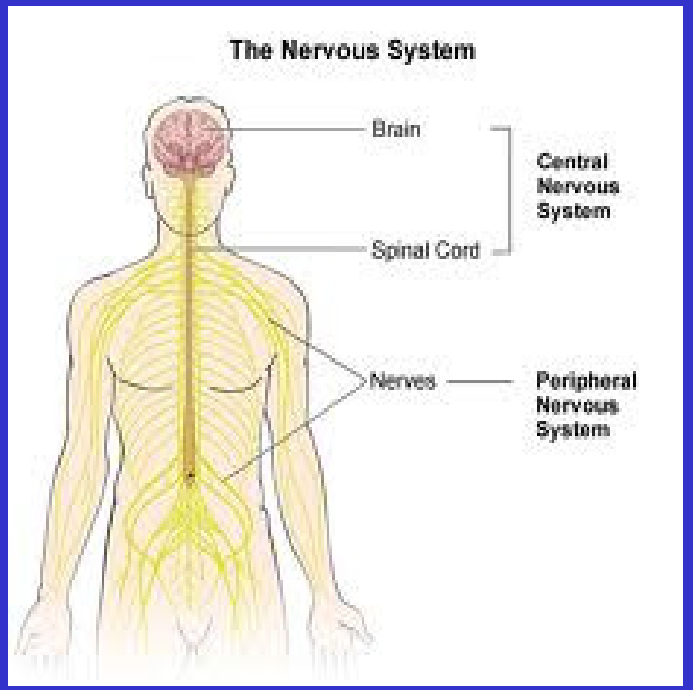
Multiple Sclerosis
CNS Demyelinating Disease

Keck School of Medicine
Department of Neurology
February 2014 - Wyoming
Leslie P. Weiner, MD

Multiple Sclerosis

- Multiple sclerosis is a chronic, often disabling disease that attacks the central nervous system*
  - Brain, spinal cord, and optic nerves.



