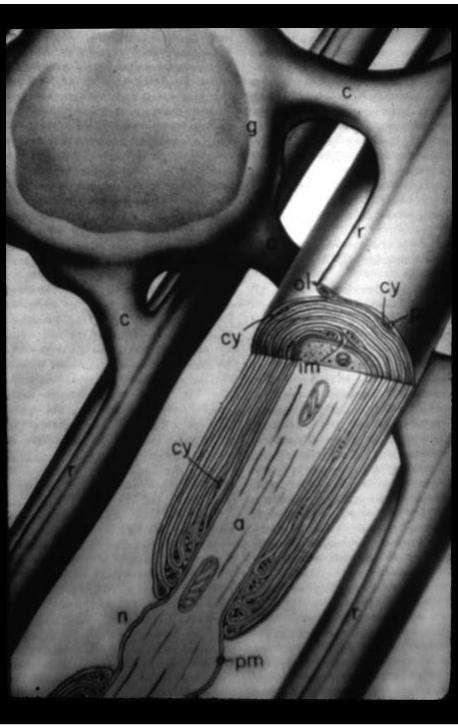
Pathologic classification of white matter disorders

- **Demyelinating -**
  loss of normal myelin
  autoimmune/inflammatory component
- **Dysmyelinating -**
  loss of chemically abnormal myelin
- **Hypomyelinating -**
  paucity of myelin formation
- **Myelinolytic (Spongiform) -**
  cytotoxic loss of myelin, intramyelinolytic edema

Oligodendrocytes make myelin in the CNS

Multiple axons are myelininated by one oligodendrocyte



Demyelinating Diseases

- Multiple Sclerosis
- Acute Disseminated Encephalomyelitis
- Acute Hemorrhagic Leukoencephalitis
- Progressive Multifocal Leukoencephalopathy
- Subacute Sclerosing Panencephalitis
- Idopathic Polyneuritis (Landry-Guillain-Barre)

Multiple Sclerosis

- Episodic neurologic signs and symptoms referable to different parts of the neuraxis ("disseminated in time and space")
- Attacks followed by complete or partial remission
- Peak age of onset is 20-40 years; more common in women
- Chronic relapsing ("classical") and rapidly progressing forms
- Diagnosis established by clinical history, MRI, CSF analysis (oligoclonal bands)

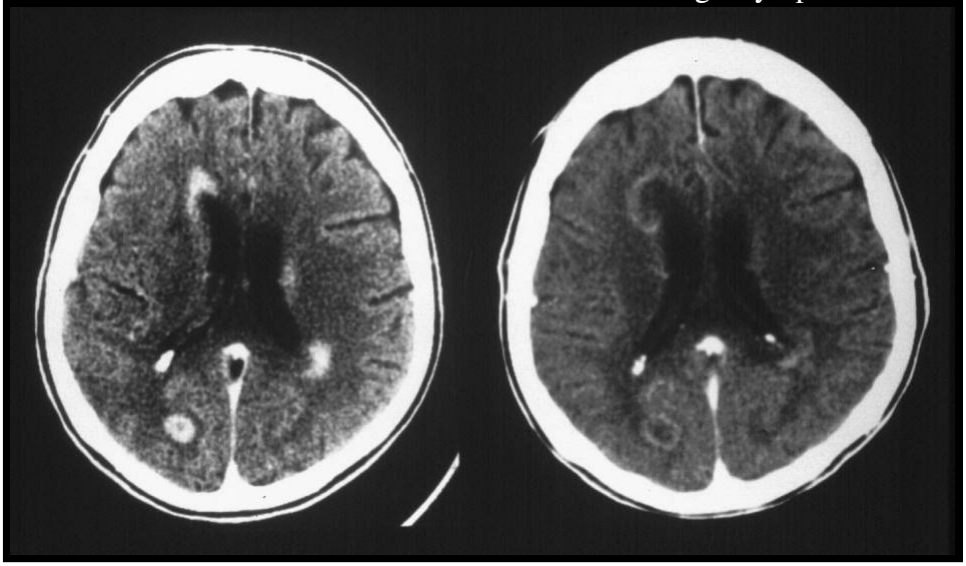
"Classical" Multiple Sclerosis

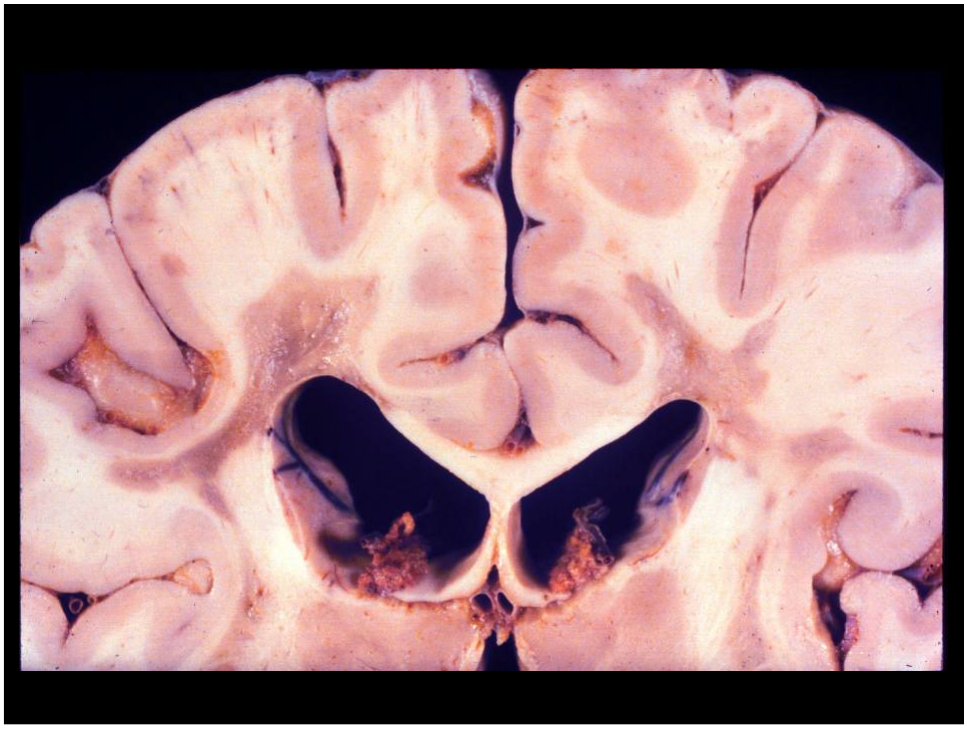
- **Prevalence:**
  - **30-120/100,000 in Northern Latitudes**
- **Etiology:**
  - **Genetic Factors**
  - **Environmental Factors**
  - **Immunologic Pathogenesis**

