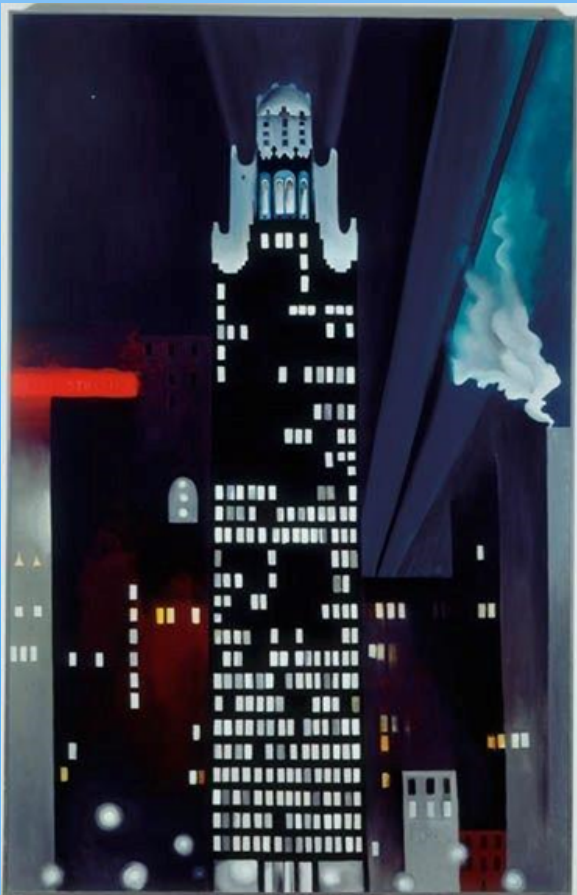


# **The Ordinary and the Fantastic:**

## **An Essential Review of Multiple Sclerosis**

**ACP Annual Scientific Meeting - October 4<sup>th</sup>, 2019**



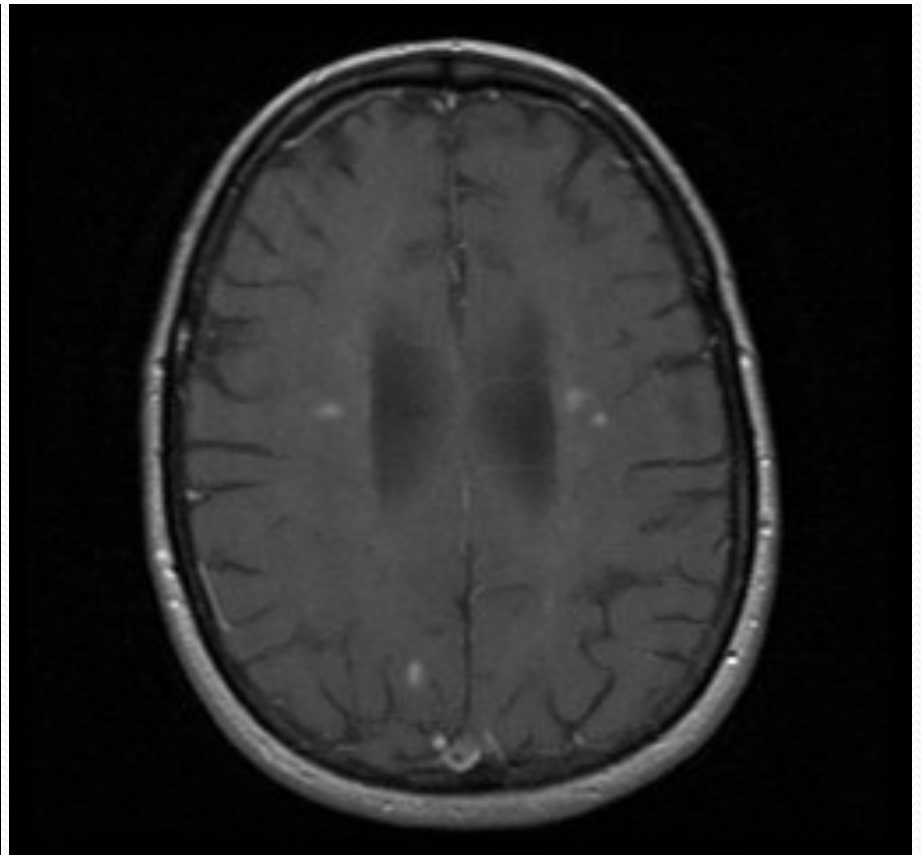
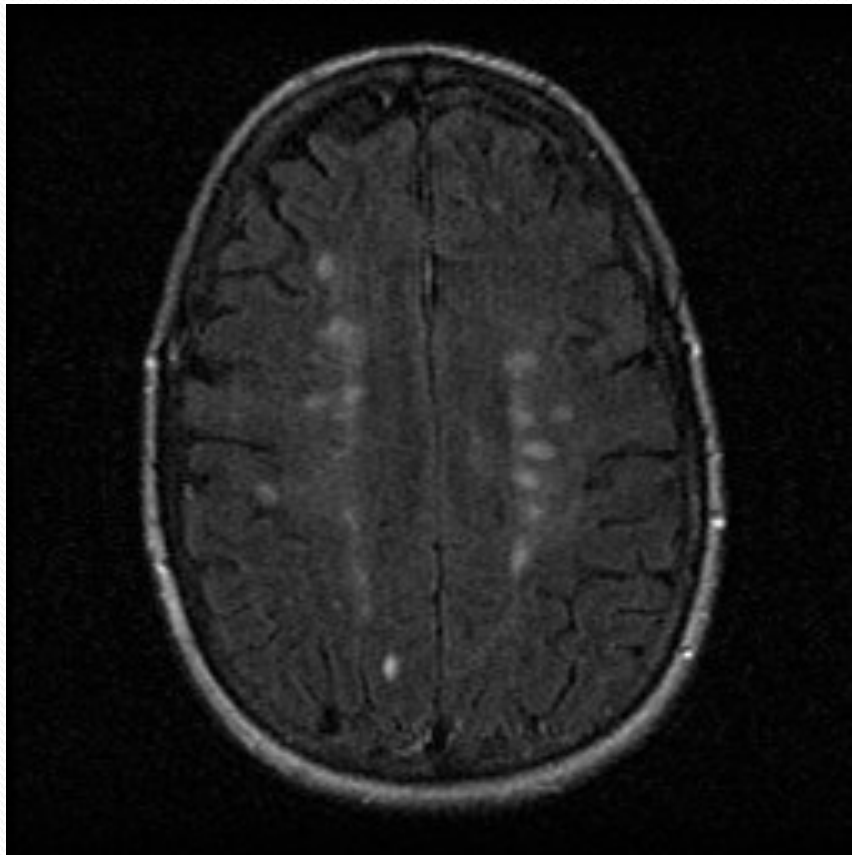
Jerome W. Freeman, M.D.  
Department of Neurosciences  
Sanford USD School of Medicine  
Sanford Clinic Neurology