*http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/what-is-ms/index.aspx

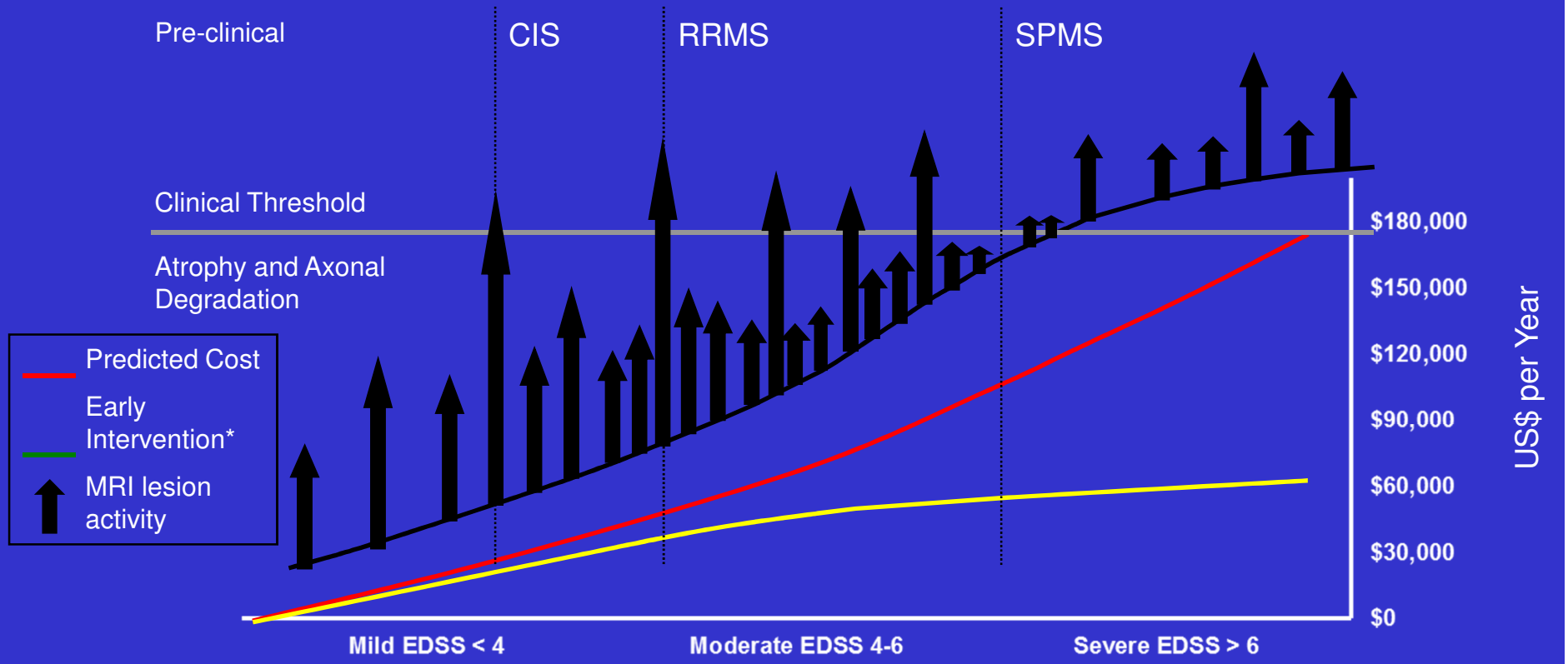
Epidemiology of Multiple Sclerosis

- The most common chronic disease affecting the CNS in young adults
- Approximately 400,000 cases in the United States
  - Estimates range from 250,000 to 500,000
- The chances of developing MS are 1:1000 in the general population
- Estimated 2.5 million cases worldwide
- Highest incidence in Caucasians of northern European ancestry
- Higher incidence in women (approximately 3:1)
- MS strikes individuals between the ages 20-50, normally a time of peak productivity

CNS = central nervous system.

Compston A, et al. *Lancet*. 2002;359(9313):1221-1231. Frohman EM. *Med Clin N Am*. 2003;87(4): 867-897. Hogancamp WE, et al. *Mayo Clin Proc.* 1997;72(9):871-878. National Multiple Sclerosis Society. Who gets MS? http://www.nationalmssociety.org/about-multiple-sclerosis/who-gets-ms/index.aspx. Accessed January 8, 2009. Lage MJ, et al. *Work*. 2006;27(2):143-151.