Multiple Sclerosis - CT Scans

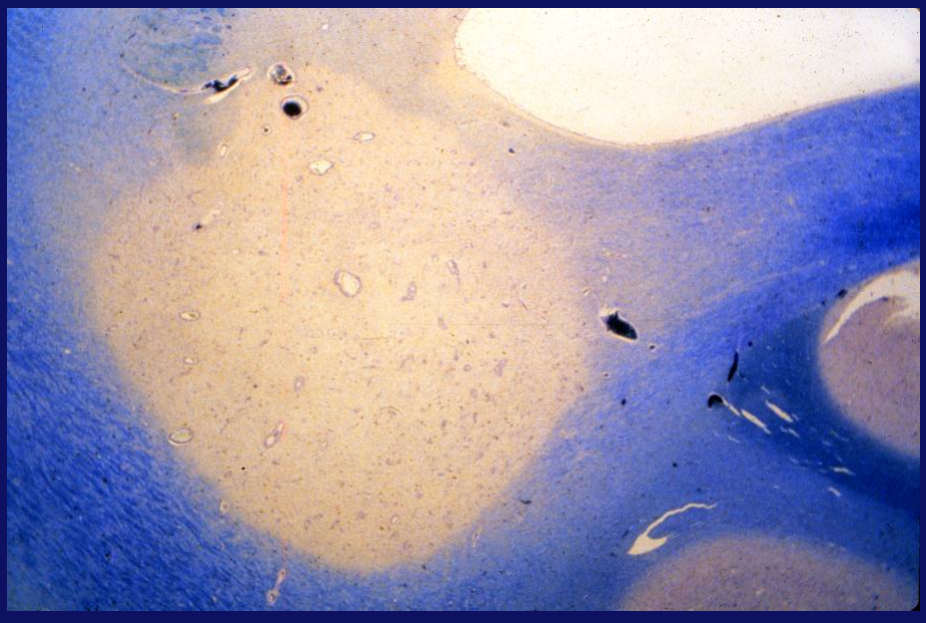
Neurologic symptoms present

Complete/partial resolution of neurologic symptoms

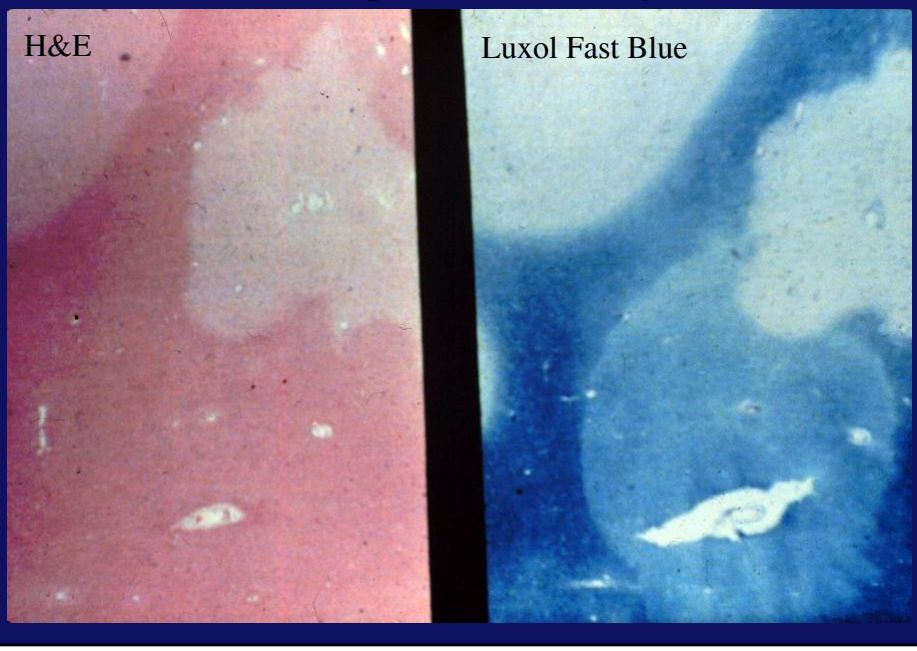




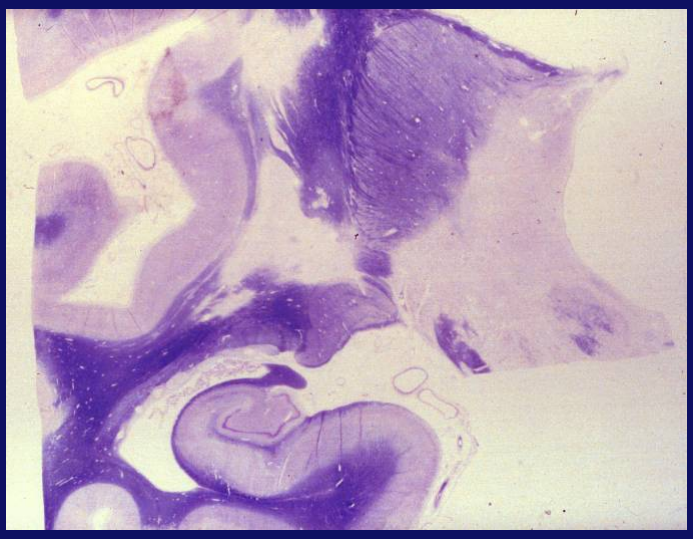
Multiple Sclerosis Plaque - periventricular



