DIFFERENTIAL DIAGNOSIS OF NEUROGENIC DISORDERS & MYOPATHIES

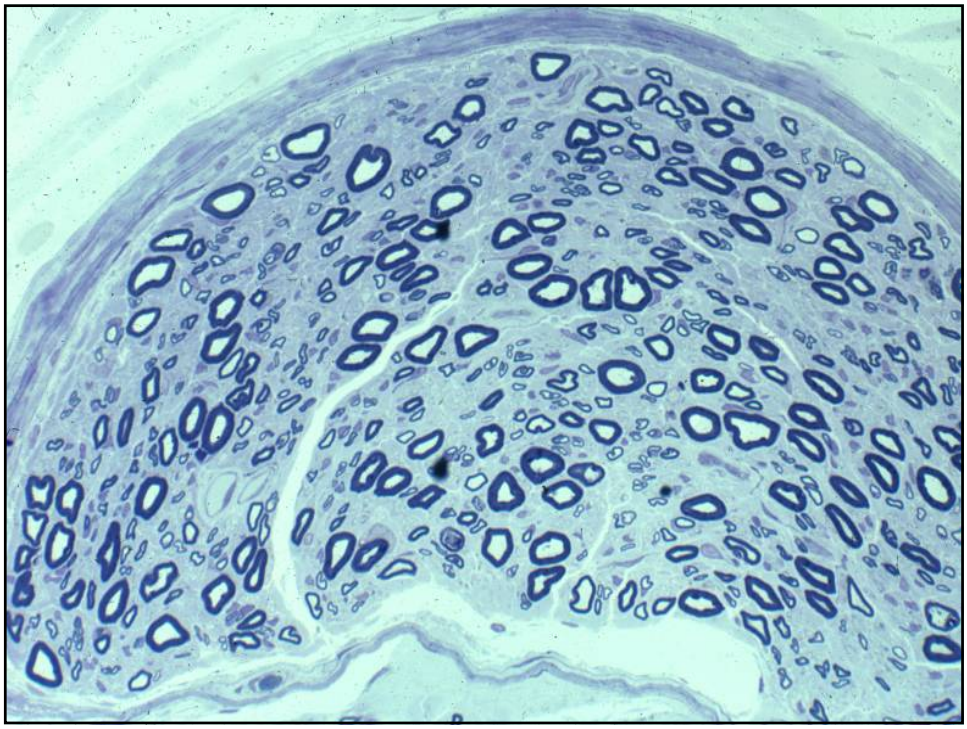
	NEUROPATHY	MYOPATHY
Weakness	distal	proximal
Sensory loss	+	0
Loss of reflexes	early	late
CSF protein	elevated	normal
Electromyography	neurogenic	myopathic
Serum enzymes	+/-	++++

CLASSIFICATION OF PERIPHERAL NERVE DISEASES

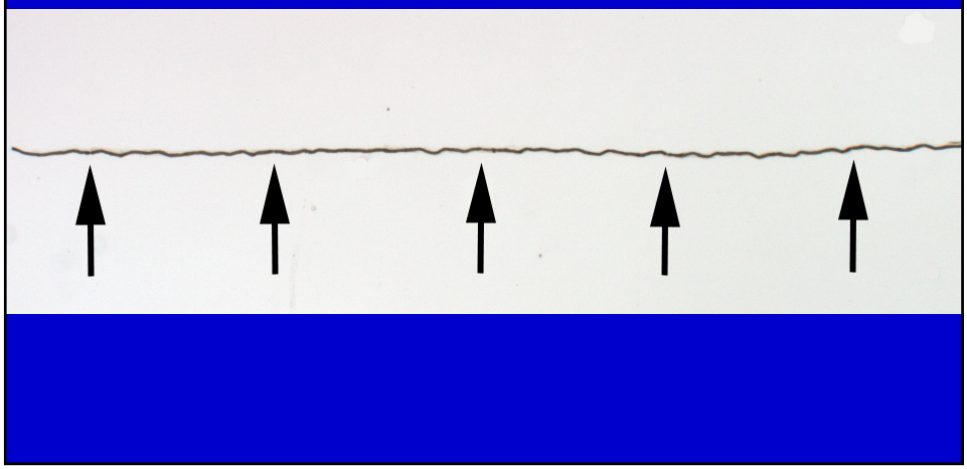
Myelinopathy
- Acute inflammatory polyneuropathy (AIP)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Charcot-Marie-Tooth, type 1 (CMT-1)

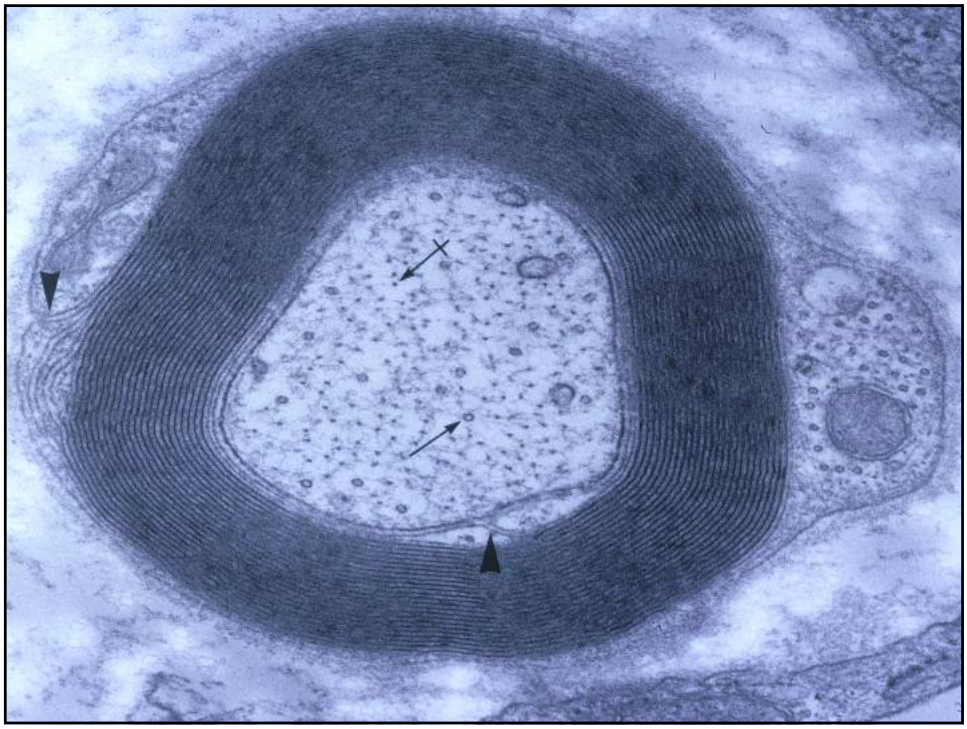
Axonopathy
- Vasculitis, amyloidosis
- Metabolic neuropathies (diabetic neuropathy)
- Toxic neuropathy (acrylamide neuropathy)

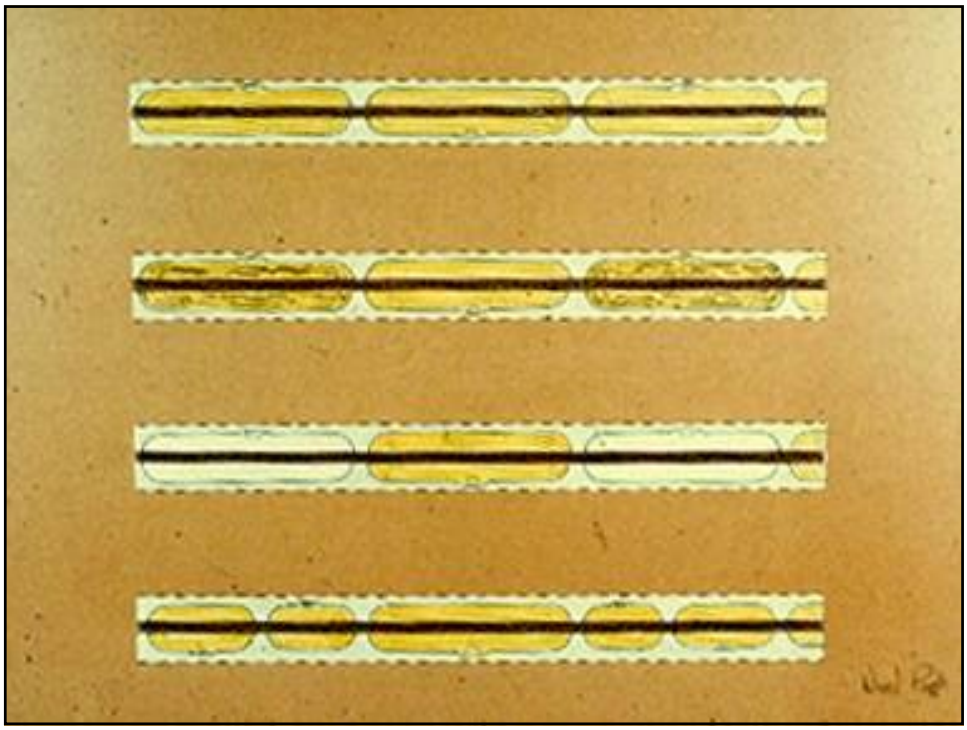
Neuronopathy
- Amyotrophic lateral sclerosis (ALS)



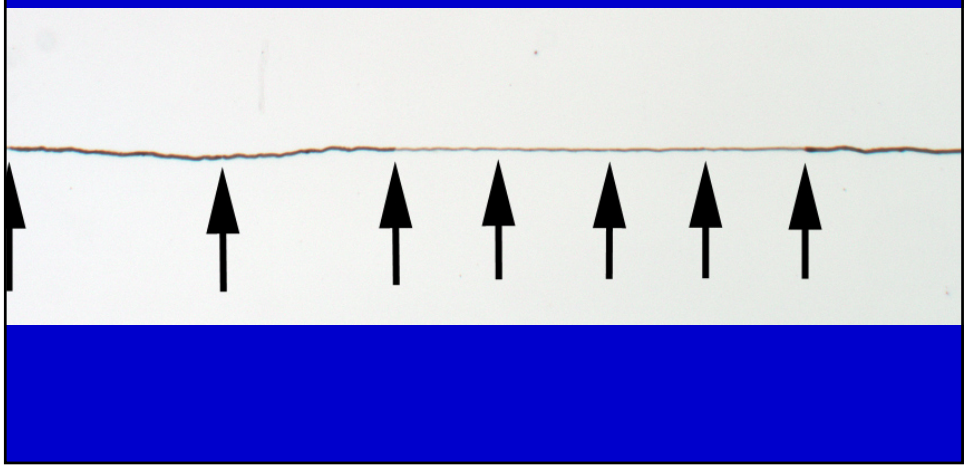
TEASED MYELINATED FIBER: NORMAL



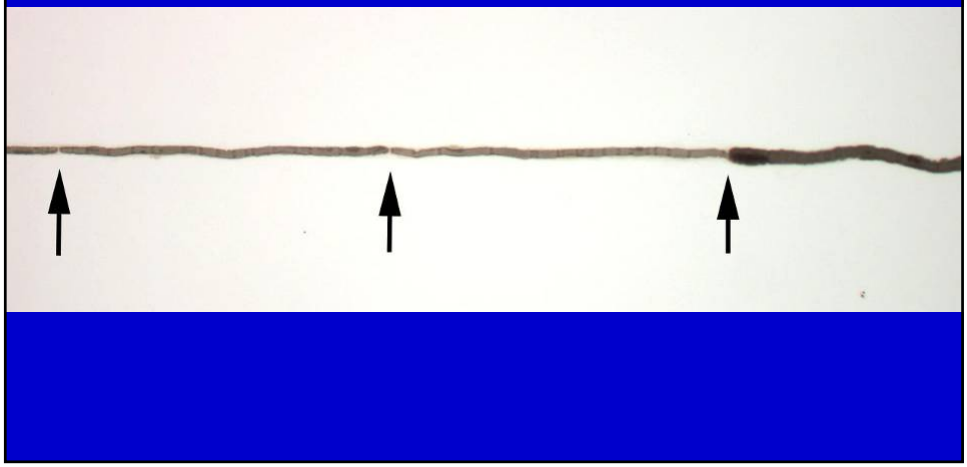


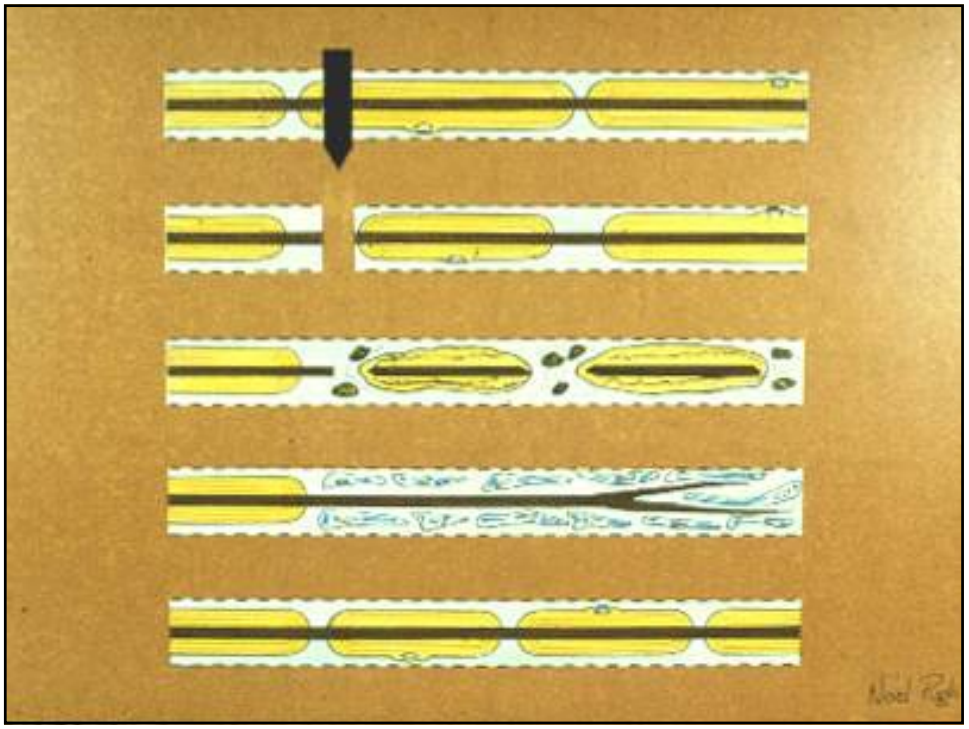


TEASED MYELINATED FIBER: SEGMENTAL REMYELINATION



SAME TEASED FIBER AT HIGHER MAGNIFICATION





TEASED MYELINATED FIBER: AXONAL DEGENERATION

CLASSIFICATION OF PERIPHERAL NERVE DISEASES

Myelinopathy

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- **Chronic inflammatory demyelinating polyneuropathy (CIDP)**
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Axonopathy