# What a Neurologist (or Internist) Does: Listens to Stories

“It is a capital mistake to theorize before you have all the evidence.”  
(Sherlock Holmes)

“For every complex problem there is an answer that is clear, simple and wrong.”  
(H.L. Menken)

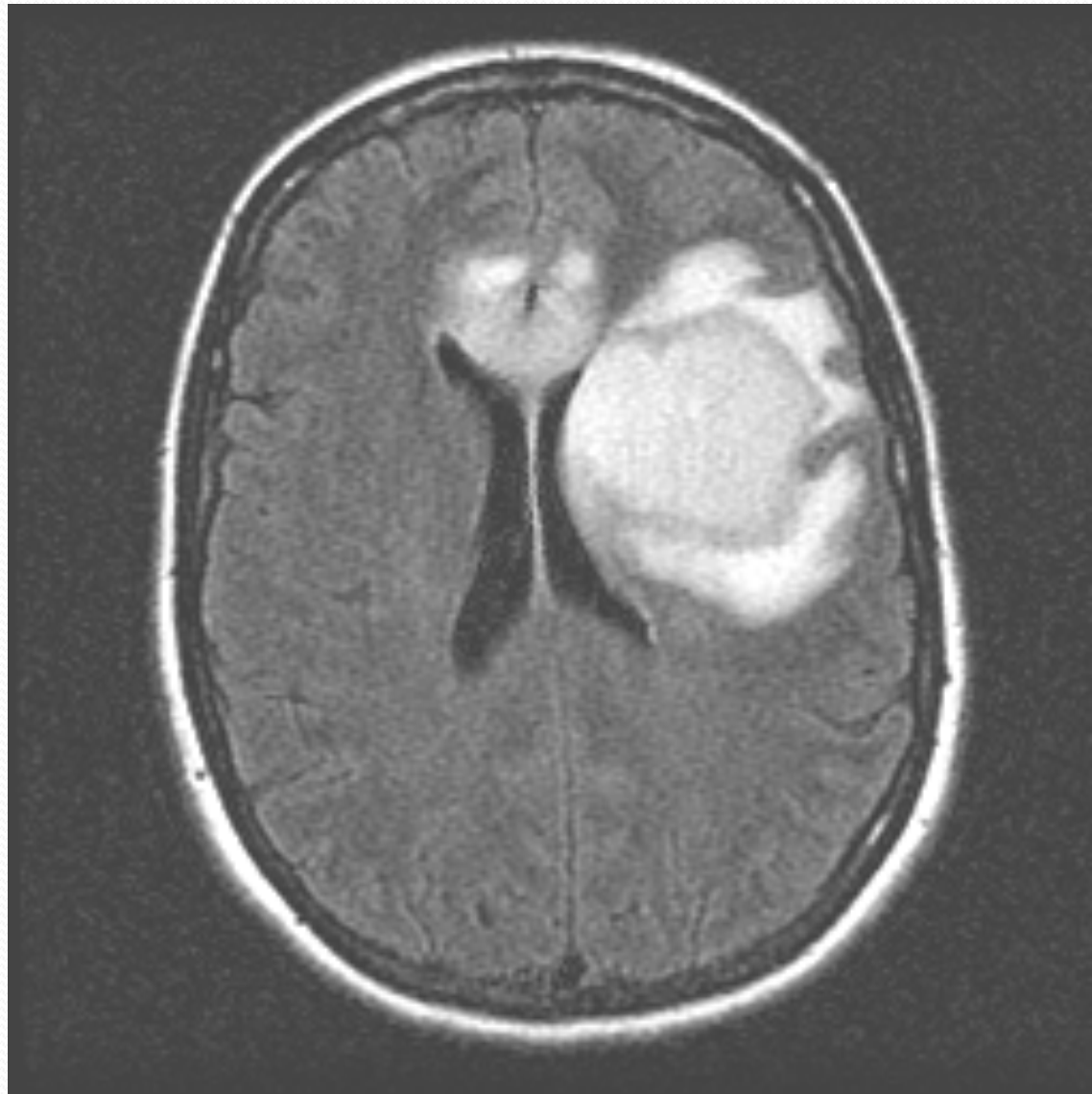
“The truth is rarely pure and never simple.” (Oscar Wilde)



# Case History – 42 y.o. female in good health except for cigarette smoking

- February 2003 – right optic neuritis; MRI normal
- June 2003 – decreased memory. MRI showed large abnormality in left frontal lobe and right pre-frontal lobe. Bx consistent with demyelinating changes. Rx with dexamethasone.
- August 2003 – dysarthria, left 6<sup>th</sup> nerve paresis, right face weakness, ataxia. Rx with methylprednisolone and cyclophosphamide. Rehab unit. Improved but residual right face weakness and dysarthria.
- October 2003 – left hemiplegia, no speech, right 6<sup>th</sup> nerve paresis, N/V. MRI new demyelinating lesion in right frontal and midbrain. Intubated after problems with secretions and respiratory failure. Tracheostomy. Rx with plasma exchange, higher doses of cyclophosphamide and methylprednisolone. Long rehab stay.
- Now stable for 16 years on glatiramer acetate. Has mild residual left leg weakness and balance issues and mild dysarthria.









# Case History – 23 y.o. female in good health – no prior pregnancies or surgeries

- 2008 Numbness left torso and leg; positive Lhermitte's  
Abnormal MRIs B/C/T  
Interferon sub cut. started
- 2009 Flare – numbness feet, perineum, urinary retention
- 2010 Self cath
- 2011 Flare – numbness from waist down  
Glatiramer sub cut started  
Second Flare – CSF abnormal; JCV positive  
Monthly IVIg + high dose steroids
- 2012 Increased MRI lesions and flares  
Natalizumab
- 2013 Fingolimod
- 2014 MRI with new enhancing lesions
- 2015 Patient first inquires about autologous stem cell therapy
- 2016 Total lymphs dropped to 100 and Fingolimod stopped  
Glatiramer restarted  
New brain lesions on MRI. IVIg and high dose steroids  
Dimethyl Fumarate started and flares continue  
ACTH started with new enhancing lesions  
Cyclophosphamide
- 2017 Mycophenolate
- 2018 Autologous stem cell transplant





