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)

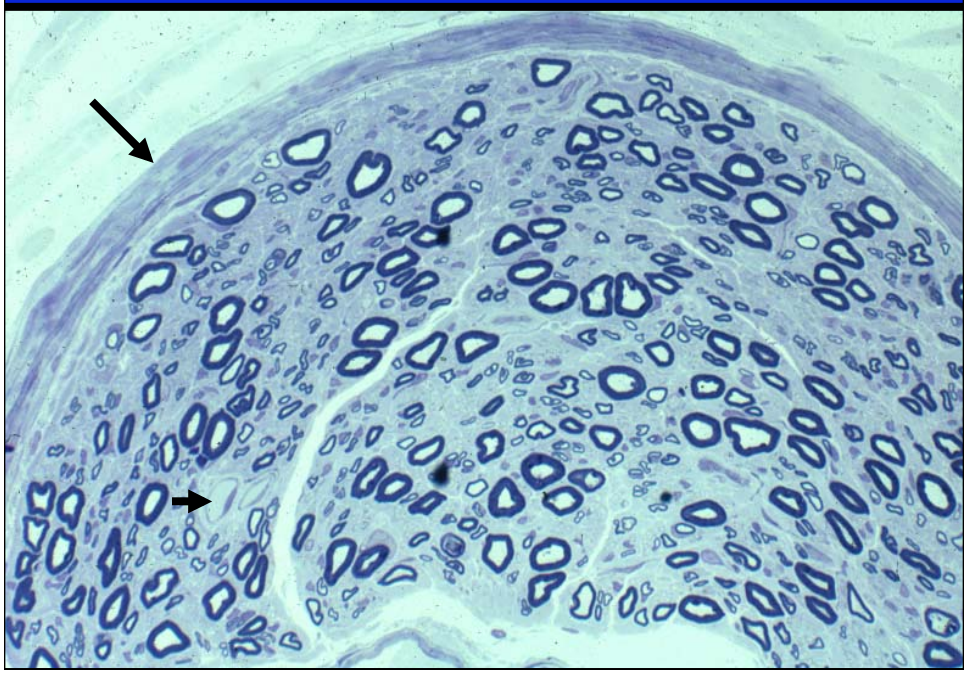
CLINICAL ROLE OF NERVE BIOPSY IS VERY LIMITED

- 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.

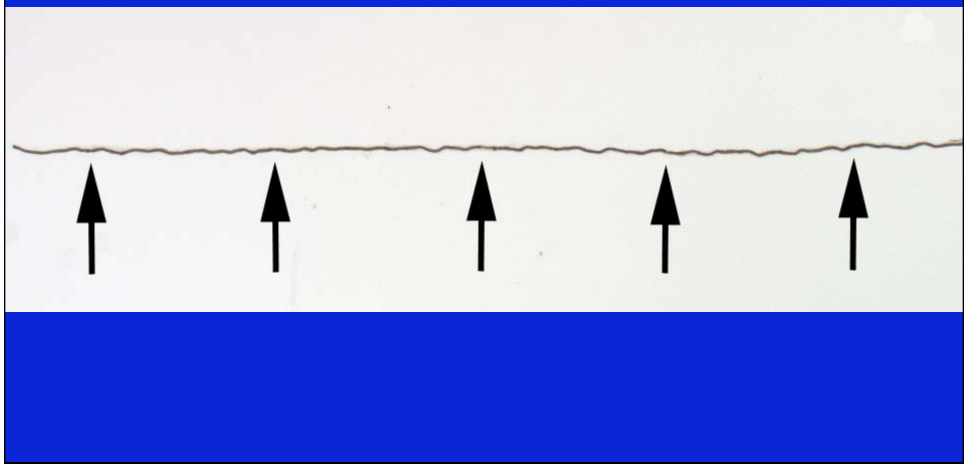
PATHOLOGICAL ANALYSIS OF SURAL NERVE BIOPSY

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

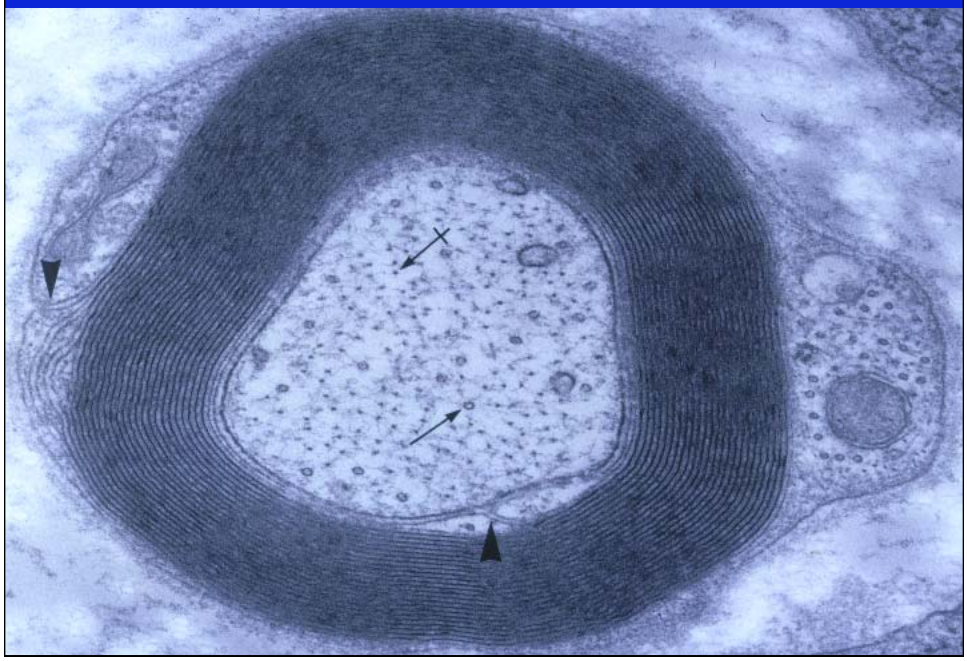
SURAL NERVE, SEMITHIN PLASTIC SECTION (TOLUIDINE BLUE)



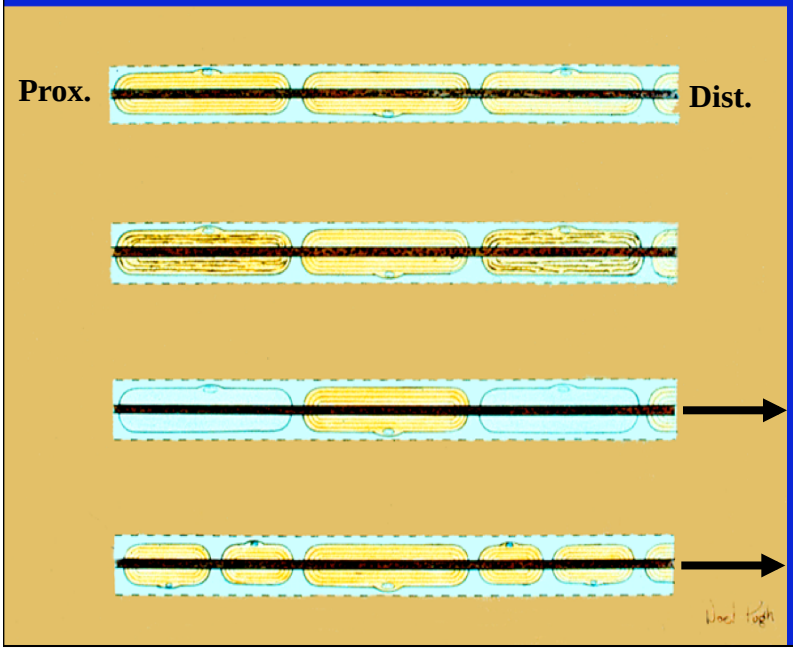
TEASED MYELINATED FIBER: NORMAL



PERIPHERAL NERVE, ELECTRON MICROGRAPH

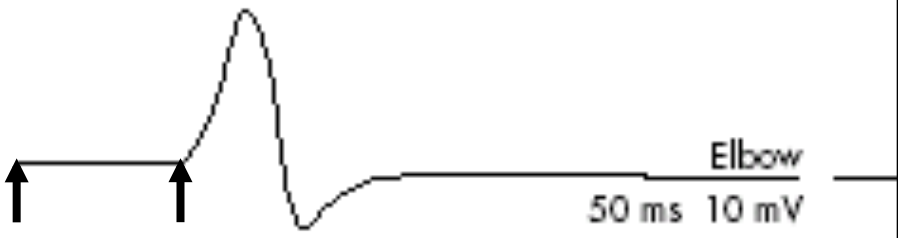


SEQUENCE OF SEGMENTAL DEMYELINATION & REMYELINATION

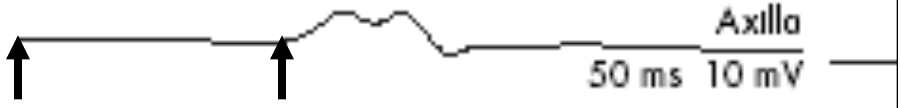


NERVE STIMULATION EVOKES ACTION POTENTIAL IN HAND MUSCLE

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

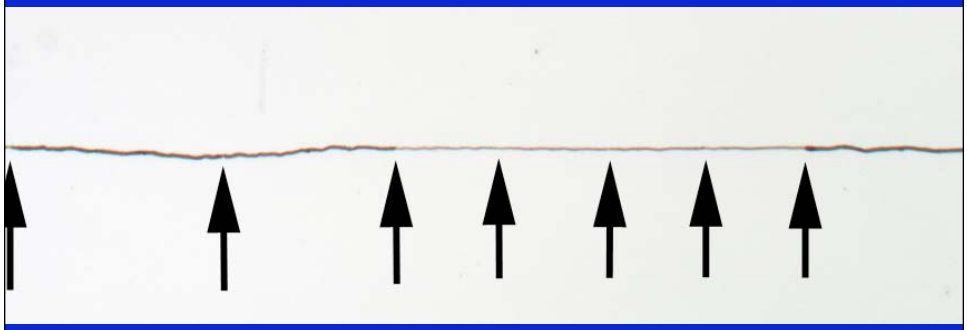


NORMAL COMPOUND MUSCLE ACTION POTENTIAL

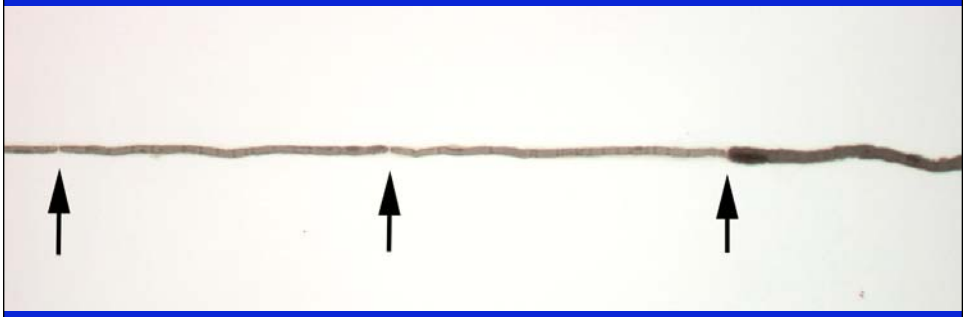


REDUCED AMPLITUDE OF CMAP

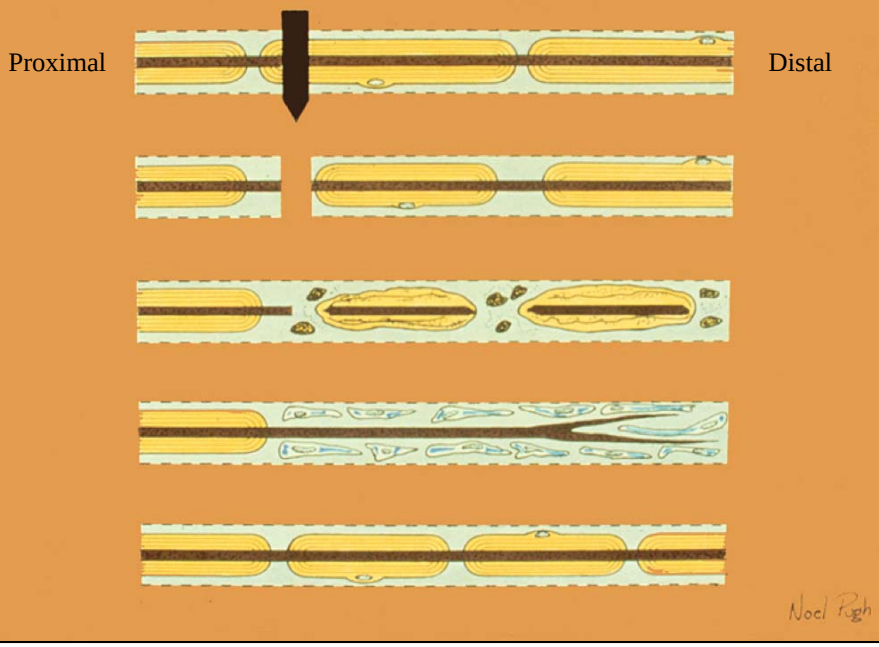
TEASED MYELINATED FIBER: SEGMENTAL REMYELINATION



SAME TEASED FIBER AT HIGHER MAGNIFICATION



SEQUENCE OF SEGMENTAL AXONAL DEGENERATION & REGENERATION



TEASED MYELINATED FIBER: AXONAL DEGENERATION

CLASSIFICATION OF PERIPHERAL NERVE DISEASES

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- **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)**

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.