Shadow Plaque = Partial remyelination



MS plaques may involve "gray matter" regions (e.g. deep nuclei in forebrain, brain stem) where there is a close mixture of myelinated axonal fibers and neuronal nuclei



LFB-PAS

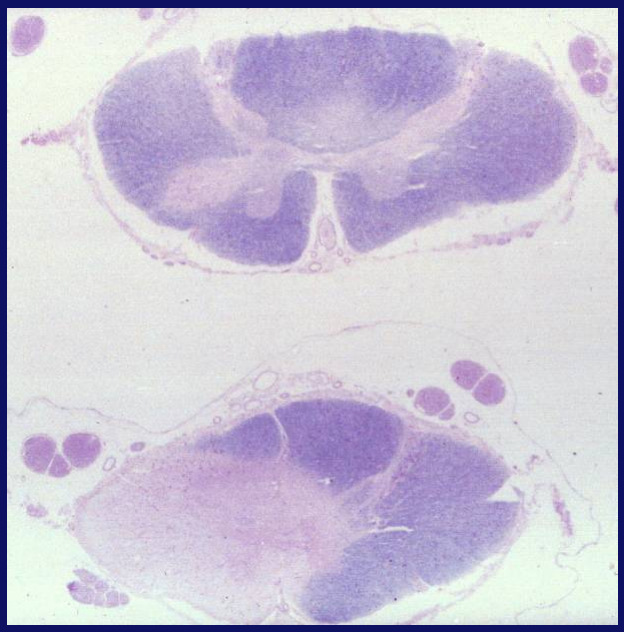
Multiple,

Asymmetric,

Non-track oriented,

in white matter =

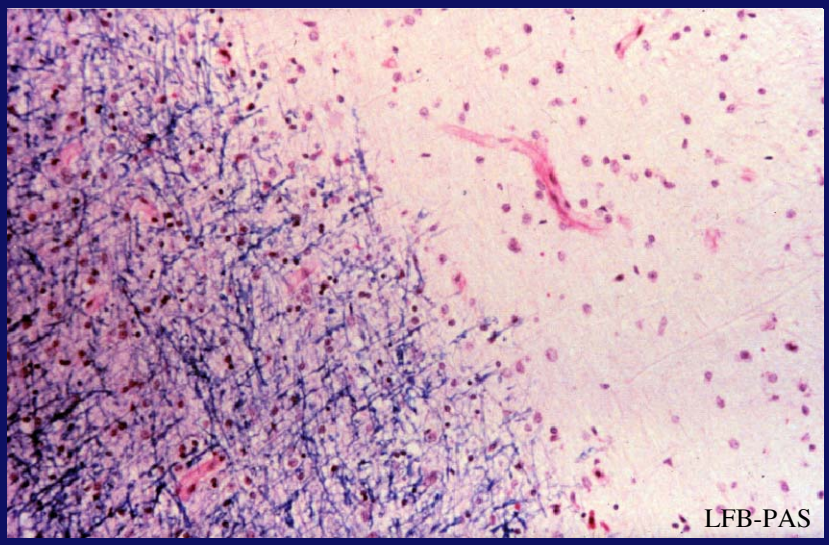
Multiple Sclerosis



LFB-PAS

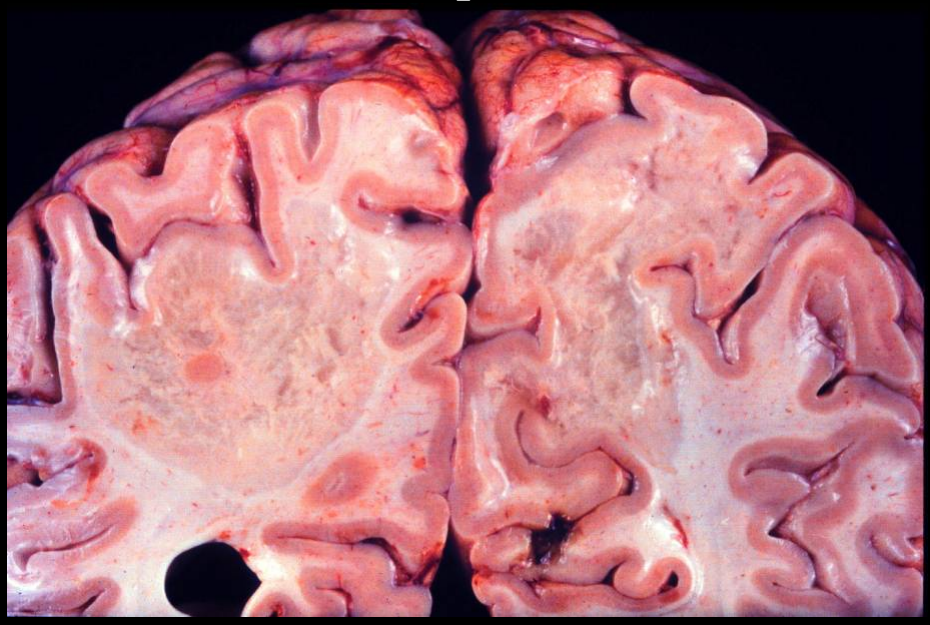
Chronic Multiple Sclerosis Plaque

Severe loss of myelin and gliosis in plaque, relative preservation of axons (not shown), sharply circumscribed border