JAMA<sup>®</sup>Journal of the  
American Medical Association

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Rik Burt and Coauthors

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A JAMA NETWORK  
PUBLICATION

# How is MS diagnosed?

- Appropriate history
- MRI (brain and spine)
- CSF Examination (oligoclonal bands, myelin basic protein)
- Evoked potentials (particularly visual)
- Exclude other “look-a-like” entities
  - SVID (DM, hypertension, smoking, hyperlipidemia)
  - Neuromyelitis optica (NMO) – anti-AQP<sub>4</sub> antibody (aquaporin 4) – NMO IgG
  - Vasculitis
  - Vitamin B<sub>12</sub> deficiency
  - ADEM

## MS Classifications:

- Relapsing/Remitting (85%)
- Primary progressive (15%)
- Secondary progressive
- Clinically isolated syndrome

# Pathology

- Presumably an autoimmune disease of CNS that results in inflammation, demyelination and axonal injury.
- Can involve both white and grey matter.
- Axonal injury can occur sometimes as an early phenomenon.
- Loss of neurons is associated with brain and spinal cord atrophy.





# **Inflammatory Mechanisms in Multiple Sclerosis**

- Predominately T-cell mediated inflammatory disorder.
- Increasing interest in B cell mechanisms

# Older Injectable Therapies

- Glatiramer
- Interferon beta

## New Oral Therapies

- Fingolimod
- Teriflunomide
- Dimethyl Fumarate
- Siponimod
- Cladribine

## New IV Therapies

- Natalizumab
- Alemtuzumab
- Ocrelizumab

# Clinical Trial Endpoints

- Primary endpoint: annualized relapse rate (ARR)
- Secondary endpoints: changes on MRIs; disability progression

## Objectives of therapy:

- Decreased inflammation leading to demyelination
- Prevent axonal loss/atrophy
- Prevent acute exacerbations
- Prevent progressive disability
- Promote remyelination

# Standard Injectable (Platform) Therapies: Interferon beta and Glatiramer acetate

## Modes of action :

- Interferon beta:
  - Inhibition of leukocyte migration across the blood-brain barrier
- Glatiramer acetate:
  - Th2 cells (anti-inflammatory or regulatory) are promoted within the CNS

\*\*\*\*\*

- These medications have been available now for over twenty years
- Interferon beta and glatiramer have similar clinical utility - - studies suggest both reduce ARR by 30%



# Fingolimod

- Drug action: A sphingosine analogue that alters lymphocyte migration (resulting in sequestration of lymphocytes in the lymph nodes). Thus it is an immune suppressant.
- ARR reduced by 54-60% and a significant reduction in gadolinium enhancing lesions
- Can cause bradycardia with the first dose and patients must be monitored in an outpatient setting for 6 hours.
- A small number of deaths have occurred with the use of the drug due to cardiac events or for unexplained reasons. As of 2019, 28 cases of PML have been described (in 284,000 patients).
- The ophthalmology evaluation prior to initiation of therapy to check for macular edema.
- If no history of chicken pox or vaccination against varicella zoster virus (VZV) the patient should be tested for antibodies to VZV. If antibodies are negative a VZV vaccination is required and the subsequent delay of starting treatment for a month
- There can be a major rebound of MS activity after stopping this therapy and paradoxically with initiation of the therapy. A recent report noted the onset of tumefactive MS upon initiation.
- Once daily oral dose

# Siponimod

# Teriflunomide

- Drug action: Inhibits pyrimidine biosynthesis and disrupts the interaction of T cells with antigen presenting cells. May limit proliferation of B cells as well as T cells
- 31.5 % reduction in ARR
- Significant pregnancy risk (category X)
- After product is discontinued it may persist in the body for up to two years. Therapies such as cholestyramine and activated charcoal may speed wash out.
- Once daily oral dose

# Dimethyl Fumarate

- Drug action: Induces T-helper cell-like cytokines that suppress activated T cells. Makes it more difficult for cells to leave blood vessels that enter tissues
- 53% reduction in ARR. Also 38% reduced risk of disability progression. Also drug reduces the number of new brain lesions seen on MRI
- Two most common side effects are diarrhea and flushing
- Rare association with PML (seven cases worldwide in 400,000 patients)
- Can see fairly severe falls in white blood cell counts (especially lymphocytes). Some experts advocate monitoring CD4 and CD8 counts
- Twice daily dose

# Natalizumab

- The precise mechanism of action for tysabri is unknown. It is a humanized anti- $\alpha_4$  integrin monoclonal antibody. Binds the  $\alpha_4$  integrin on WBCs ultimately inhibiting white cell migration across the blood-brain barrier. It can actually increase the number of circulating leukocytes due to inhibition of transmigration out of the vascular space.
- An extremely effective agent for aggressive MS. Estimated ARR reduction is 68%.
- Must be used with caution as the drug has been associated with instances of progressive multi-focal leukoencephathy (PML).
- Virtually all cases of PML occur in patients are carriers (have antibodies) to JC virus. 50% of the population has these antibodies.
- Risk factors for PML include James Cunningham (JC virus positivity; use of prior chemotherapies; duration of tysabri treatment).
- Risk of PML in the first two years (even if JC virus positive) is low (in the range of 1/1000).



# Alemtuzumab

- Monoclonal antibody
- Binds to CD 52 molecules on surface of B&T cells leading to their depletion (prolonged reductions in CD4+ lymphocyte counts)
- Reduces relapses and progression when compared to interferon beta (30-50%) but ARR not reported
- Serious autoimmune side effects include: ITP, autoimmune thyroid disorders (34%), glomerular nephropathies
- Initial 5 day infusion: repeat 3 day infusion in 1 year

# Ocrelizumab

- Humanized monoclonal antibody that selectively targets CD20 on B lymphocytes
- Lower rates of disease activity and progression more than interferon beta-1a (i.e. for relapsing MS)
- In a trial vs placebo, Ocrelizumab reduced progression in primary progressive MS
- Dose is 600mg IV every 24 weeks
- Side effects fairly manageable but include some increased risk of infusion reaction, infection, neoplasm (rarely). Serious adverse events were estimated to be 6.9% as opposed to 7.8% in the trial interferon bata-1a

# MS and Pregnancy

- Women often do well during pregnancy with no exacerbations
- None of the MS drugs approved during pregnancy
- Risk of exacerbations post-partum



# The cost of MS drugs is reasonable and appropriate:

- True \_\_
- False \_\_



# Cost of MS Drugs in the U.S.

(from an article and editorial in *Neurology* May 26, 2015)