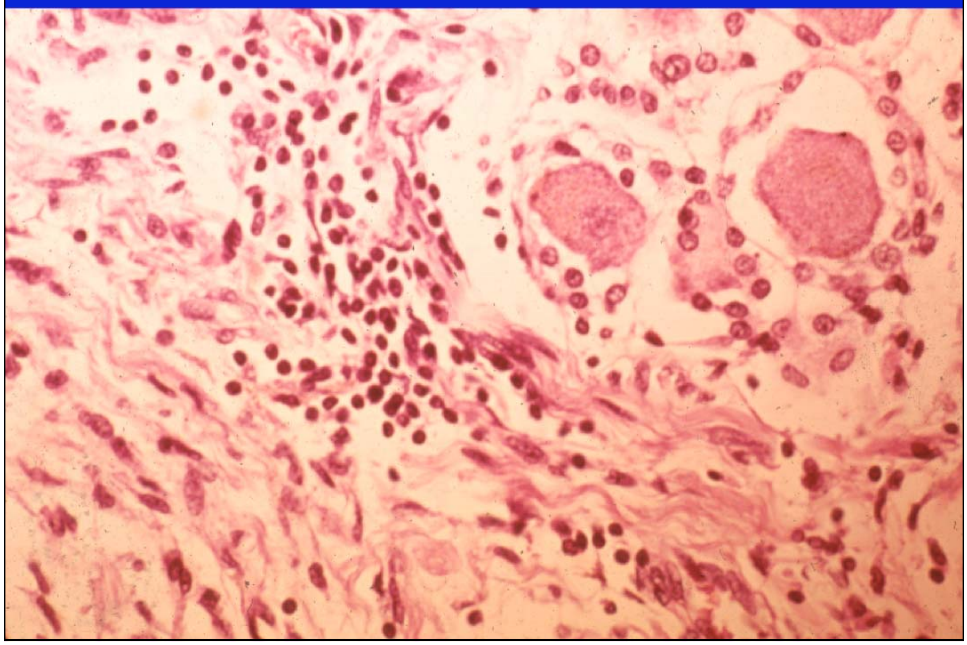
GBS: DIAGNOSIS & TREATMENT

- 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.

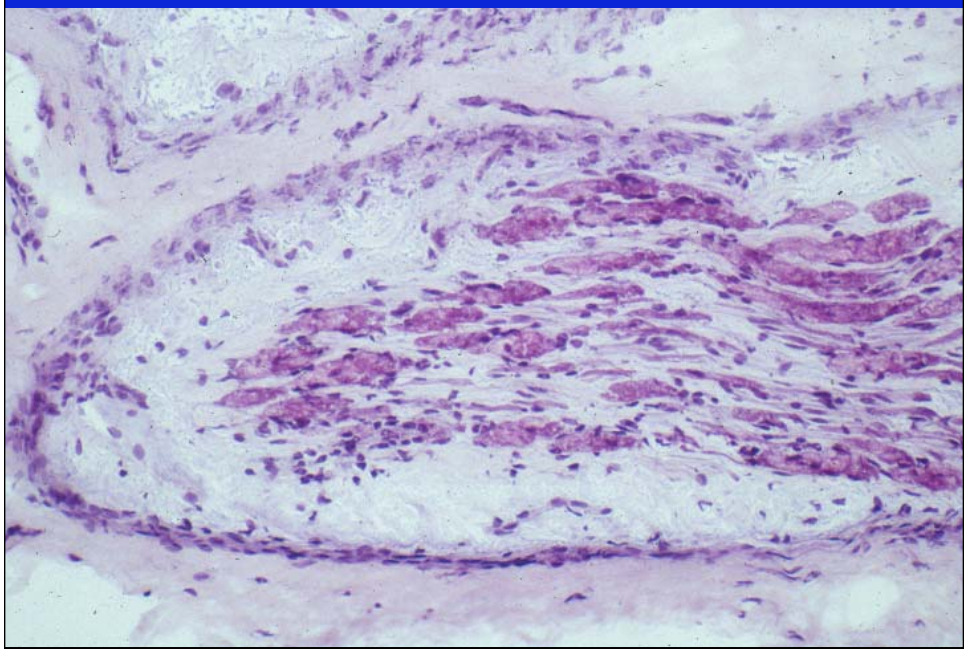
PATHOLOGY OF GUILLAIN-BARRÉ SYNDROME

- 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.

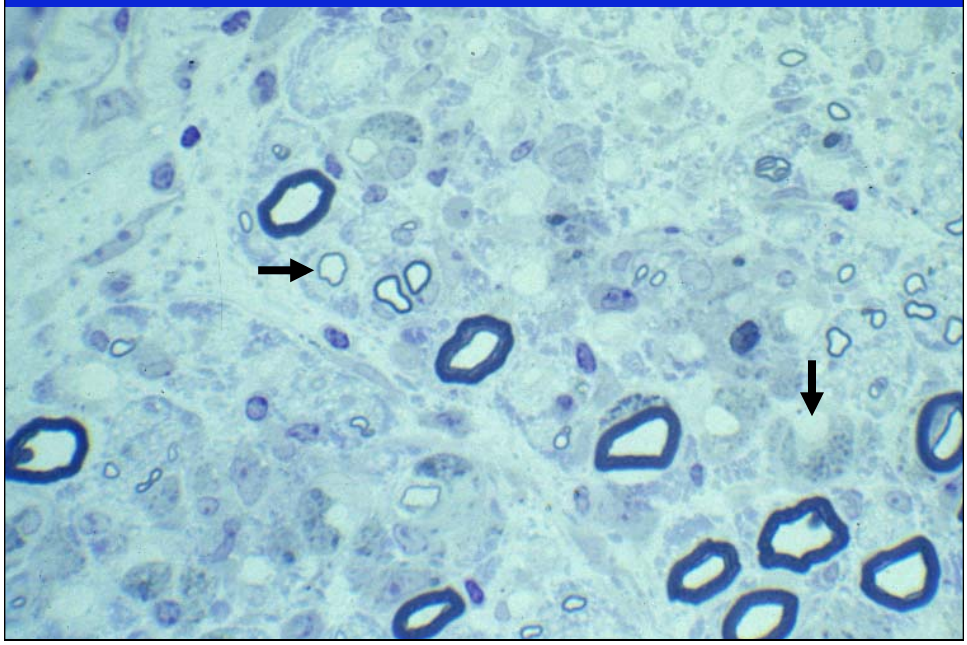
GBS, DORSAL ROOT GANGLION, H&E



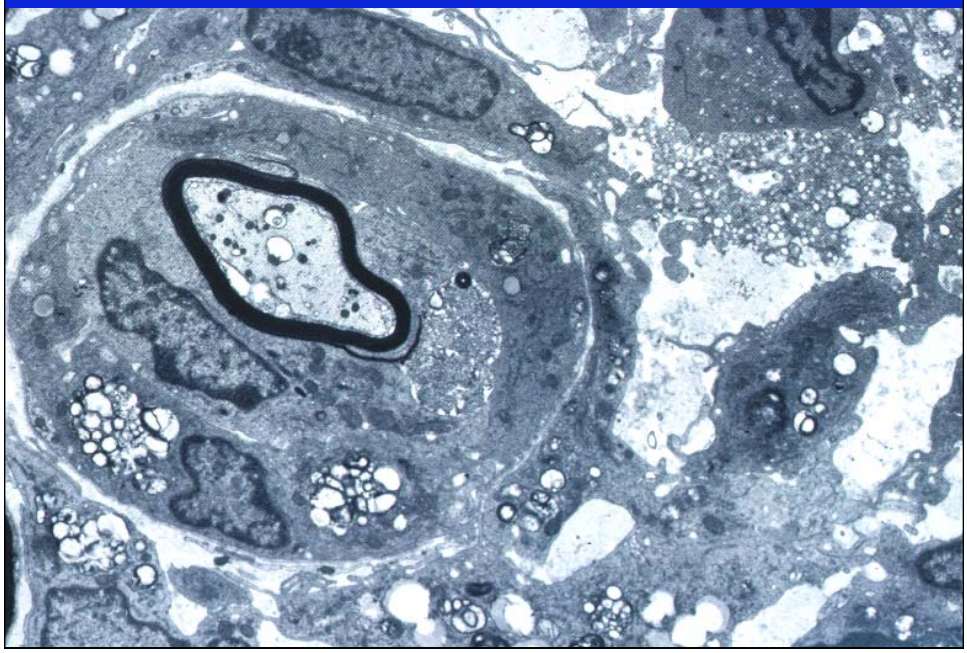
GBS, MOTOR NERVE, H&E



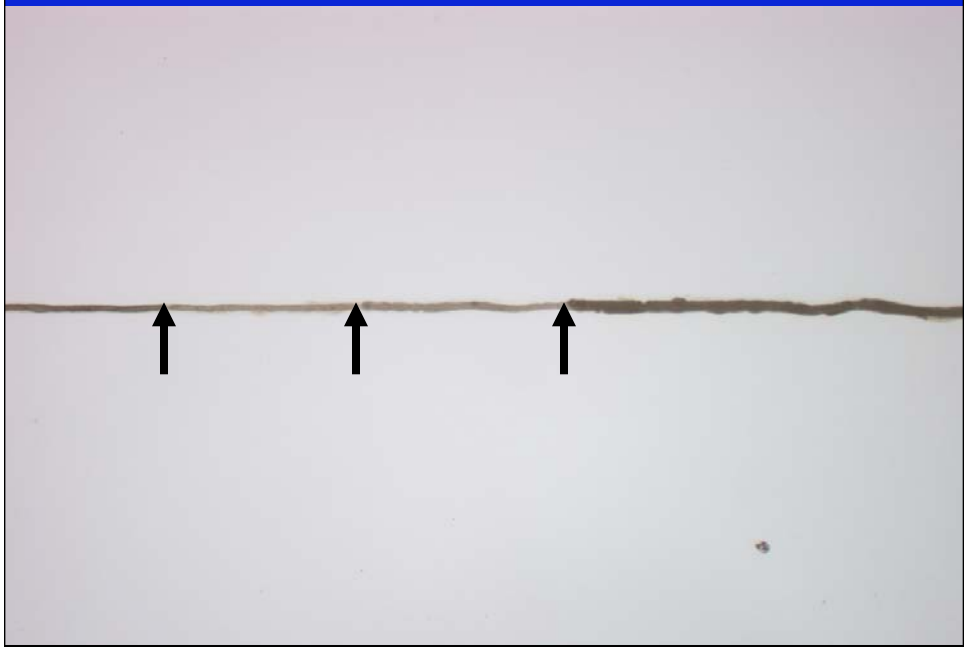
GBS, MOTOR NERVE, SEMITHIN SECTION



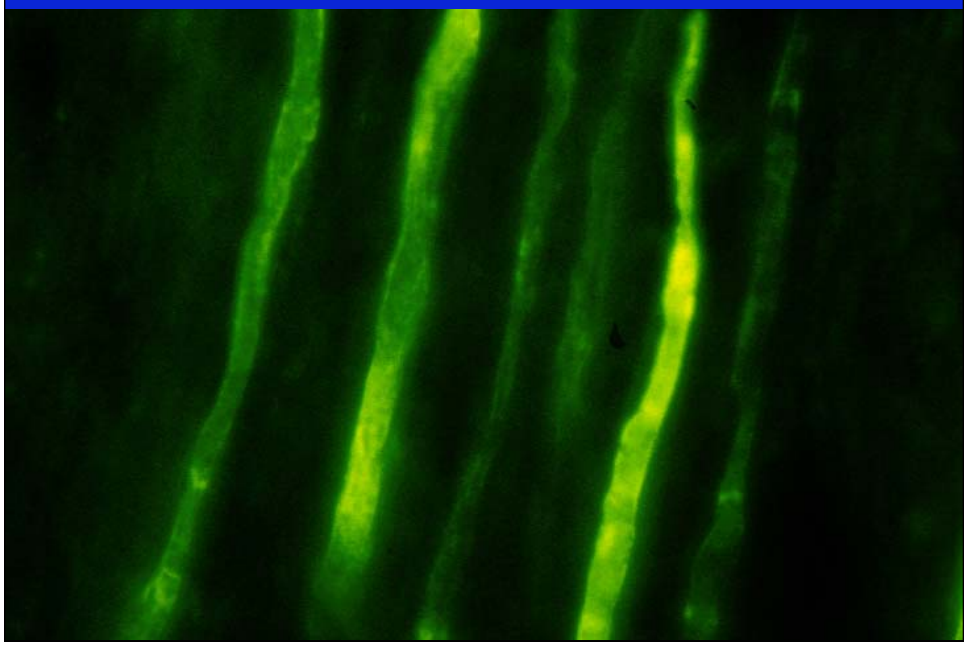
GBS, ELECTRON MICROGRAPH



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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Neuronopathy