Natural History of MS and Cost of MS

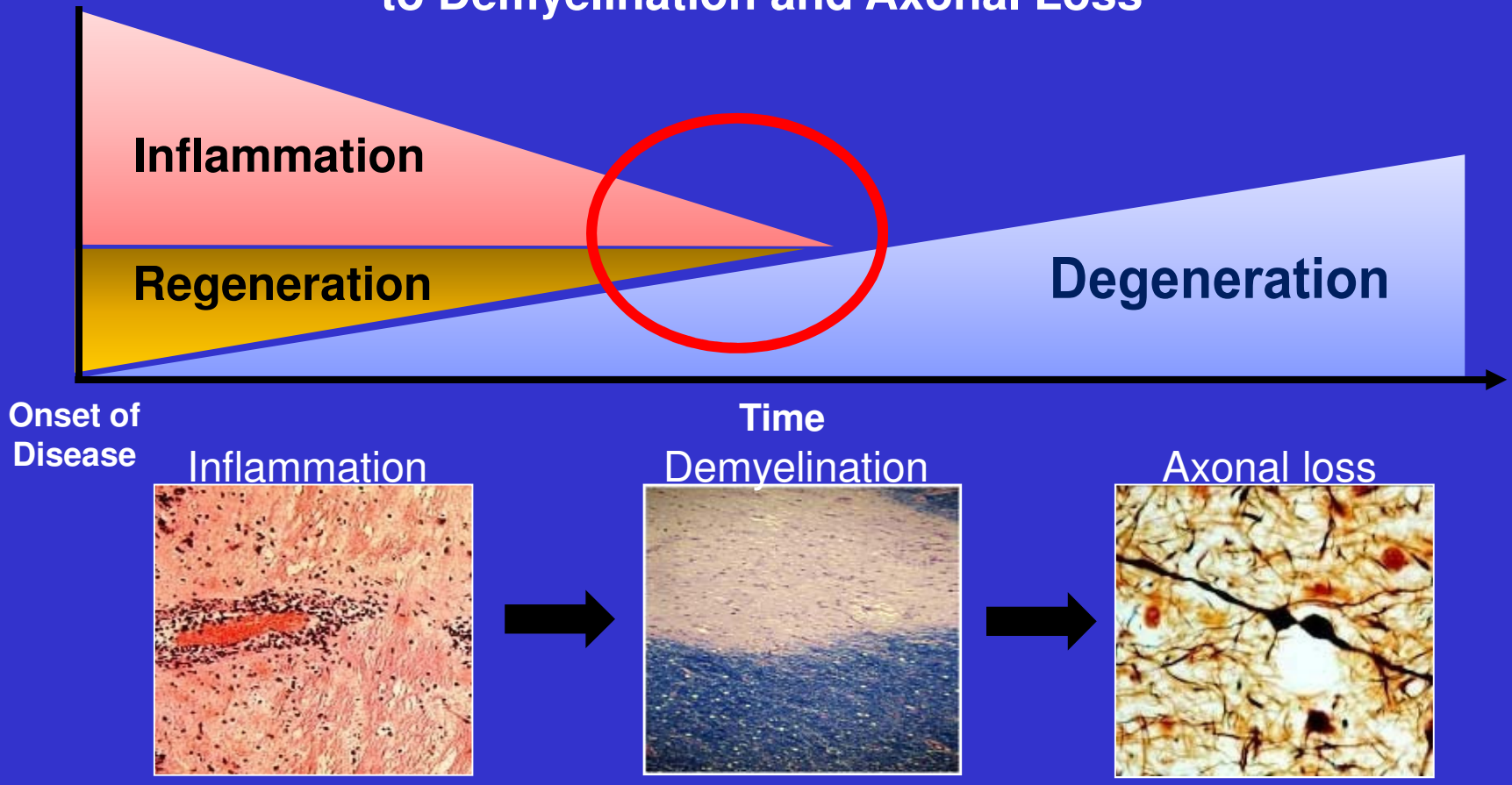


*Curve is based on an estimation of the decrease in cost for early treatment of about 40% at each range of EDSS

Burks J. *J Manag Care Med*. 2008;12(1):26-31. [Exhibit 8].
Comi G. *Neurol Sci*. 2006;27:S8-S12.
Kobelt G, et al. *Neurology*. 2006;66(11):1696-1702.

Immunopathogenesis of MS

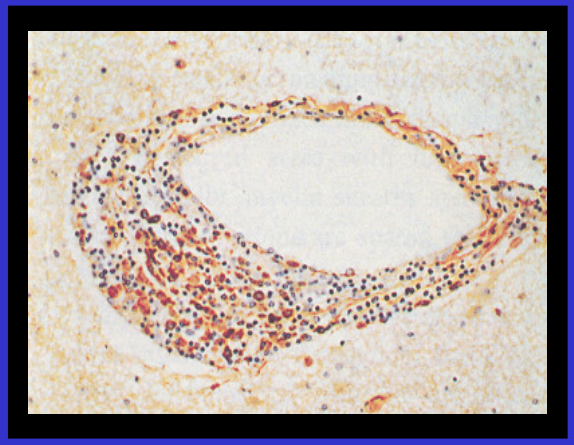
Inflammatory Processes Occurring Early in MS Lead to Demyelination and Axonal Loss



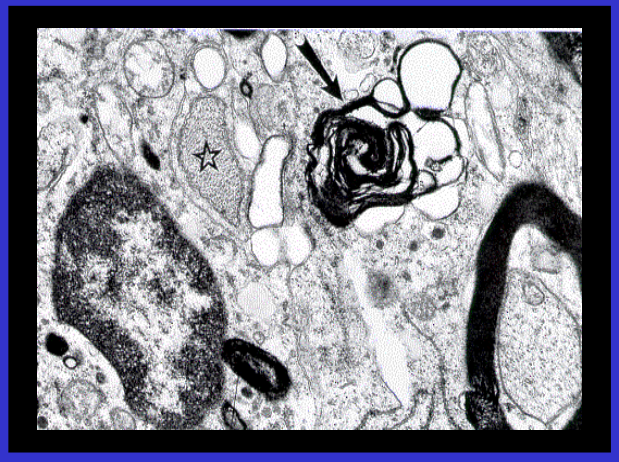
Compston A, et al. Lancet. 2008;372:1502-1517.
Kuhlmann T, et al. Brain. 2002;125:2202-2212.
Paolilo A, et al. J Neurol. 2004;251:432-439.
Trapp BD, et al. Curr Opin Neurol. 1999;12:295-302.

