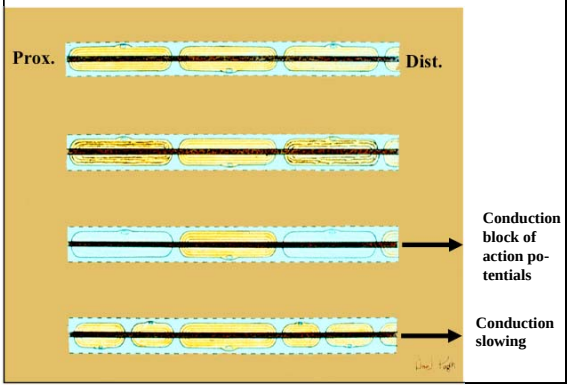
TEASED MYELINATED FIBER: NORMAL



PERIPHERAL NERVE, ELECTRON MICROGRAPH

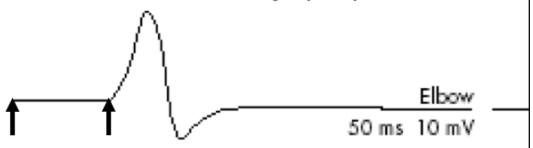


SEQUENCE OF SEGMENTAL DEMYELINATION & REMYELINATION

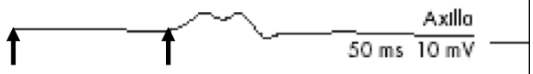


NERVE STIMULATION EVOKES ACTION POTENTIAL IN HAND MUSCLE

J. Neurol. Neurosurg. Psychiatry 2005;76;1269-1272

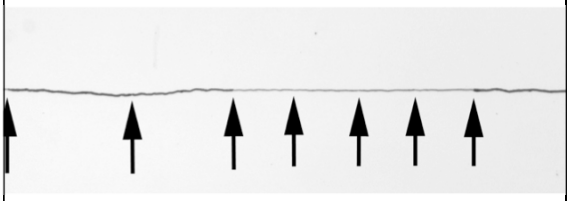


NORMAL COMPOUND MUSCLE ACTION POTENTIAL

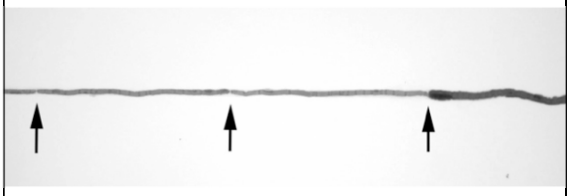


REDUCED AMPLITUDE OF CMAP

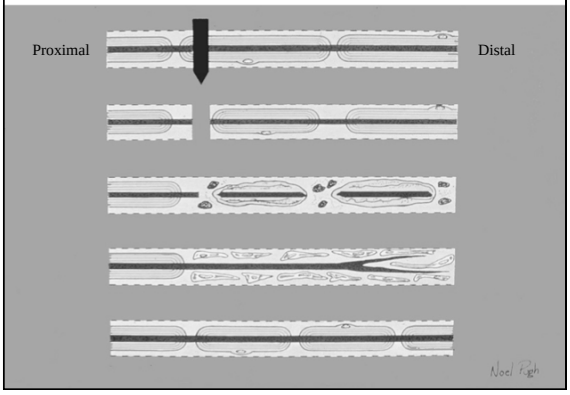
TEASED MYELINATED FIBER: SEGMENTAL REMYELINATION



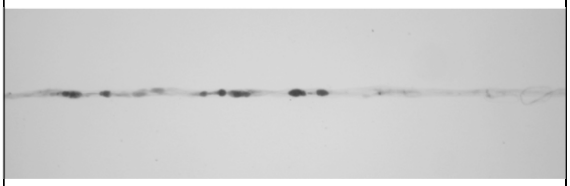
SAME TEASED FIBER AT HIGHER MAGNIFICATION



SEQUENCE OF SEGMENTAL AXONAL DEGENERATION & REGENERATION



TEASED MYELINATED FIBER: AXONAL DEGENERATION



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Axonopathy
- **Wallerian degeneration (trauma, vasculitis etc.)**
- **Distal axonopathies (dying back neuropathies)**

Neuronopathy
- **Amyotrophic lateral sclerosis (ALS)**

ACUTE INFLAMMATORY POLYNEUROPATHY (GUILLAIN-BARRE SYNDROME OR GBS)

- **Rapidly progressive neuropathy, chiefly motor, reaching maximum weakness usually within 1 to 2 weeks.**
- **Severe respiratory weakness is a major danger and may require treatment in an intensive care unit.**
- **An acute infectious illness precedes weakness in two thirds, consisting of influenza-like symptoms or diarrhea. The respiratory disorder is linked to infection by viruses whereas diarrhea is often caused by *Campylobacter jejuni.***
- **Recovery takes weeks or months. Permanent handicap occurs in 15%-20% of patients.**

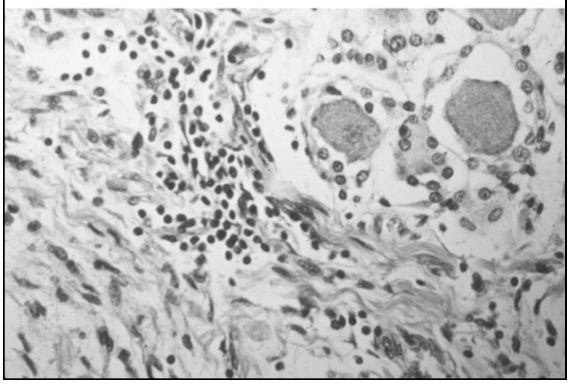
GBS: DIAGNOSIS & TREATMENT

- **Electrophysiology: early block of conduction of action potentials along motor nerves. Slowing of conduction velocity develops later as segmental remyelination appears.**
- **Electrodiagnostic studies often show evidence of co-existing axonal degeneration, usually of mild degree.**
- **Cerebrospinal fluid typically has mildly elevated protein and no cells.**
- **Sural nerve biopsy does not have a role in diagnosis but has provided information about etiology and pathogenesis.**
- **Plasmapheresis or intravenous gamma globulin speeds recovery.**