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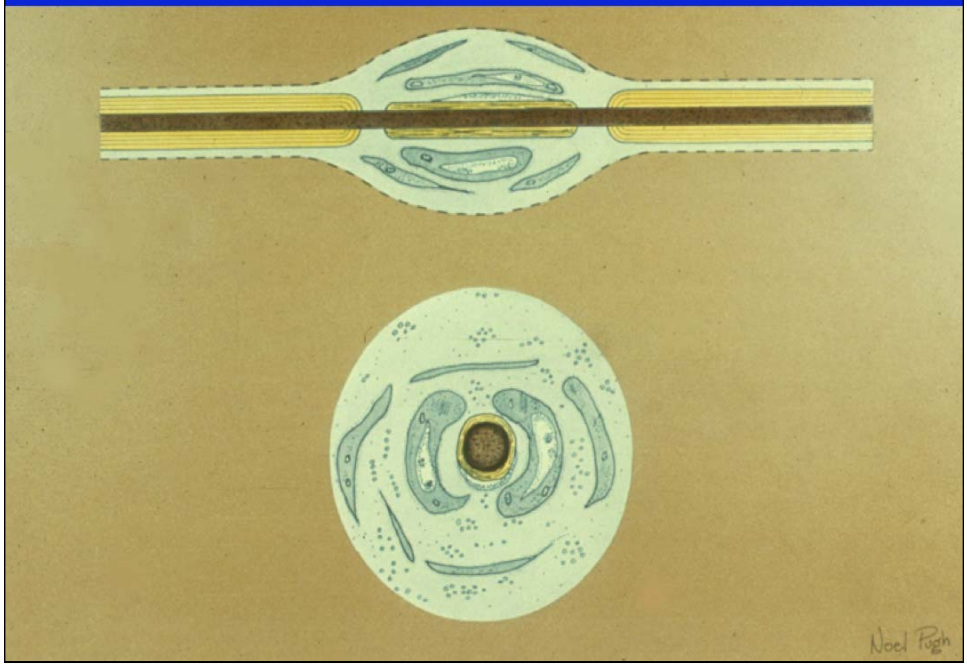
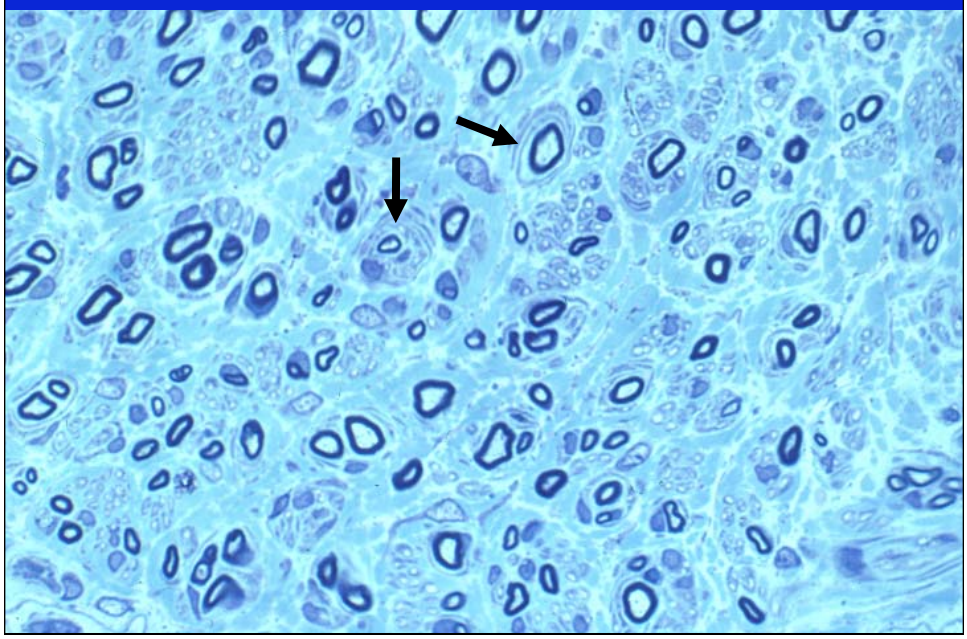
CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

- **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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CHARCOT-MARIE-TOOTH, TYPE I

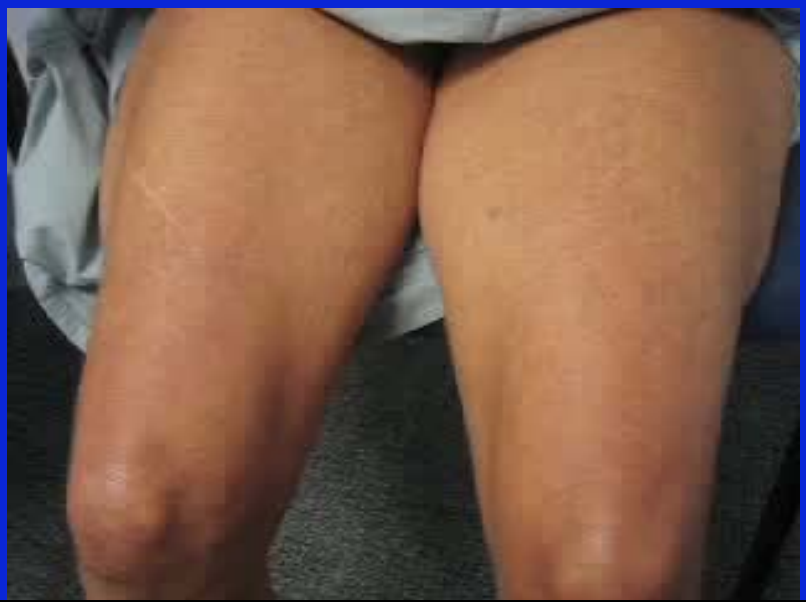
- **Slowly progressive distal limb weakness begins in first decade with great variation in onset; few sensory complaints.**
- **Autosomal dominant, mutations commonly affect *PMP22*.**
- **Neurological exam:**
  - **Atrophy of distal leg muscles (stork leg appearance).**
  - **Palpable nerve enlargement 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.

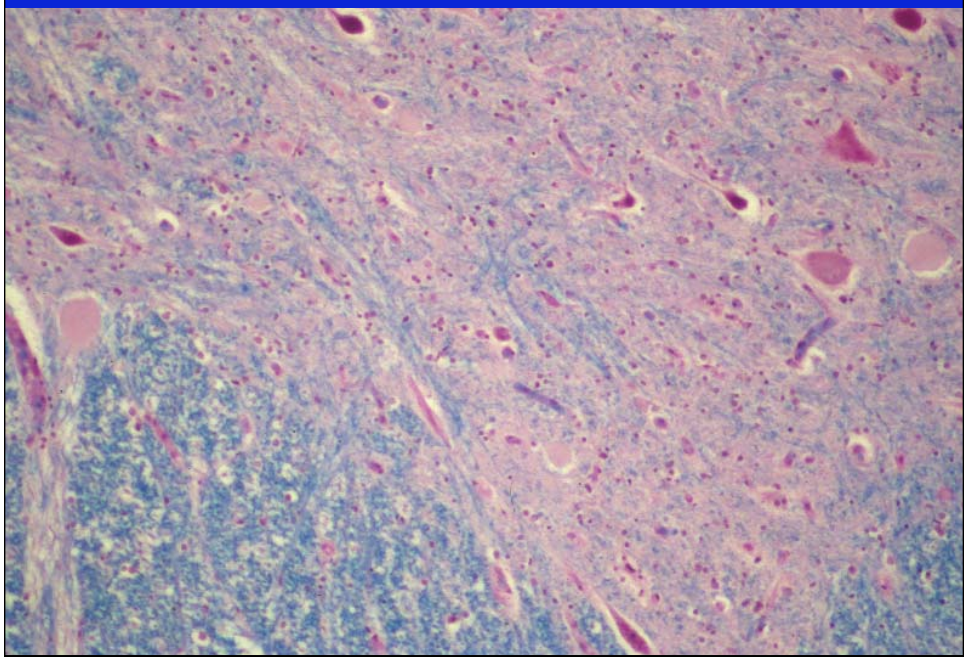
ALS: FASCICULATIONS & BABINSKY REFLEXES



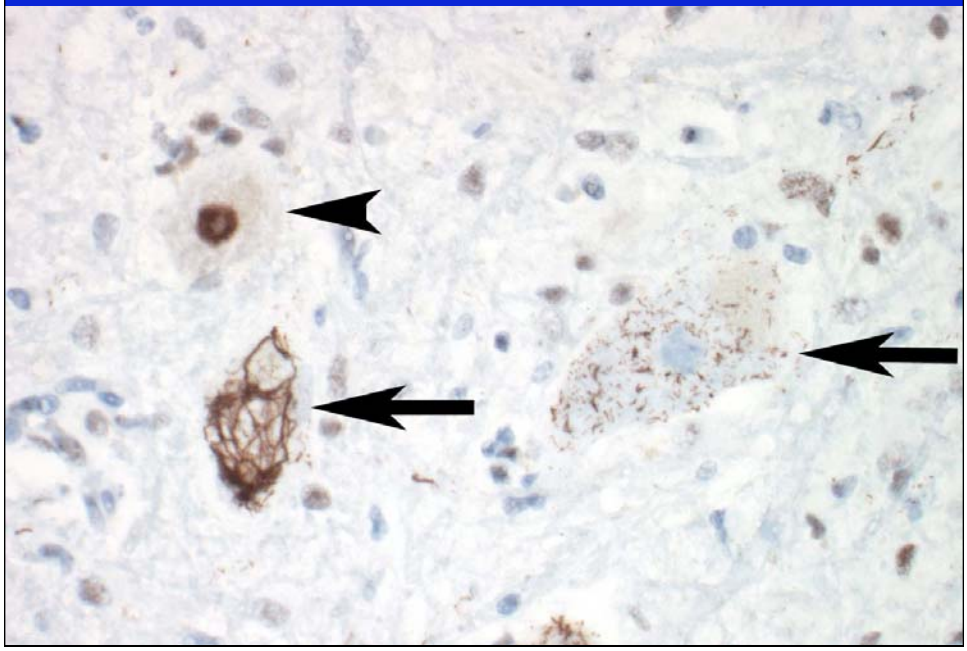
ALS: LOWER MOTOR NEURON PATHOLOGY

- 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.

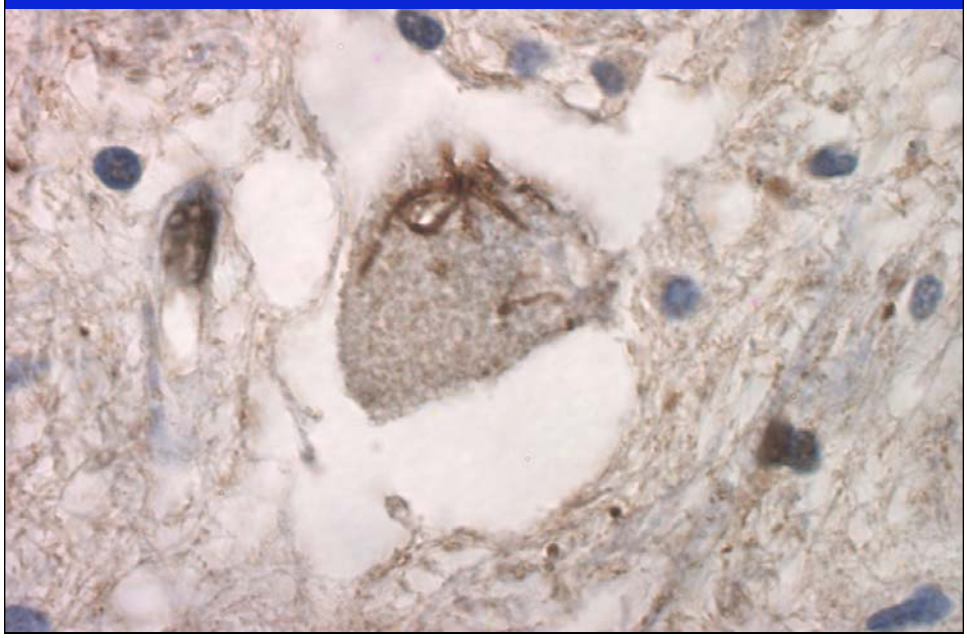
ALS: LOSS OF MOTOR NEURONS IN VENTRAL HORN



ALS & SARCOIDOSIS, SPINAL CORD, TDP-43



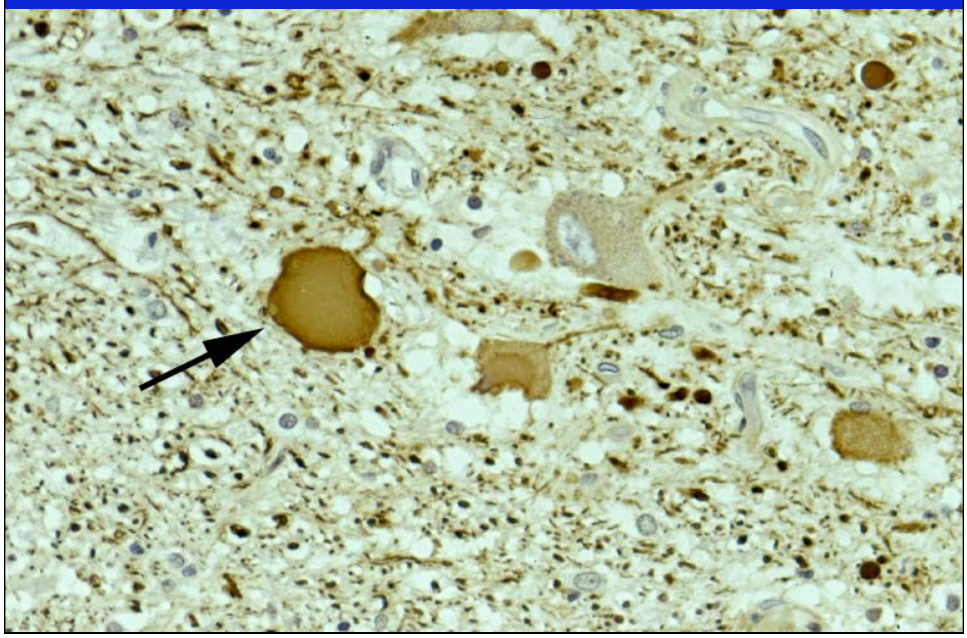
ALS, SKEIN-LIKE INCLUSIONS, UBIQUITIN



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%.