- **Vasculitis, amyloidosis**
- **Metabolic neuropathies (diabetic neuropathy)**
- **Toxic neuropathy (acrylamide neuropathy)**

Neuronopathy

- **Amyotrophic lateral sclerosis (ALS)**

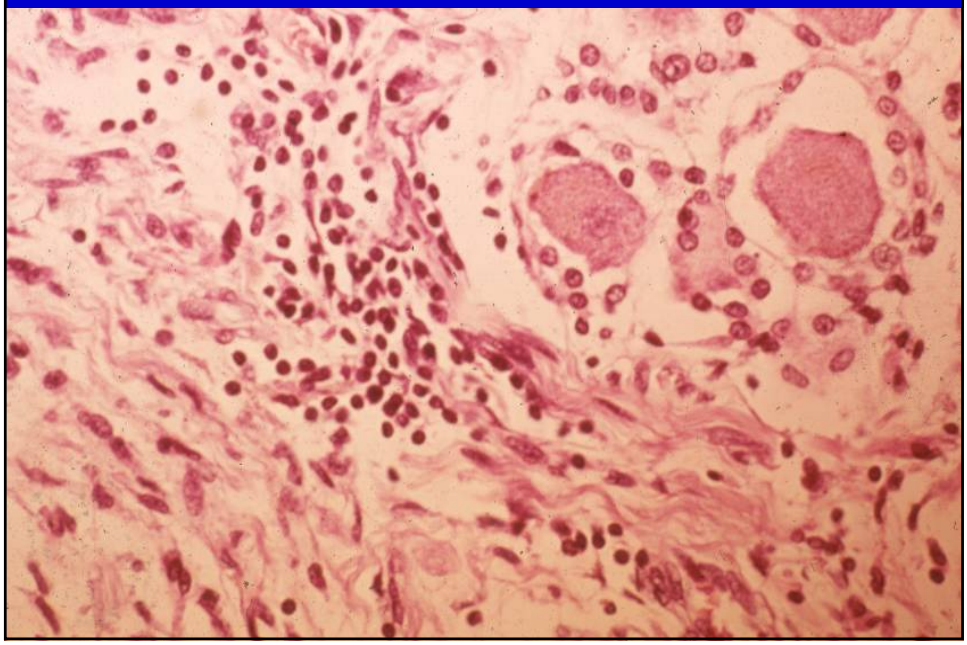
ACUTE INFLAMMATORY POLYNEUROPATHY (GUILLAIN-BARRE SYNDROME [GBS])

- **Rapidly progressive neuropathy, chiefly motor, reaching maximum weakness usually within 1 to 2 weeks.**
- **An acute infectious illness precedes weakness in two thirds.**
- **Electrophysiology: slow conduction velocity & conduction block but also show axonal degeneration, usually of mild degree.**
- **Recovery takes weeks or months. Permanent handicap in 5%.**
- **Plasmapheresis or intravenous gamma globulin speeds recovery.**

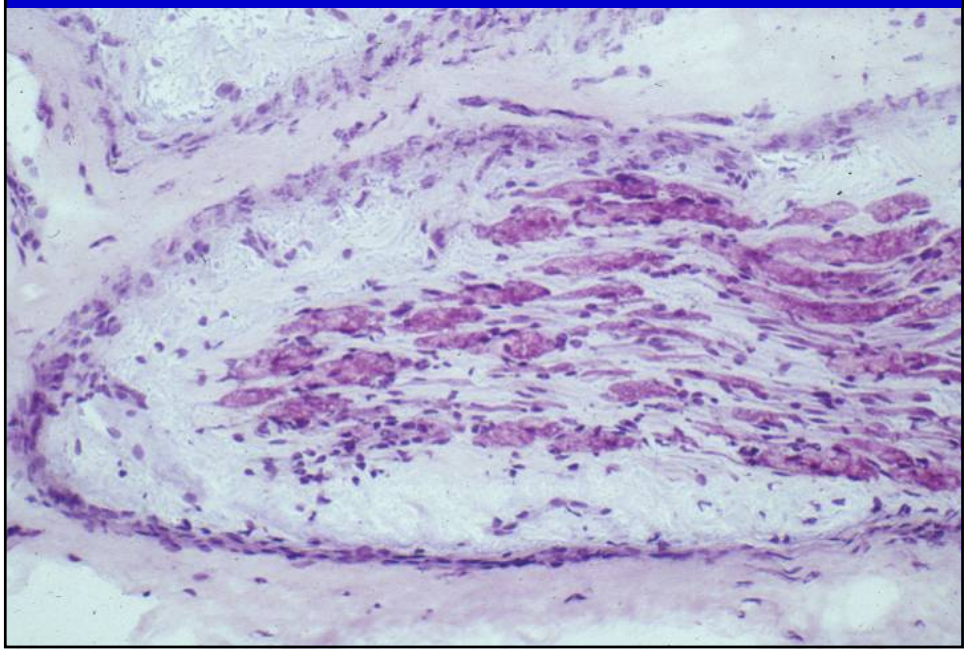
PATHOLOGY OF ACUTE INFLAMMATORY POLYNEUROPATHY (GBS)

- Immune complexes (C3, IgG, IgM) are detectable on the surface of myelin sheaths in the early stage.
- 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.

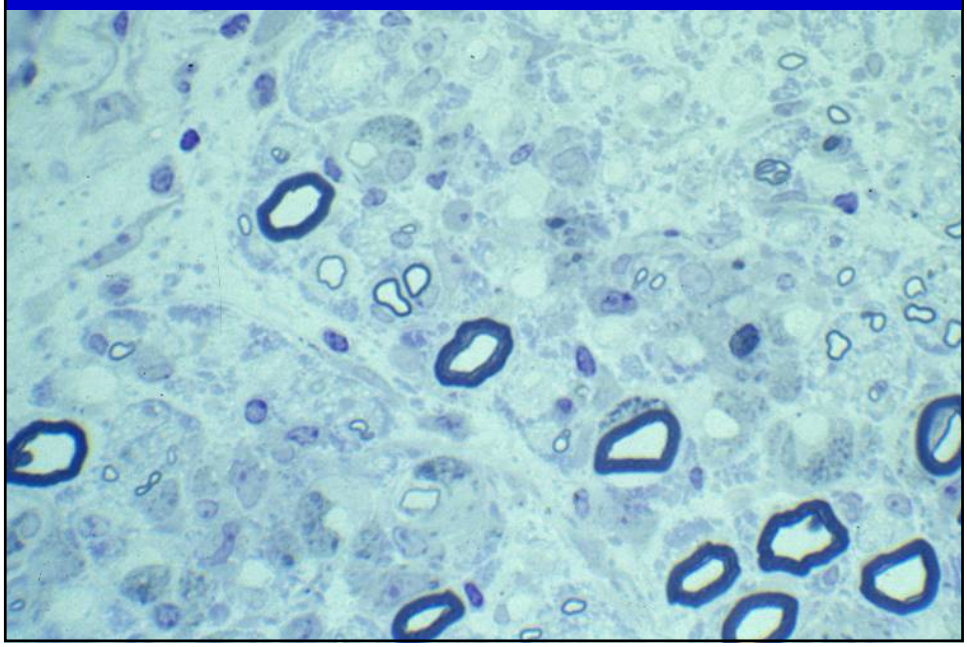
GBS, DORSAL ROOT GANGLION, H&E



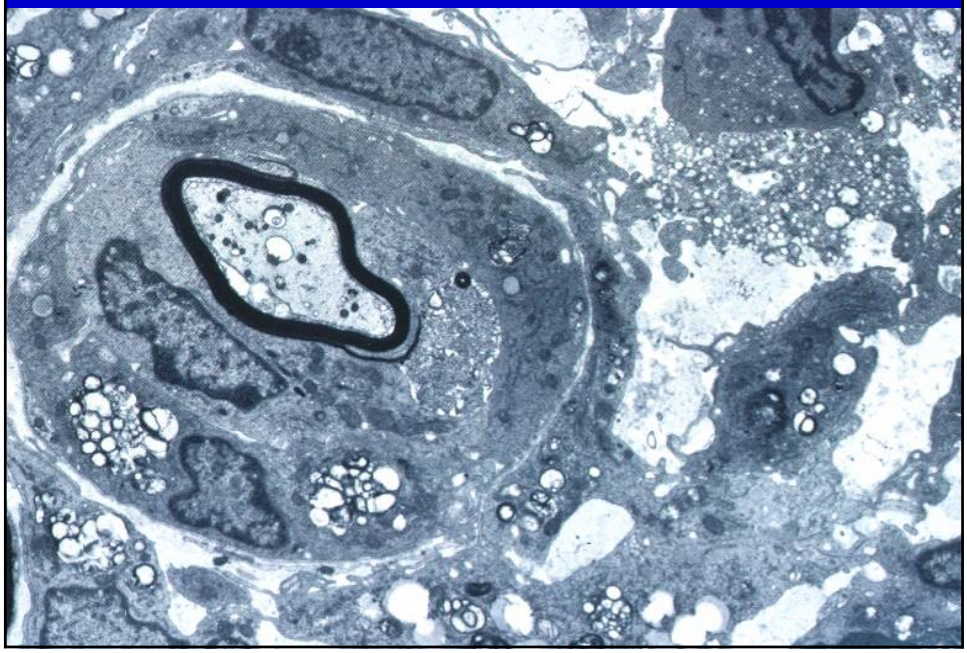
GBS, MOTOR NERVE, H&E



GBS, MOTOR NERVE, SEMITHIN SECTION

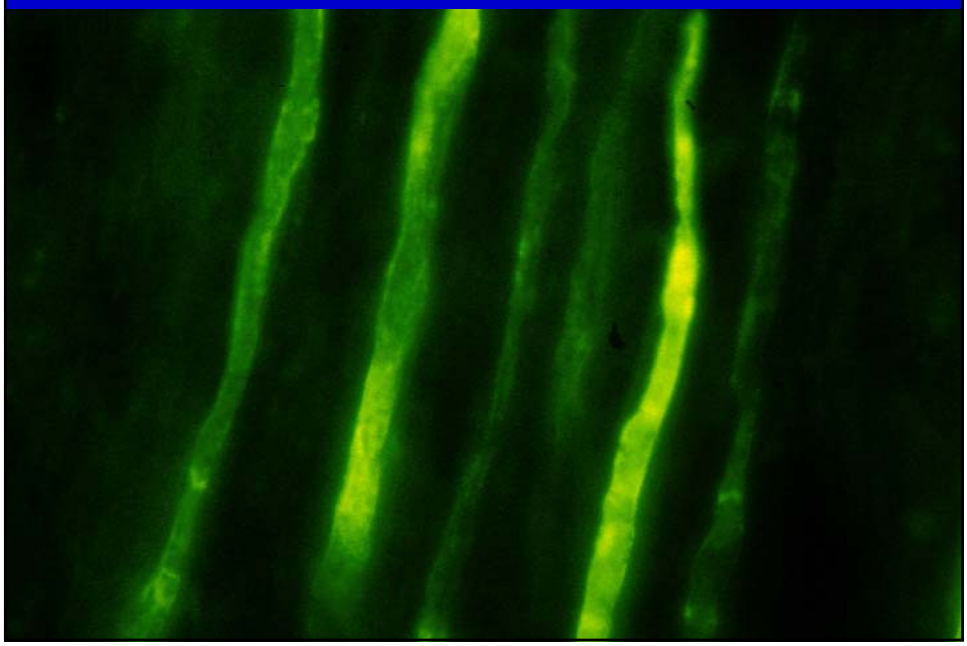


GBS, ELECTRON MICROGRAPH



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, P_2 myelin basic protein or galactocerebroside.
- Antibody titers to nerve myelin in patient correlate with disease activity.
- The antibodies recognize glycolipids of peripheral myelin.
- Immune complexes are found at the 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 was first described in children in China by investigators from John Griffin and others from Johns Hopkins.
- Electrodiagnostic studies suggested a purely axonal disorder with little slowing of conduction velocity or block.
- Some of the patients died within a few days of the onset of weakness allowing autopsy study of the nerves.

AXONAL VARIANT OF GUILLAIN-BARRE SYNDROME

- Autopsy showed axonal degeneration with little or no demyelination or lymphocytic infiltration.
- Immune complexes were found at the nodes of Ranvier.
- The disorder was often preceded by a gastrointestinal illness caused by the bacterium, *Campylobacter jejuni.*
- Elevated serum antibodies to GD1 & GM1 ganglioside; these antibodies recognized the terminal oligosaccharide chain, which is a component of both gangliosides.