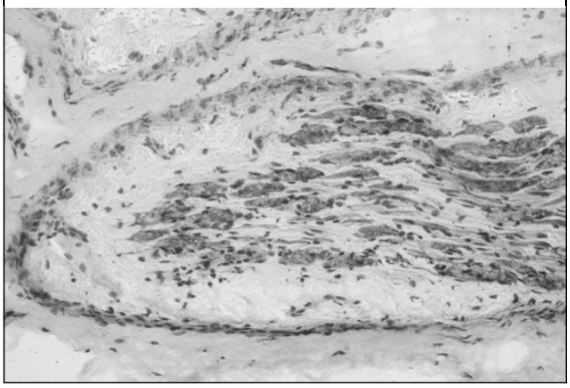
PATHOLOGY OF GUILLAIN-BARRÉ SYNDROME

- **Immune complexes (C3, IgG, IgM) are detectable on the surface of myelin sheaths in the early stage.**
- **Sparse T cells, chiefly CD4 subset, infiltrate endoneurium.**
- **Monocytes and macrophages appear to attack myelin sheaths.**
- **Myelinated fibers show segmental demyelination during the first few days. Segmental remyelination occurs subsequently.**
- **The lesions have a perivenular distribution and tend to affect the DRG, nerve roots and adjacent nerves where blood-nerve barrier is normally more permeable than elsewhere.**

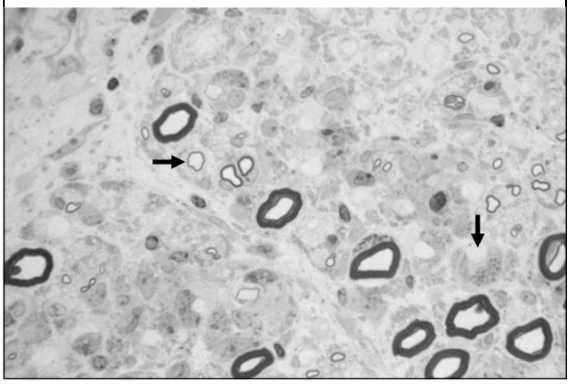
GBS, DORSAL ROOT GANGLION, H&E



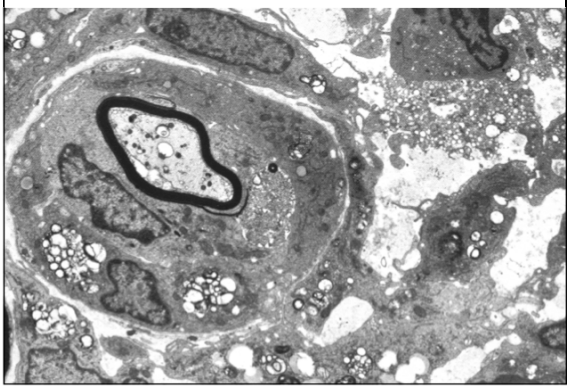
GBS, MOTOR NERVE, H&E



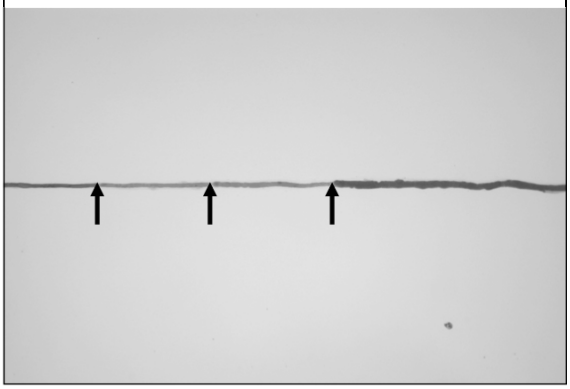
GBS, MOTOR NERVE, SEMITHIN SECTION



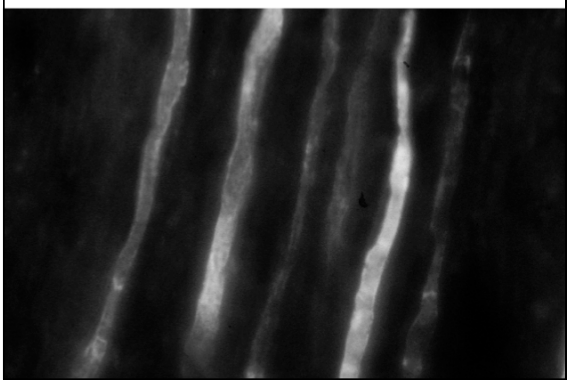
GBS, ELECTRON MICROGRAPH



GBS, SEGMENTAL REMYELINATION



GBS, C3 COMPONENT ON MYELIN SHEATHS



EVIDENCE FOR AUTOIMMUNE ETIOLOGY IN GUILLAIN-BARRE SYNDROME

- **Demyelinating neuropathy can be induced in experimental animals by immunization with myelin, purified myelin protein or galactocerebroside.**
- **Antibody titers to nerve myelin in patients correlate with disease activity.**
- **The antibodies recognize specific glycolipids or glycoproteins of peripheral myelin in a minority of patients.**
- **Immune complexes are found at surface of myelin sheaths.**
- **Plasmapheresis or intravenous gamma globulin speeds recovery when treatment is started early.**

AXONAL VARIANT OF GUILLAIN-BARRE SYNDROME

- Clinical syndrome resembles Guillain-Barre syndrome, but is often purely motor.
- It is common in Asia and other countries but accounts for only 5% of patients in the US or Europe.

AXONAL VARIANT OF GBS, Possible molecular mimicry

- The patients often have elevated serum autoantibodies that recognize the terminal oligosaccharide of GM1 & GD1a ganglioside.
- The chemical structure of lipopolysaccharide of *C. jejuni* has the same oligosaccharide chain present in GD1a and GM1.
- This suggests that the immune response to *C. jejuni* induces antibodies that crossreact to a self-antigen of the axolemma. This axonal variant of autoimmune neuropathy is postulated to be caused through molecular mimicry.