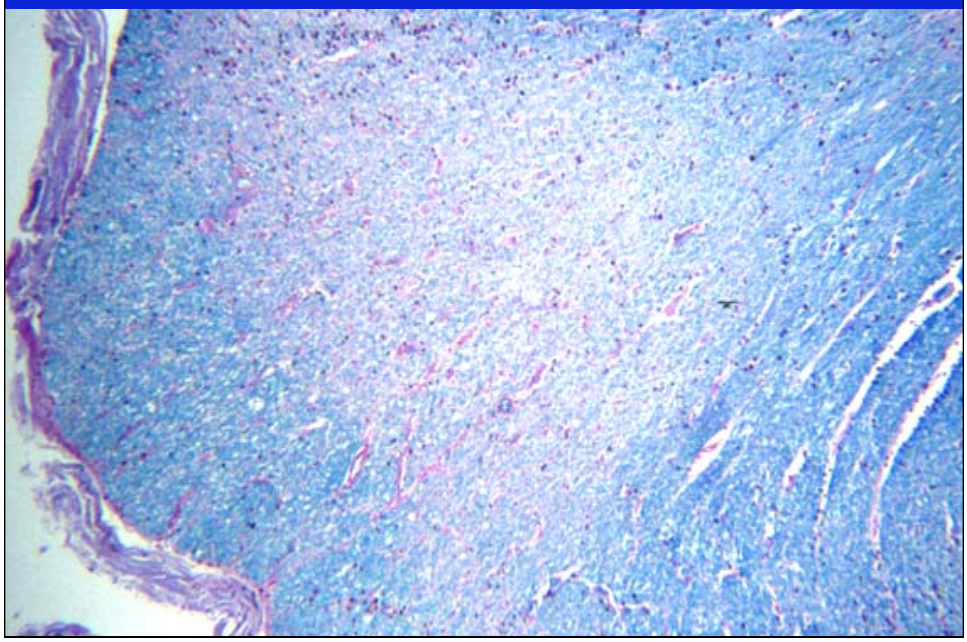
ALS, NEUROFILAMENT PROTEIN



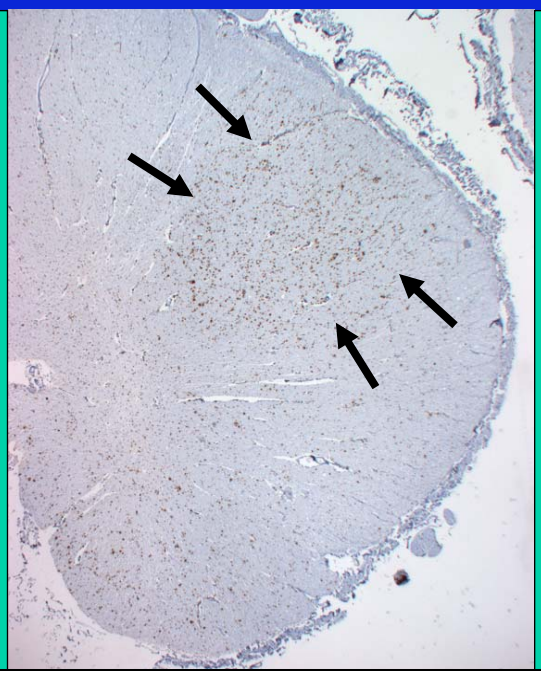
ALS: UPPER MOTOR NEURON PATHOLOGY

- 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

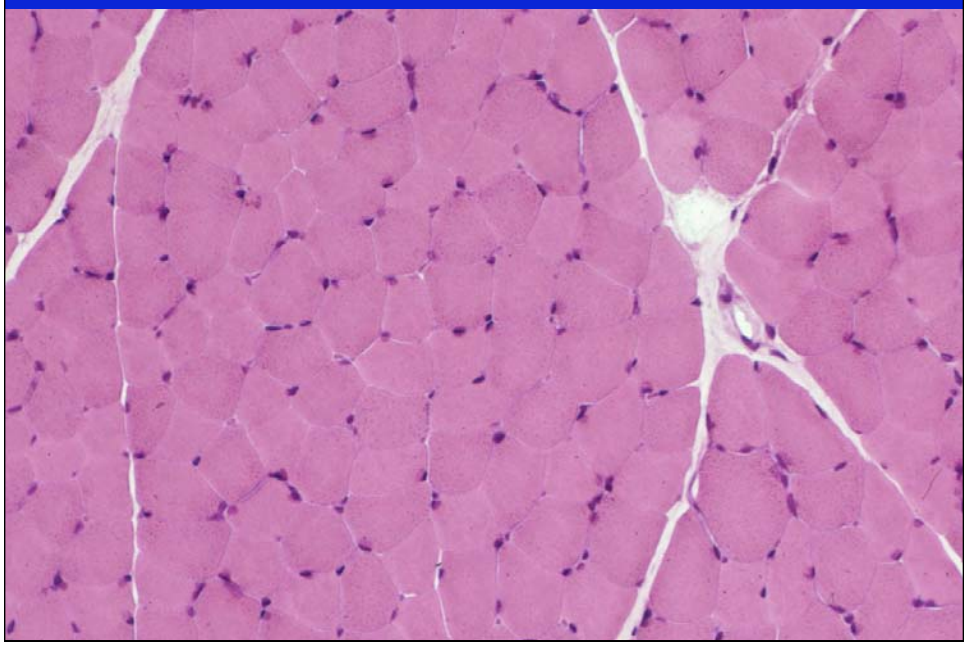
Mutations of the Cu/Zn superoxide dismutase (SOD1) cause ALS of 20% of familial cases. Expression of mutant human SOD1 in transgenic mice produces MND by a toxic or gain of function mechanism. This mouse model has yielded two major hypotheses of toxicity:

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

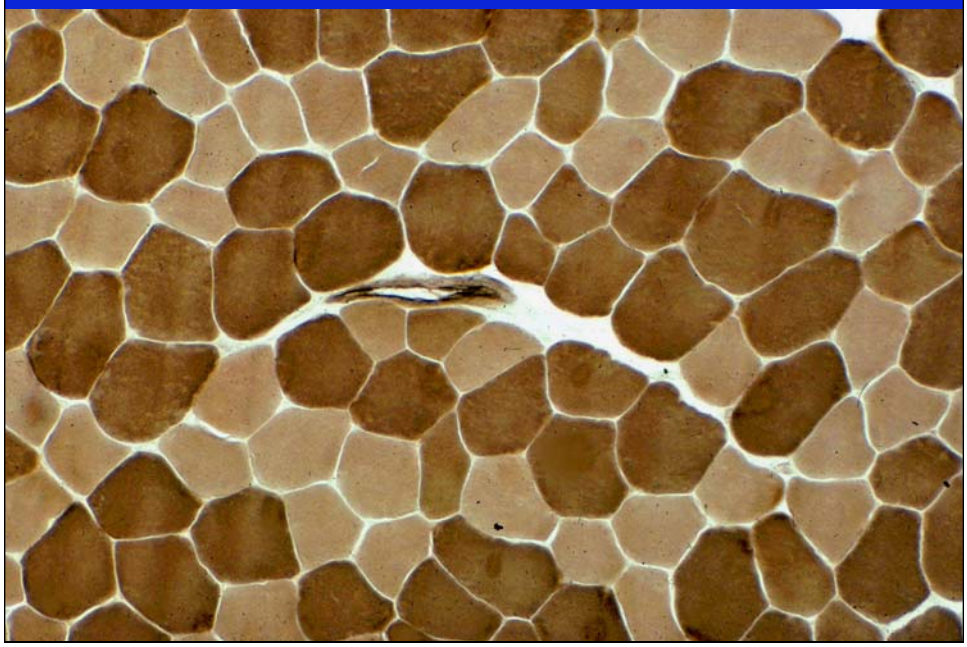
AIMS OF MUSCLE BIOPSY

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

CRYOSECTIONS OF SKELETAL MUSCLE, H&E

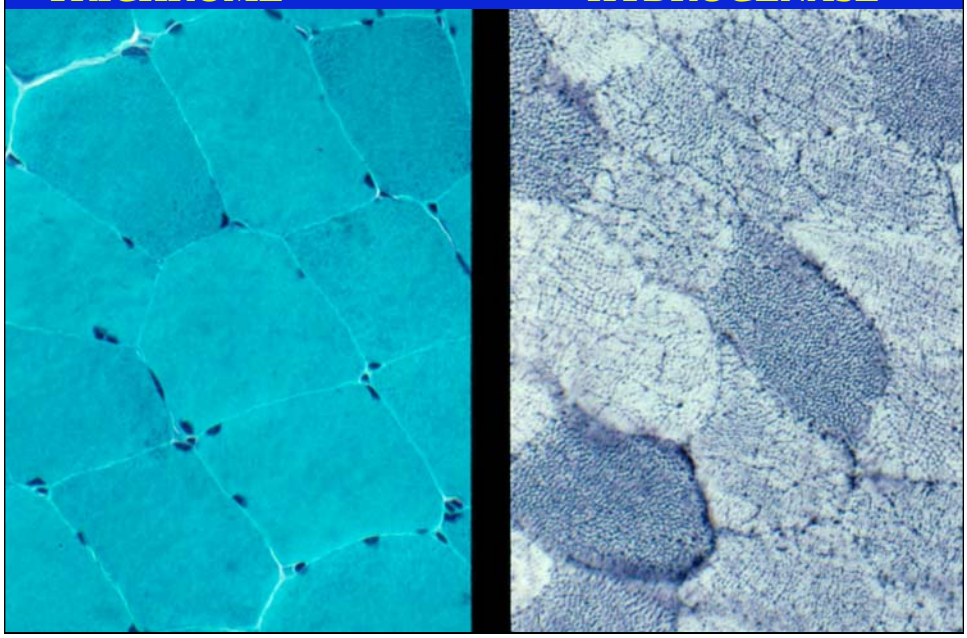


CRYOSECTIONS OF SKELETAL MUSCLE, ATPase



MODIFIED GOMORI TRICHROME

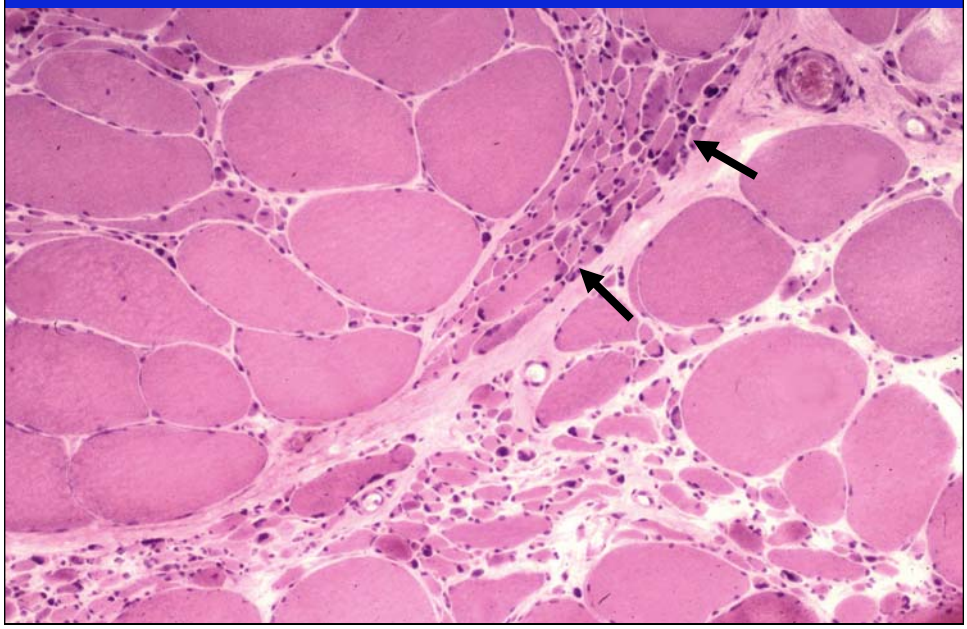
SUCCINATE DE-HYDROGENASE



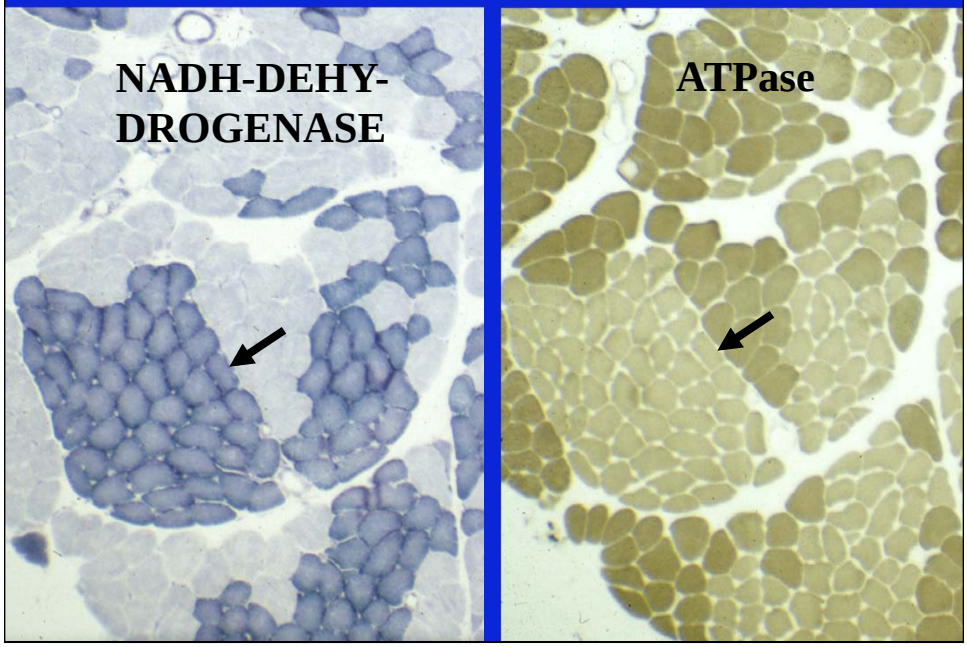
DIAGNOSTIC HISTOLOGICAL FEATURES OF A NEUROGENIC DISORDER