Interferon sub cut betaseron-1b

approved July 1993-insufficient supply-lottery used(\$11,532 —→ \$61,529)

Interferon-1a (\$8,000 —→ \$62,000)

Avonex (\$8,723 —→ \$62,394)

Glatiramer acetate (\$8,295 —→ \$66,394)

\*Costs in Canada, Australia, UK are  $\frac{1}{2}$  to  $\frac{1}{3}$

\*\*\*\*\*

## From other sources:

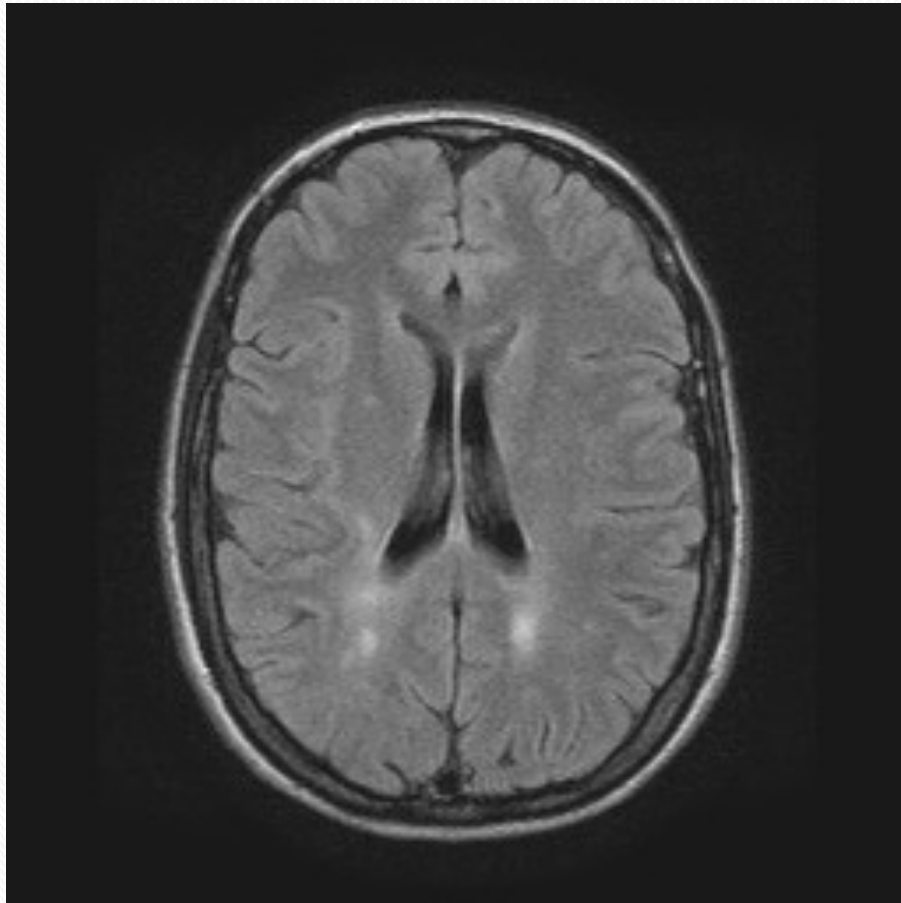
Alemtuzumab (\$158,000 for initial 5 day infusion followed by a 3 day infusion in one year)

Fingolimod (\$61,000)

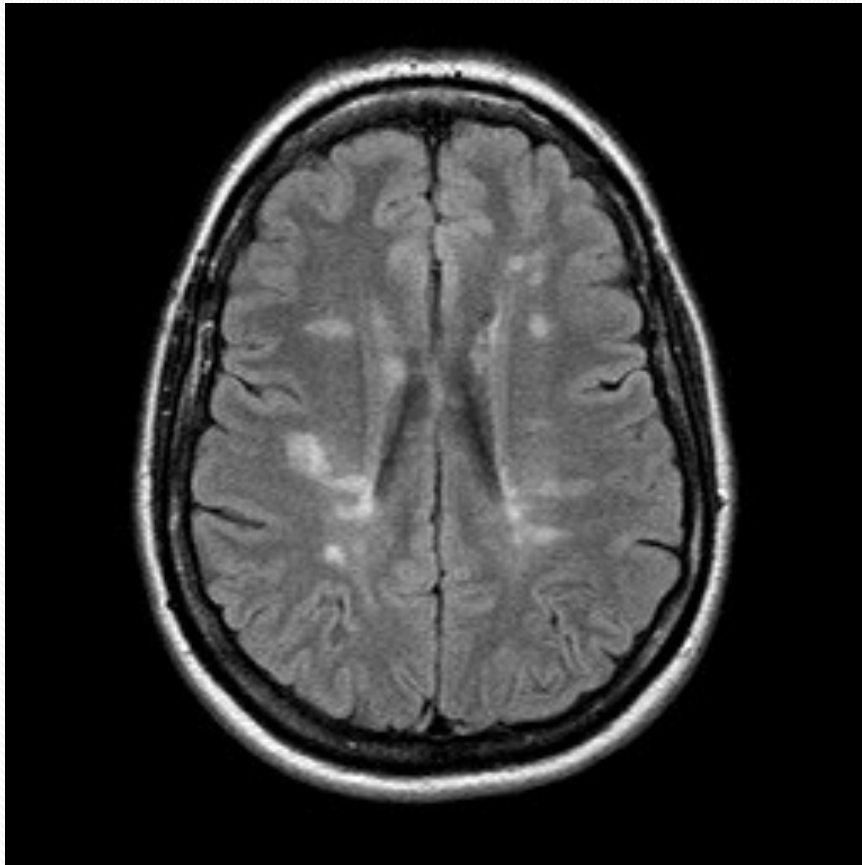
Dimethyl Fumarate (\$60,000)

Teriflunomide (\$54,300)

**Case #1- - A 37 year old female had a 3 week history of leg and perineum numbness. She had experienced a prior numbness from the waist down through the legs at age 24. MS had been suspected, but she declined treatment. Her mother has MS.**