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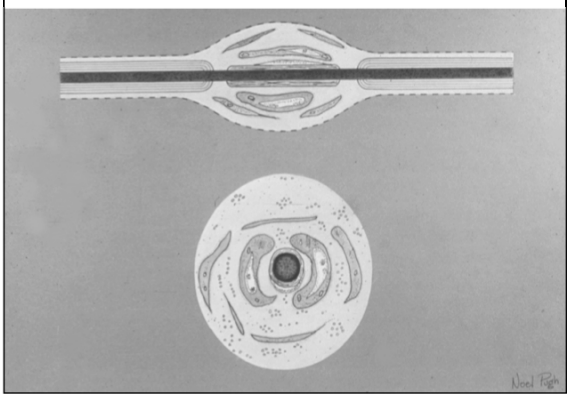
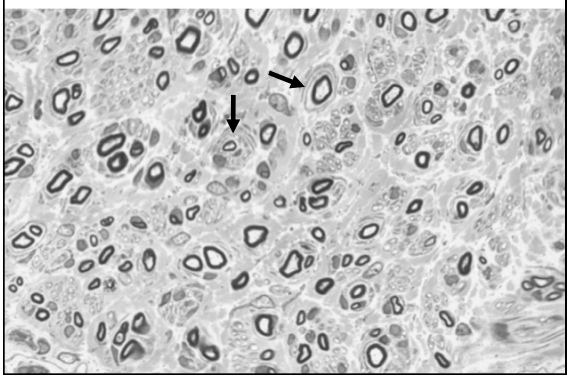
CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

- Chronic progressive or relapsing neuropathy, motor > sensory.
- An antecedent infectious illness is uncommon.
- Electrophysiology: conduction block and slowing of velocity.
- Pathology: segmental demyelination and remyelination, onion bulbs, fibrosis and little or no lymphocytic infiltration of tissue.
- Probably an autoimmune disorder of myelin but pathogenesis is not well understood.
- Patients respond to plasmapheresis, intravenous gamma globulin or corticosteroid treatment.

ONION BULB



CIDP WITH ONION BULBS



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Neuronopathy
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CHARCOT-MARIE-TOOTH, TYPE I

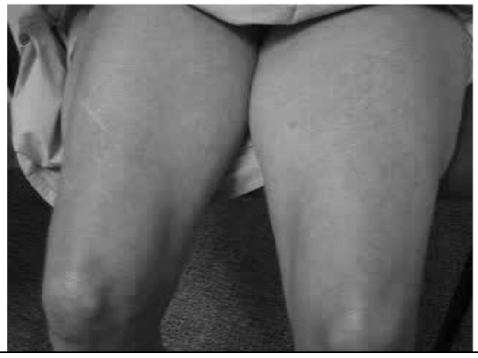
- **Slowly progressive distal limb weakness begins in first decade with great variation in onset; few sensory complaints.**
- **Autosomal dominant, mutations commonly affect *PMP22*.**
- **Neurological exam:**
  - **Atrophy of distal leg muscles (stork leg appearance).**
  - **Palpable nerve enlargement in 50%.**
  - **Pes cavus and hammer toes is common.**
- **Electrophysiology: Uniform slowing of conduction velocity. No conduction block.**
- **Pathology: similar to CIDP.**

Lou Gehrig

AMYOTROPHIC LATERAL SCLEROSIS (LOU GEHRIG'S DISEASE)

- **Progressive weakness, muscle wasting and fasciculations; often asymmetrical in the beginning.**
- **Symptoms usually begin after the age of 40.**
- **Hyperactive tendon reflexes, clonus and Babinski signs.**
- **Electromyogram: Signs of denervation in muscle. Normal or slightly reduced conductions.**
- **Most are sporadic; about 10% are familial.**
- **Death occurs usually within 3 to 5 years from onset.**

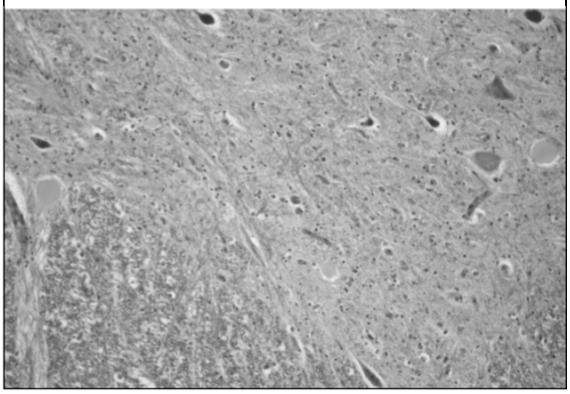
ALS: FASCICULATIONS & BABINSKY REFLEXES



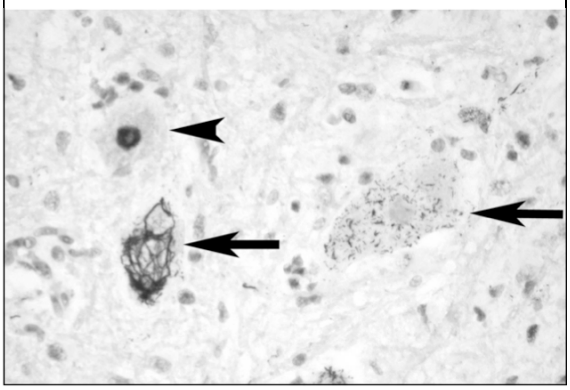
ALS: LOWER MOTOR NEURON PATHOLOGY

- **Loss of motor neurons in ventral horns and nuclei of cranial nerve V, VII, IX-XII.**
- **Sparing of motor nuclei of cranial nerves III, IV & VI and Onuf's nucleus.**
- **Surviving motor neurons show atrophy & inclusions.**
- **Few chromatolytic-like nerve cells.**
- **Little or no evidence of axonal regeneration.**

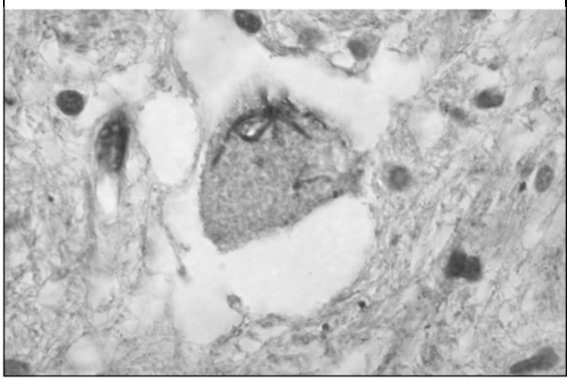
ALS: LOSS OF MOTOR NEURONS IN VENTRAL HORN