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

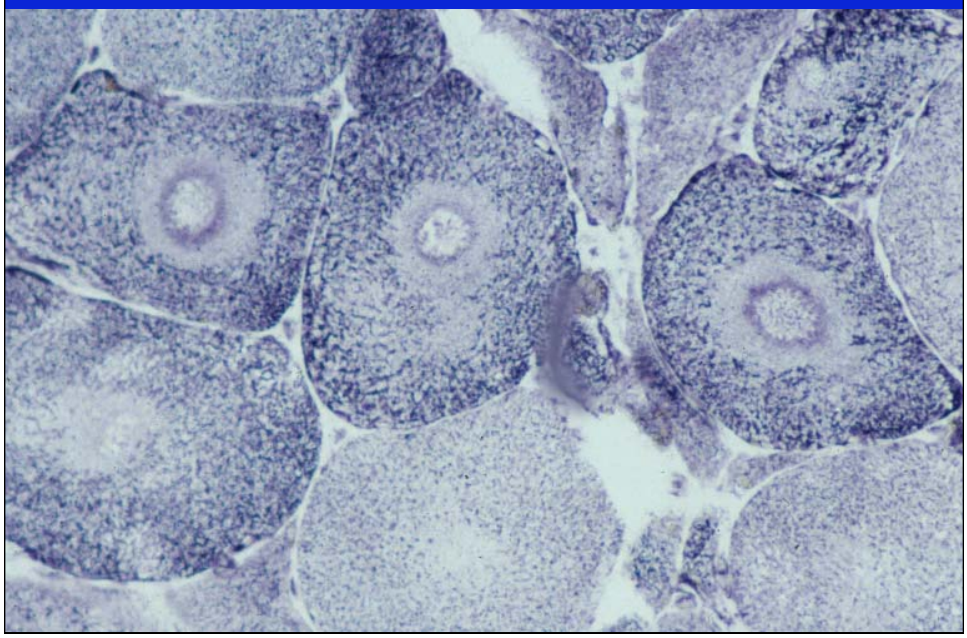
GROUPS OF ATROPHIC MYOFIBERS, H&E



FIBER TYPE GROUPING



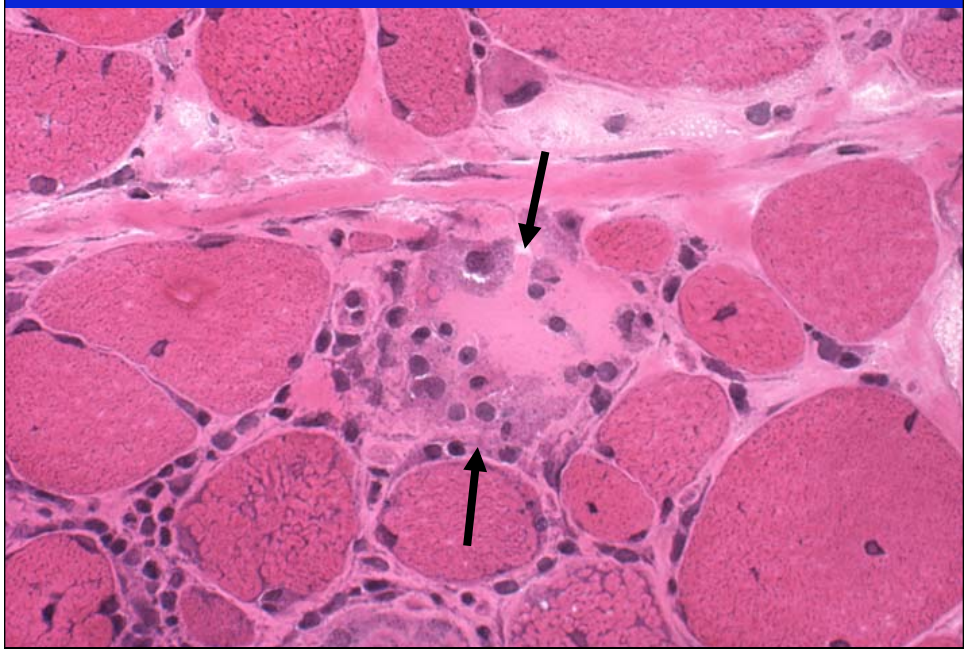
TARGET FIBERS, NADH DEHYDROGENASE



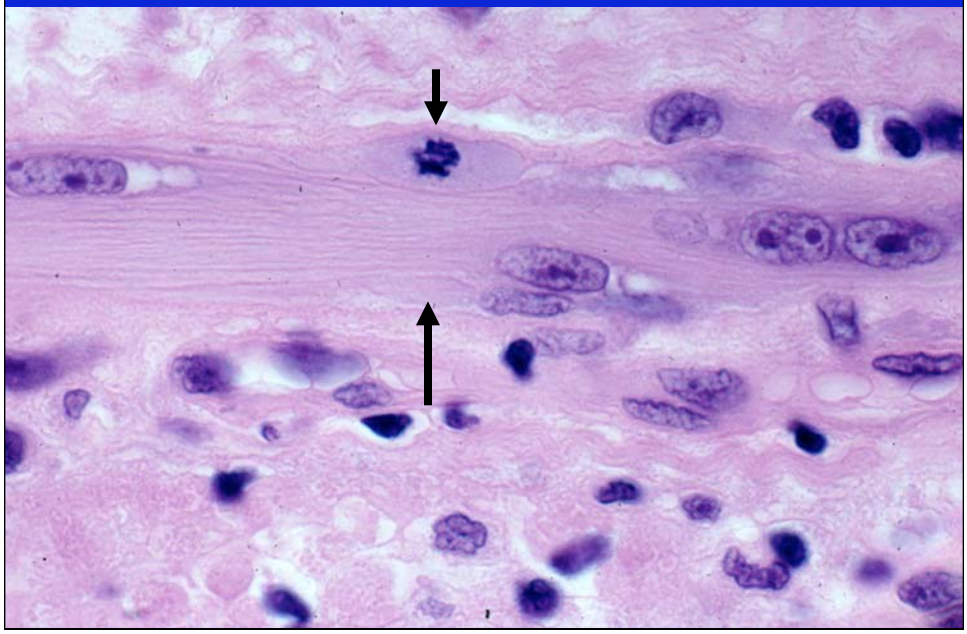
DIAGNOSTIC HISTOLOGICAL FEATURES OF MYOPATHIES