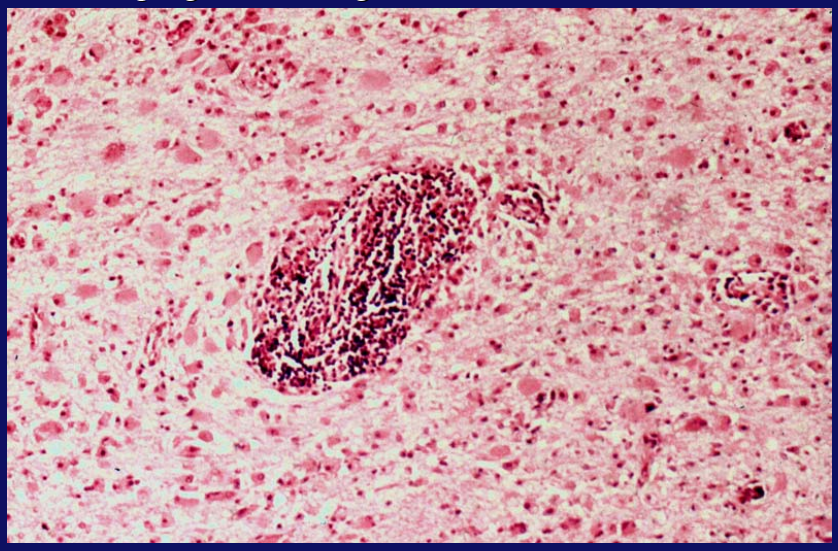
LFB-PAS

Acute Multiple Sclerosis



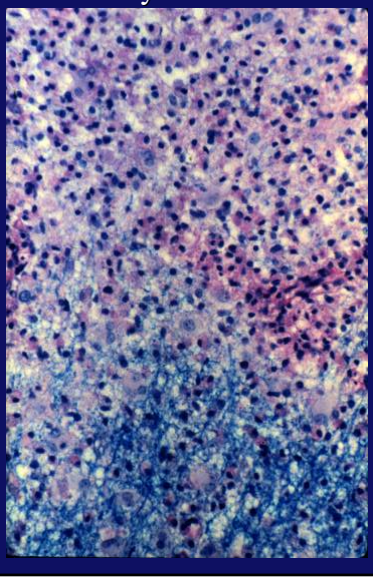
Acute Multiple Sclerosis Plaque

Loss of myelin, perivascular lymphocytes, many macrophages infiltrating lesion and "reactive"

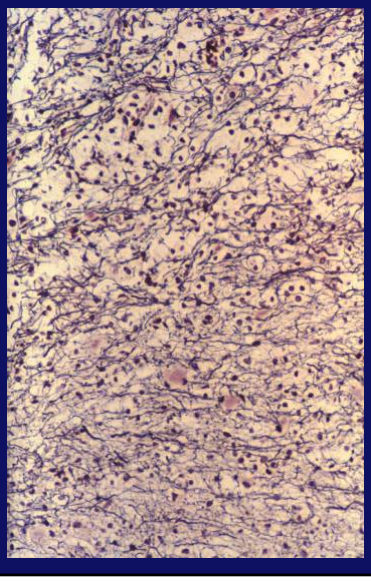


Relative axonal sparing in multiple sclerosis

Luxol fast blue (LFB) myelin stain



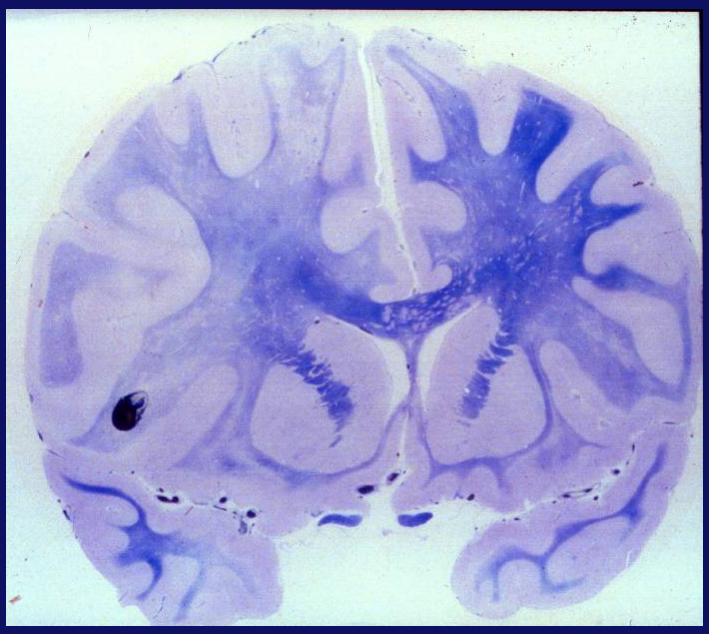
Bielschowsky axonal stain



Acute Disseminated Encephalomyelitis

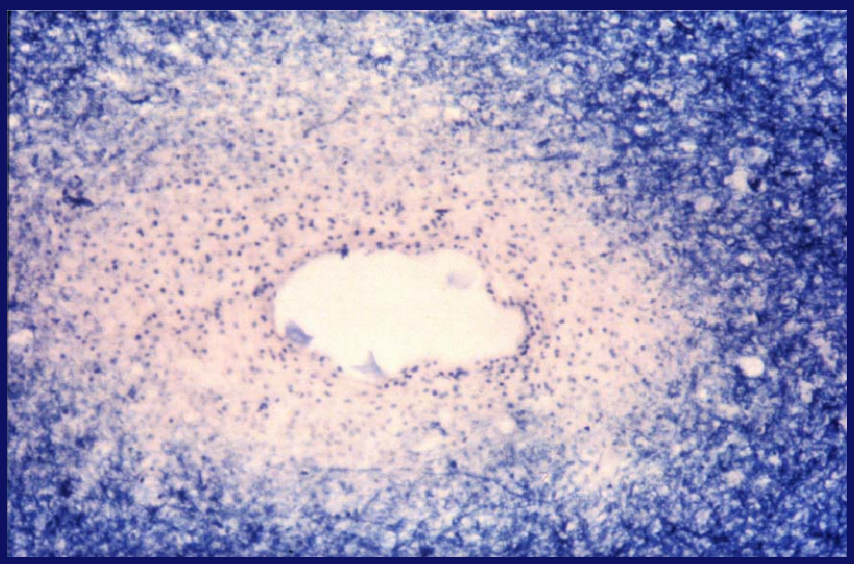
- Monophasic illness, lasting ~2 to 4 weeks
- Affects predominantly children and young adults
- Usually follows an infection, also immunizations
  - Immune mediated complication
- Acute onset of multifocal neurologic disturbances
- Most patients recover (early recognition and steroid treatment)
- Perivenous inflammation and demyelination, punctate to confluent, widespread in neuraxis