Multiple Sclerosis
Components of Tissue Injury

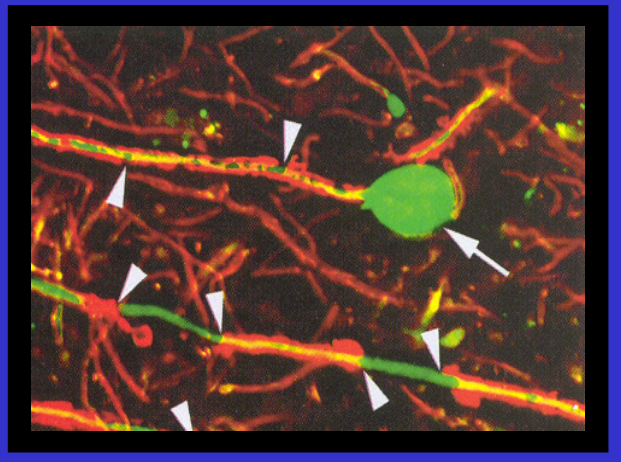
Inflammation



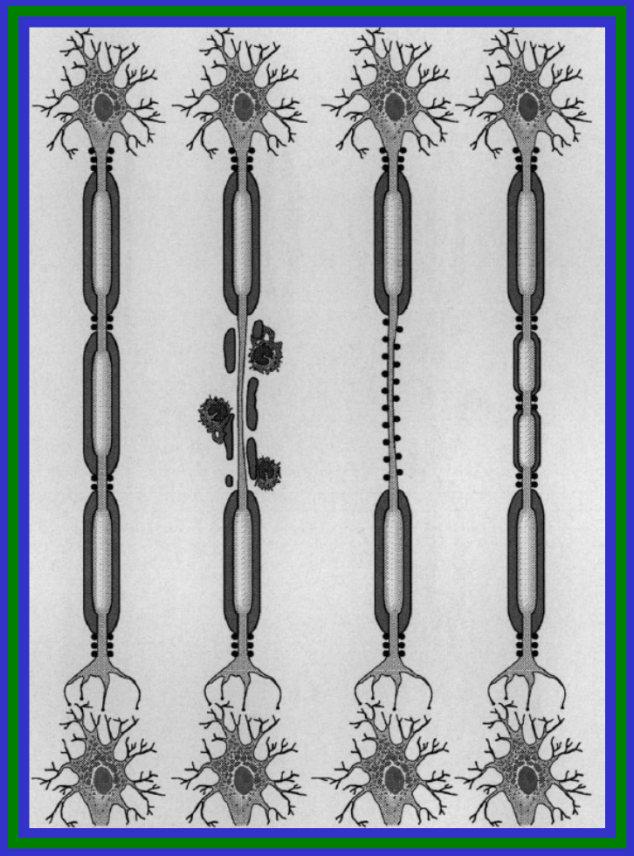
Demyelination



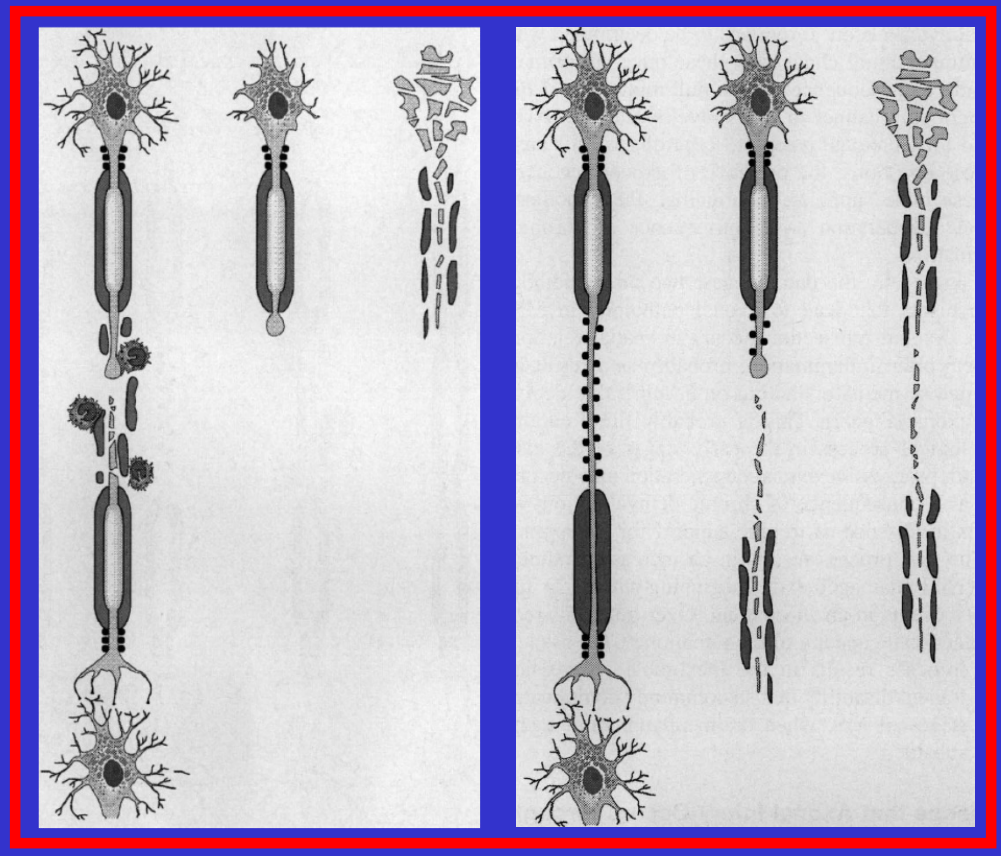
Axonal Loss



Pathogenesis of Neurological Dysfunction: Axonal Transection and Degeneration



Inflammatory demyelination followed by Na+ channel redistribution and remyelination leading to restoration of conduction and clinical remission



Axonal transection resulting in degeneration of the distal axonal segment or loss of trophic support of demyelinated axons leads to loss of neuronal function.