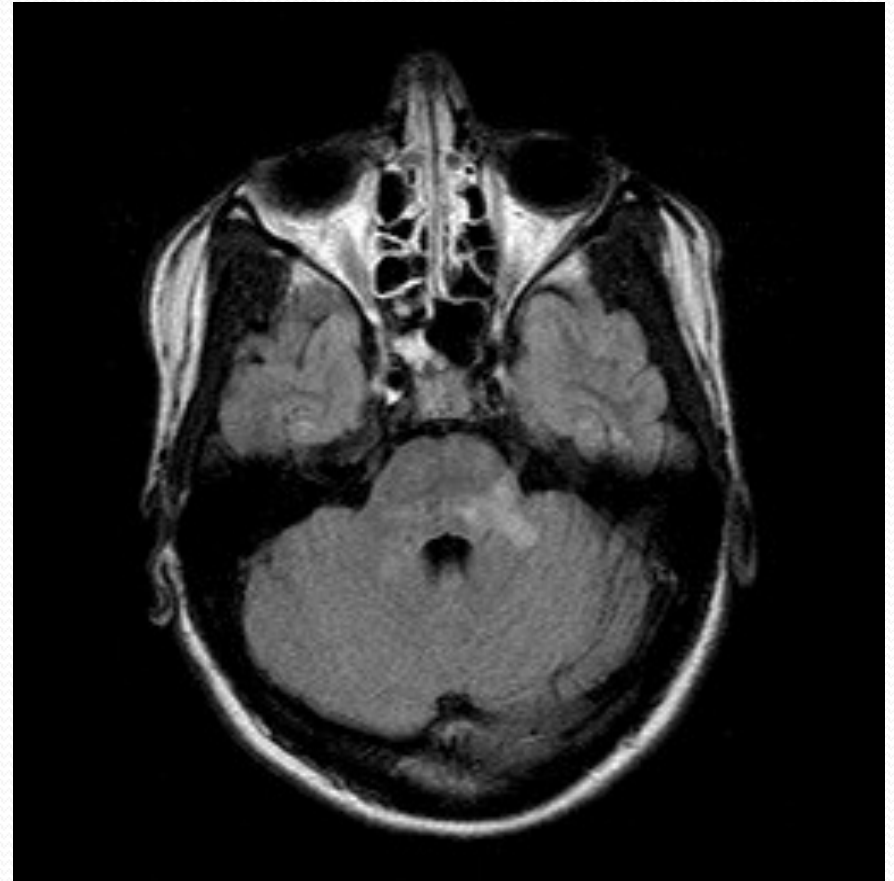
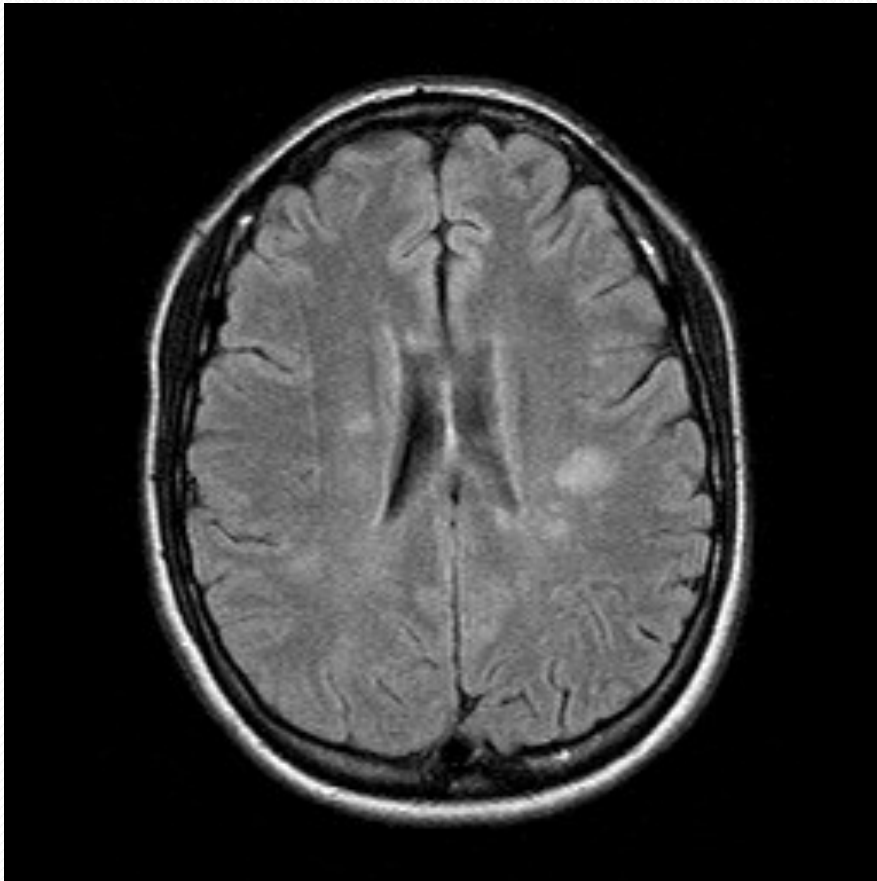


**Case #3 - - This 45 year old woman experienced left eye pain and decreased vision. It improved with high dose steroids. At age 42 she had presented with an acute left optic neuritis and numbness in the left arm and leg for four months. MS was diagnosed and glatiramer was started.**