ALS & SARCOIDOSIS, SPINAL CORD, TDP-43



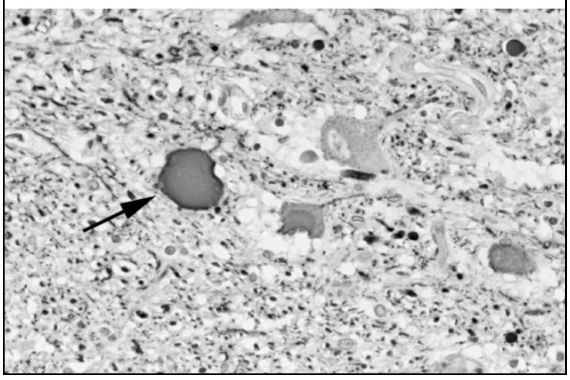
ALS, SKEIN-LIKE INCLUSIONS, UBIQUITIN



SKEIN-LIKE INCLUSIONS

- **Intracytoplasmic aggregates of granules and loosely-arranged fibrils (skein-like inclusions) occur in motor neurons of spinal cord and brain stem. Rare in Betz motor cells of precentral gyrus.**
- **Invisible in routine histology (H&E) and are not argyrophilic.**
- **The inclusions are composed of TDP-43, a protein that is normally expressed in the nucleus.**
- **The skein-like inclusions are ubiquinated.**
- **Sensitivity: 90-100%; specificity: >95%.**

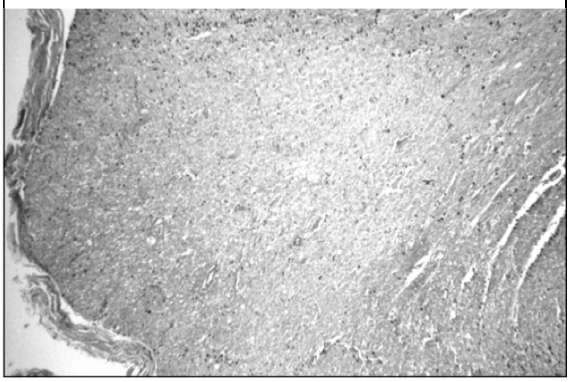
ALS, NEUROFILAMENT PROTEIN



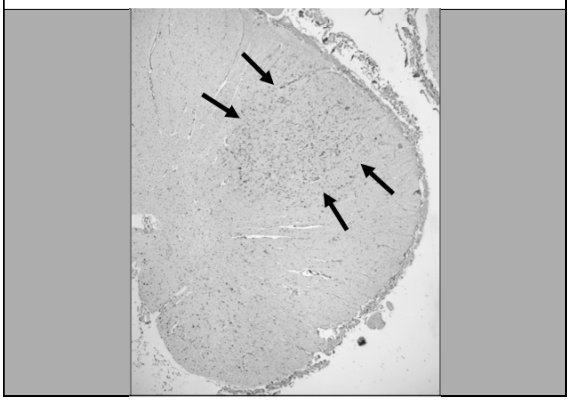
ALS: UPPER MOTOR NEURON PATHOLOGY

- **Loss of Betz cells (upper motor neurons) in pre-central gyrus.**
- **Pyramidal degeneration with gradually increasing myelin pallor in a caudal direction due to loss of axons.**
- **The tract degeneration is marked by macrophages (removing myelin debris) and numerous activated microglia.**

ALS, MYELIN PALLOR IN PYRAMIDAL TRACT, LFB-PAS



ALS, PYRAMIDAL TRACT, CD68



PATHOGENESIS OF ALS

Mutations of the Cu/Zn superoxide dismutase (SOD1) cause ALS of 20% of familial cases. Expression of mutant human SOD1 in transgenic mice produces MND by a toxic or gain of function mechanism. This mouse model has yielded two major hypotheses of toxicity:

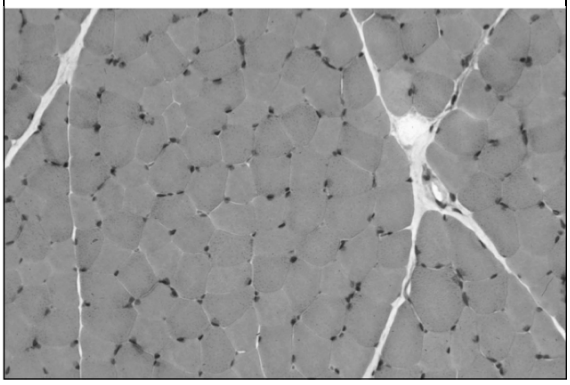
aberrant oxidation ⟷ intracellular aggregates

glutamate toxicity, disrupted calcium homeostasis, abnormal nitration and glycation of proteins, apoptotic death

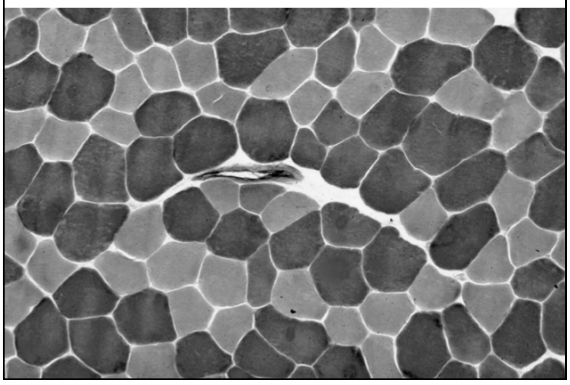
AIMS OF MUSCLE BIOPSY

- **Distinguish a neurogenic disorder from a myopathy.**
- **Screen inherited myopathies for molecular analysis.**
- **Subclassify acquired myopathies.**

