Pathogensis of Multiple Sclerosis

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Disclosures

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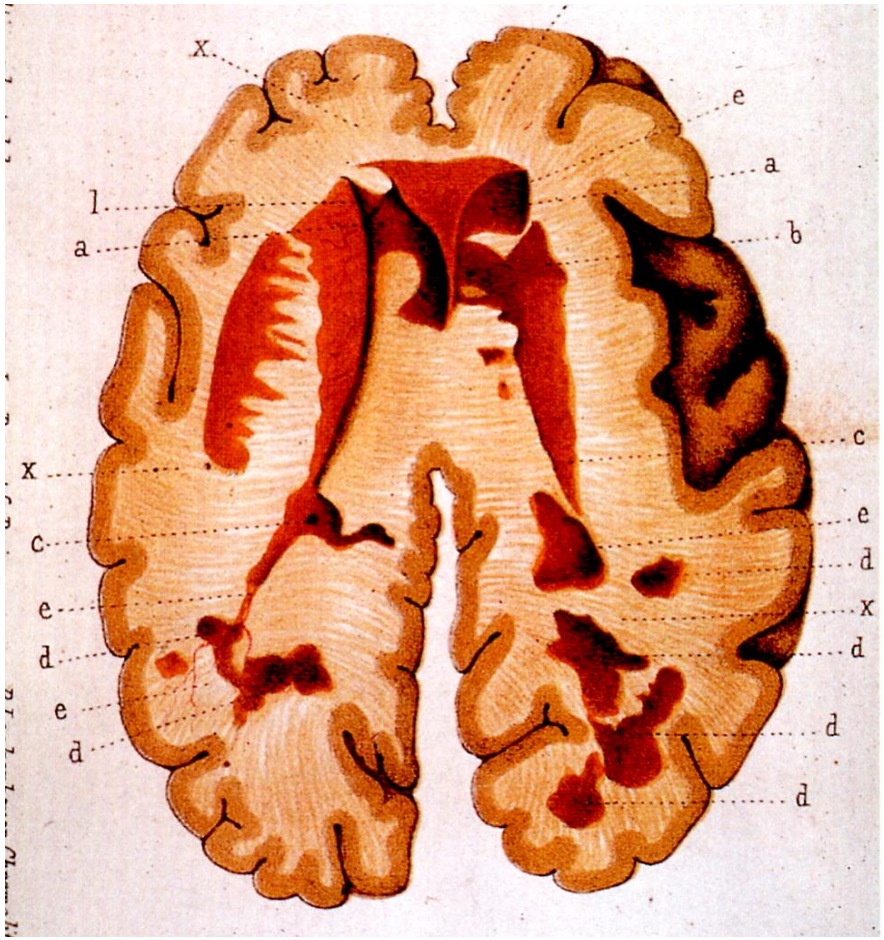