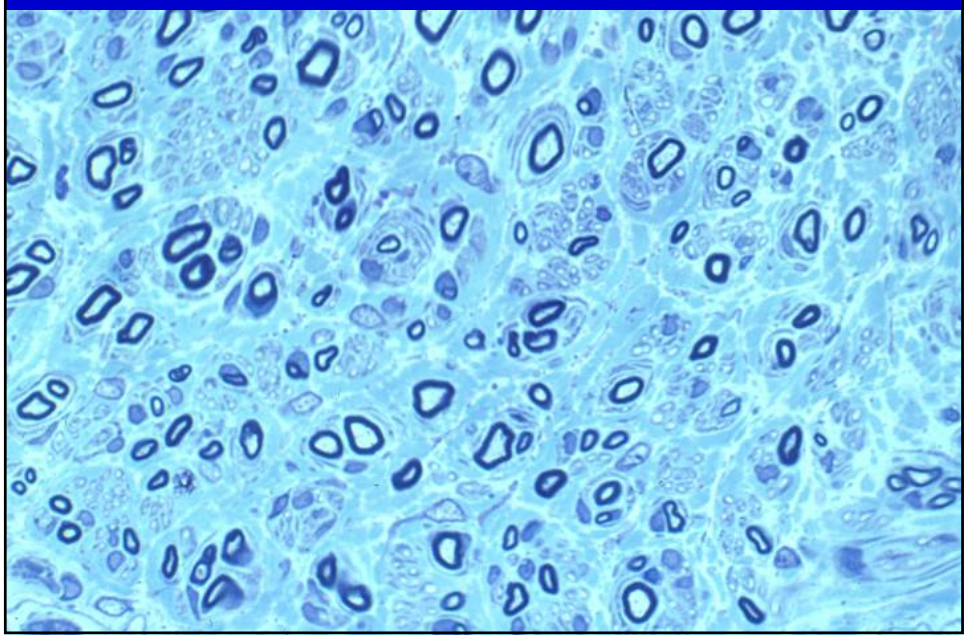
AXONAL VARIANT OF GUILLAIN-BARRE SYNDROME

- It turned out that the chemical structure of the lipopolysaccharide of the bacterium includes the same oligosaccharide chain present in GD1a and GM1.
- This suggests that the immune response to the infection could react to both *Campylobacter jejuni* and gangliosides expressed on axons.
- This data provides support for the idea that molecular mimicry can be the basis for this autoimmune neuropathy.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

- Chronic progressive or relapsing neuropathy, motor > sensory.
- An antecedent infectious illness is uncommon.
- Electrophysiology: slow conduction velocity & conduction block.
- Pathology: segmental demyelination and remyelination, onion bulbs, fibrosis and little or no lymphocytic infiltration of tissue.
- Autoimmune disorder of myelin, probably antibody-mediated.
- Patients respond to plasmapheresis, intravenous gamma globulin or corticosteroid treatment.

CIDP WITH ONION BULBS



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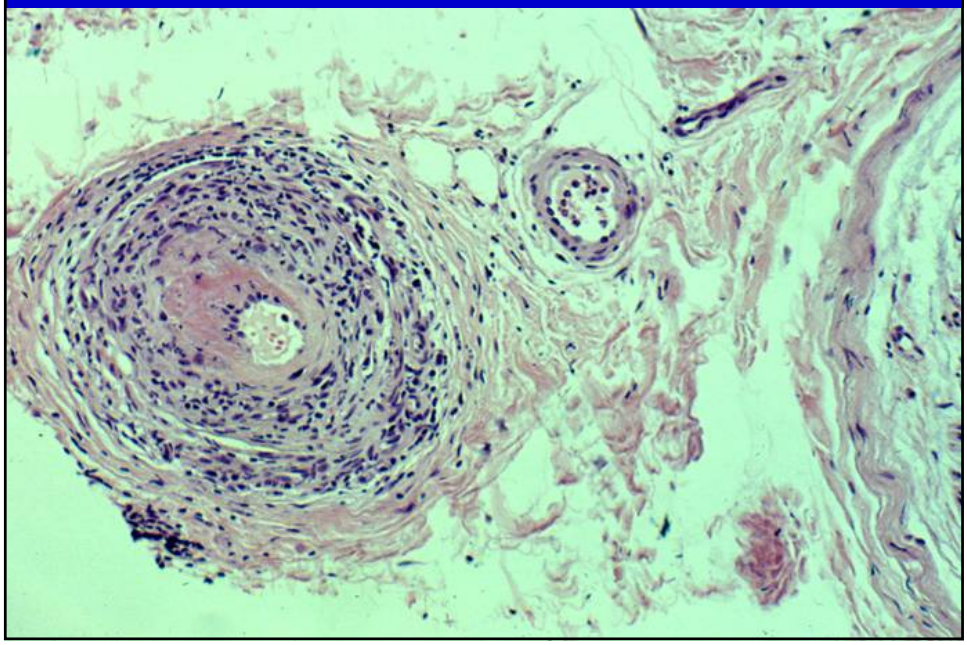
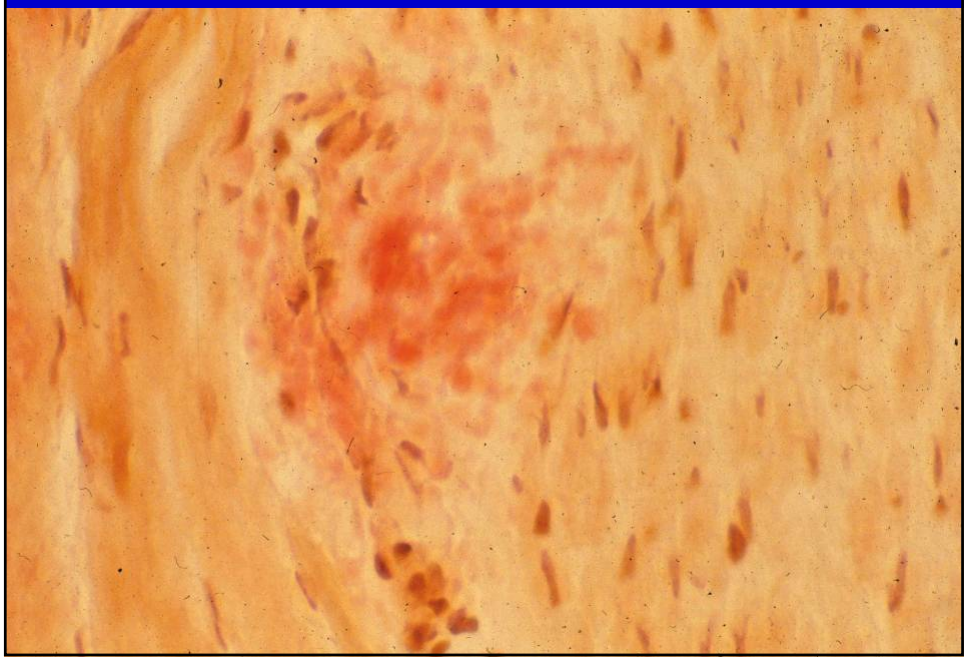
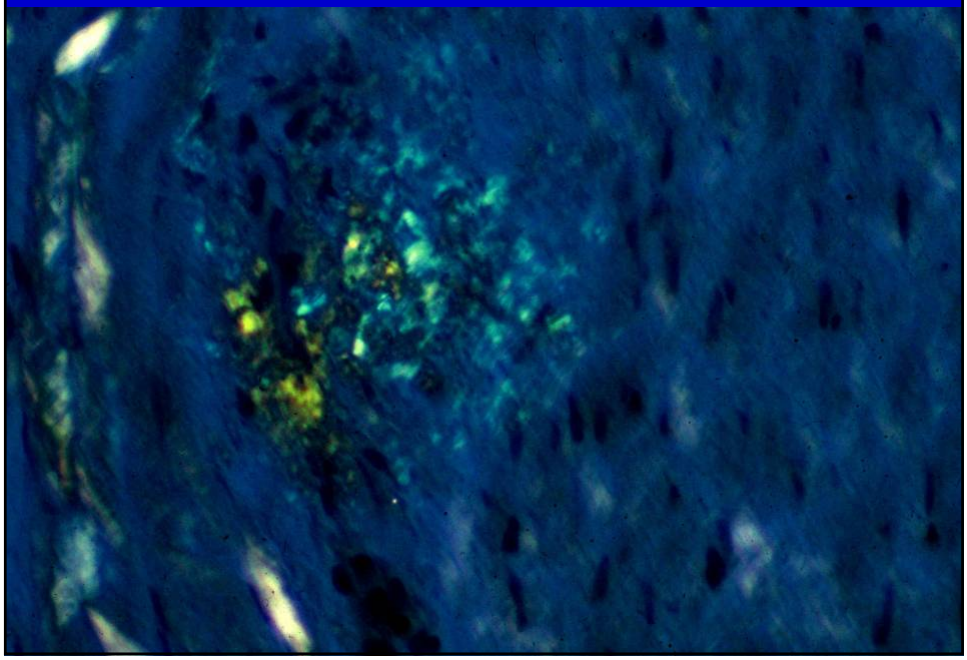
VASCULITIC NEUROPATHY



SURAL NERVE BIOSY, CONGO RED



SURAL NERVE BIOSY, CONGO RED, BIREFRINGENCE



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Lou Gehrig

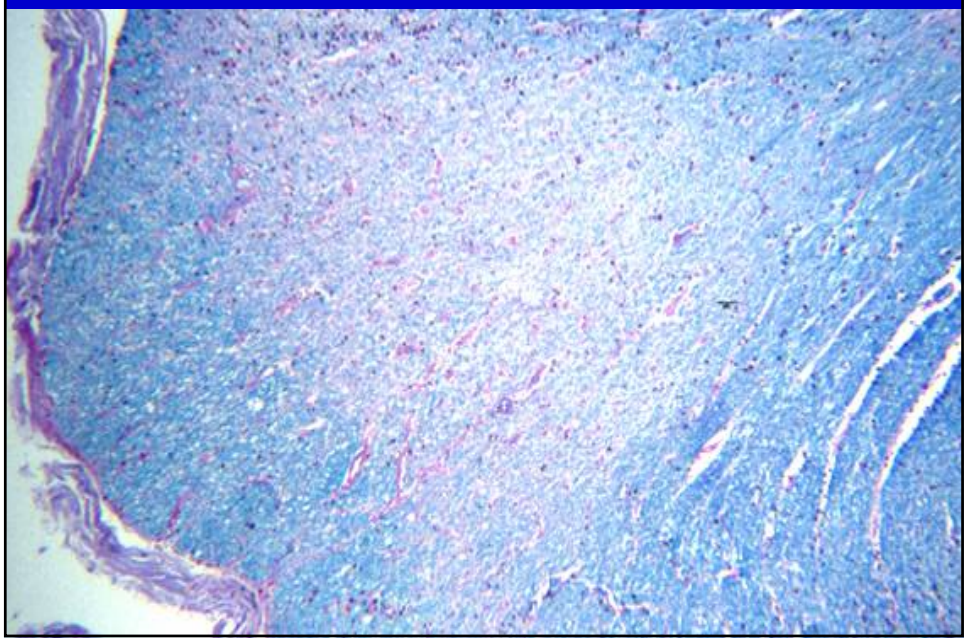
AMYOTROPHIC LATERAL SCLEROSIS (LOU GEHRIG'S DISEASE)

- Progressive weakness and wasting with fasciculations, often asymmetrical in the beginning.
- Hyperactive tendon reflexes, clonus and Babinski signs.
- Symptoms usually begin after the age of 40.
- Electrodiagnostic: denervation & normal nerve conductions.
- Most are sporadic; 5-10% are familial.
- Death usually within 3 to 5 years from onset.

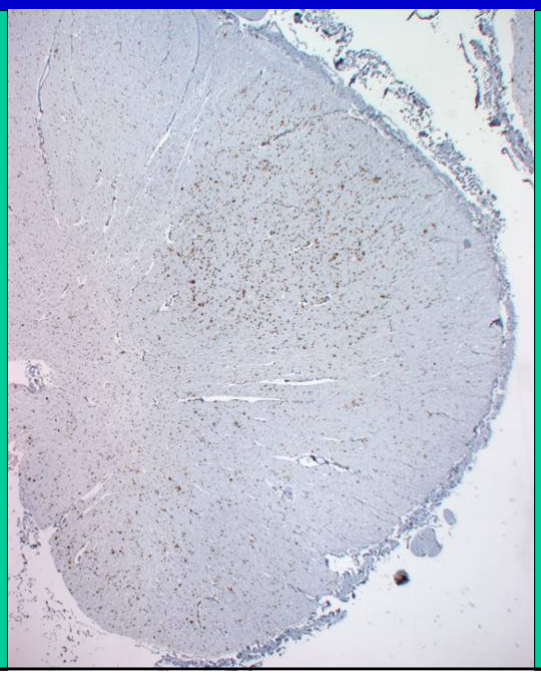
ALS: UPPER MOTOR NEURON PATHOLOGY

- Loss of Betz cells in precentral gyrus.
- Pyramidal degeneration with gradually increasing myelin pallor in 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