CRYOSECTIONS OF SKELETAL MUSCLE, H&E

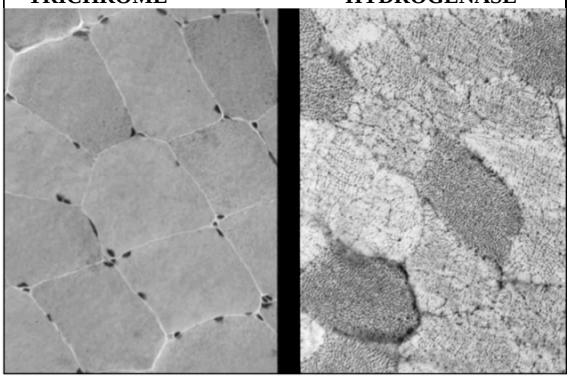


CRYOSECTIONS OF SKELETAL MUSCLE, ATPase



MODIFIED GOMORI TRICHROME

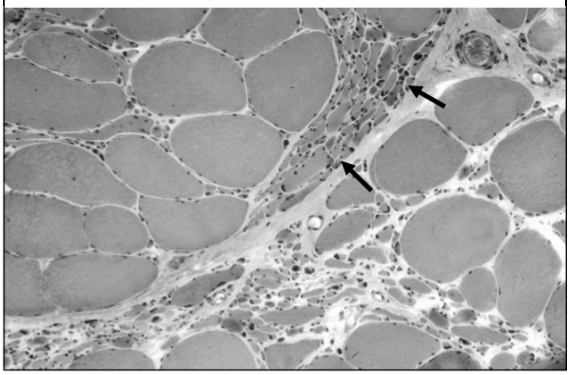
SUCCINATE DE-HYDROGENASE



DIAGNOSTIC HISTOLOGICAL FEATURES OF A NEUROGENIC DISORDER

- LARGE GROUPS OF ATROPHIC FIBERS
- FIBER TYPE GROUPING
- TARGET FIBERS

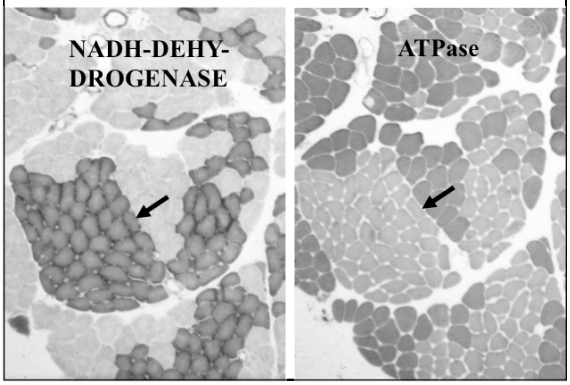
GROUPS OF ATROPHIC MYOFIBERS, H&E



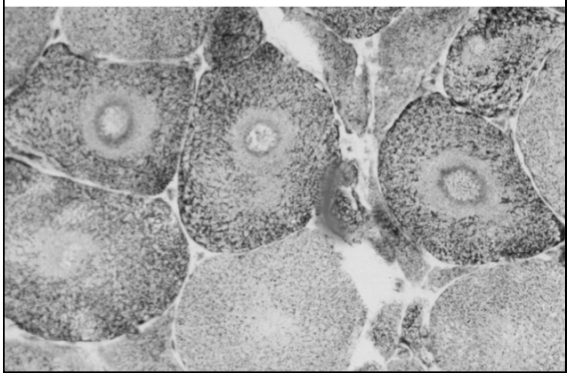
FIBER TYPE GROUPING

NADH-DEHY-DROGENASE

ATPase



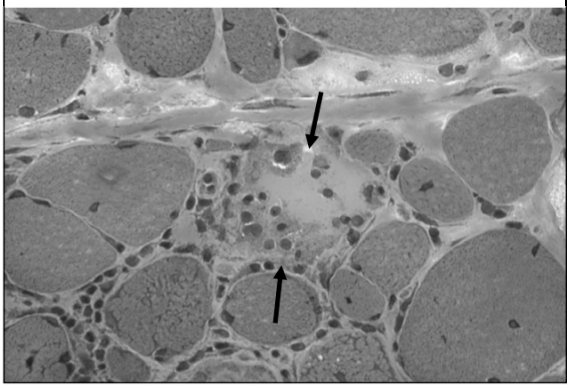
TARGET FIBERS, NADH DEHYDROGENASE



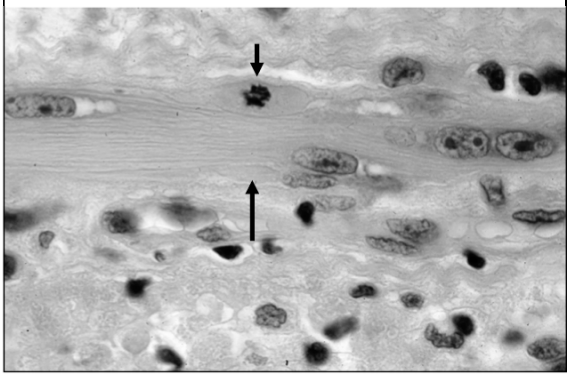
DIAGNOSTIC HISTOLOGICAL FEATURES OF MYOPATHIES

- ABSENCE OF NEUROGENIC ABNORMALITIES
- NECROTIC MUSCLE FIBERS
- BASOPHILIC (REGENERATING) MYOFIBERS
- FIBROSIS OF THE ENDOMYSIUM
- SPECIAL PATHOLOGICAL FEATURES (INFLAMMATORY CELLS, RAGGED RED FIBERS ETC.)

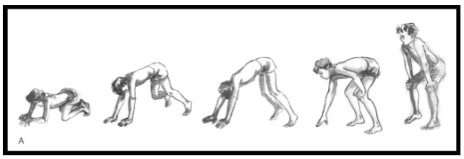
NECROTIC FIBER, H&E



REGENERATING FIBER, H&E



GOWER'S SIGN

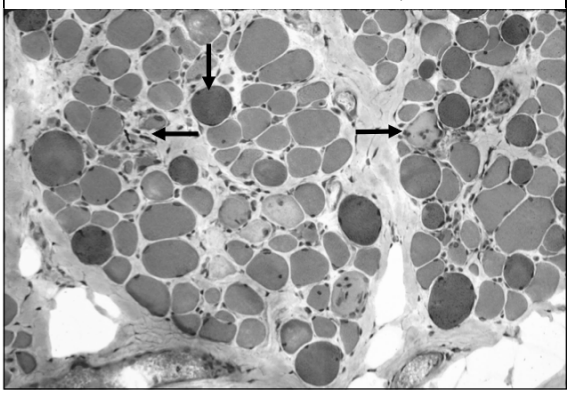


Gowers, 1879

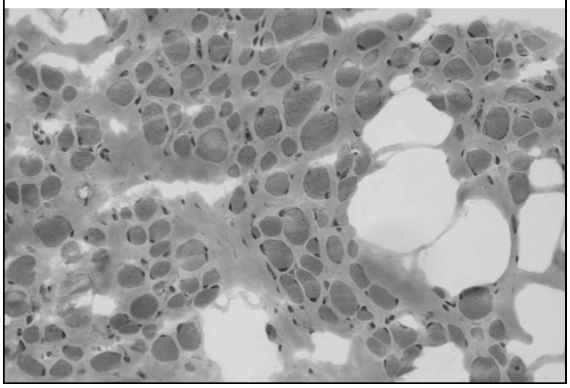
DUCHENNE MUSCULAR DYSTROPHY

- X-linked recessive inheritance
- Onset of weakness noticeable at 2-5 years of age.
- Progressive weakness, proximal>distal
- Hypertrophy of calves
- High serum creatine kinase activity
- Fatal in 3rd decade