Dr. Rose is a member of the Utah/Southern Idaho Chapter Board of the National Multiple Sclerosis Society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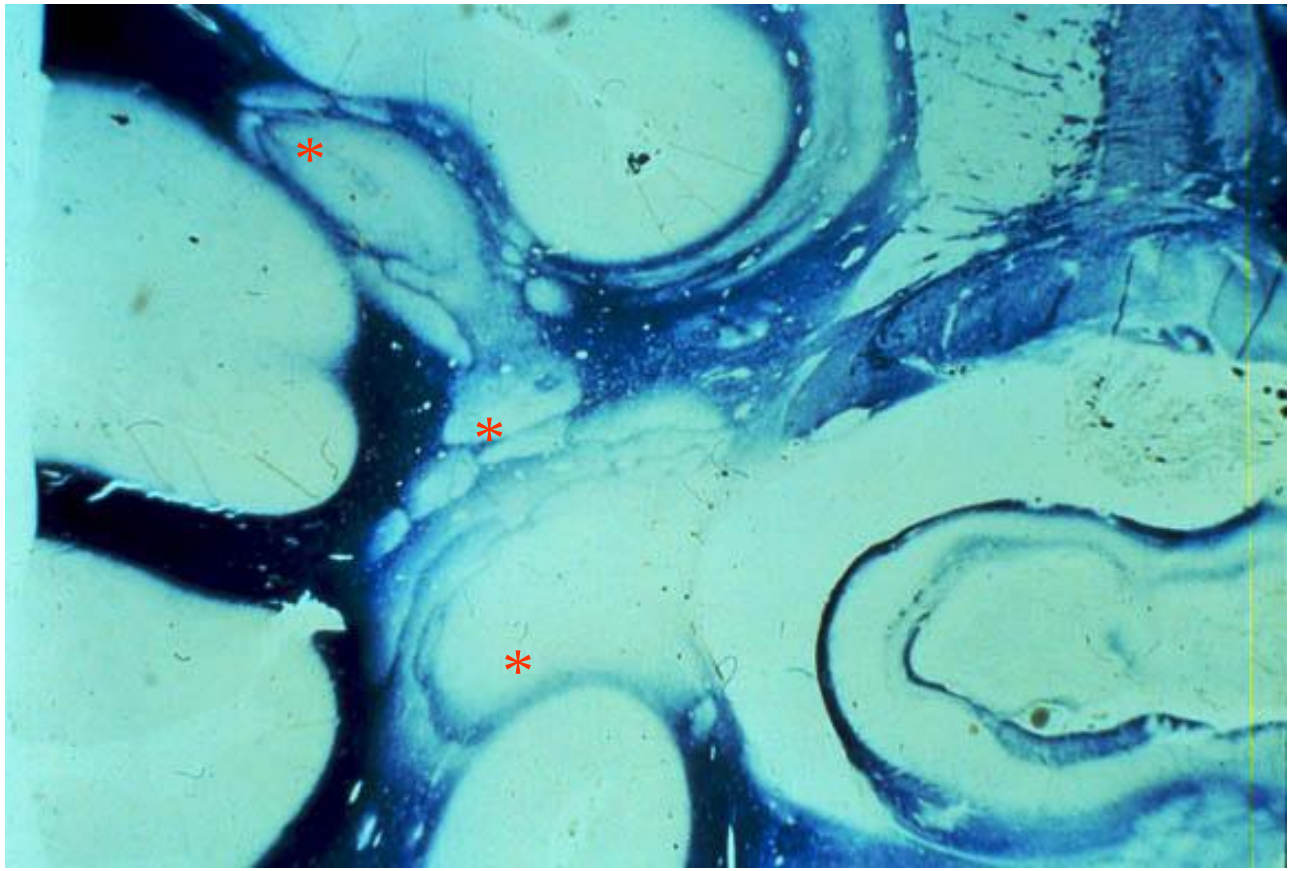
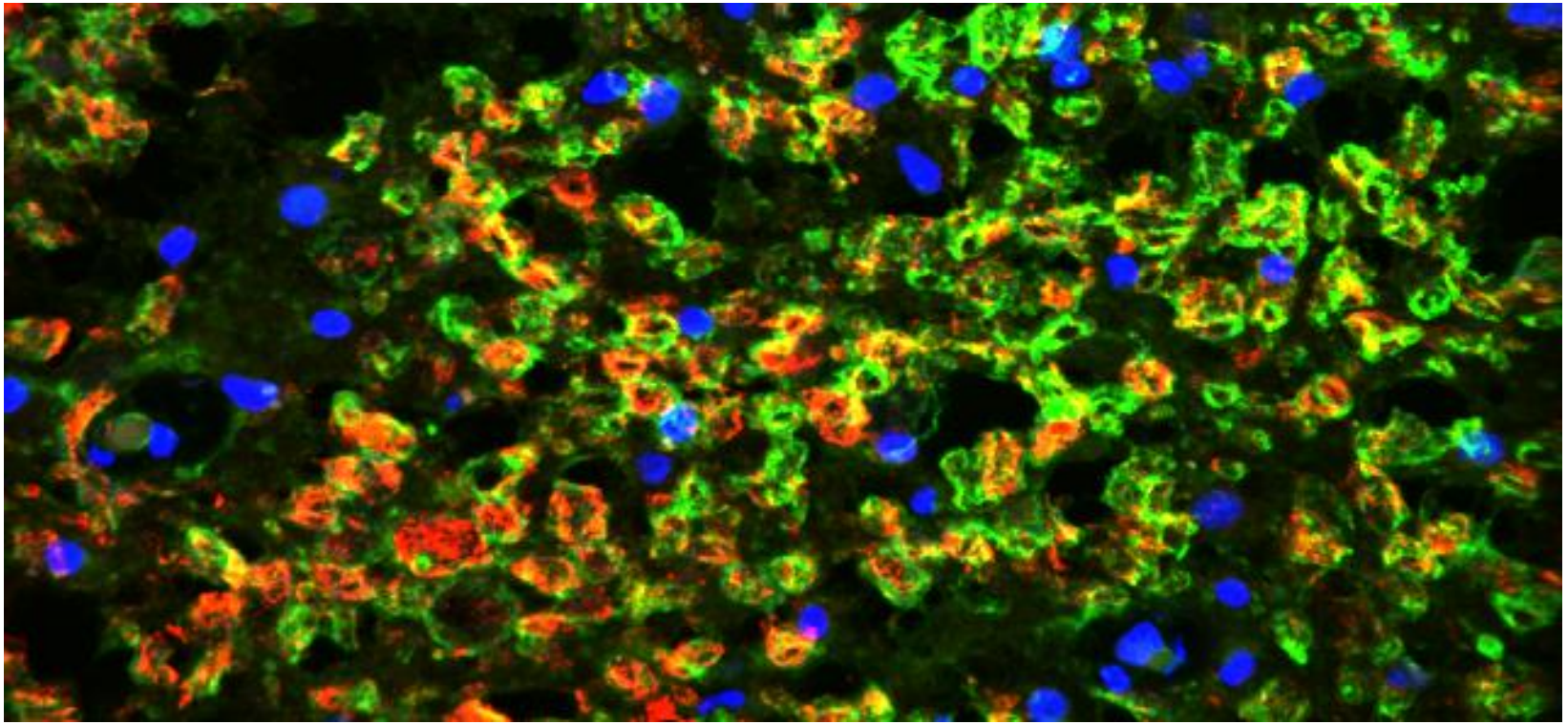
MS Demyelination *