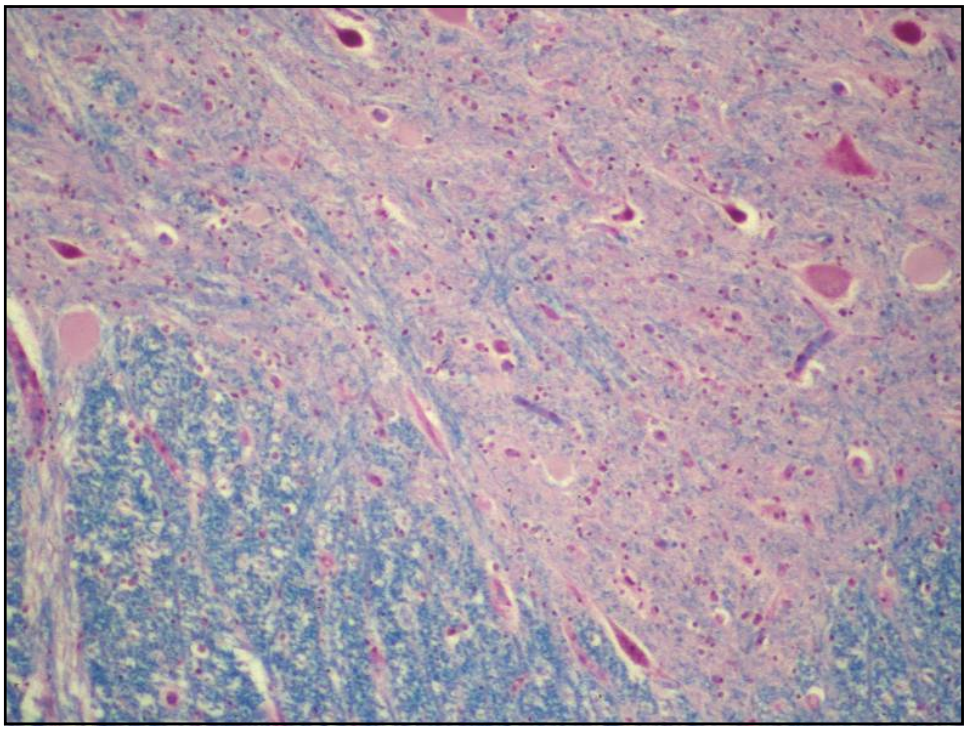


ALS, PYRAMIDAL TRACT, CD68

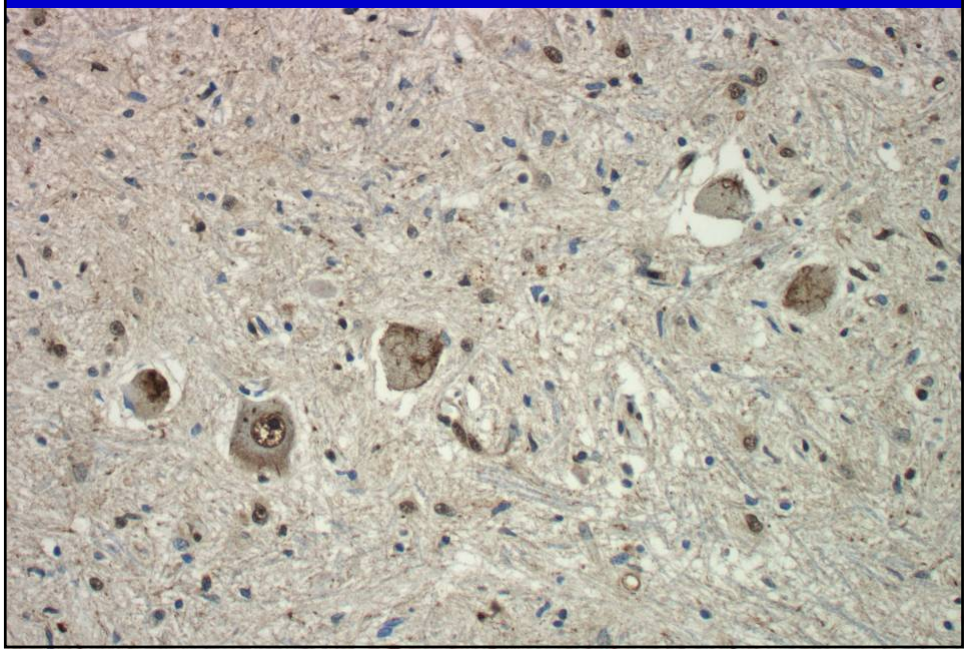


ALS: LOWER MOTOR NEURON PATHOLOGY

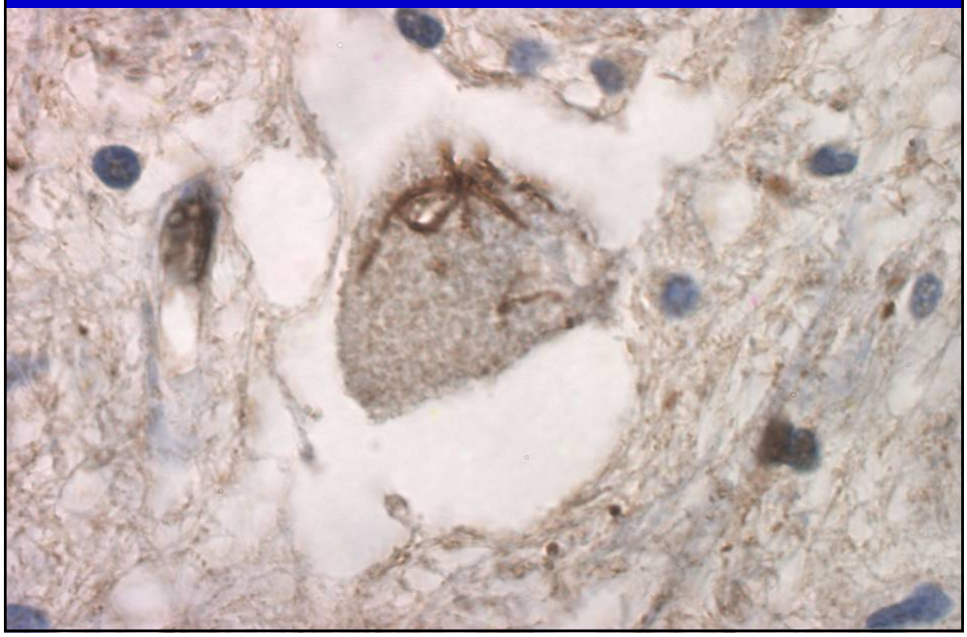
- Loss of motor neurons in ventral horns and nuclei of cranial nerve V, VII, IX-XII.
- Sparing of motor nuclei of cranial nerves III, IV & VI and Onuf's nucleus.
- Motor neurons show atrophy & inclusions.
- Few, if any, chromatolytic nerve cells.
- Little or no evidence of axonal regeneration.



ALS, SKEIN-LIKE INCLUSIONS, UBIQUITIN



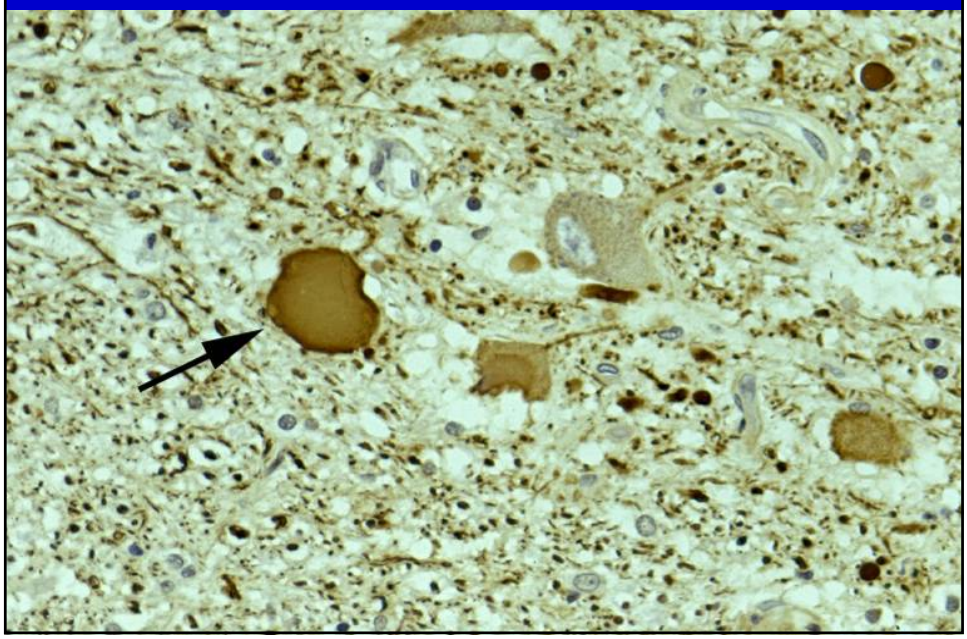
ALS, SKEIN-LIKE INCLUSIONS, UBIQUITIN



UBIQUINATED SKEIN-LIKE INCLUSIONS

- Intracytoplasmic aggregates of loosely-arranged fibrils in motor neurons of spinal cord and brain stem. Rare in Betz cells.
- Invisible in routine histology (H&E) and are not argyrophilic.
- Ubiquitin presumably conjugated to a protein but not identified yet.
- Sensitivity: 90-100%.
- Specificity: >95%.

ALS, NEUROFILAMENT PROTEIN



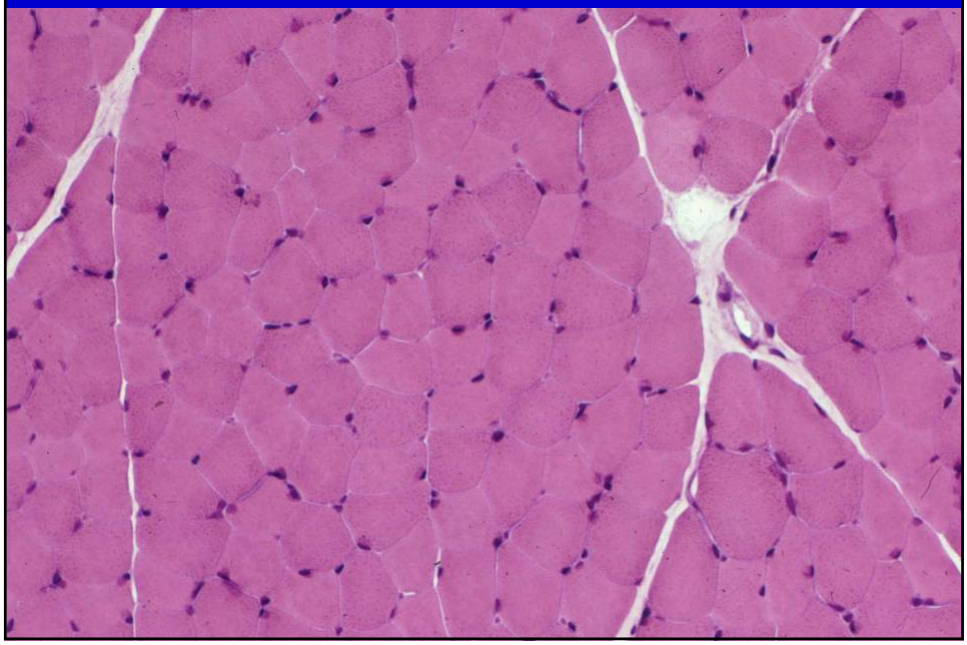
PATHOGENESIS OF ALS

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

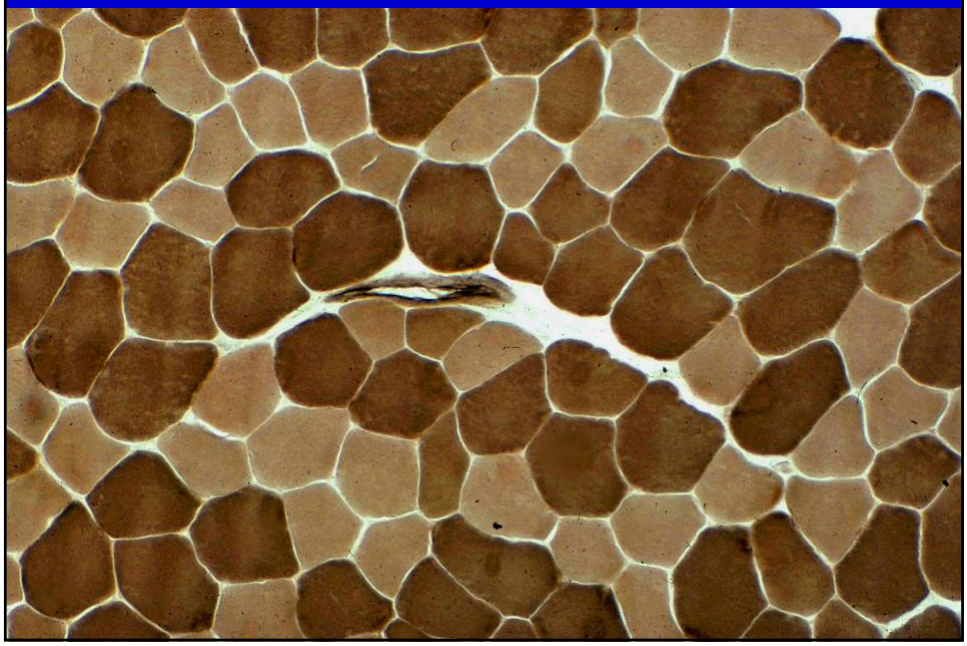
aberrant oxidation ◄·····► intracellular aggregates