Acute Disseminated Encephalomyelitis



LFB-PAS

ADEM - **perivenous demyelination and inflammatory infiltrate containing largely lymphocytes**

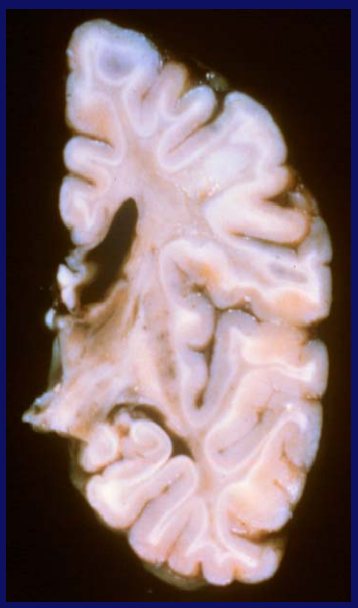


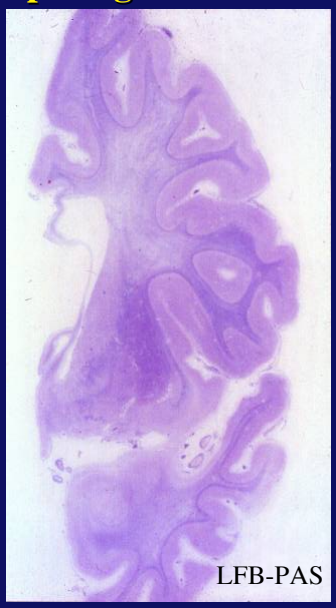
Dysmyelinating Diseases

- inherited disorders
- chemically abnormal myelin

- Metachromatic Leukodystrophy
- Globoid Cell Leukodystrophy
- Adrenoleukodystrophy

Leukodystrophy = widespread, confluent loss of myelin relative sparing of cortical U-fibers

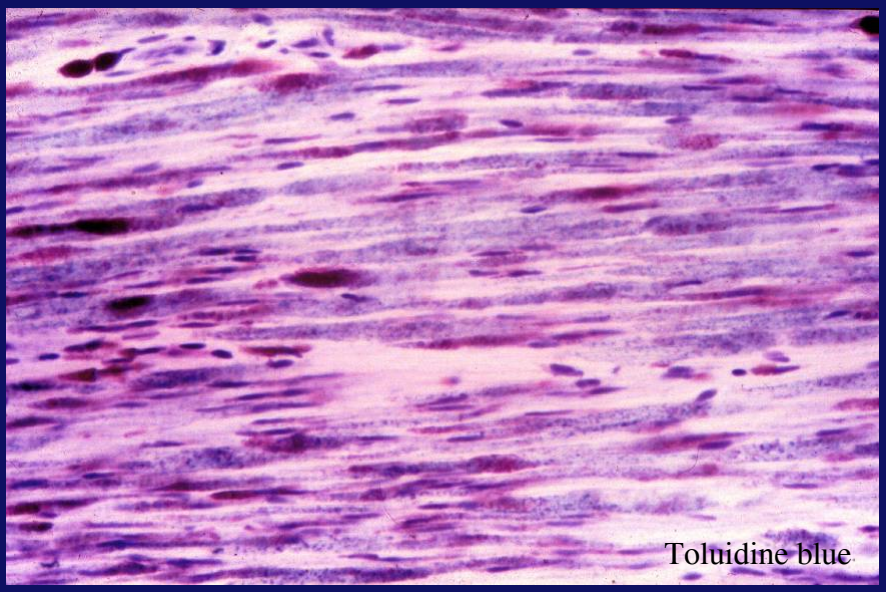




Metachromatic Leukodystrophy

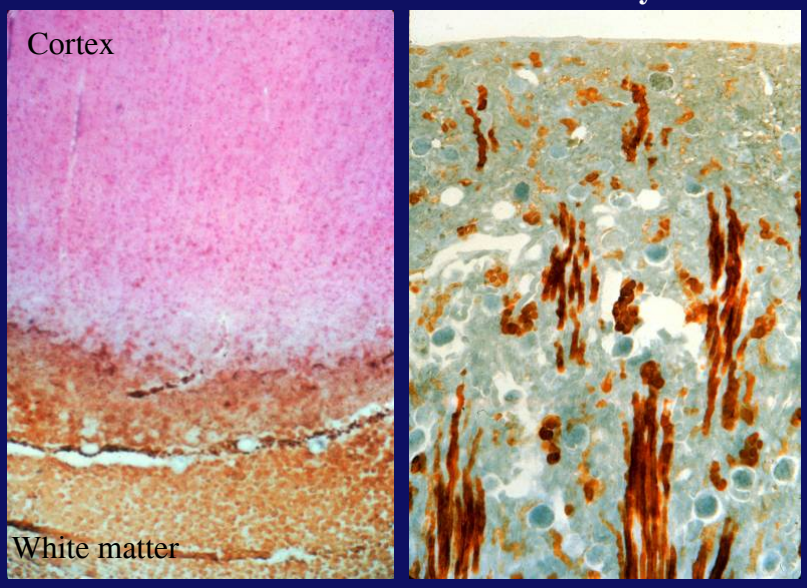
- Deficiency of the lysosomal enzyme arylsulfatase A; autosomal recessive
- Late infantile form most common, onset 1-2 years; progressive motor disability, intellectual decline, rapid demise
- "Metachromatic" deposits of sulfatide in CNS, PNS, and kidney
- Diagnosis made by measurement of enzyme activity, urinary sulfatide excretion; prenatal diagnosis is possible