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

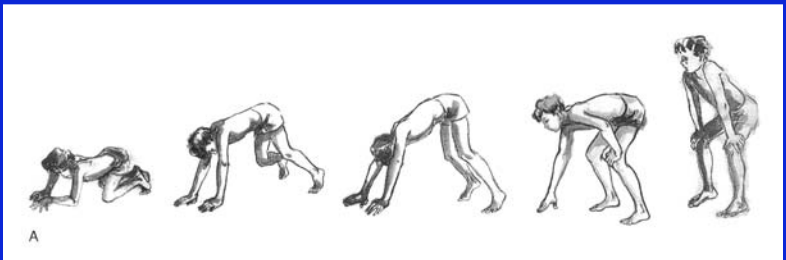
NECROTIC FIBER, H&E



REGENERATING FIBER, H&E



GOWER'S SIGN

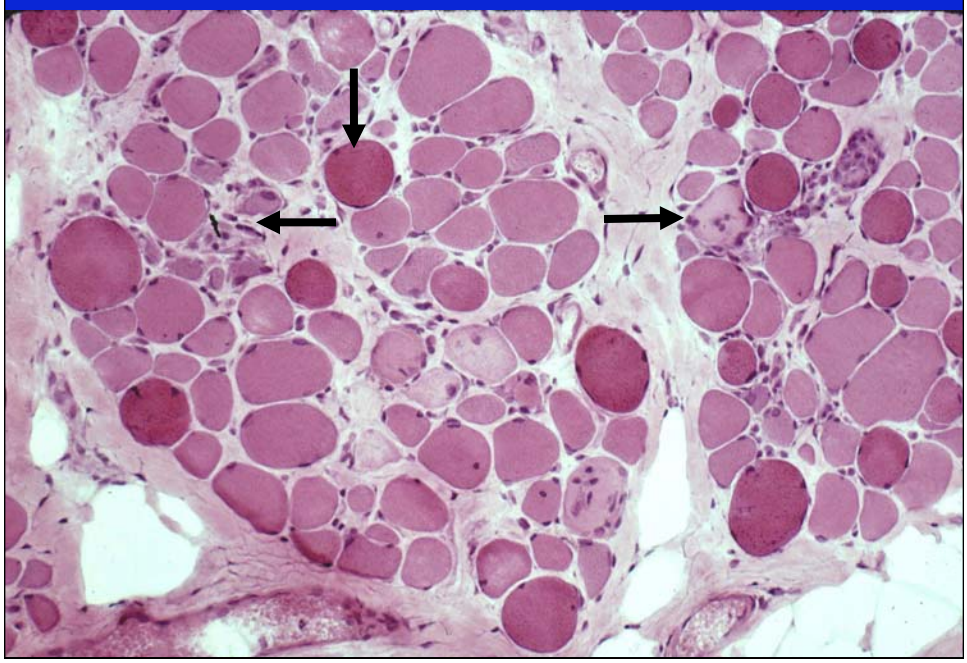


Gowers, 1879

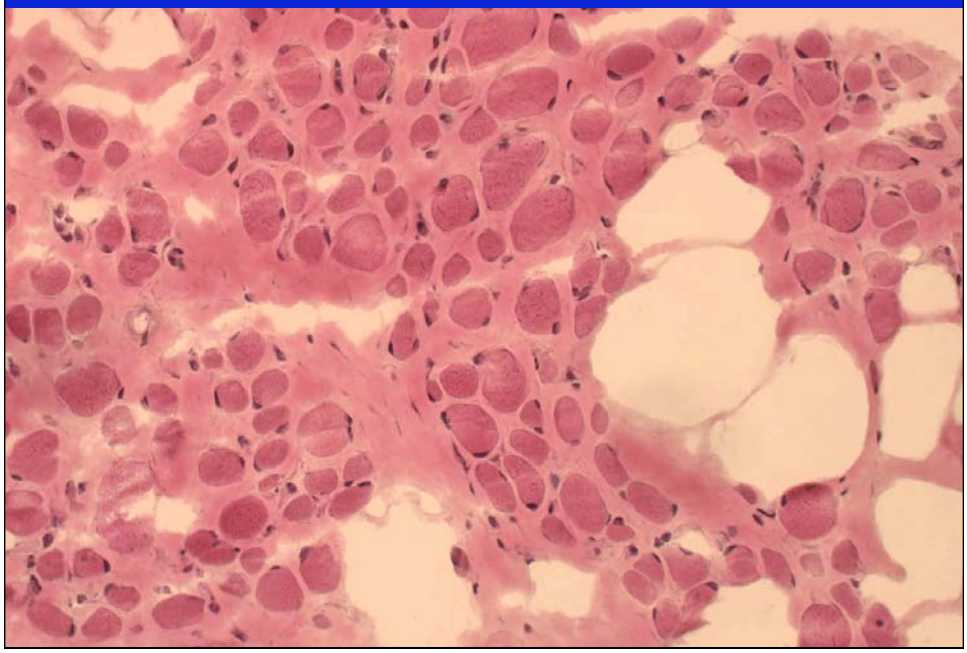
DUCHENNE MUSCULAR DYSTROPHY

- 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

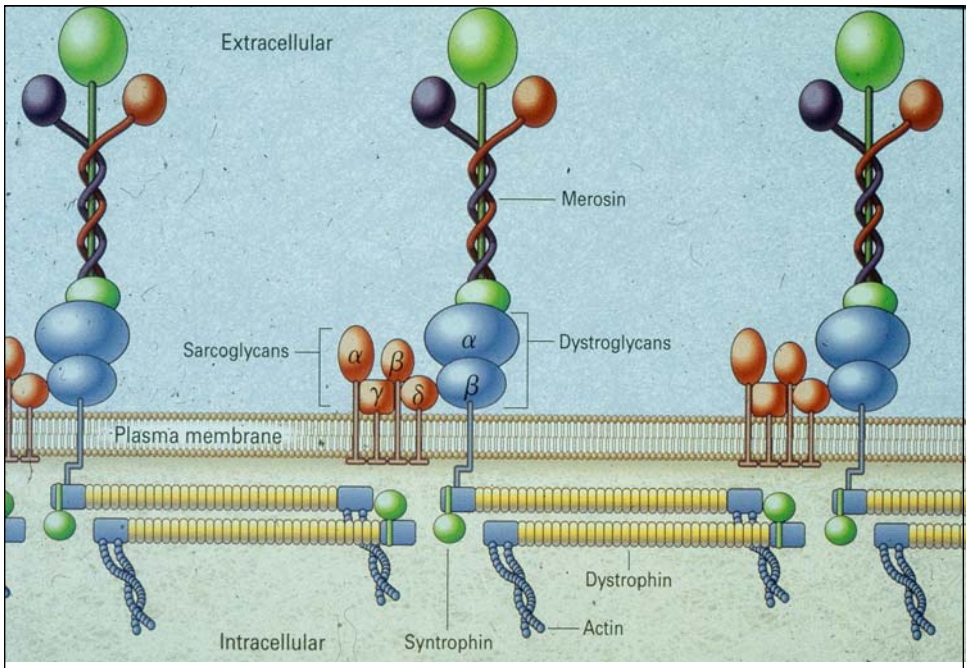


DUCHENNE DYSTROPHY, LATER STAGE



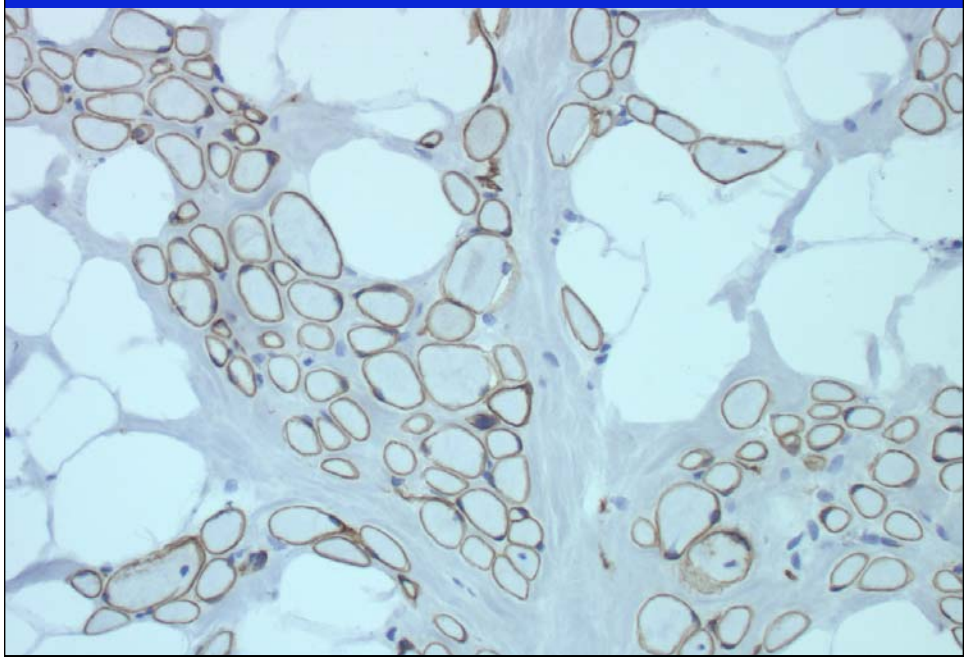
DUCHENNE MUSCULAR DYSTROPHY

- 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.

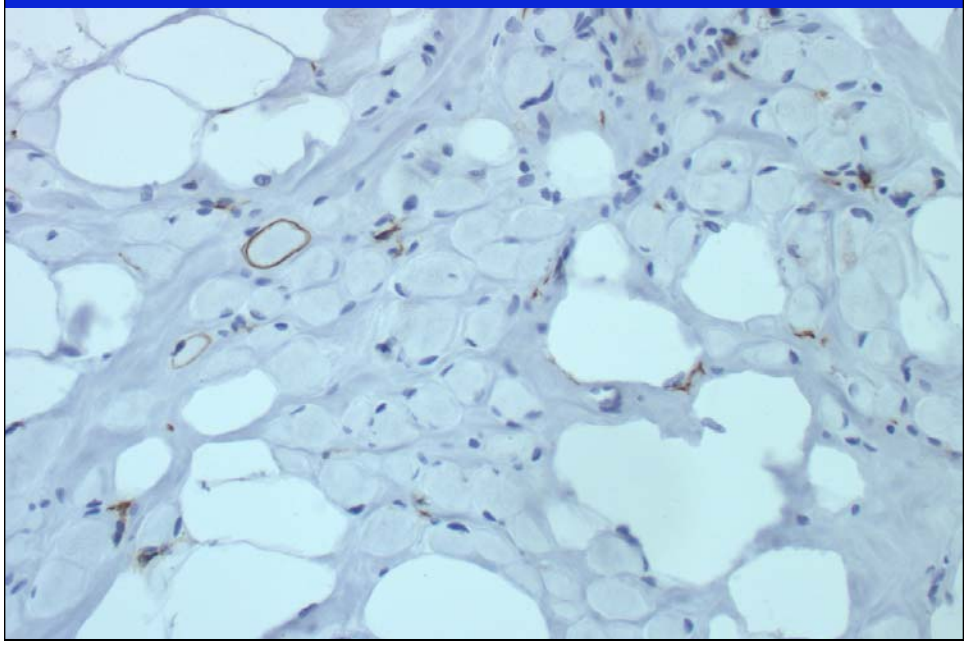


Duggan et al. Mutations in the sarcoglycan genes in patients with myopathy. N Engl J Med 1997;336:618

DUCHENNE DYSTROPHY, SPECTRIN



DUCHENNE DYSTROPHY, DYSTROPHIN



INFLAMMATORY MYOPATHIES

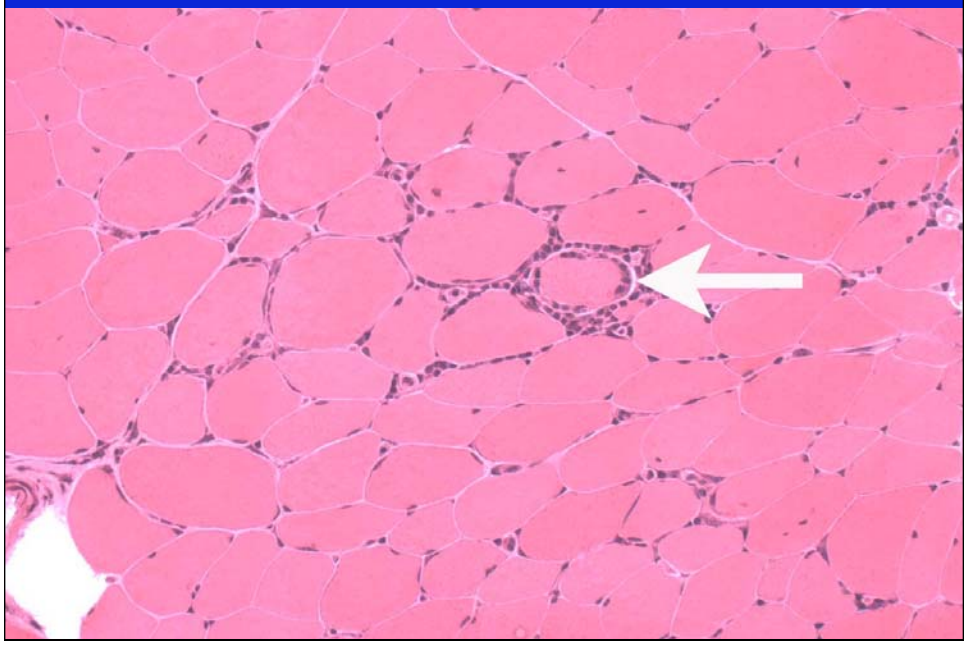
- Polymyositis
- Inclusion body myositis
- Dermatomyositis

POLYMYOSITIS

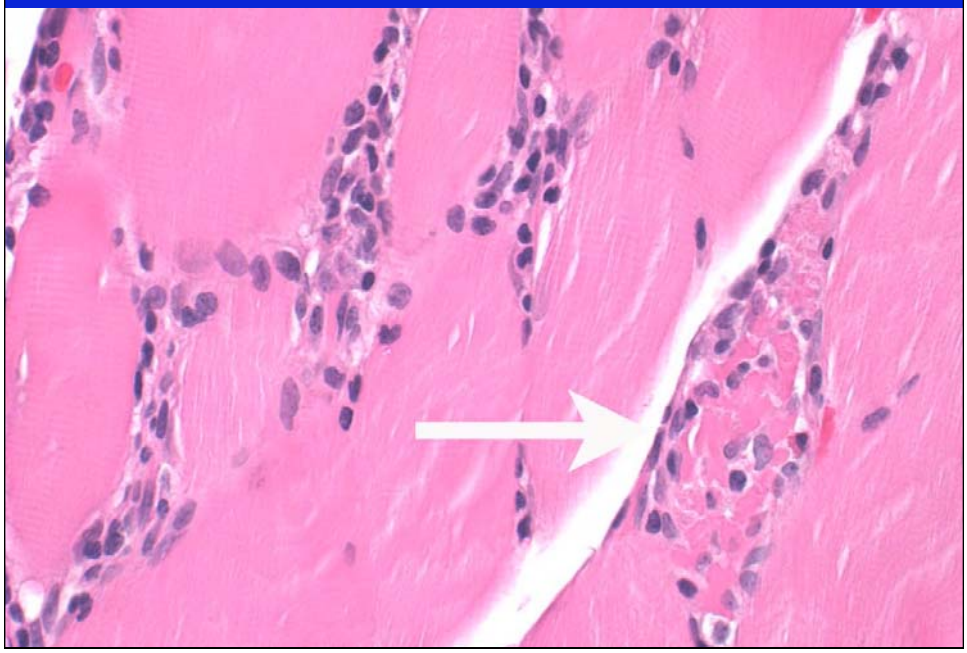
DIAGNOSTIC FEATURES OF POLYMYOSITIS

- 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.