DUCHENNE DYSTROPHY, H&E

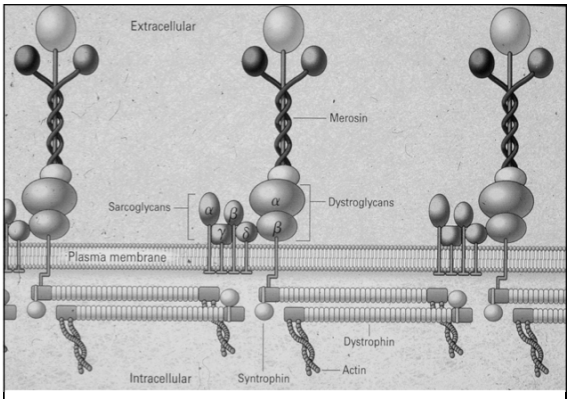


DUCHENNE DYSTROPHY, LATER STAGE



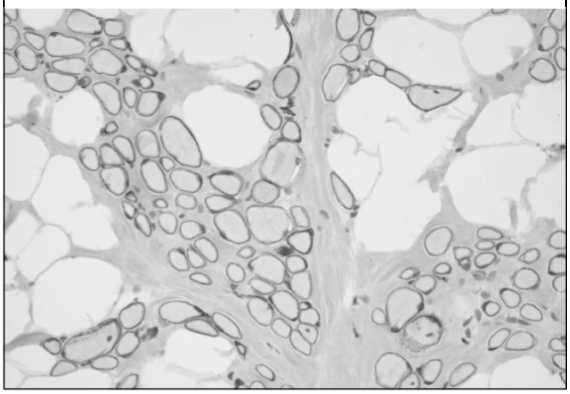
DUCHENNE MUSCULAR DYSTROPHY

- **Dystrophin is a 427 kD protein that binds to the inner face of the surface membrane.**
- **The protein has amino acid sequence similarities with alpha-actinin, an actin binding protein.**
- **The protein links actin to the surface membrane and the basal lamina acting through dystroglycan and merosin (alpha 2-laminin).**
- **Interrupting this linkage causes the surface membrane to be unstable leading to fiber injury.**

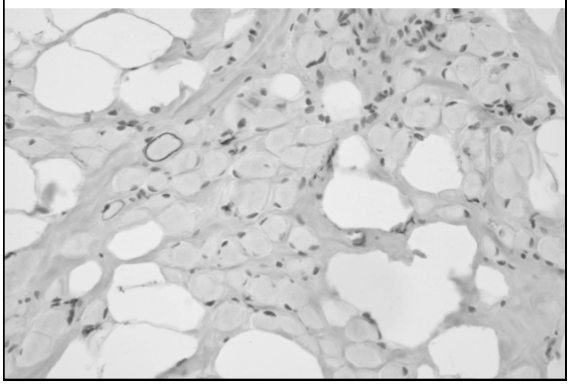


Duggan et al. Mutations in the sarcoglycan genes in patients with myopathy. N Engl J Med 1997;336:618

DUCHENNE DYSTROPHY, SPECTRIN



DUCHENNE DYSTROPHY, DYSTROPHIN



INFLAMMATORY MYOPATHIES

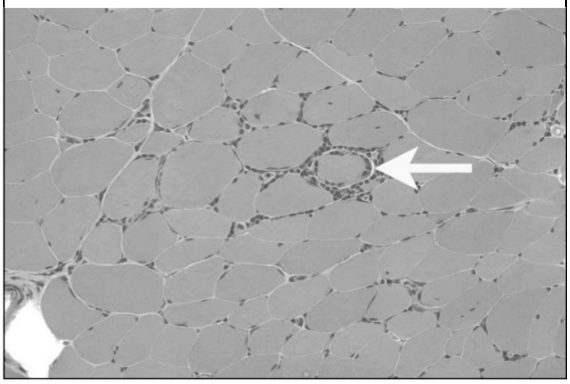
- **Polymyositis**
- **Inclusion body myositis**
- **Dermatomyositis**

POLYMYOSITIS

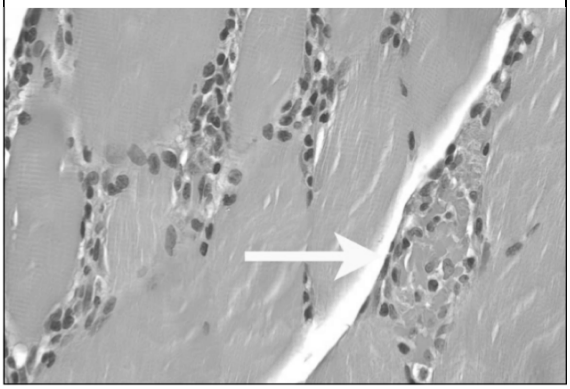
DIAGNOSTIC FEATURES OF POLYMYOSITIS

- **Subacute progressive weakness, proximal>distal. Usually adults, women more common than men.**
- **Elevated serum creatine kinase activity.**
- **Electromyogram: myopathic potentials, spontaneous activity.**
- **Muscle biopsy: inflammatory myopathy affecting chiefly the endomysium.**
- **Usually respond to glucocorticoids.**

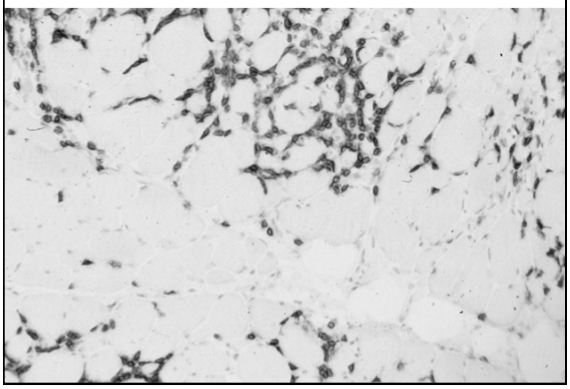
POLMYOSITIS, H&E



POLMYOSITIS, PARAFFIN SECTION, H&E



POLMYOSITIS, IMMUNOPEROXIDASE, CD8



POLYMYOSITIS: PATHOLOGY

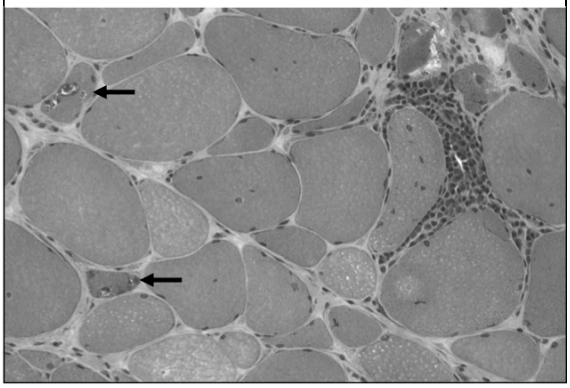
- **Necrotic fibers and regenerating fibers randomly distributed throughout the muscle specimen.**
- **CD8 cytotoxic cells infiltrate predominantly the endomysium with invasion of rare myofibers.**
- **Little fibrosis or myofiber hypertrophy, consistent with a subacute disorder.**