Brownish, "metachromatic" deposits in peripheral nerve



Metachromatic Leukodystrophy

Brain **Kidney**

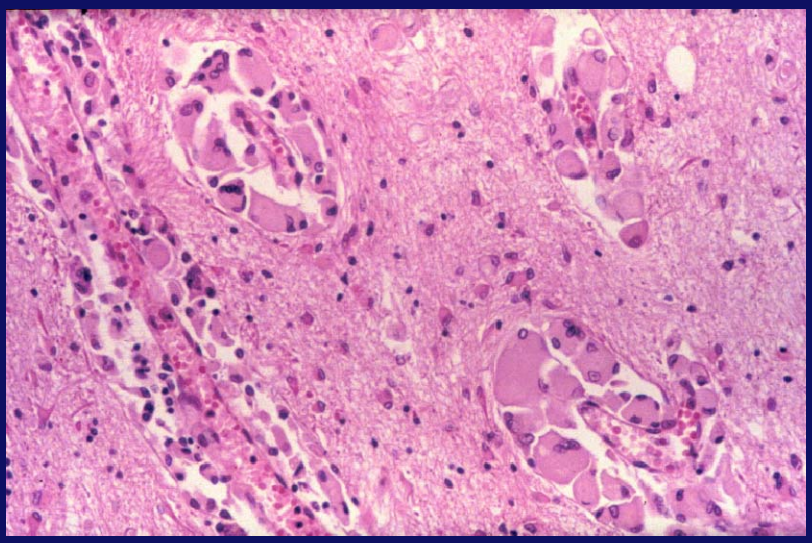


Globoid cell Leukodystrophy (Krabbe's disease)

- Deficiency of the lysosomal enzyme beta-galactocerebrosidase; autosomal recessive
- Onset and symptoms:
  - Late infancy most common (80%), usually before 6 months
    - developmental arrest
    - extreme irritability and crying followed by rigidity and tonic spasms;
    - frequent episodes of pyrexia
    - death by 1-2 years with continued seizures and opisthotonus
  - CNS pathology due to accumulation of psychosine
  - May also affect the peripheral nervous system

Krabbe's disease

- Clusters of globoid cells in pale, gliotic white matter
- Globoid cells are monocyte derived



Adrenoleukodystrophy

• INHERITANCE:	X-linked recessive (Xq28)
• ONSET:	4-8 years (childhood cerebral form)
• SYMPTOMOTOLOGY:	Disturbances in affective behavior Neurologic deficits Adrenal insufficiency
• AVG AGE AT DEATH:	10 years
• BIOCHEMICAL DEFECT:	Peroxisomal disorder Accumulation of VLCFA (>C22:0) due to defective beta-oxidation Mutations in ALDP gene, an ABC transporter

Adrenoleukodystrophy

Childhood cerebral (peak age of onset 4-8 years)
Age of onset and extent of lesions at presentation (by MRI scans) are predictive of clinical course

Adrenomyeloneuropathy (peak age of onset 20-30 years)
Slowly progressive (over decades) spastic paraparesis, sphincter disturbance due to spinal cord involvement; variable cerebral involvement

Adult cerebral
Cerebral symptoms after age 21, no spinal involvement

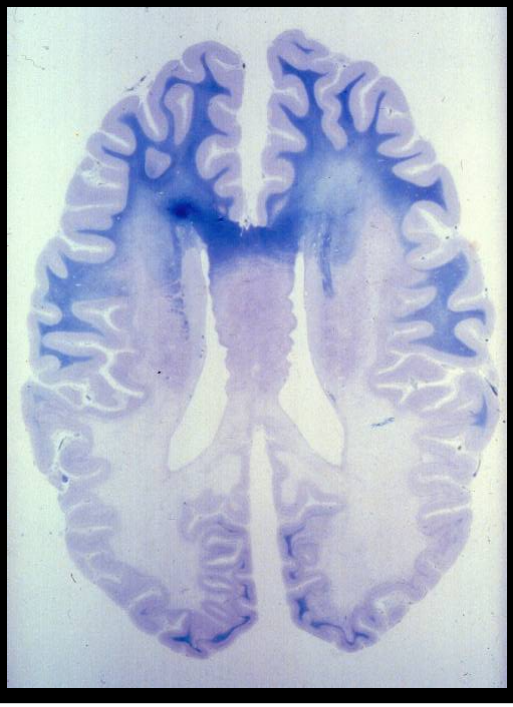
Adrenal insufficiency only ("Addison disease" in men)

Symptomatic ALD Heterozygotes (women age 25-55 years)
61% with "neurologic abnormality", widely varying severity

Adrenoleukodystrophy (cerebral form)

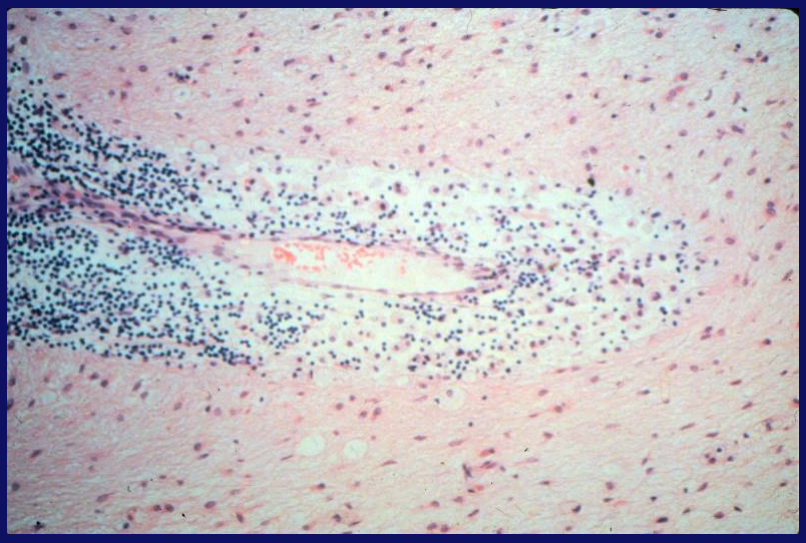
Often begins in posterior, occipital lobe and progresses to involve more frontal regions (generally more rapid progression)