Trapp; Neurocscientist 5:48

Clinical Manifestations of MS

- Fatigue
- Pain
- Depression
- Numbness/paresthesias
- Cognitive dysfunction
- Weakness
- Spasticity
- Optic neuritis
- Bladder dysfunction
- Bowel dysfunction
- Cerebellar dysfunction
- Sexual dysfunction
- Gait abnormalities
- Partial/complete paralysis

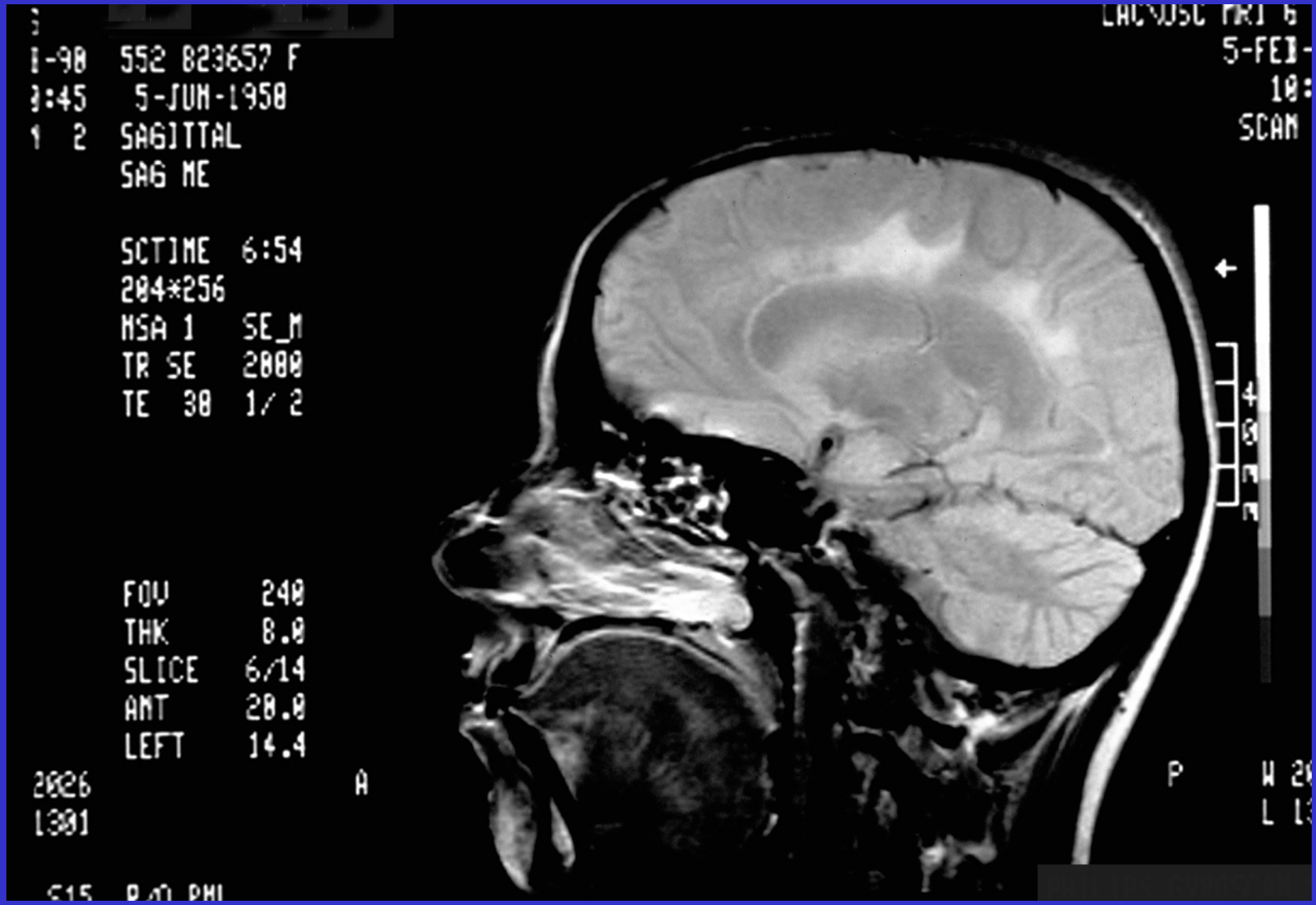
National Multiple Sclerosis Society. http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/symptoms/index.aspx. Accessed February 21, 2010.