INCLUSION BODY MYOSITIS

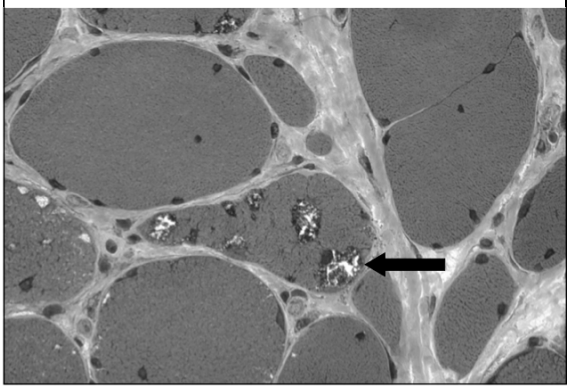
DIAGNOSTIC FEATURES OF IBM

- **Most common inflammatory myopathy in patients over the age of 50 years and affects mostly men.**
- **Slowly progressive weakness, proximal and distal.**
- **Mildly elevated serum creatine kinase or normal.**
- **Electromyogram: myopathic potentials, spontaneous activity.**
- **Muscle biopsy: resembles polymyosits, but chronic and exhibits rimmed vacuoles and amyloid inclusions.**
- **Usually does not respond to glucocorticoids.**

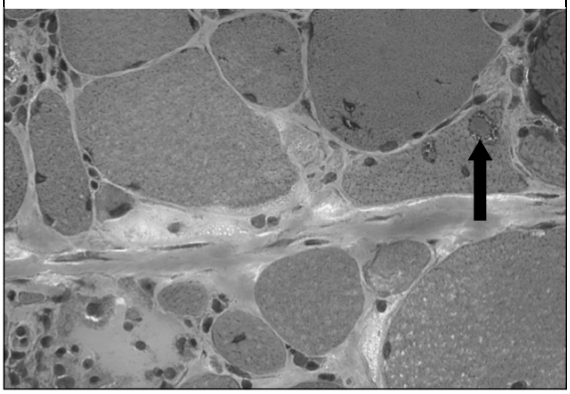
INCLUSION BODY MYOSITIS, H&E



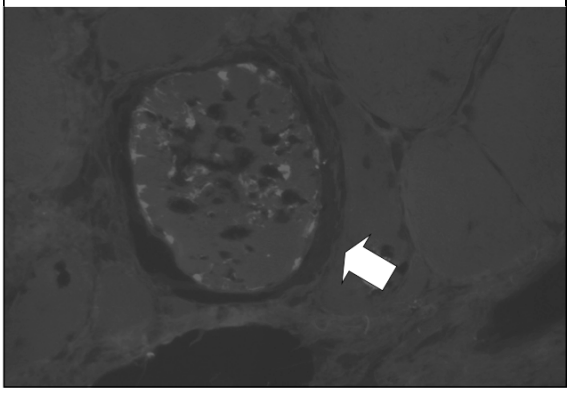
IBM, RIMMED VACUOLES, H&E



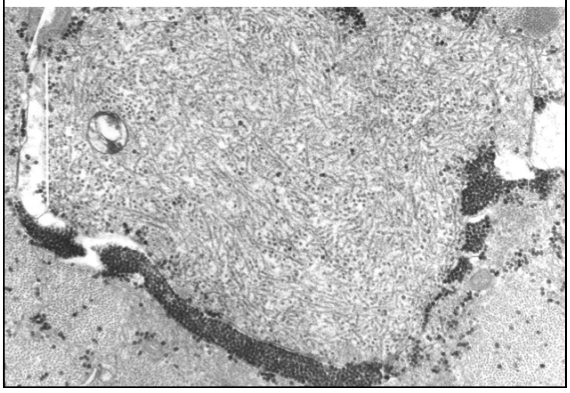
IBM, EOSINOPHILIC INCLUSION IN A RIMMED VACUOLE



IBM, CONGO RED, FLUORESCENCE, RHODAMINE OPTICS



ELECTRON MICROSCOPY, 15-20 nm FILAMENTS



IBM PATHOLOGY

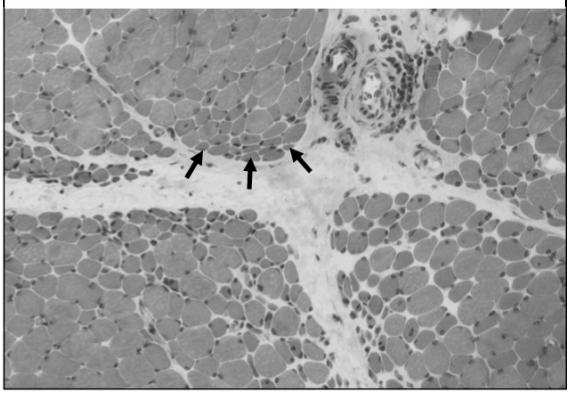
- IBM resembles polymyositis but has hyper- trophic fibers and prominent endomysial fibrosis indicating it is chronic.
- Rimmed vacuoles.
- Congophilic fibrillar inclusions, composed of abnormal (? paired-helical) filaments.
- Lymphocytic infiltration suggests an auto-immune disorder, but disorder is usually unresponsive to immunosuppression.

DERMATOMYOSITIS

DIAGNOSTIC FEATURES OF DERMATOMYOSITIS

- Subacute progressive weakness, proximal>distal. Children and adults, women more common than men.
- Characteristic rash on face, chest & extensor surfaces.
- Elevated serum creatine kinase activity.
- Electromyogram: myopathic potentials, spontaneous activity.
- Muscle biopsy: inflammatory myopathy affecting chiefly the perimysium with perifascicular atrophy.
- Usually respond to glucocorticoids or IVGG.