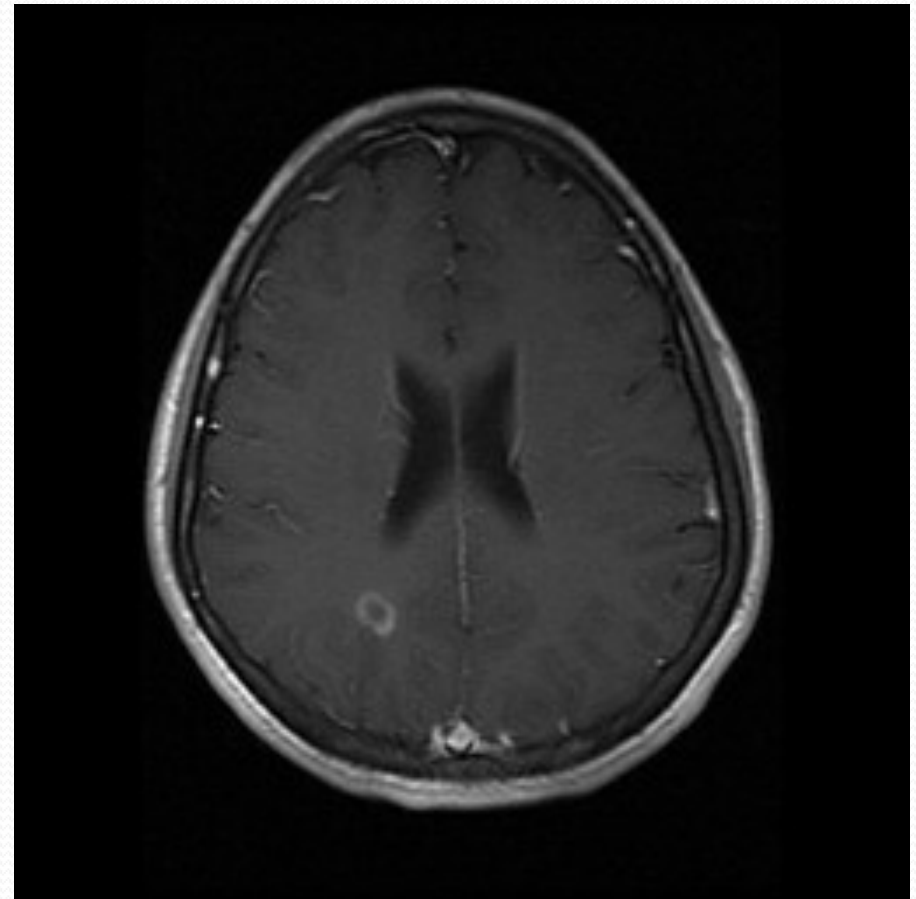
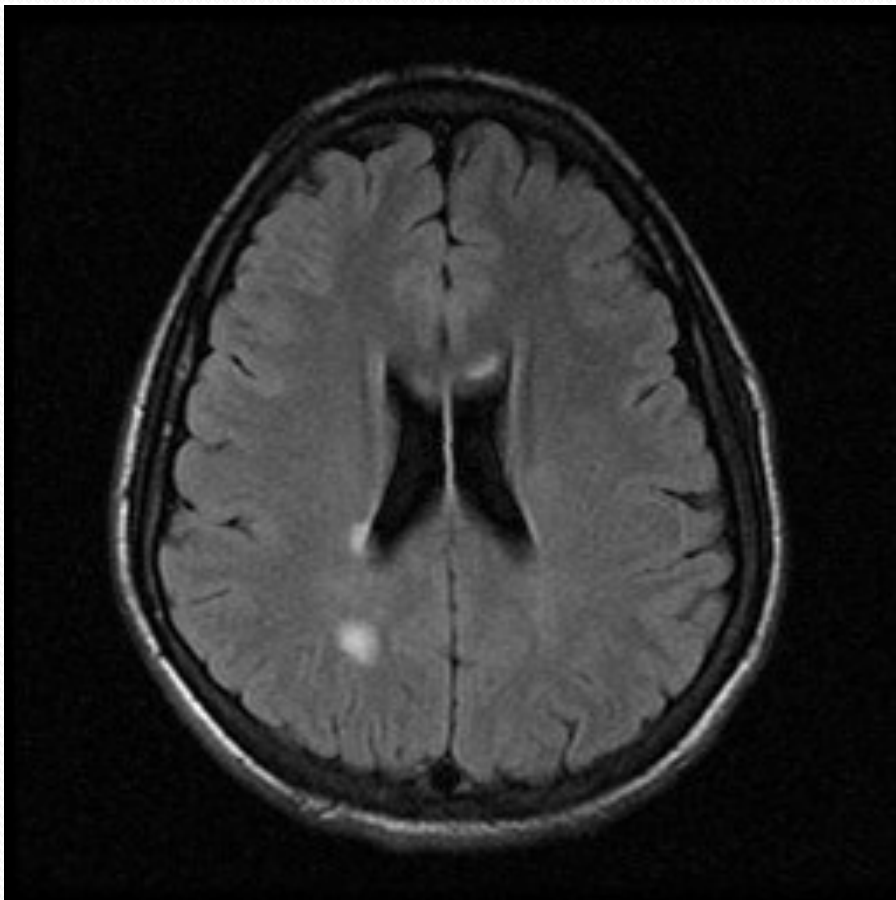


**Case #4 - - This 20 year old college athlete experienced left face and right body numbness for five days. She was mildly unsteady and had some right leg weakness.**

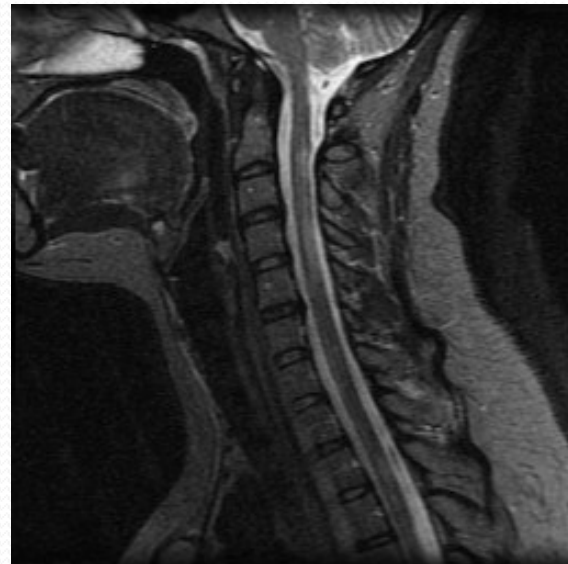
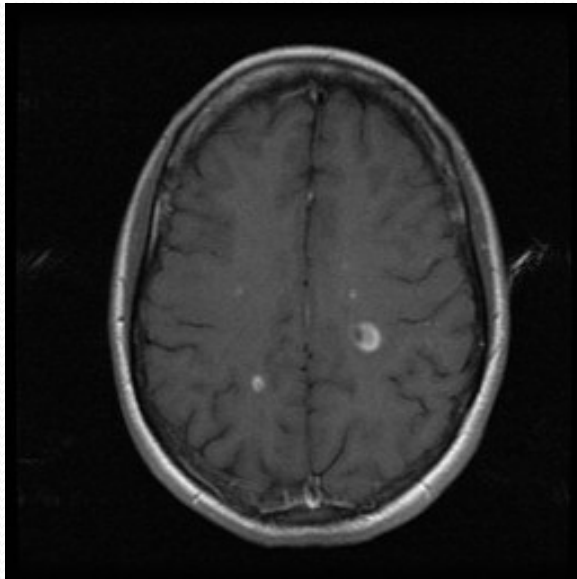
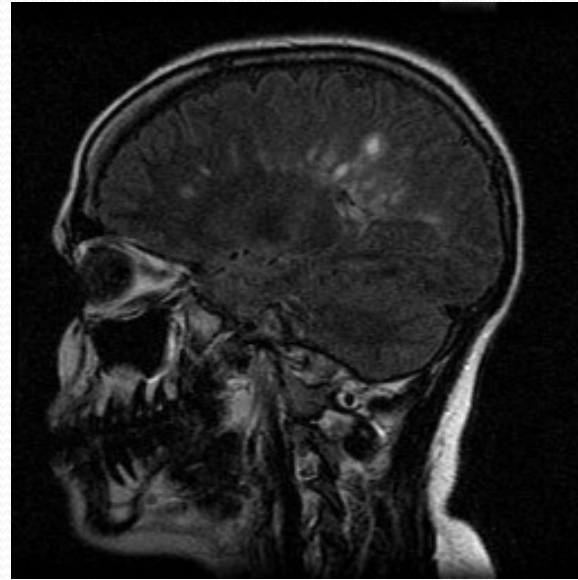
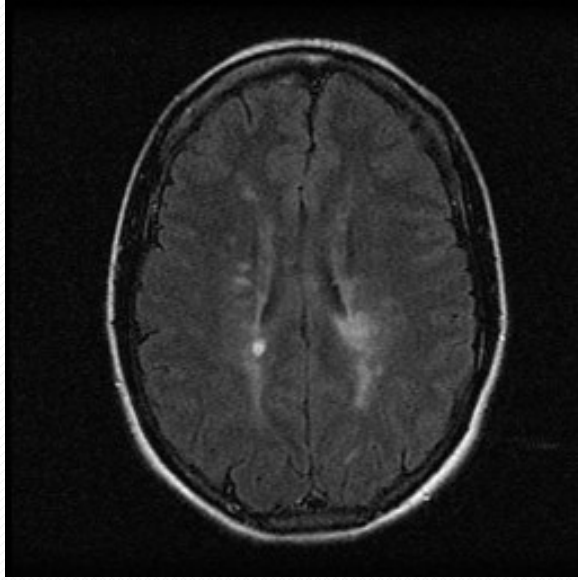