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

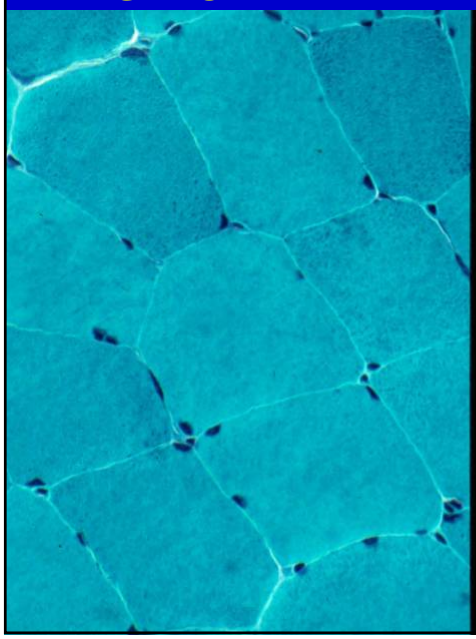
CRYOSECTIONS OF SKELETAL MUSCLE, H&E



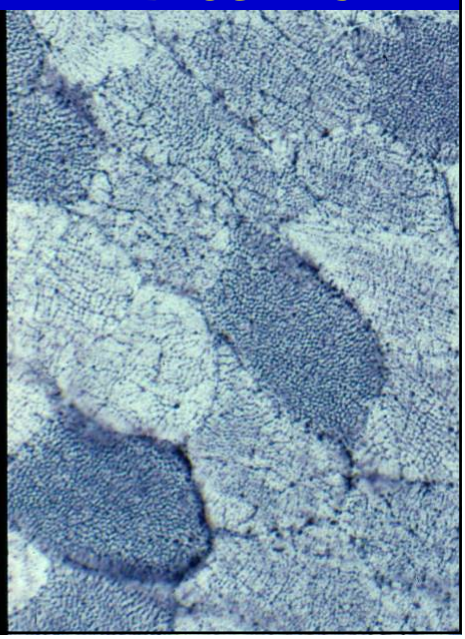
CRYOSECTIONS OF SKELETAL MUSCLE, ATPase



MODIFIED GOMORI TRICHROME



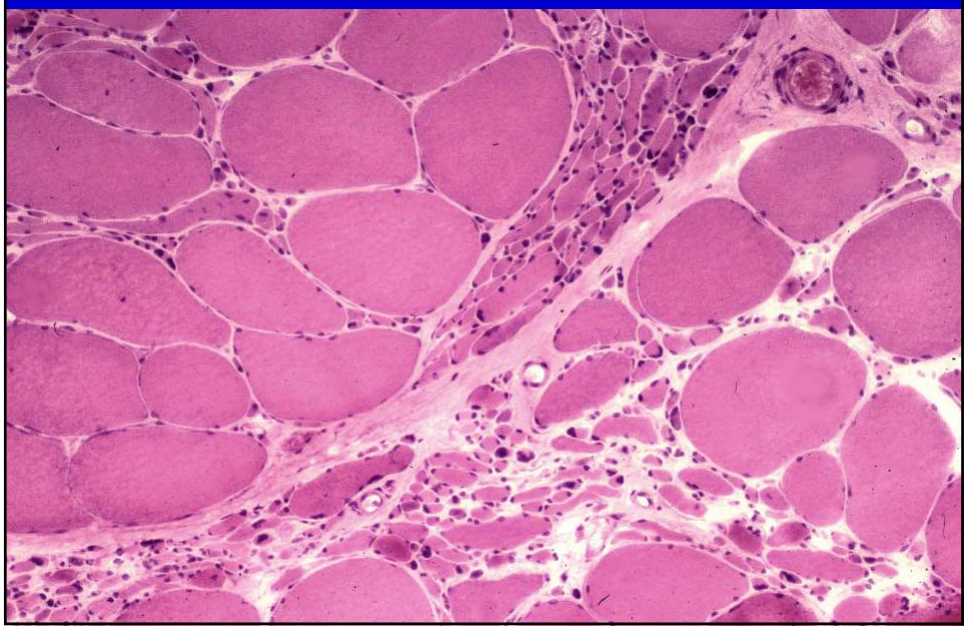
SUCCINATE DE-HYDROGENASE



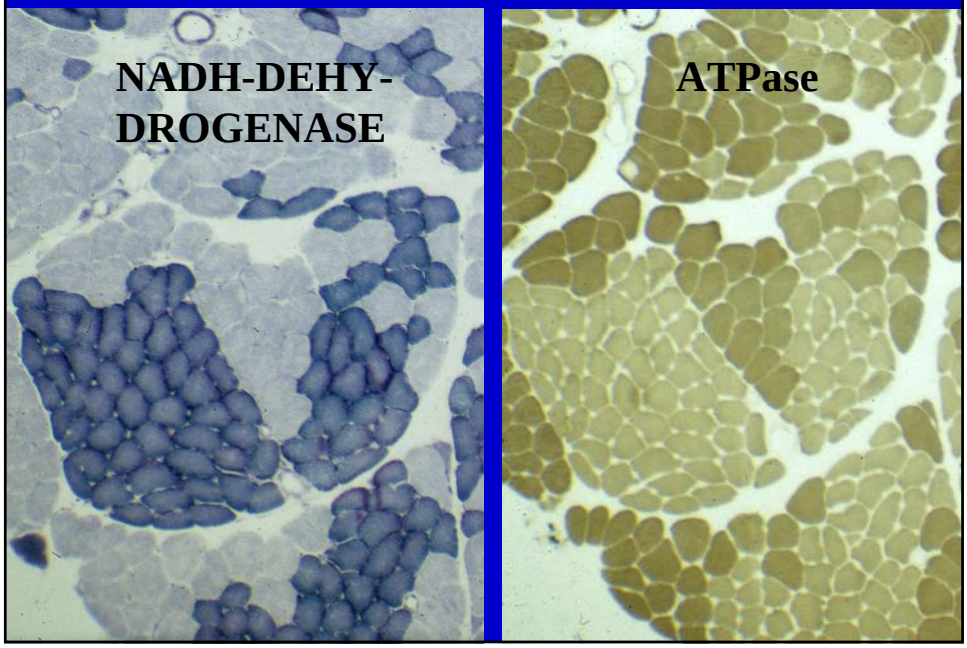
DIAGNOSTIC HISTOLOGICAL FEATURES OF A NEUROGENIC DISORDER

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

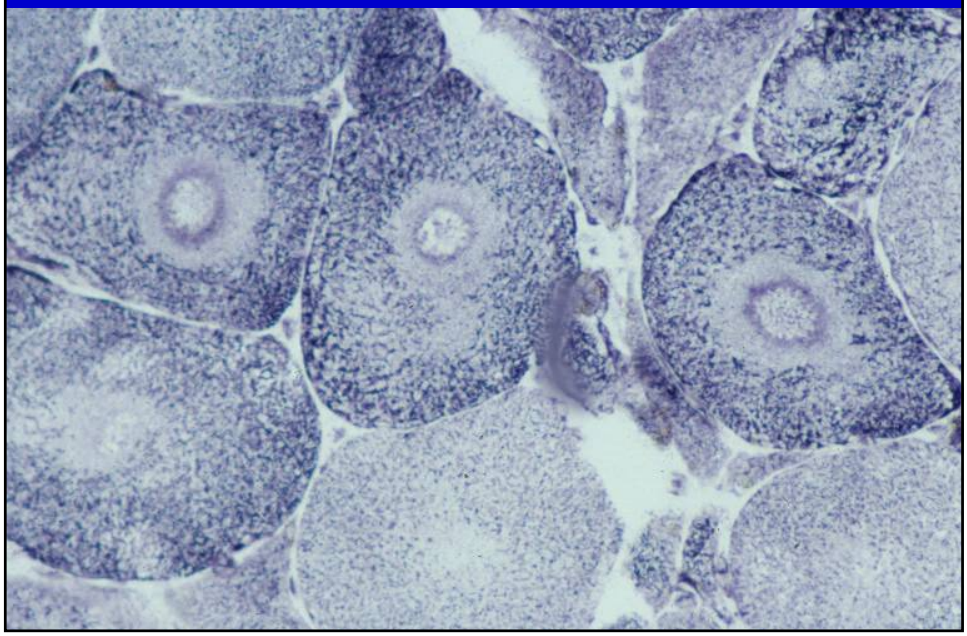
GROUPS OF ATROPHIC MYOFIBERS, H&E



FIBER TYPE GROUPING



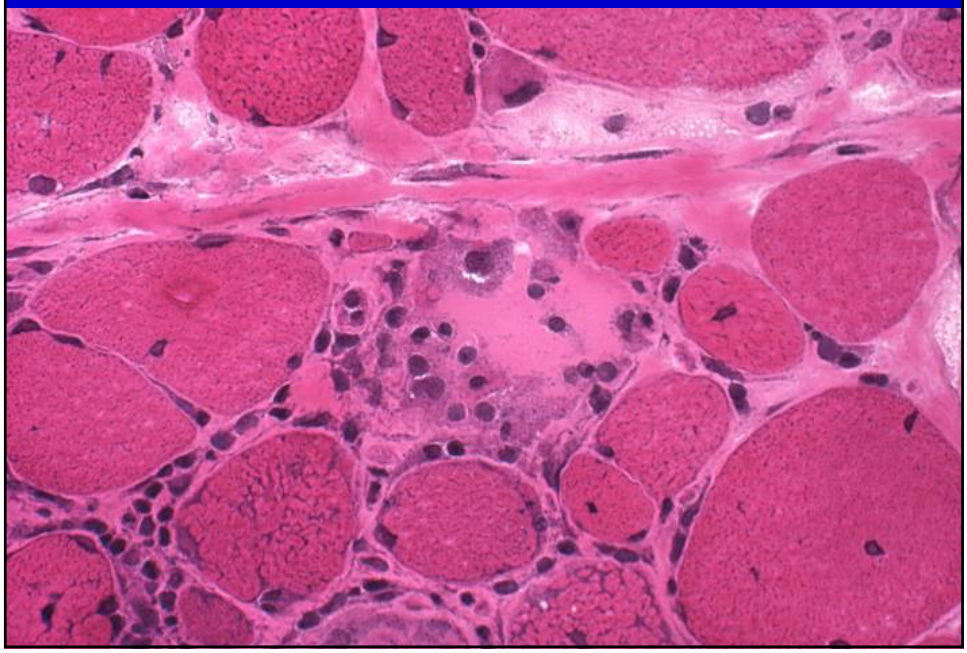
TARGET FIBERS, NADH DEHYDROGENASE



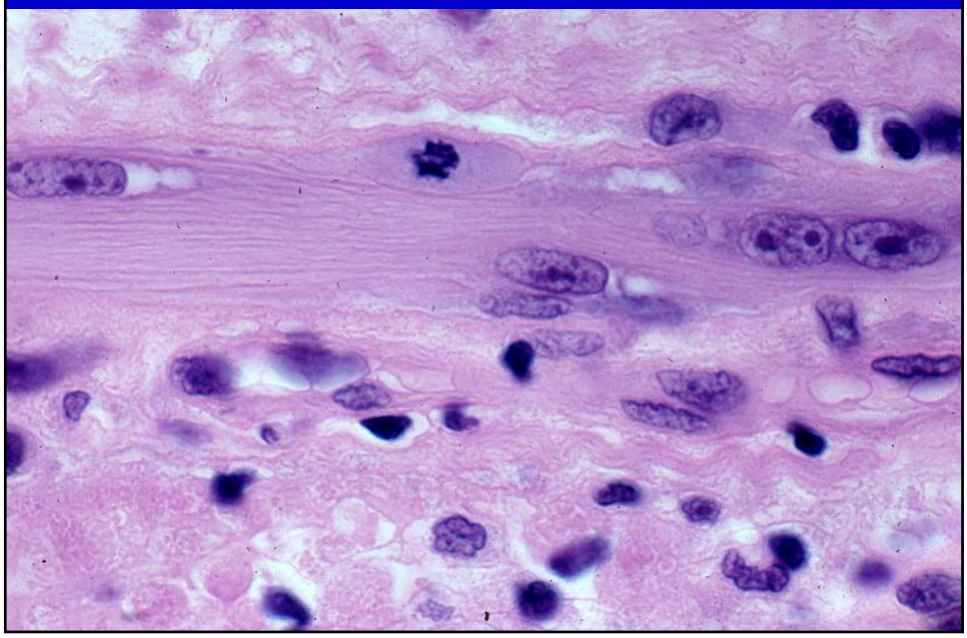
DIAGNOSTIC HISTOLOGICAL FEATURES OF MYOPATHIES