In some patients, begins in frontal lobe and progresses to posterior regions (slower progression)

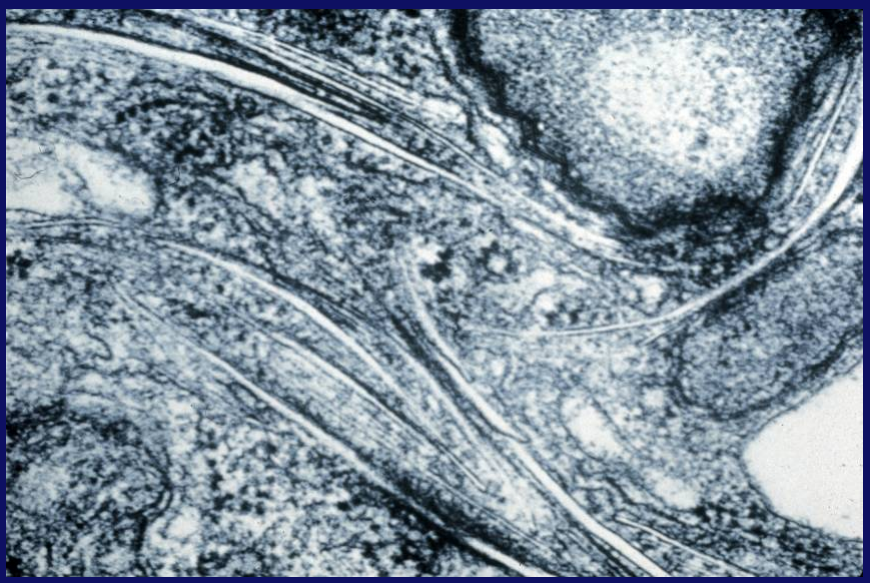


Cerebral Adrenoleukodystrophy

Inflammatory demyelination



Lamellar lipid inclusions in Adrenoleukodystrophy



Treatment options in leukodystrophy

- Palliative measures
- Lorenzo's oil for ALD may slow progression of childhood cerebral form when started before symptomatic; debate about utility in AMN patients
- Bone marrow transplantation, used in childhood cerebral ALD, globoid cell leukodystrophy and metachromatic leukodystrophy
  - early transplantation and careful selection of patients
  - successfully treated patients have shown arrest and/or reversal of CNS pathology
- Many experimental protocols:
  - peroxisome proliferator drugs in ALD: 4-phenylbutyrate
  - combining gene transfer with bone marrow transplantation
  - gene transfer to the nervous system, stem cells (!!!)

Hypomyelinating Diseases

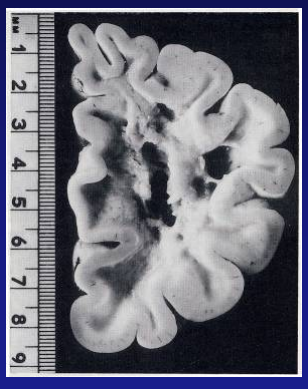
- Pelizaeus-Merzbacher Disease
- Alexander Disease
- CACH (Vanishing White Matter)

Alexander's Disease

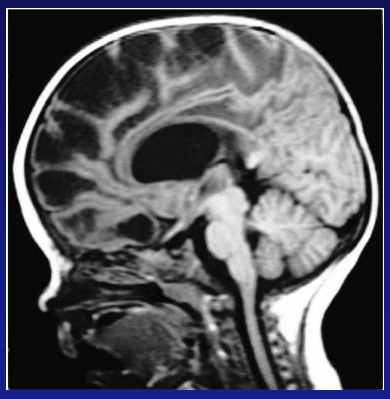
- Most often presents in infancy with increased head size, psychomotor retardation, spasticity; rapidly progressive
- Widespread demyelination in CNS with Rosenthal fibers in astrocytic processes
- Usually sporadic; autosomal recessive
- Majority of patients have mutations in glial fibrillary acidic protein, an intermediate filament protein of astrocytes

Alexander Disease

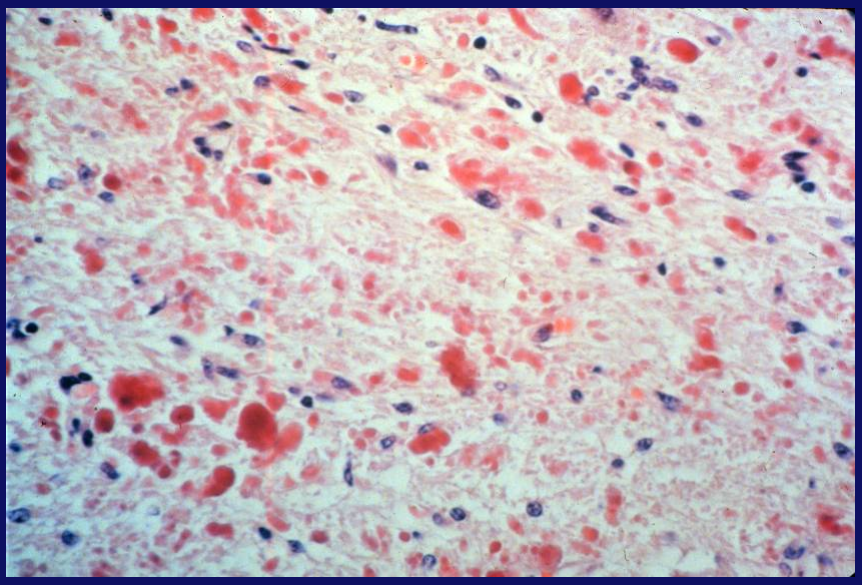
Coronal section showing a near total lack of white matter