Key Mechanisms

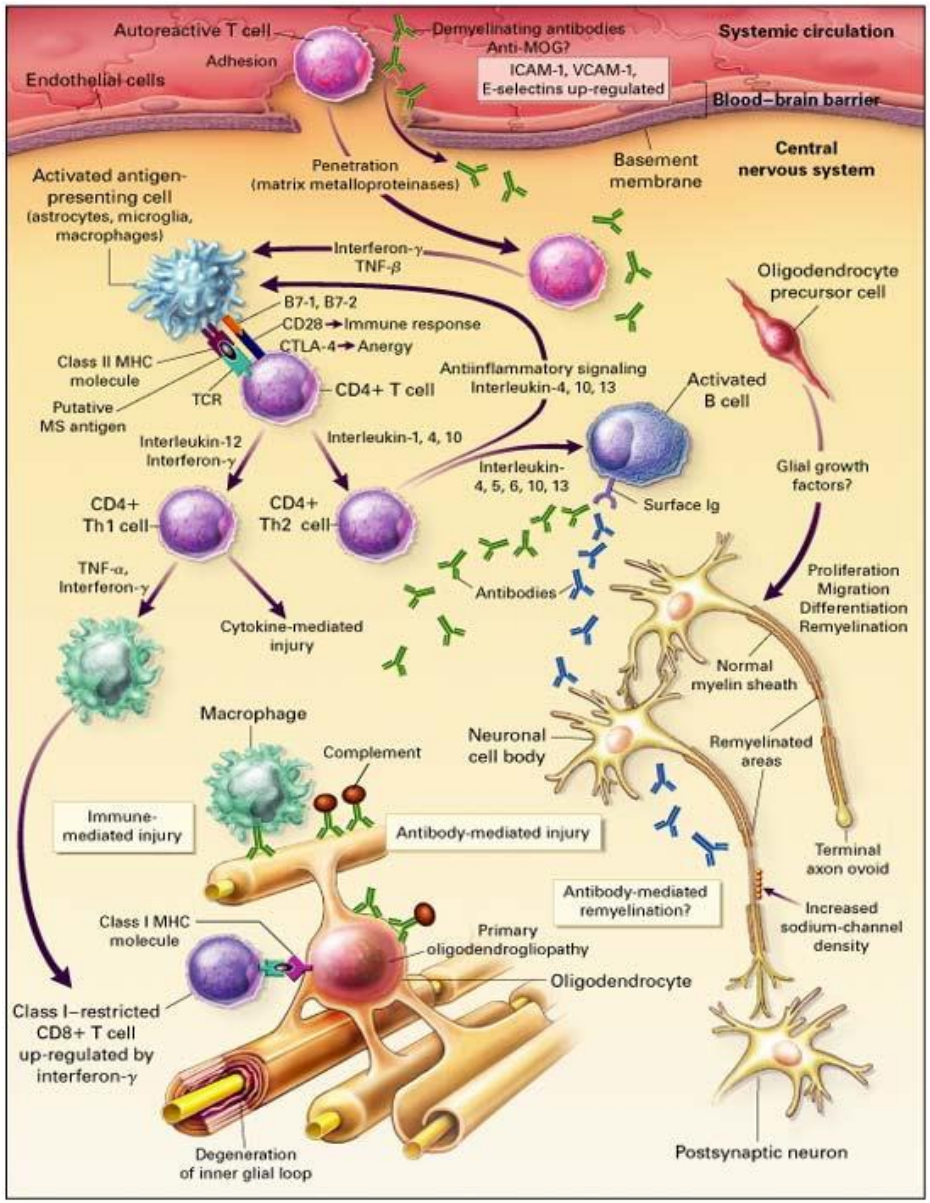
- Inflammation
- Demyelination
- Axonal Injury
- Neurodegeneration
- Remyelination