- 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



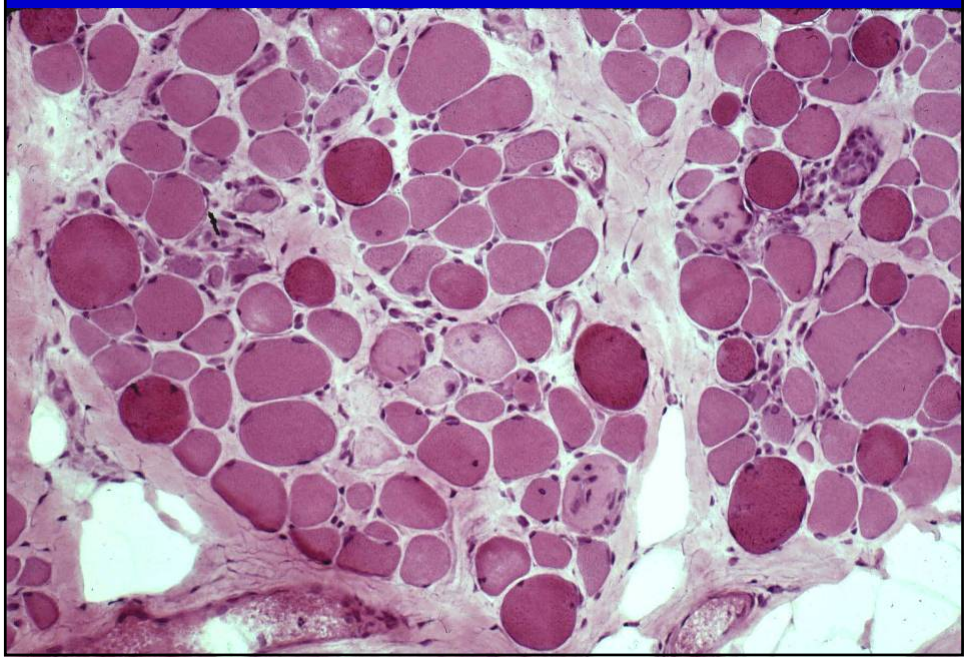
REGENERATING FIBER, H&E



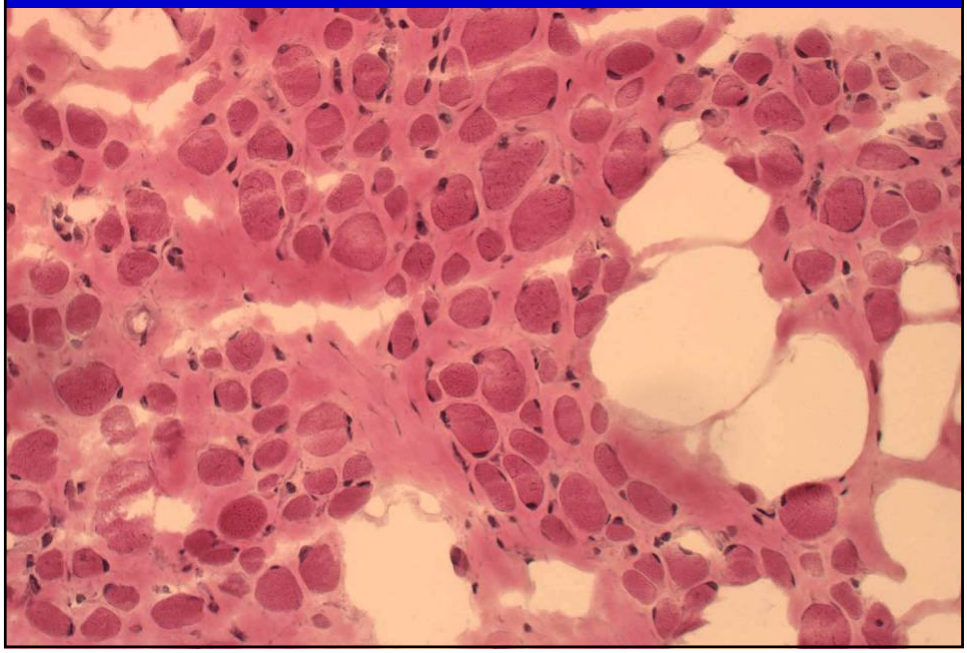
DUCHENNE MUSCULAR DYSTROPHY

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

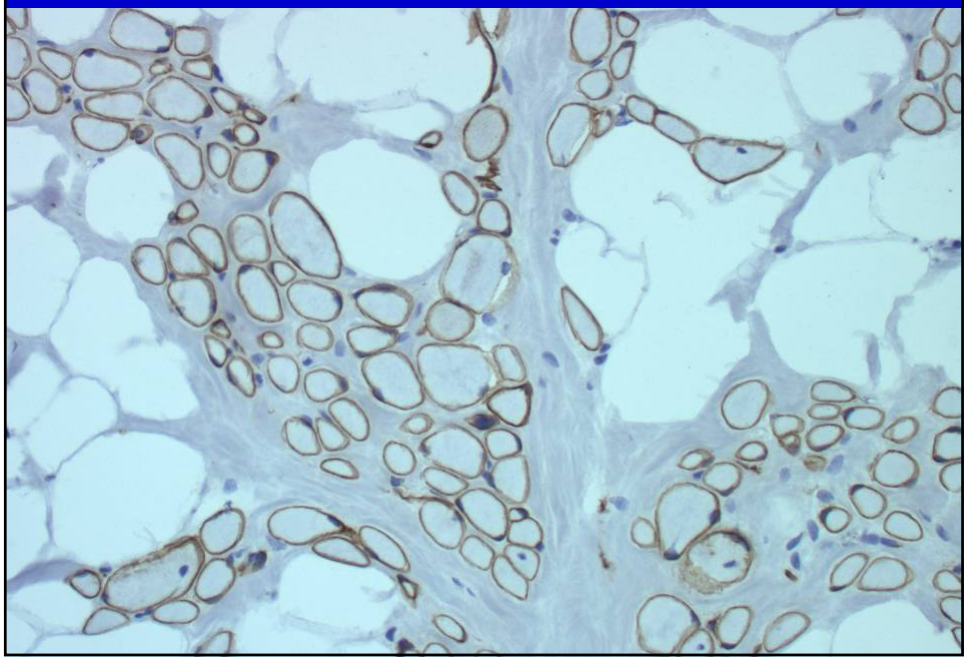
DUCHENNE DYSTROPHY, H&E



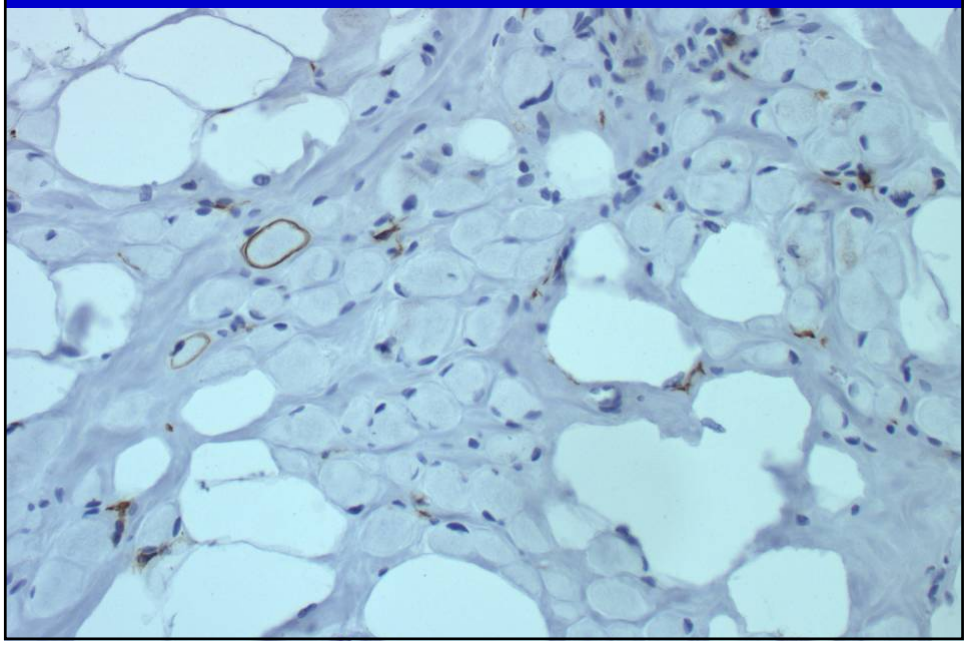
DUCHENNE DYSTROPHY, LATER STAGE

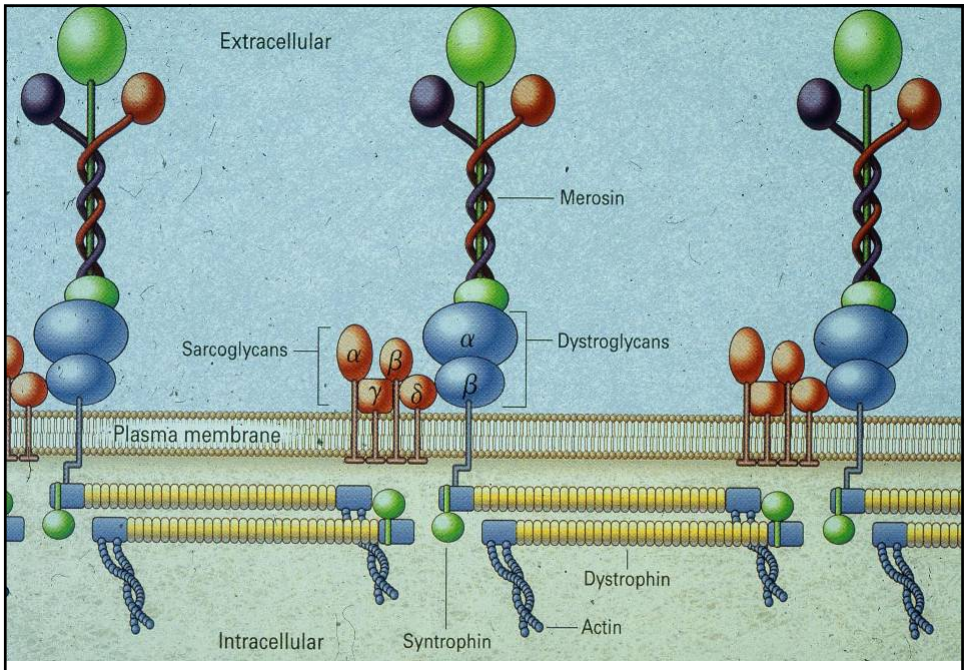


DUCHENNE DYSTROPHY, SPECTRIN



DUCHENNE DYSTROPHY, DYSTROPHIN





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

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.**

INFLAMMATORY MYOPATHIES

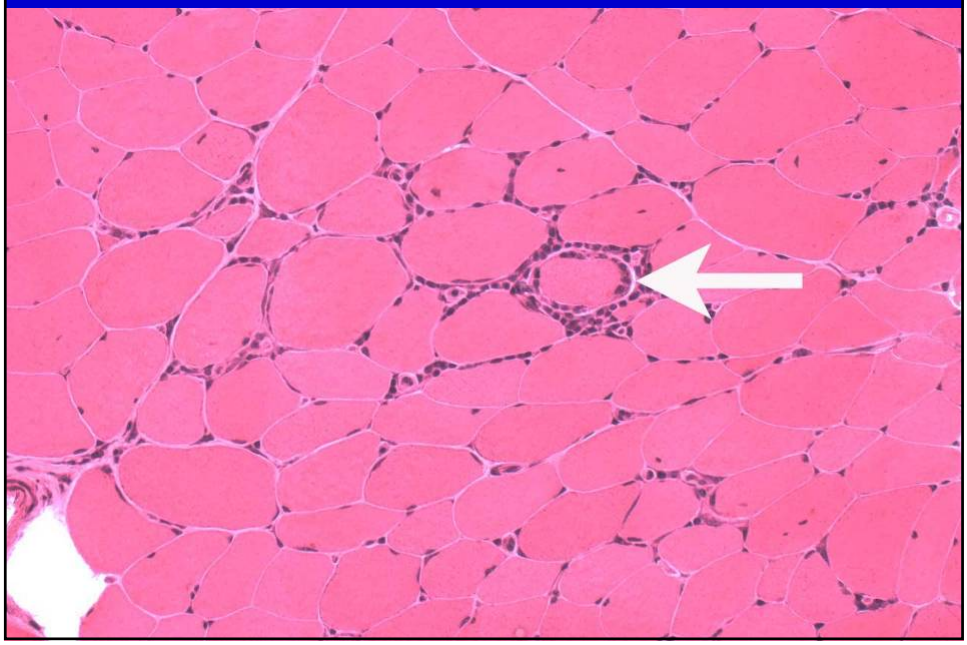
- Polymyositis
- Inclusion body myositis
- Dermatomyositis

POLYMYOSITIS

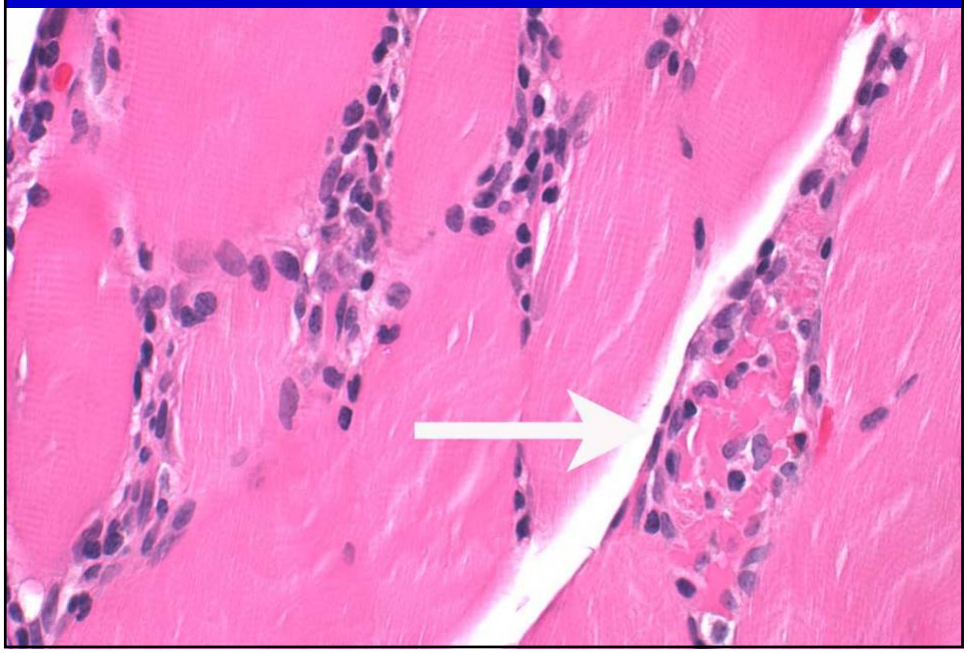
DIAGNOSTIC FEATURES OF POLYMYOSITIS

- 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.