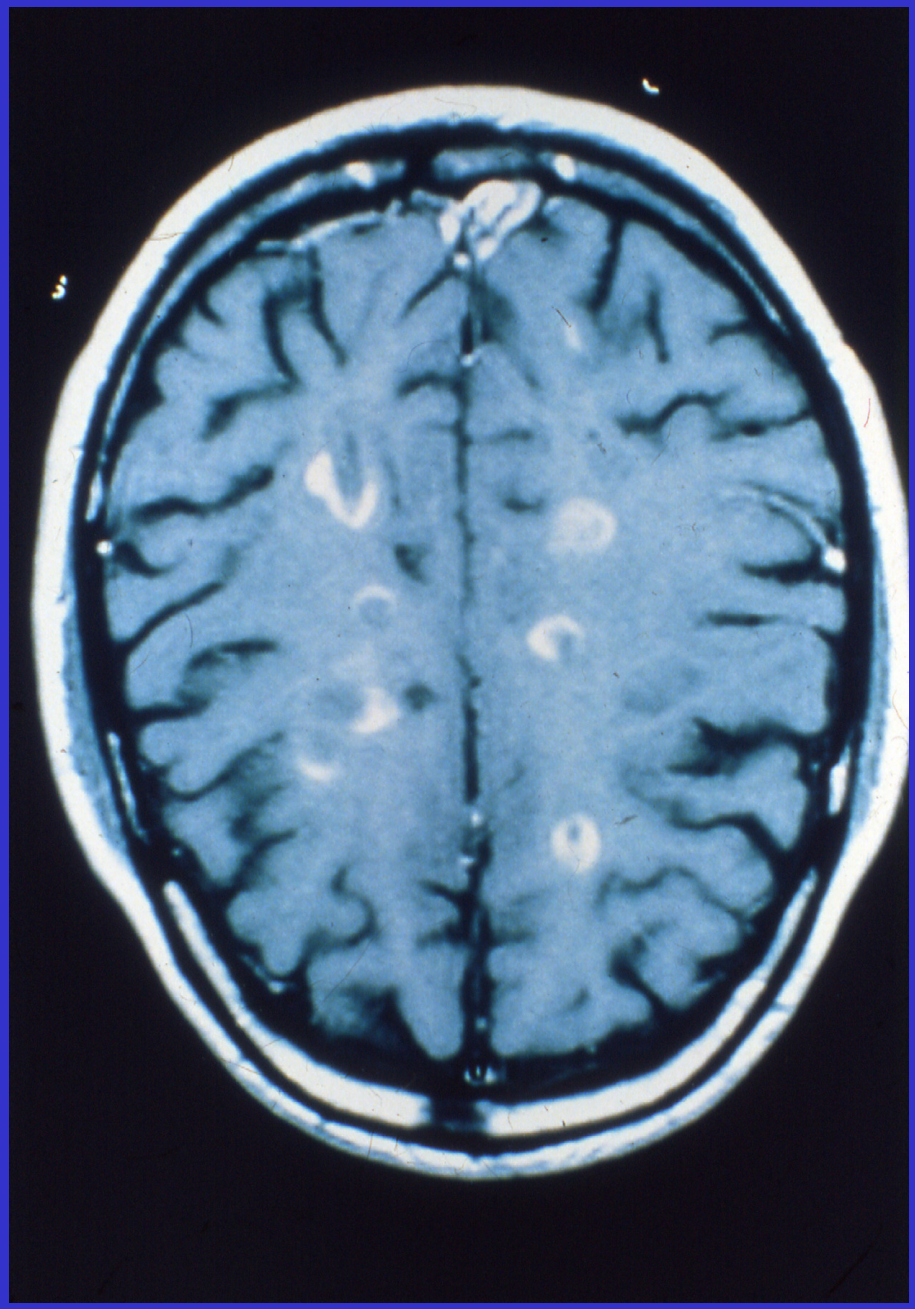
These are some of the genes found to have associations