Neuropathology Of Multiple Sclerosis: Inflammation, Demyelination, Axonal Injury



Inflammatory Cell Nuclei, Myelin Basic Protein, Axonal Neurofilaments

Mechanisms of Injury and Repair in Multiple Sclerosis



- T Cell Infiltration
- Stimulation
- Inflammatory Cytokine Expression
- Immunoglobulin Production
- Recruitment of Microglia & Macrophages

Noseworthy JH et al. N Engl J Med 2000;343:938-952.

Heterogeneity of MS Lesions

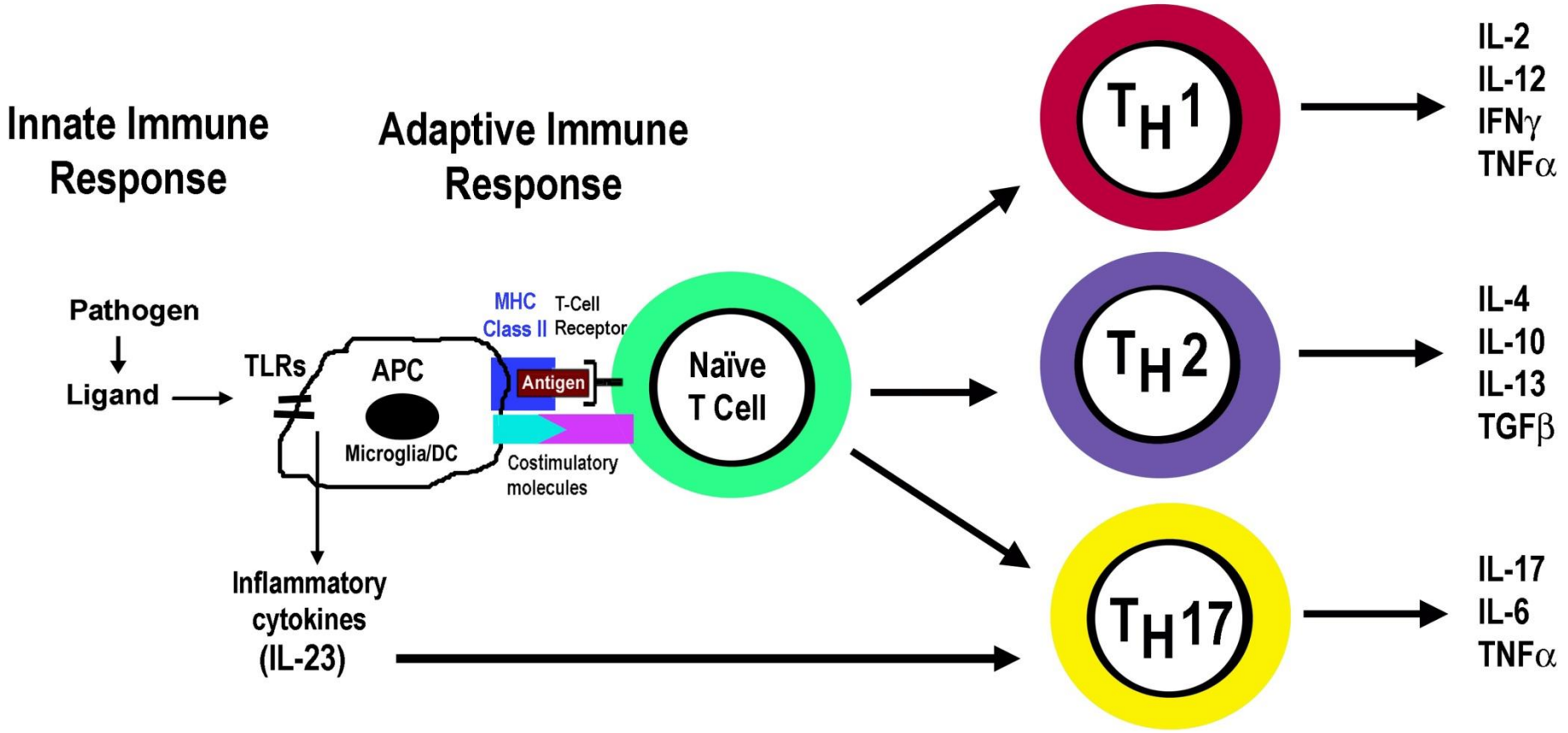
Lesion Pattern

Feature	I	II	III	IV
T cells	197	133	145	134
Pl. cells	6	9	5	4
μΦ/μγ	1,158	931	842	1650
C9neo	-	++	-	-
Oligo #	295	249	51*	55
Remyel.	++	++	-	-

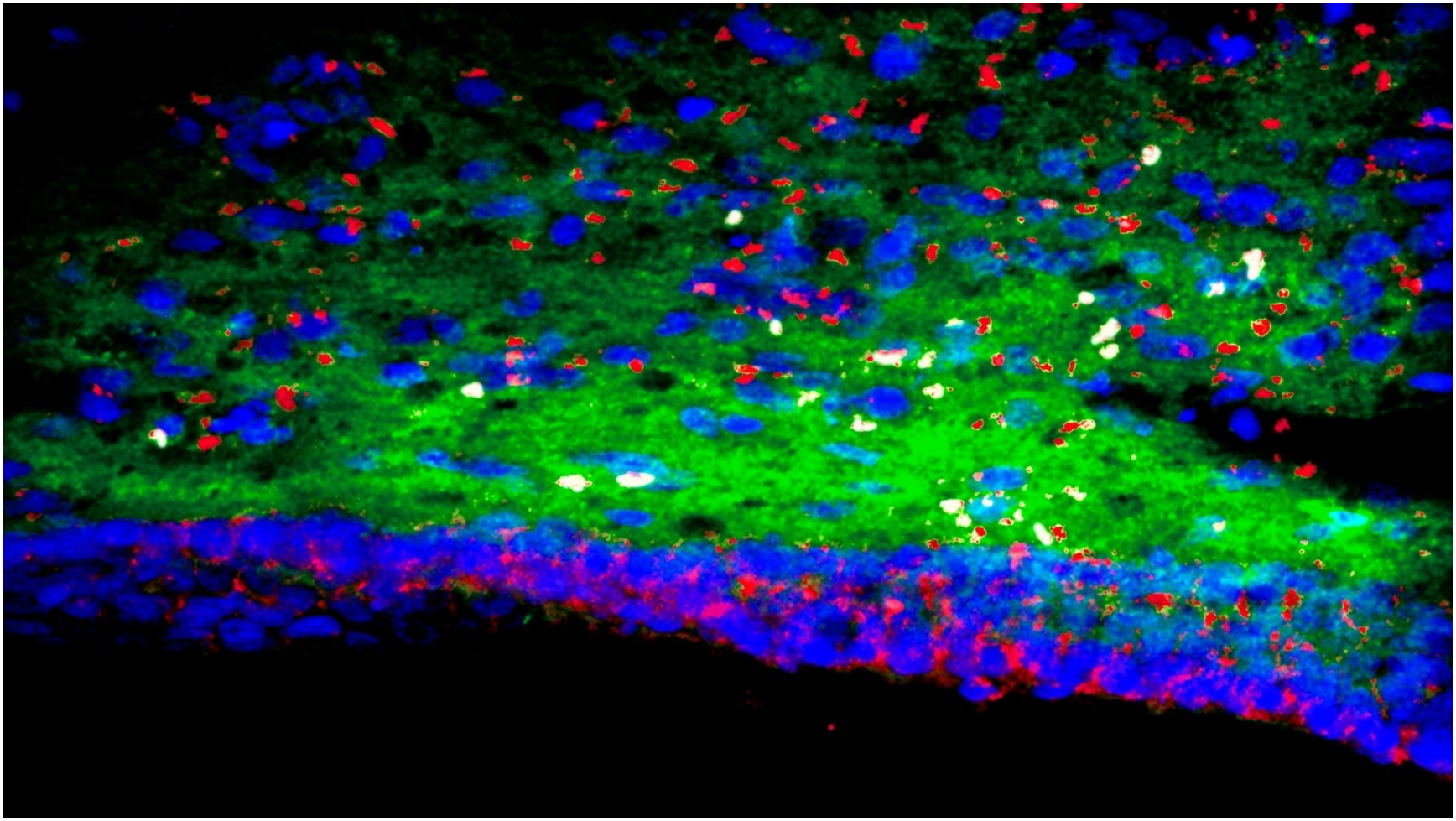
High Consistency of Lesion Pattern In Each Patient