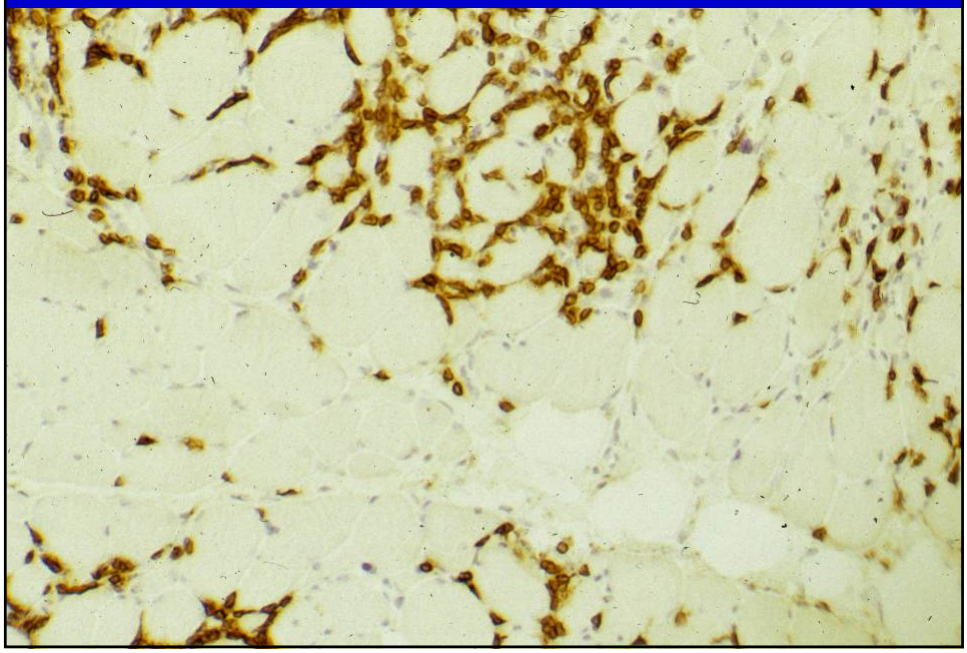
POLMYOSITIS, H&E



POLMYOSITIS, PARAFFIN SECTION, H&E



POLMYOSITIS, IMMUNOPEROXIDASE, CD8



MUSCLE BIOPSY DIAGNOSES OF POLYMYOSITIS (46 CASES)

Inflammatory myopathy	52%
Myopathy	10%
Muscle fiber atrophy	15%
Normal	23%

POLYMYOSITIS: PATHOLOGY

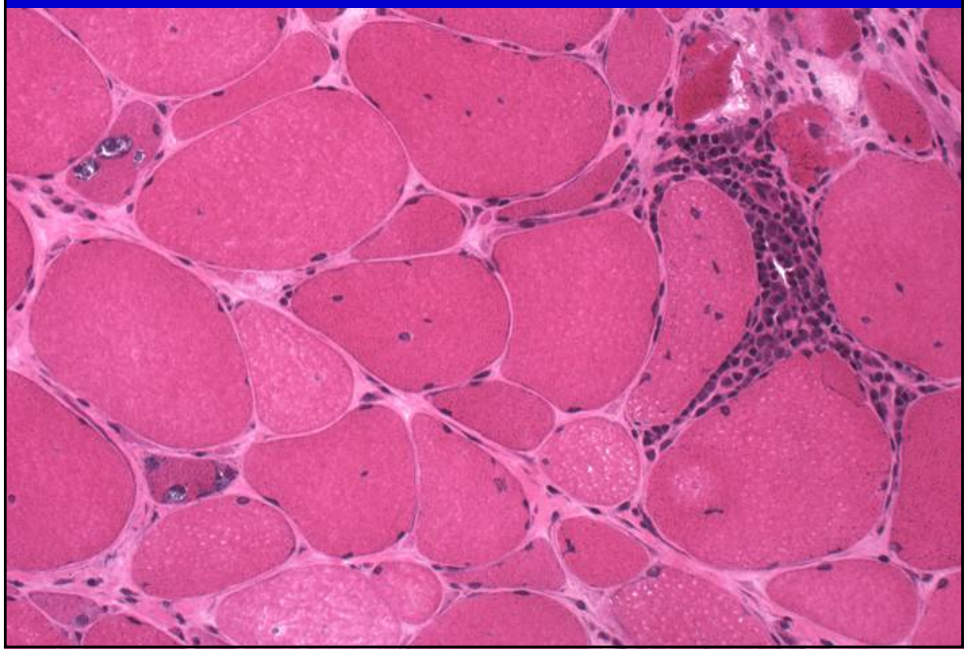
- Necrotic fibers and regenerating fibers randomly distributed throughout the muscle specimen.
- CD8 cytotoxic cells infiltrate predominantly the endomysium with invasion of rare myofibers.
- Little fibrosis or myofiber hypertrophy, consistent with a subacute disorder.

INCLUSION BODY MYOSITIS

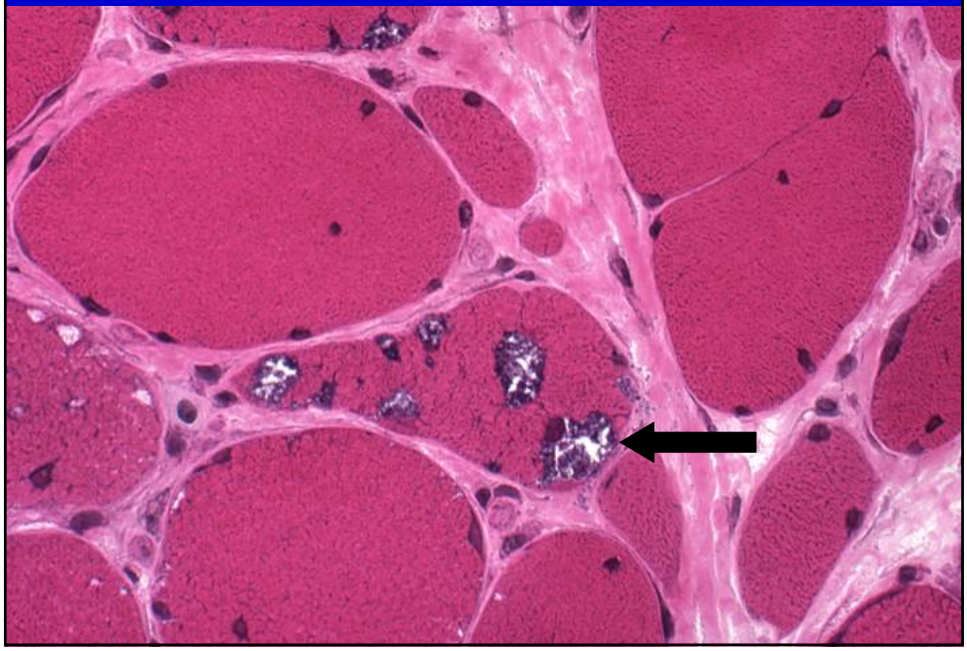
DIAGNOSTIC FEATURES OF IBM

- **Slowly progressive weakness, proximal and distal. Usually in adults, mostly men.**
- **Mildly elevated serum creatine kinase or normal.**
- **Electromyogram: myopathic potentials, spontaneous activity.**
- **Muscle biopsy: inflammatory myopathy affecting chiefly the endomysium, but chronic and has rimmed vacuoles and amyloid inclusions.**
- **Usually does not respond to glucocorticoids.**

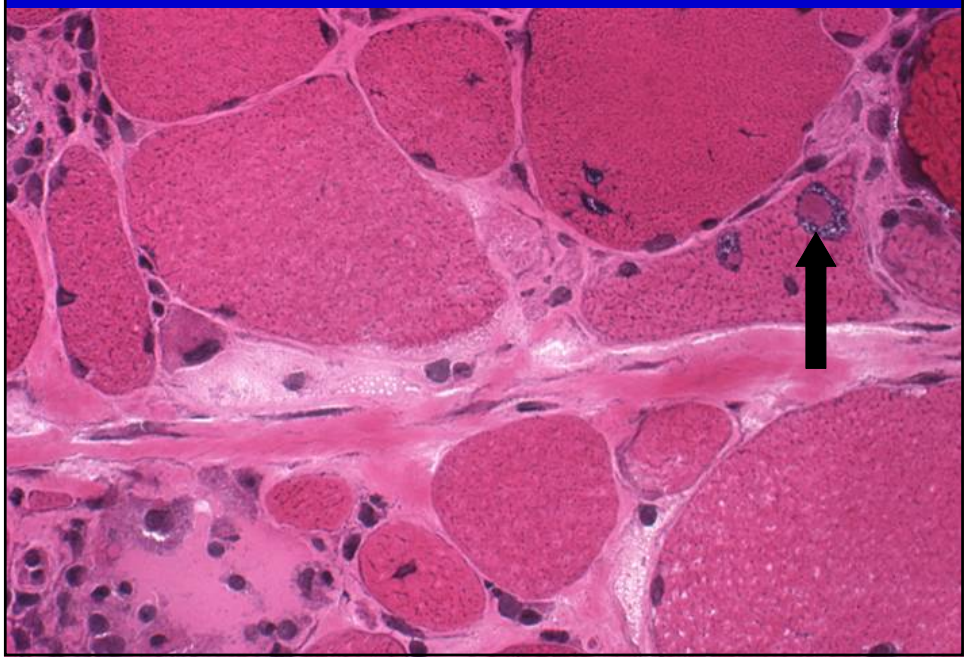
INCLUSION BODY MYOSITIS, H&E



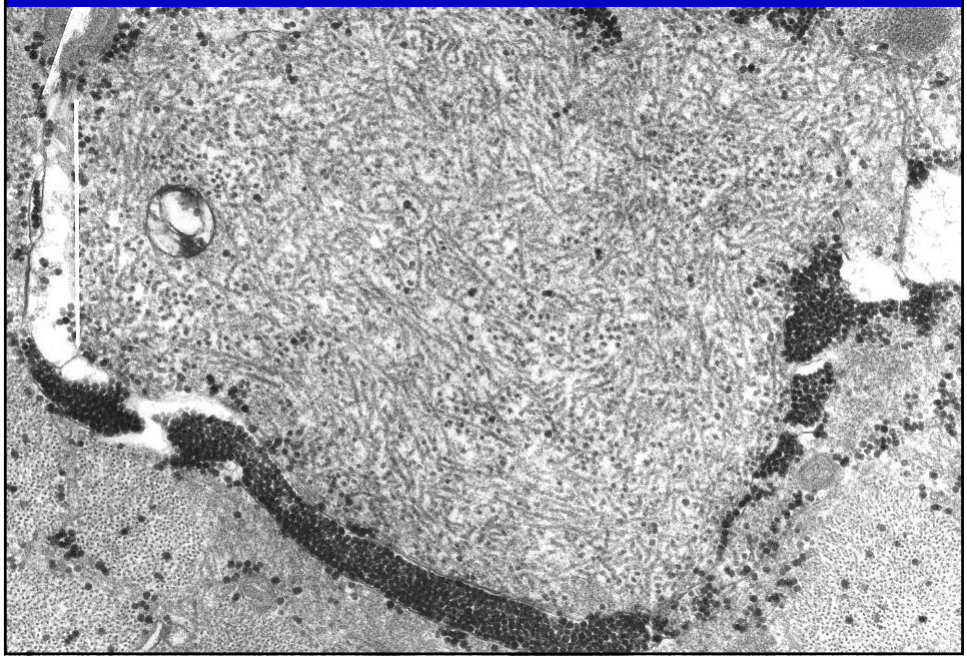
IBM, RIMMED VACUOLES, H&E



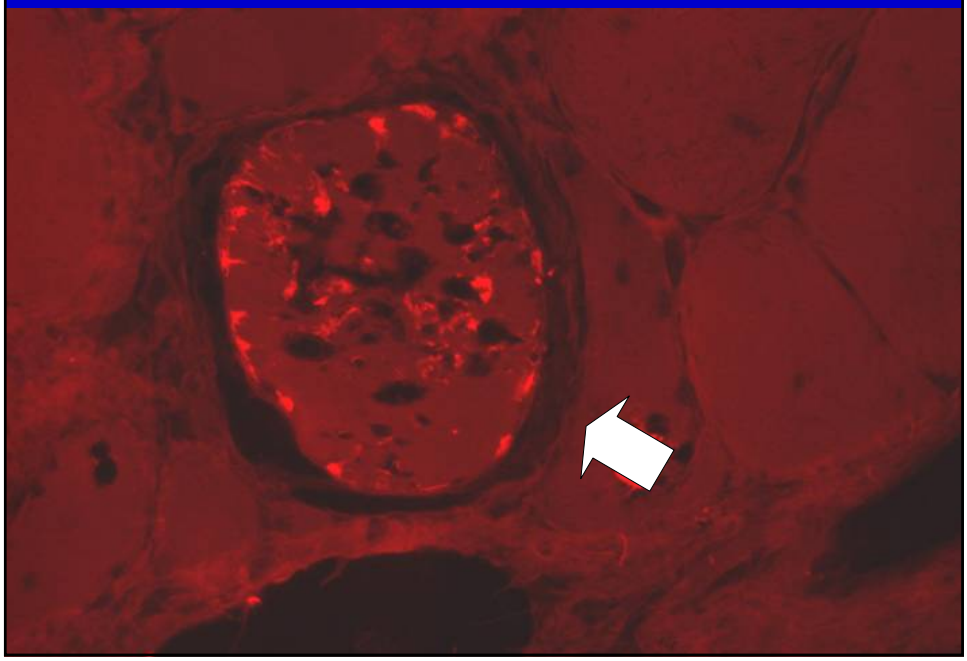
IBM, EOSINOPHILIC INCLUSION IN A RIMMED VACUOLE



ELECTRON MICROSCOPY, 15-20 nm FILAMENTS



IBM, CONGO RED, FLUORESCENCE, RHODAMINE OPTICS



IBM PATHOLOGY

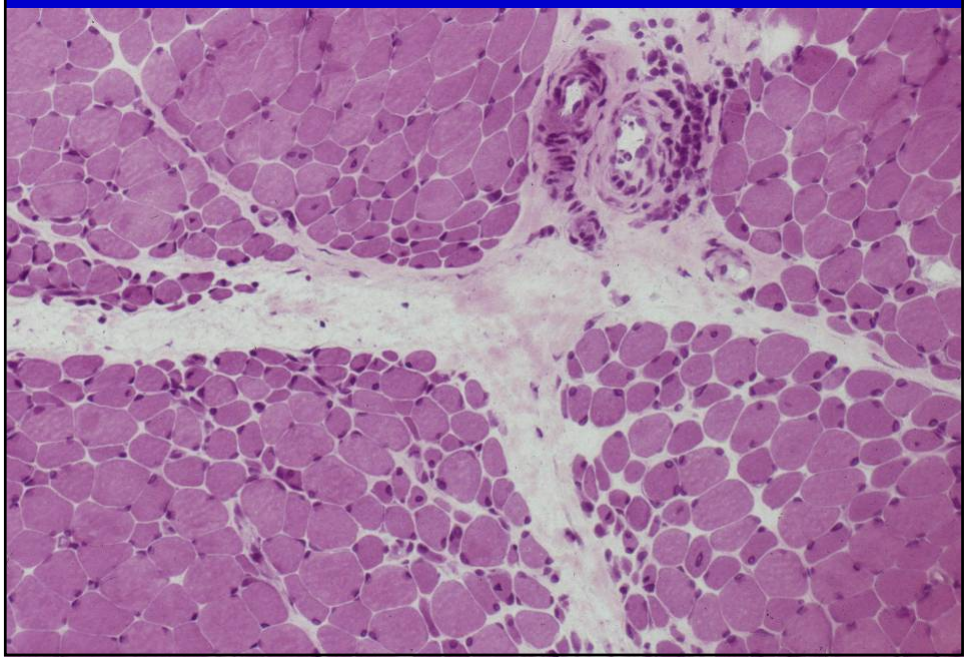
- IBM resembles polymyositis but has hypertrophic fibers and prominent endomysial fibrosis indicating it is chronic.
- Rimmed vacuoles.
- Congophilic fibrillar inclusions, composed of abnormal (paired-helical) filaments.