- Genes associated with risk
  - **MHC region on ch6p21: HLA-DRA,DQ**
  - **IL-2 receptor alpha & IL-7 receptor alpha**
  - **Polymorphisms in CCR5, IL-10, IL4Rα, IL2Rβ, IFNγ, vitamin D receptor, estrogen receptor have also been identified**
  - **Altered "CNS genes": Notch 4, CNTF, MBP**
- Genes associated with protection (HLA-A201) and with poor clinical status (HLA-DR4)

The Diagnosis of MS

- Abnormal neurologic exam
- MRI (10% normal on presentation)
- Evoked potentials particularly visual , but also somatosensory
- CSF with evidence of inflammation such as increased IgG synthesis and oligoclonal bands in the CSF
- Fluctuating symptoms and signs after an acute event

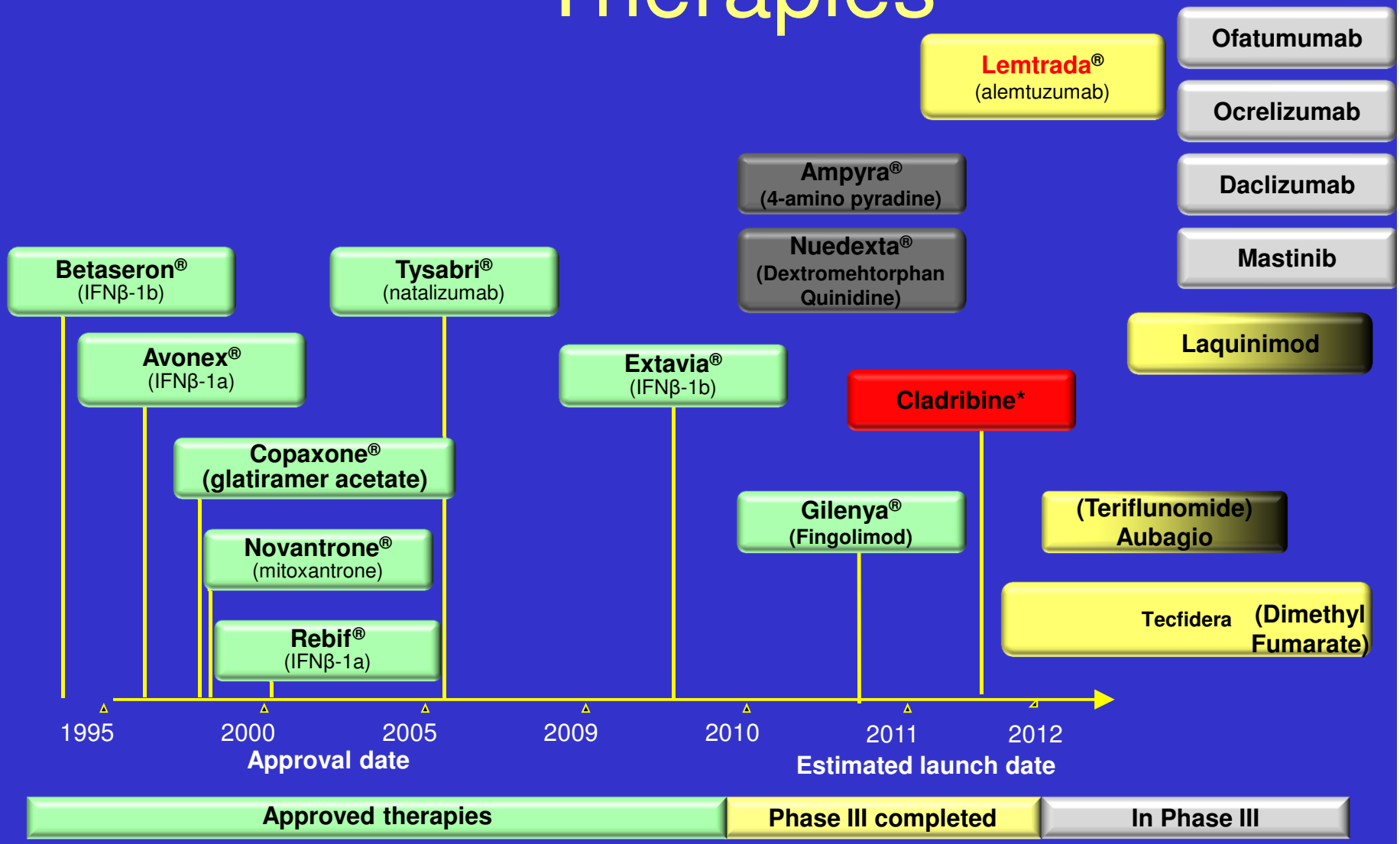

552 823657 F
5-JUN-1958
SAGITTAL
SAG ME
SCTIME 6:54
204*256
MSA 1 SE_M
TR SE 2000
TE 30 1/ 2
FOV 240
THK 8.0
SLICE 6/14
AMT 28.0
LEFT 14.4
SCAN
P
A