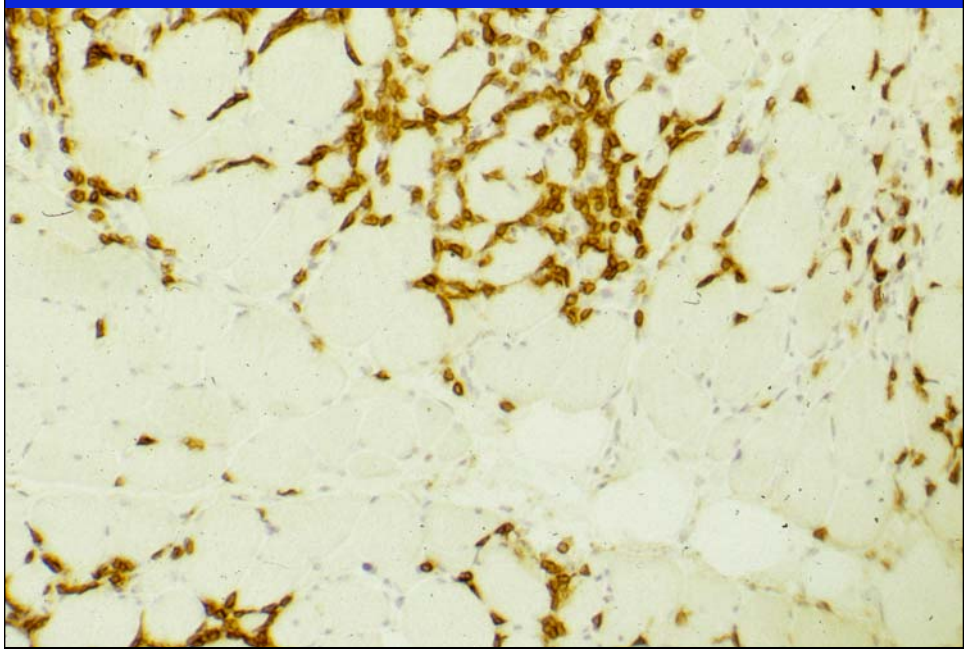
POLMYOSITIS, H&E



POLMYOSITIS, PARAFFIN SECTION, H&E



POLMYOSITIS, IMMUNOPEROXIDASE, CD8



POLYMYOSITIS: PATHOLOGY

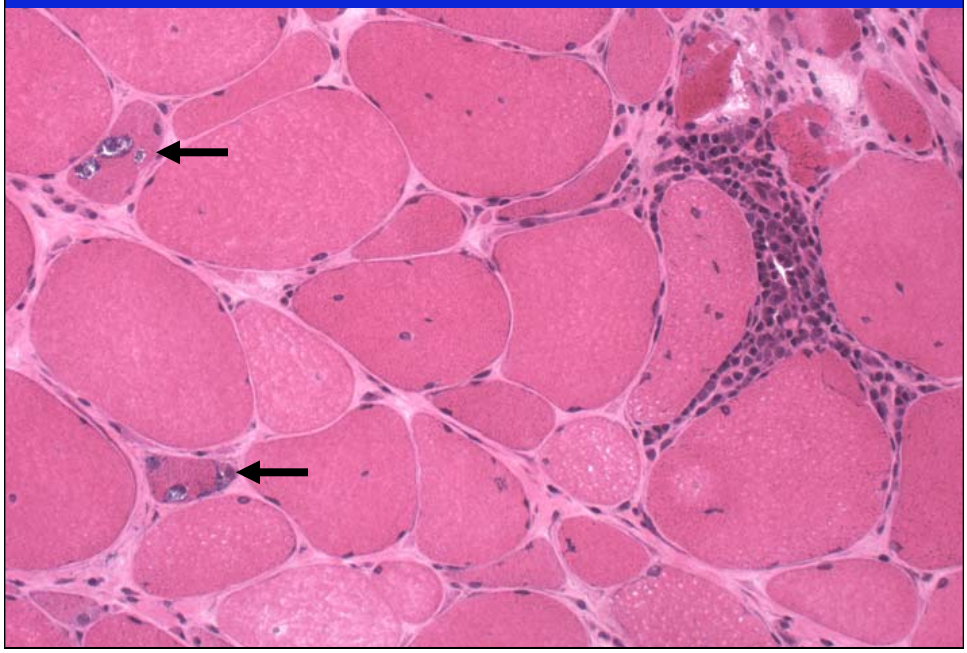
- Necrotic fibers and regenerating fibers randomly distributed throughout the muscle specimen.
- CD8 cytotoxic cells infiltrate predominantly the endomysium with invasion of rare myofibers.
- Little fibrosis or myofiber hypertrophy, consistent with a subacute disorder.

INCLUSION BODY MYOSITIS

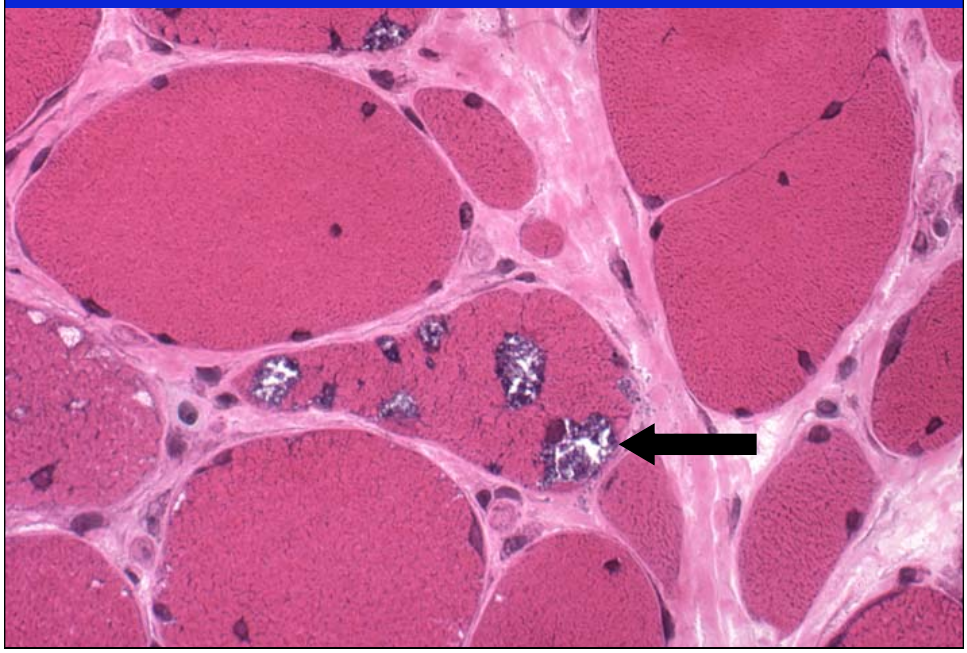
DIAGNOSTIC FEATURES OF IBM

- 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.

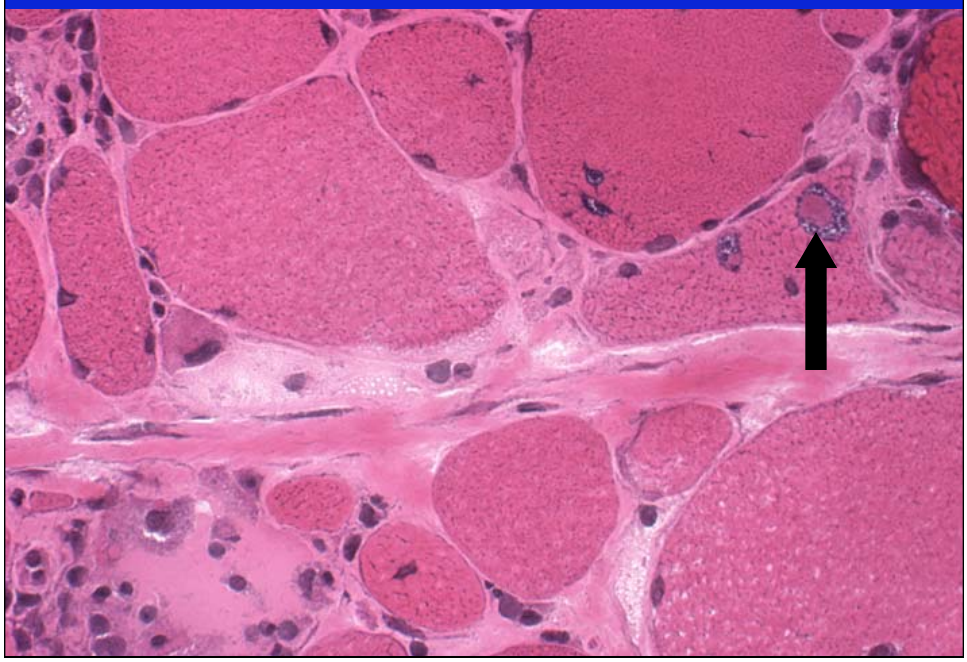
INCLUSION BODY MYOSITIS, H&E



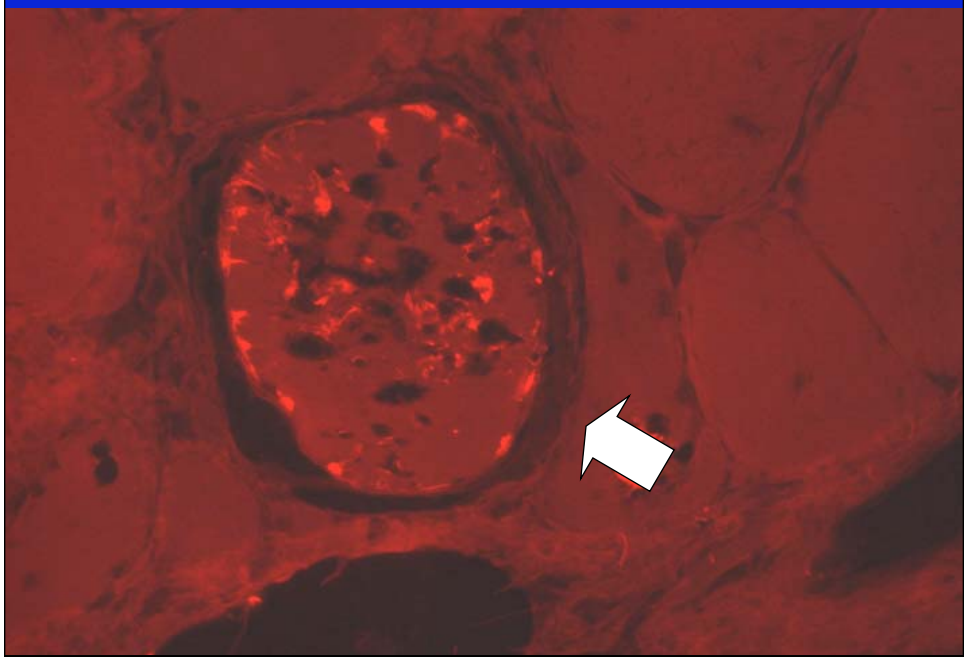
IBM, RIMMED VACUOLES, H&E



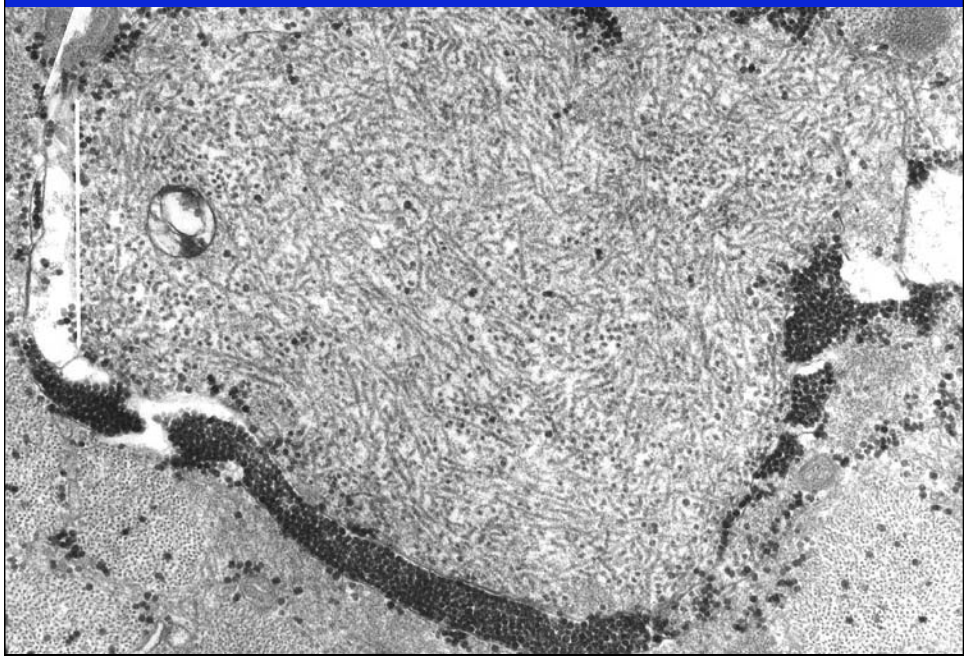
IBM, EOSINOPHILIC INCLUSION IN A RIMMED VACUOLE



IBM, CONGO RED, FLUORESCENCE, RHODAMINE OPTICS



ELECTRON MICROSCOPY, 15-20 nm FILAMENTS



IBM PATHOLOGY

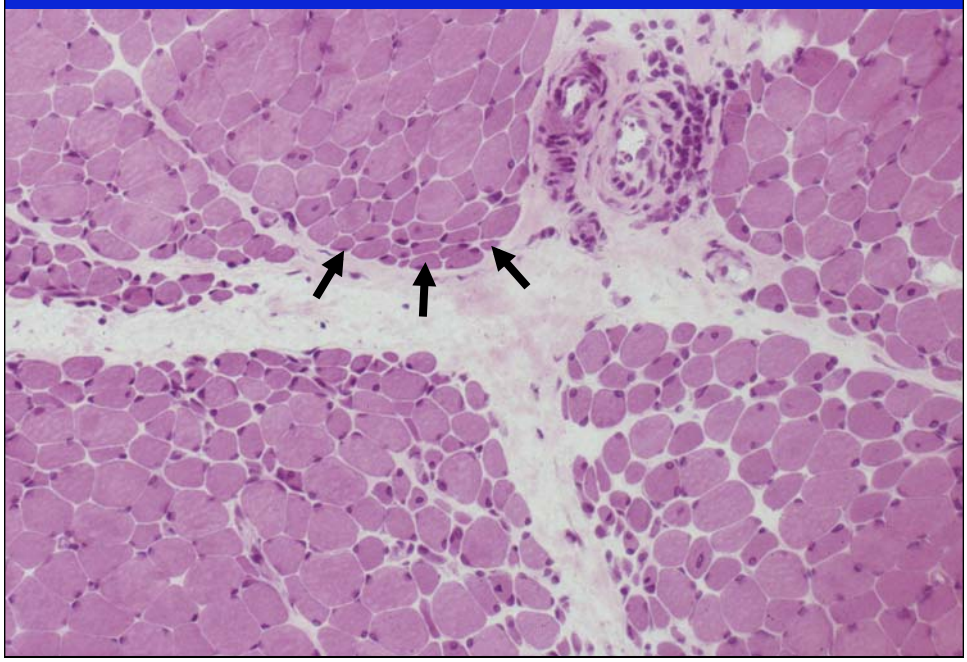
- IBM resembles polymyositis but has hyper- trophic fibers and prominent endomysial fibrosis indicating it is chronic.
- Rimmed vacuoles.
- Congophilic fibrillar inclusions, composed of abnormal (? paired-helical) filaments.
- Lymphocytic infiltration suggests an auto-immune disorder, but disorder is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