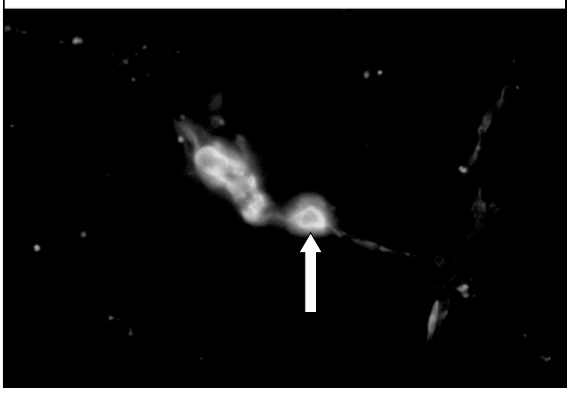
DERMATOMYOSITIS, PERIFASCICULAR ATROPHY, H&E



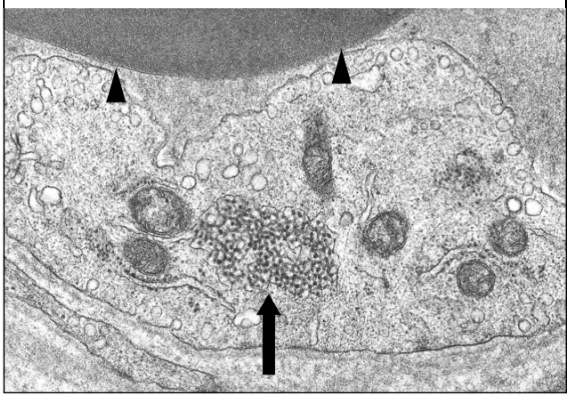
DERMATOMYOSITIS: LYMPHO-CYTE PHENOTYPES

- CD4 T cells and B cells located chiefly in connective tissue and around vessels of perimysium.
- Inconstant and usually sparse CD8 T cells located mainly in endomysium.

DM, IMMUNE COMPLEXES (C5b-9) IN BLOOD VESSEL WALL



TUBULORETICULAR AGGREGATE IN ENDOTHELIAL CELL



DERMATOMYOSITIS: PATHOLOGY

- **Perifascicular atrophy of muscle fibers, with or without necrotic fibers or regenerating fibers.**
- **Immune complexes of immunoglobulins and complement components in the walls of blood vessels.**
- **Endothelial tubuloreticular aggregates.**
- **Reduced number of capillaries at periphery of fascicle.**
- **Lymphocytes are often sparse and located in chiefly perimysium.**

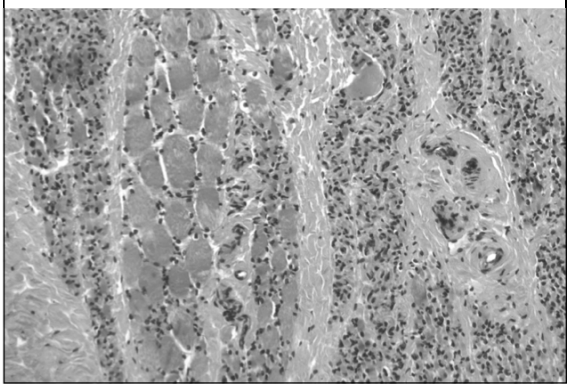
INFLAMMATORY MYOPATHIES: PATHOPHYSIOLOGY

- **Polymyositis and inclusion body myositis (IBM) have autoaggressive CD8 lymphocytes that appear to attack myofibers and suggest an autoimmune role. However, a major question exists about the etiology and pathogenesis of IBM.**
- **Dermatomyositis is thought to be caused by autoantibodies, possibly targeting an antigen of the endothelium. The pathological findings suggest that myofiber injury may be caused by ischemia.**

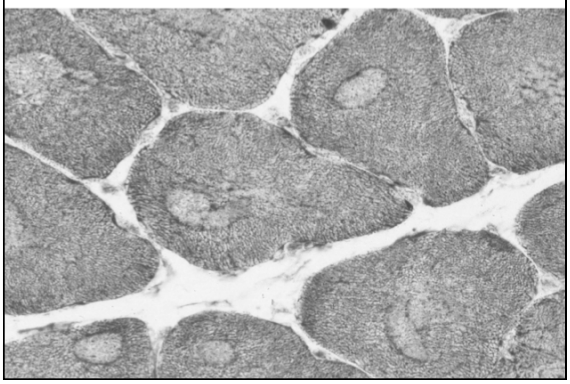
HYPOTONIA IN INFANCY

DISEASE	INHERITED	PROGNOSIS
Werdnig-Hoffmann disease	Autosomal recessive	Fatal
Central core disease	Autosomal	Not pro-
Nemaline myopathy	Variable	Variable
Mitochondrial disorder	Maternal or autosomal	Variable

WERDNIG-HOFFMANN DISEASE

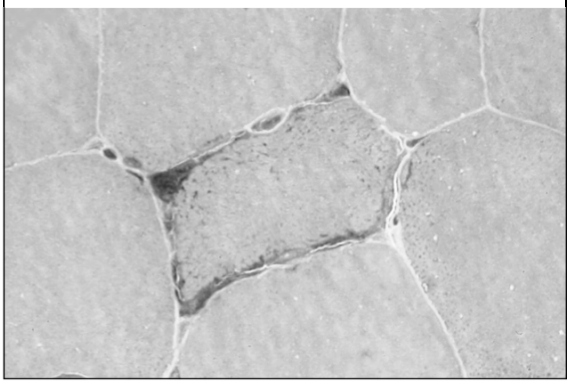


CENTRAL CORE DISEASE, NADH DEHYDROGENASE

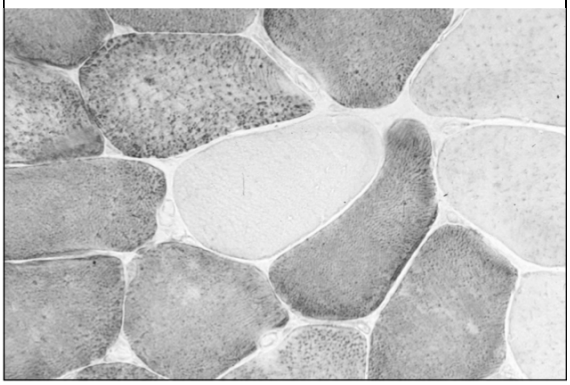


MITOCHONDRIAL MYOPATHY

MUTATIONS OF mtDNA RAGGED "RED" FIBER



CYTOCHROME C OXIDASE DEFICIENT MYOFIBER



RRF, SUCCINATE DEHYDROGENASE