Treatment Targets

- Antigen presentation
- Decreased Th1 cytokines
- Th1 to Th2 deviation
- B cells
- Leukocyte trafficking across the BBB
- Events in the CNS such as Bystander suppression and neuroprotection
- Increasing regulatory T cells

Existing and Emerging MS Therapies



*In March 2011, the FDA did not approve cladribine and requested Merck KGaA provide an improved understanding of its safety risks and overall benefit-risk profile

GLATIRAMER ACETATE

- Evidence for bystander suppression and shift to TH2 (Allie et al Arch Neurol 62:858 2005.
- Down regulation of Th1 associated chemokine receptors CXCR3, CXCR6 and CCR5 after 12 months
- All interferons reduce relapses but in an open label study GA significantly higher in reduction rate over 24 months (Haas and Firzlaff Eur J Neurol 12:425-31 2005
- Induction of CD4+CD25 regulatory T cells (Hong et al (PNAS 102:6449-6454 2005)

INTERFERON BETA - 1a

- Reduces clinical relapse rate
- Reduces development of new MRI lesions
- Delays increase of MRI lesion volume
- Prevents Brain Atrophy
- May delay disability progression
- Licensed for Clinical Isolated Syndromes
- AVONEX

INTERFERON BETA - 1a

- Appears to have a dose-related benefit for more disabled patients
- More efficacious than AVONEX
- Neutralizing antibody
- REBIF

INTERFERON BETA - 1b

- Reduces clinical relapse rate
- May delay disability progression
- Reduces development of new MRI lesions
- Delays development of new lesion volume
- Question of duration and clinical significance of benefit
- Neutralizing antibody
- BETASERON

MITOXANTRONE

- Reduces attack rate in RRMS
- Appears to have effect on disease progression and is used in SPMS
- Potential side effects considerable
- NOVANTRONE
- We don’t use this drug any longer

Tysabri

- Natalizumab – Anti adhesion MAB still most effective therapy for RRMS
- 65% reduction in acute attacks
- 80 % reduction in new MRI lesions saves axons and neurons
- No long term data
- PML JCVirus (55% positive by antibody)
- Risk of PML influenced by length of time treatment given (1:1000) in first year, to 1 to 300 in third year if patient is positive for the JCV. If negative 1:10000

Gilenya (fingolimod)

- This is a sphingosine 1-phosphate receptor modulator
- First oral therapy
- Prevents lymphocyte egress from secondary lymphoid tissues producing lymphopenia
- Requires monitoring with first dose
- Many side effects but effective in RRMS
- No long term data

Aubagio (teriflunomide)

- Terflutamide related to anti cancer drug
- Efficacious but more like glatiramer
- X rated for pregnancy
- Oral once a day
- Side effects, liver, hair loss
- Have to do TB test prior to treatment

Tecfidera (BG-12)

- Dimethyl Fumarate
- Oral twice a day
- Few side effects (primarily GI)
- Efficacy like Gilenya
- Just licensed, long term effects not known

GLUCOCORTICOIDS

- Demonstrated to have short –term benefit on the speed of functional recovery with acute attacks
- No long term benefit from treatment of acute attacks
- Primary add on rescue therapy for both attacks and progression
- Evidence that regular pulse therapy may be useful in prevention of disability

EXPERIMENTAL THERAPIES

- Lemtrada (Compath-1H- Lymphocyte depleting MAB anti CD52 monoclonal antibody* Just turned down by FDA
- Estriol (Trial assessed in APRIL)
- Testosterone
- Stem Cell, umbilical cord, mesenchymal stem cells and Bone Marrow Transplants

EXPERIMENTAL THERAPIES

- Rituximab (Rituxan) antiCD20 monoclonal Ab in PPMS and RRMS * Genentech
- Laquinimod, small molecule NFkB inhibitor* Teva
- Abatacept CTLA4Ig interferes with costimulatory molecules CD28 and CD80 and 86* NIH
- DNA MBP Vaccine*
- T Cell Receptor Peptide Vaccine*
- Cell based Gene Therapy*

CURRENT APPROACHES

- Early diagnosis and early treatment prevent disability
- Exacerbations in the presence of sustained infections lead to more damage than attacks without obvious infection.
- Degenerative stage of the disease does not respond to immune modulation
- Disability correlates with cerebral atrophy and axonal degeneration