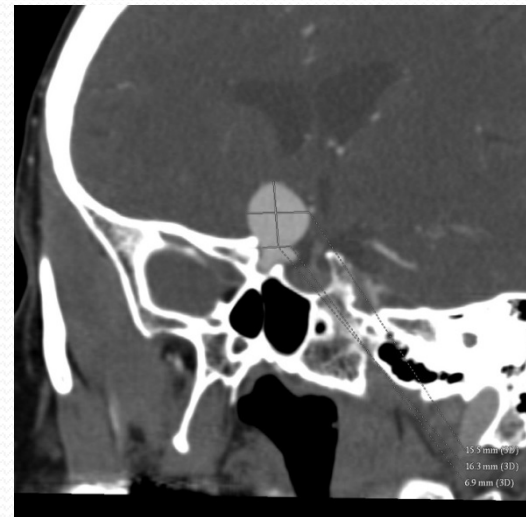
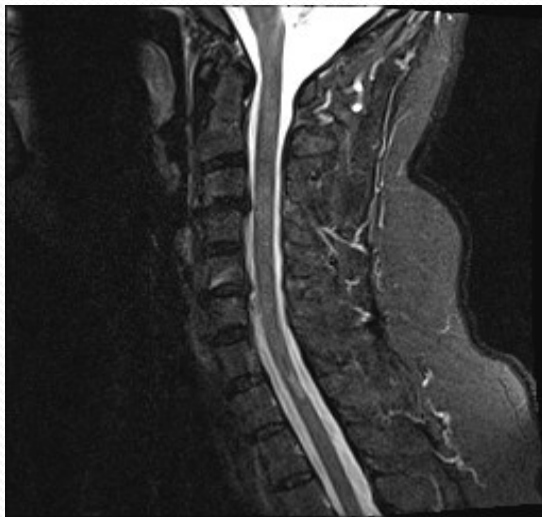
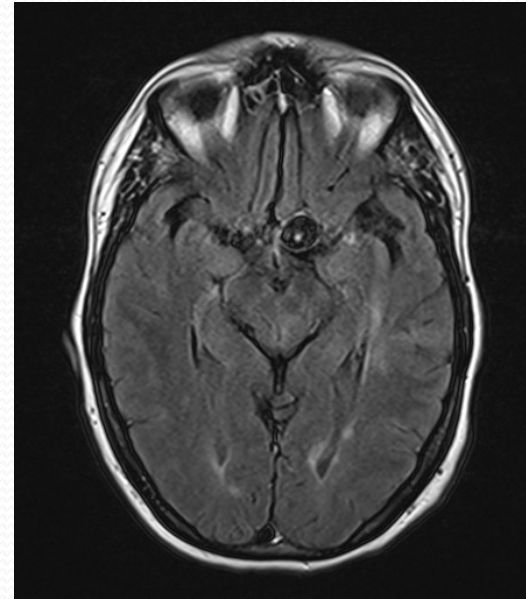
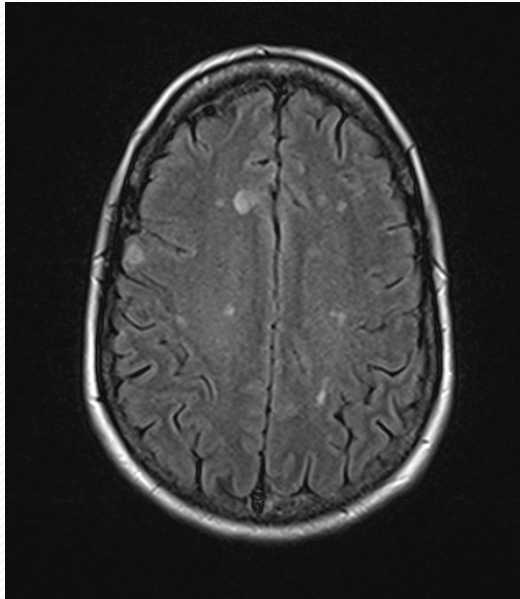
**Case #5 - - This 14 year old male experienced some numbness in his right arm, leg and chest region. He was unable to run. His spinal fluid showed oligoclonal bands and increased myelin basic protein. His symptoms resolved with high dose steroids. The image on the right is with contrast.**