DERMATOMYOSITIS

DIAGNOSTIC FEATURES OF DERMATOMYOSITIS

- **Subacute progressive weakness, proximal>distal. Children and adults, women more common than men.**
- **Characteristic rash and periorbital heliotrope.**
- **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.**

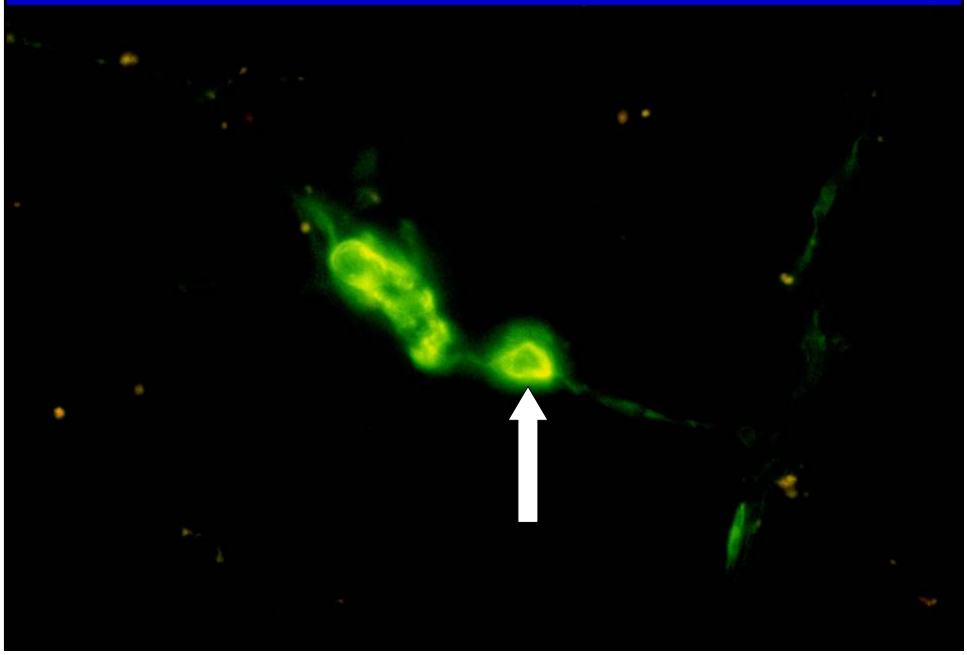
DERMATOMYOSITIS, PERIFASCICULAR ATROPHY, H&E



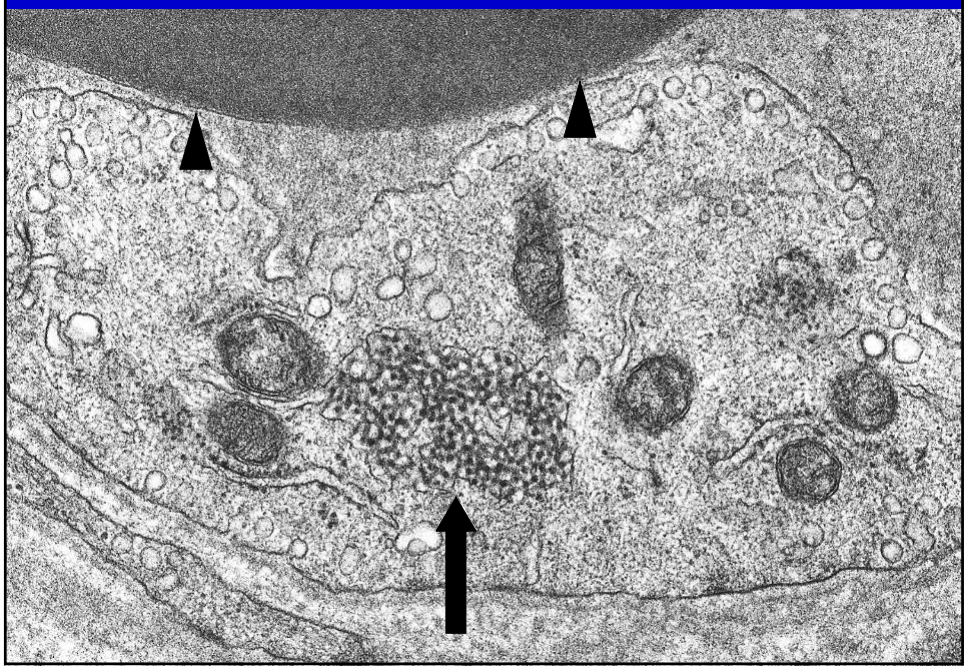
DERMATOMYOSITIS: LYMPHO-CYTE PHENOTYPES

- 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 endomyisum.

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.
- Tubuloreticular aggregates (undulating tubules).
- Reduced number of capillaries at periphery of fascicle.
- Lymphocytes are often sparse and located in chiefly perimysium.

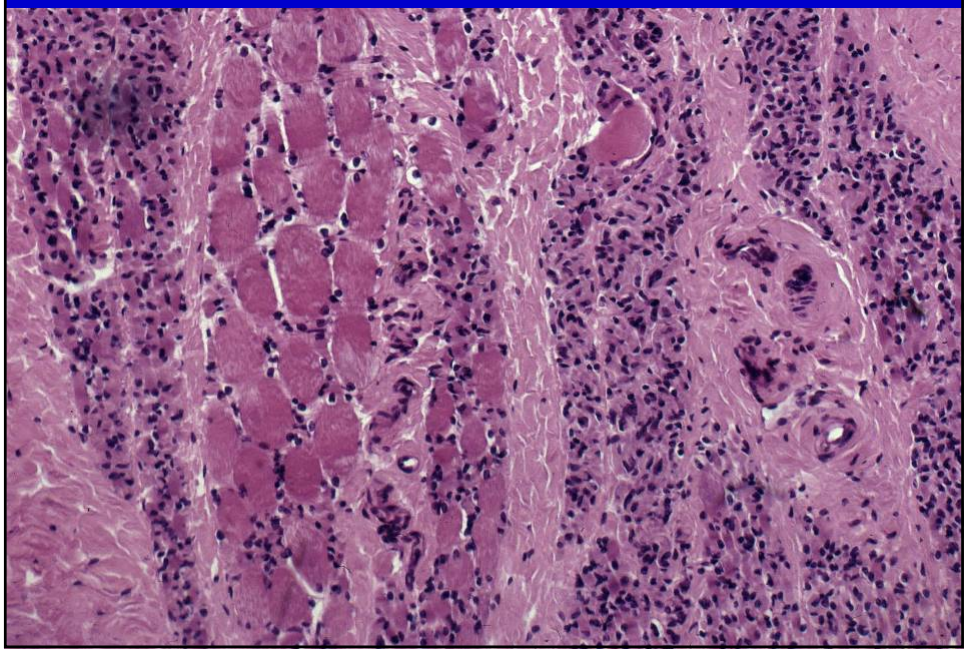
INFLAMMATORY MYOPATHIES: PATHOPHYSIOLOGY

- 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 of IBM.
- Dermatomyositis is thought to be caused by autoantibodies, possibly targeting an antigen of the endothelium. Fiber injury may be caused by ischemia.

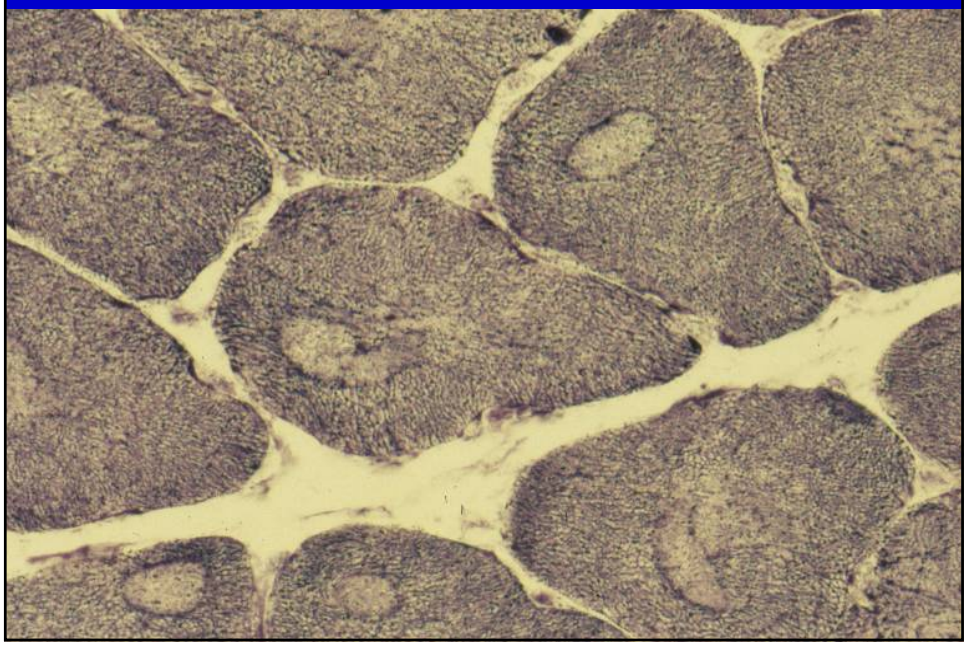
HYPOTONIA IN INFANCY

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

WERDNIG-HOFFMANN DISEASE

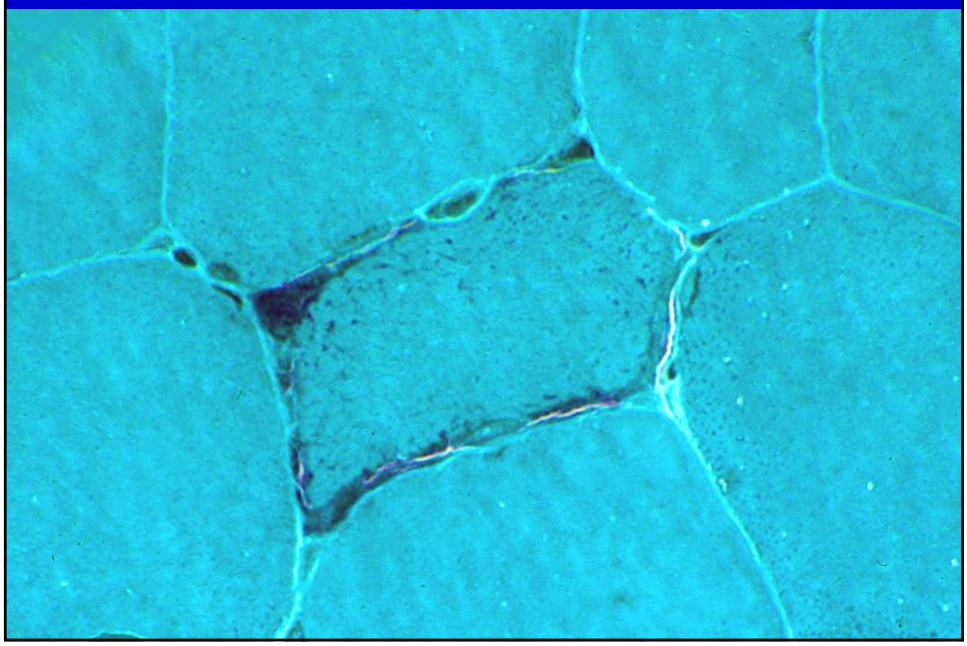


CENTRAL CORE DISEASE, NADH DEHYDROGENASE

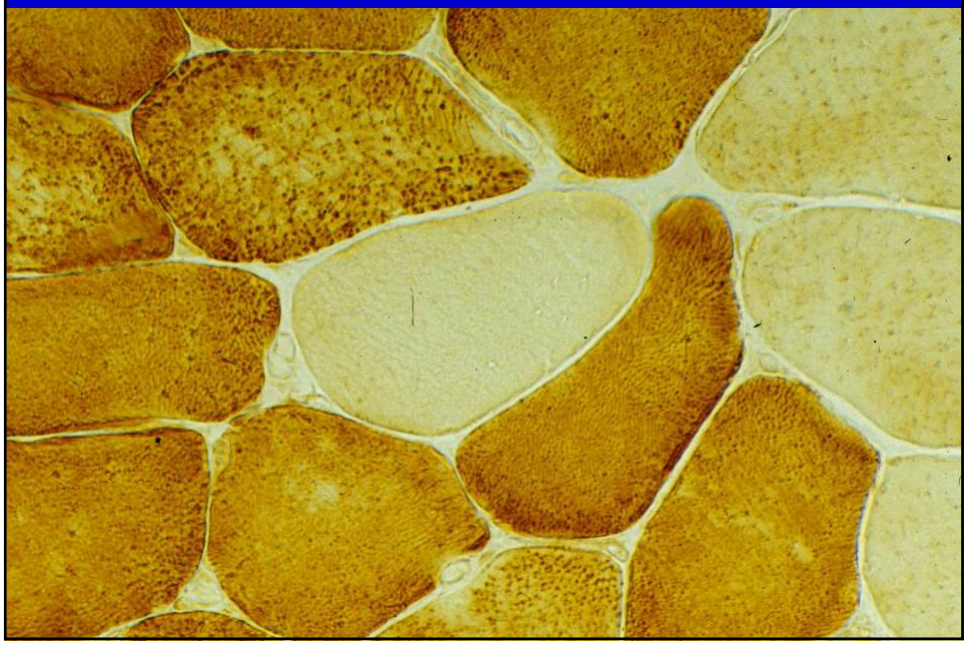


MITOCHONDRIAL MYOPATHY

MUTATIONS OF mtDNA RAGGED “RED” FIBER



CYTOCHROME C OXIDASE DEFICIENT MYOFIBER



RRF, SUCCINATE DEHYDROGENASE