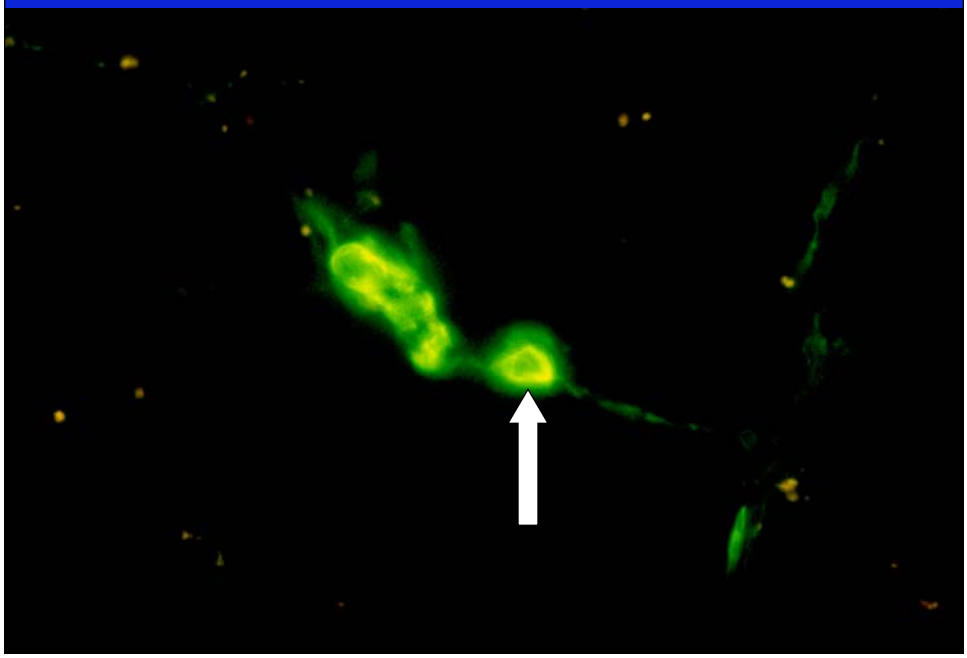
DERMATOMYOSITIS, PERIFASCICULAR ATROPHY, H&E



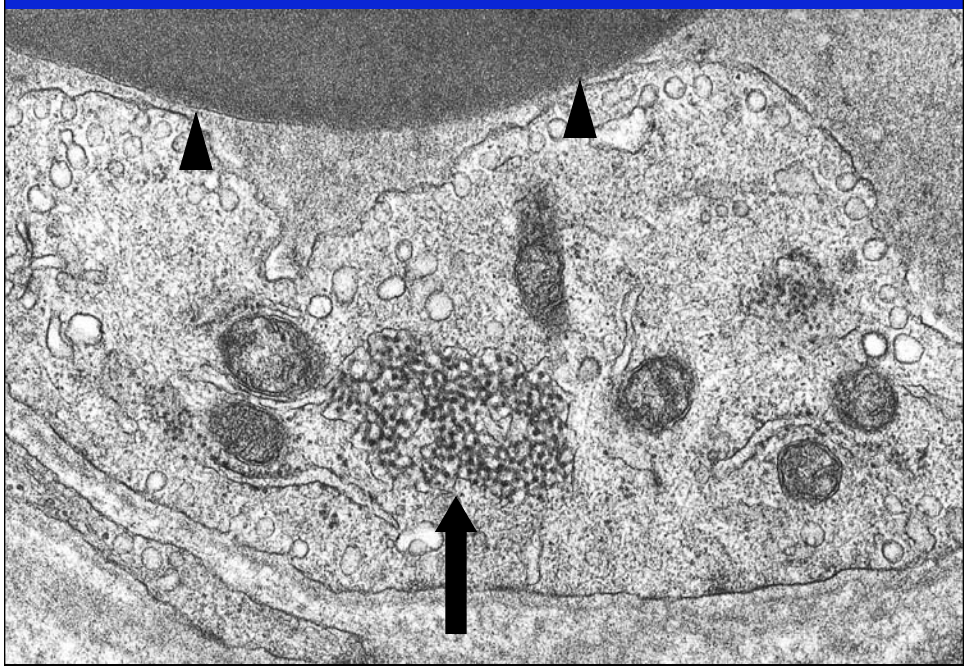
DERMATOMYOSITIS: LYMPHO-CYTE PHENOTYPES

- 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.

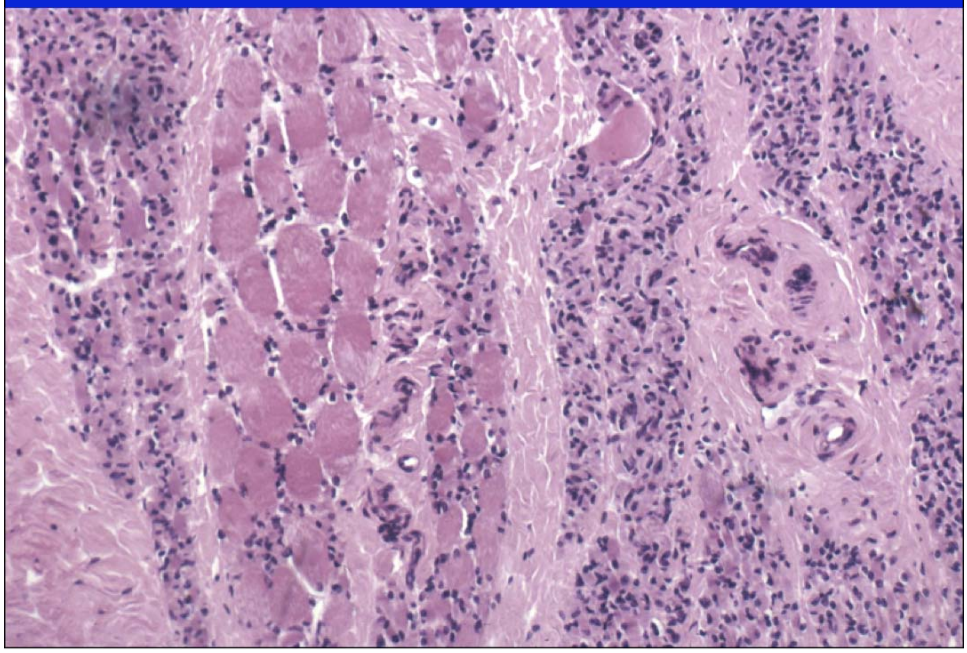
INFLAMMATORY MYOPATHIES: PATHOPHYSIOLOGY

- 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.

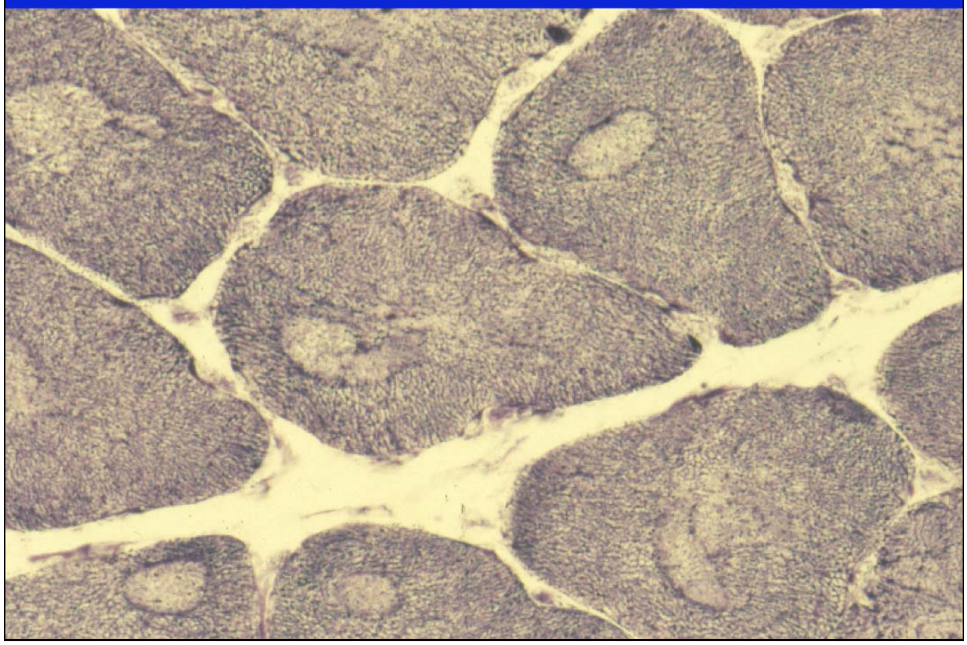
HYPOTONIA IN INFANCY

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

WERDNIG-HOFFMANN DISEASE

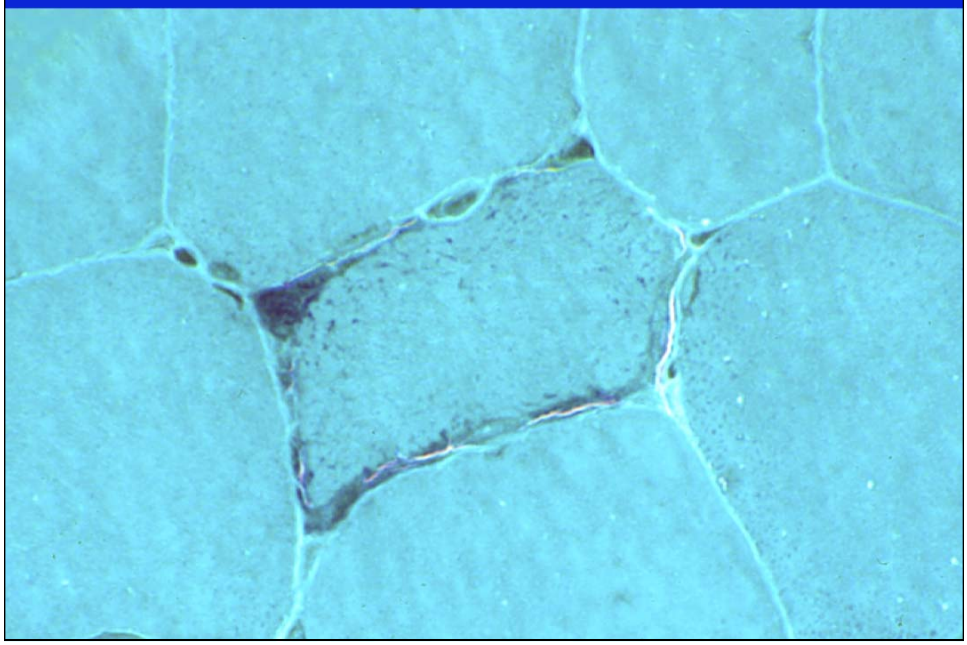


CENTRAL CORE DISEASE, NADH DEHYDROGENASE

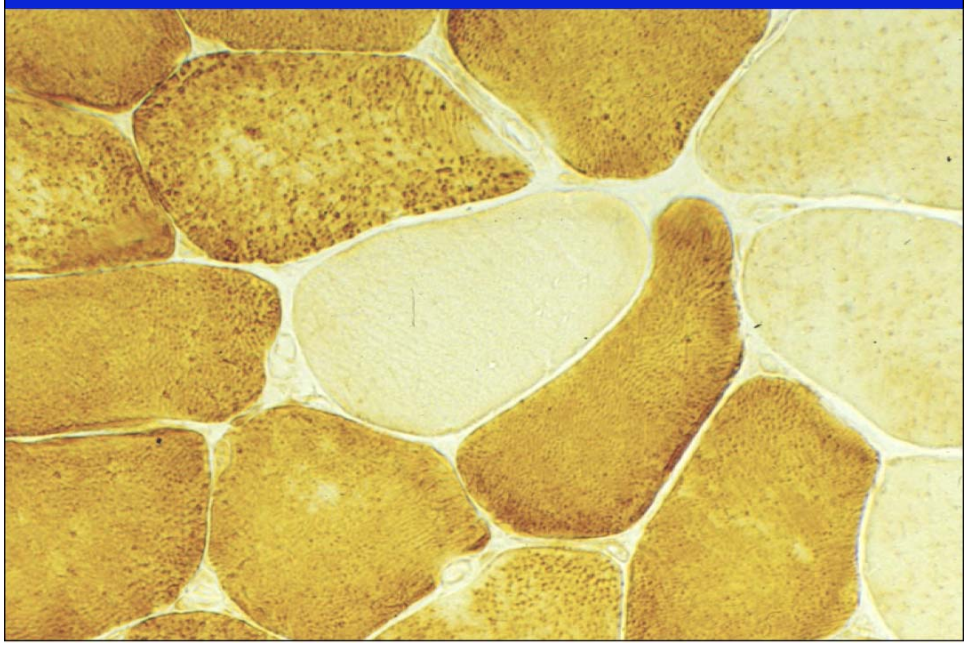


MITOCHONDRIAL MYOPATHY

MUTATIONS OF mtDNA RAGGED "RED" FIBER



CYTOCHROME C OXIDASE DEFICIENT MYOFIBER



RRF, SUCCINATE DEHYDROGENASE