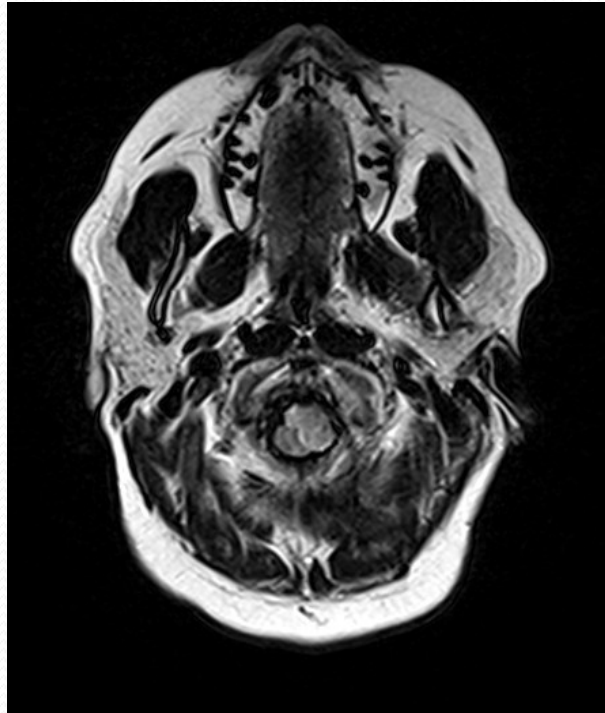
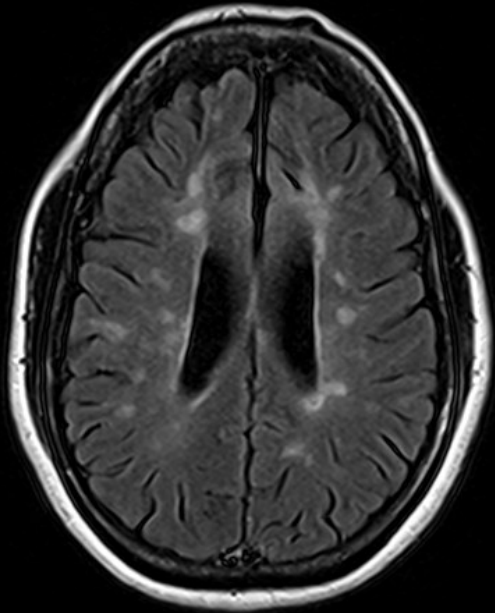
**Case #7 - - This 34 year old woman is experiencing some new gait unsteadiness and numbness in her legs. At age 20, five months after pregnancy, she developed blurred vision and tingling in her feet. At that time a diagnosis of MS was made. Image #3 is with contrast.**



**Case #9 - - This 51 one year old woman had been experiencing progressive difficulties with gait and balance. She had some leg numbness. Examination showed bilateral Babinski signs and a broad based gait. She had been diagnosed 13 years earlier with MS when she had presented with tingling in the extremities and fatigue. At that time she had declined treatment. At the time of this MRI her aneurysm was noted also.**

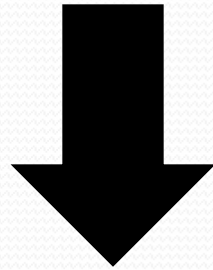


**Case #10 - - This 53 year old woman had been diagnosed to have multiple sclerosis at age 37 when she presented with double vision. At the time of this MRI she had been complaining gradually worsening weakness and fatigue. Her gait was broad based and slow. In addition to her MS, the lesion in the upper cervical region was found. Images #2 and #3 are with contrast. At surgery this lesion proved to be a meningioma. Her gait improved post operatively.**





# The Ordinary and Fantastic



## Kindness



Premise:  
There is insufficient kindness in medicine



# Kindness Initiative at SSOM

A specific focus on kindness for our medical school is unique and profound. While a few institutions stipulate kind behavior as a desired attribute, no other medical school explicitly champions kindness as an overarching value and expectation intended to transform how patients and colleagues are treated. A culture of kindness can make us exceptional.



Kindness = *what we do* and *how we do it*



# Kindness

## *What we do*

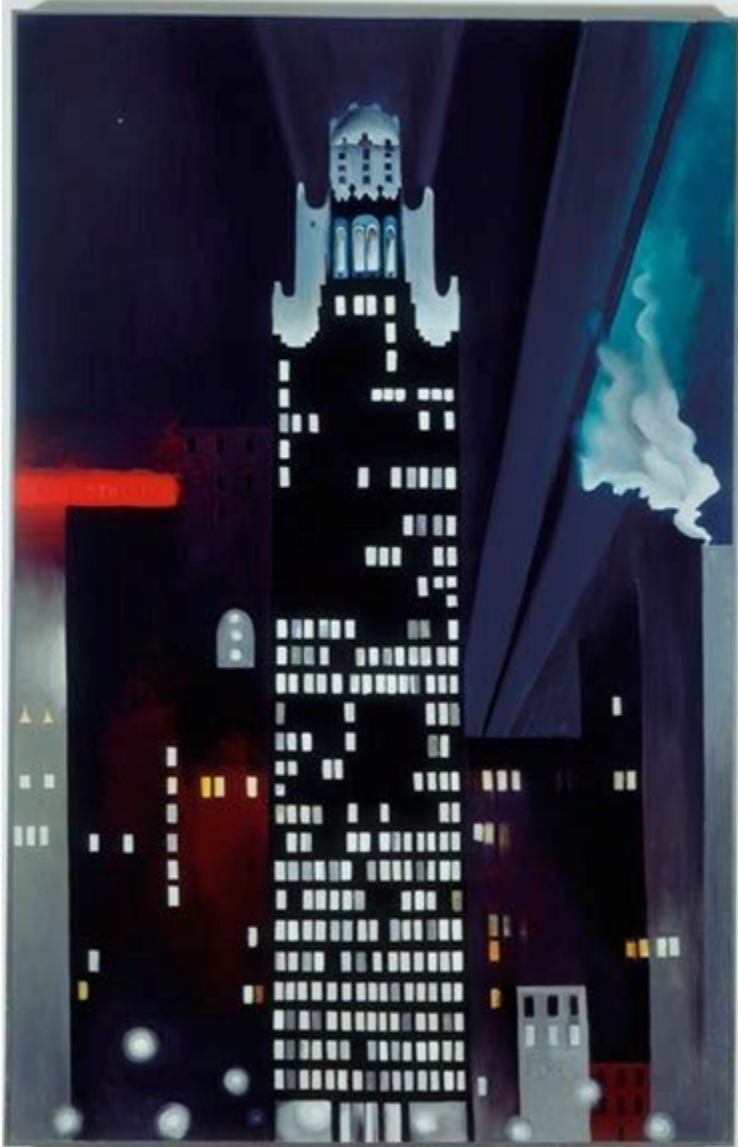
- Evidence-based medicine/scientific excellence
- Collaboration and teamwork
- Recognition of ethics/value issues and conflicts

## *How we do it*

- Consensus professional attributes (ABIM, ACGME, GMC, Royal College, IIMEE and WHO)
- Altruism
- Honor and Integrity
- Caring and Compassion
- Respect
- Responsibility and Accountability
- Excellence and Scholarship
- Leadership

# Examples of Kindness (or lack of it) from the MS world

- Patient told on the phone “your MRI looks like MS”
- “Read about these 4 drugs and let me know which one you want.”
- CCSVI



“The truth is rarely pure and never simple.”