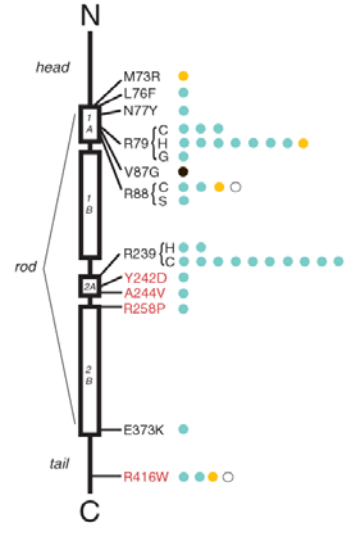
Sagittal T1-weighted MRI scan of an 8-month-old patient showing abnormal frontal and parietal white matter



Rosenthal fibers in Alexander disease



GFAP mutations in Alexander disease



- infantile onset
- juvenile onset
- uncertain onset

GFAP gene has missense mutations that are heterozygous (dominant) and arise de novo

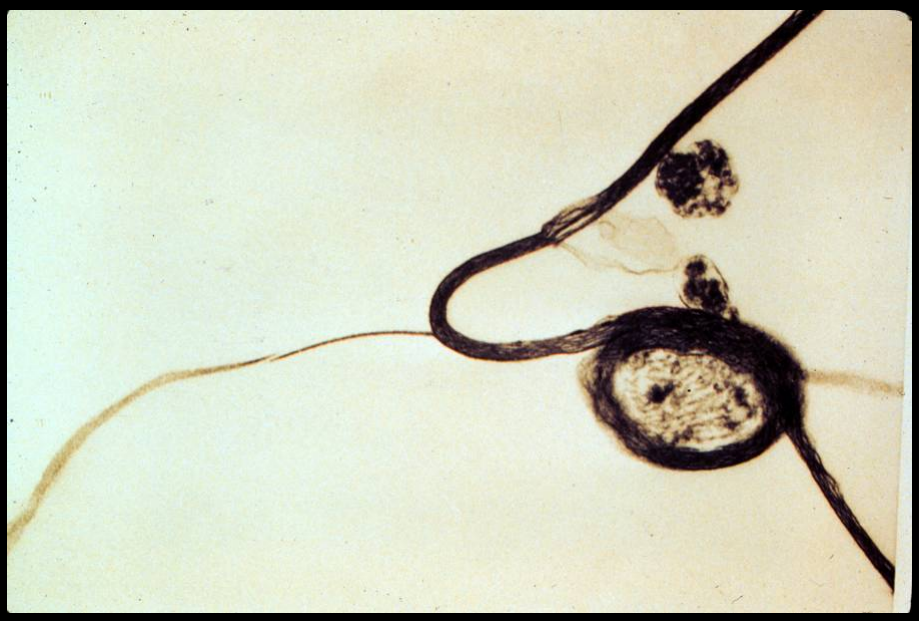
R79 patients tend to have mildest clinical course, R239 patients have severe disease

Mutations result in defective protein with altered oligomerization or solubility. Astrocyte stress response induced leading to secondary loss of oligodendrocytes/myelin.

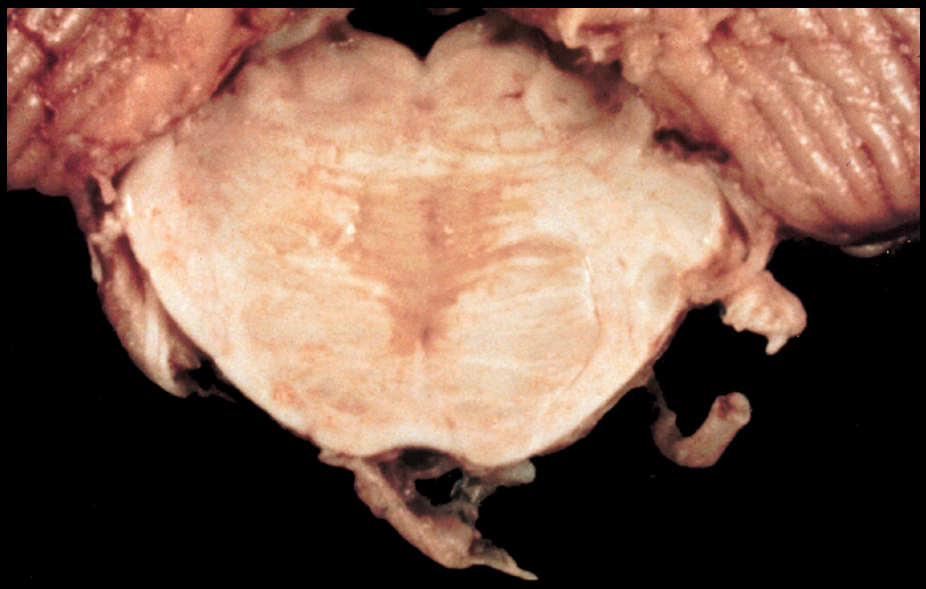
Myelinolytic Diseases

- Central Pontine Myelinolysis
- Marchiafava-Bignami Disease
- Aminoacidurias
- Spongy Degeneration of Infancy (Canavan)
- Vacuolating Leukoencephalopathy
- Hexachlorophene Toxicity
- Heroin toxicity (“chasing the dragon”)

Intramyelinolytic edema



Central Pontine Myelinolysis



Canavan's Disease

- Deficiency of the lysosomal enzyme aspartoacylase; N-acetyl-aspartic acid accumulates in brain
- Autosomal recessive; most common in Ashkenazi Jews
- Presents at 2-6 months of age with psychomotor retardation, hypotonia; blindness, megalencephaly, seizures occur
- Vacuolar change ("spongy") in CNS due to intramyelinic edema in white matter of cerebrum and cerebellum