Lucchinetti, Ann. Neurol. 47: 707, 2000

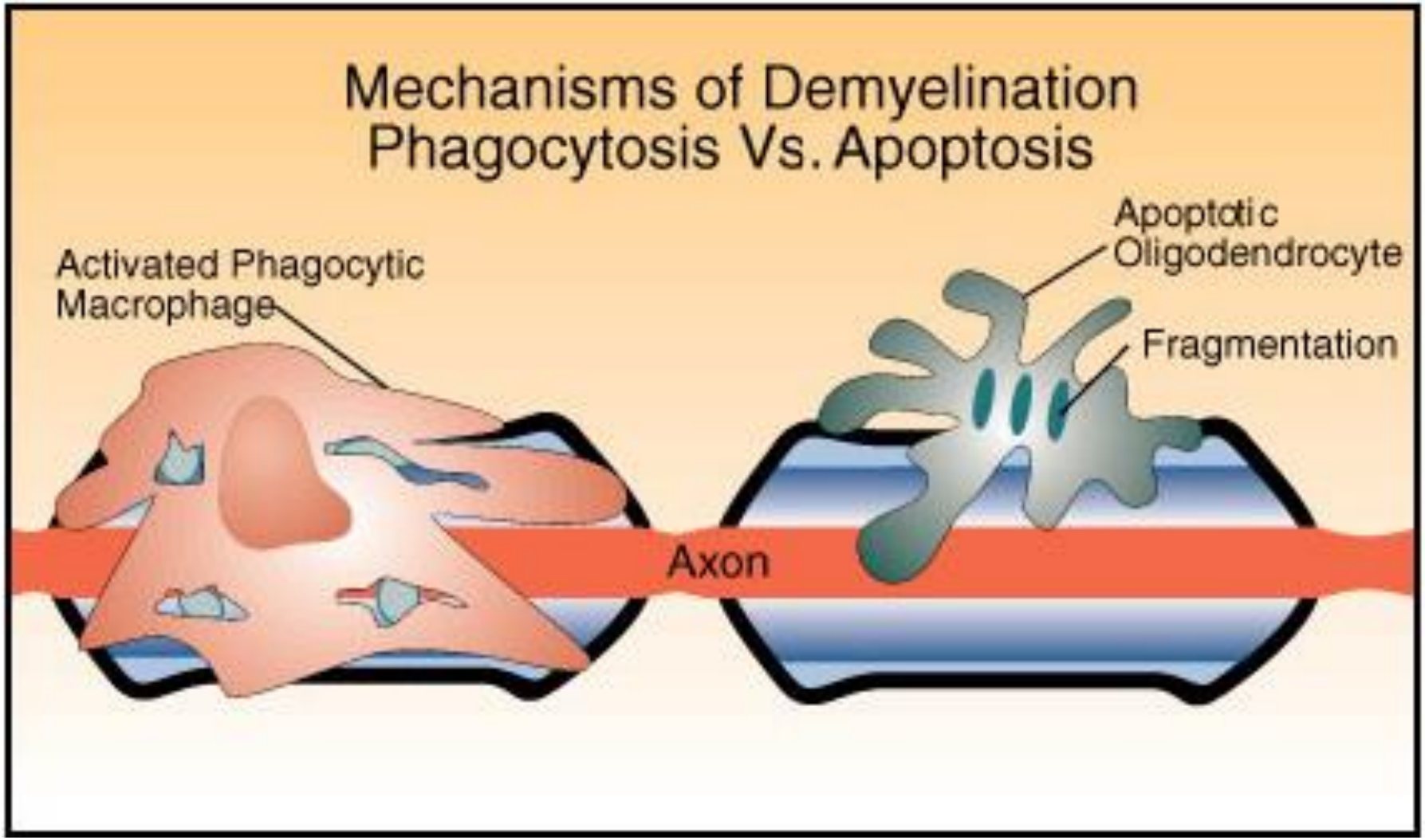
Immune Response: Pathways to Autoimmunity



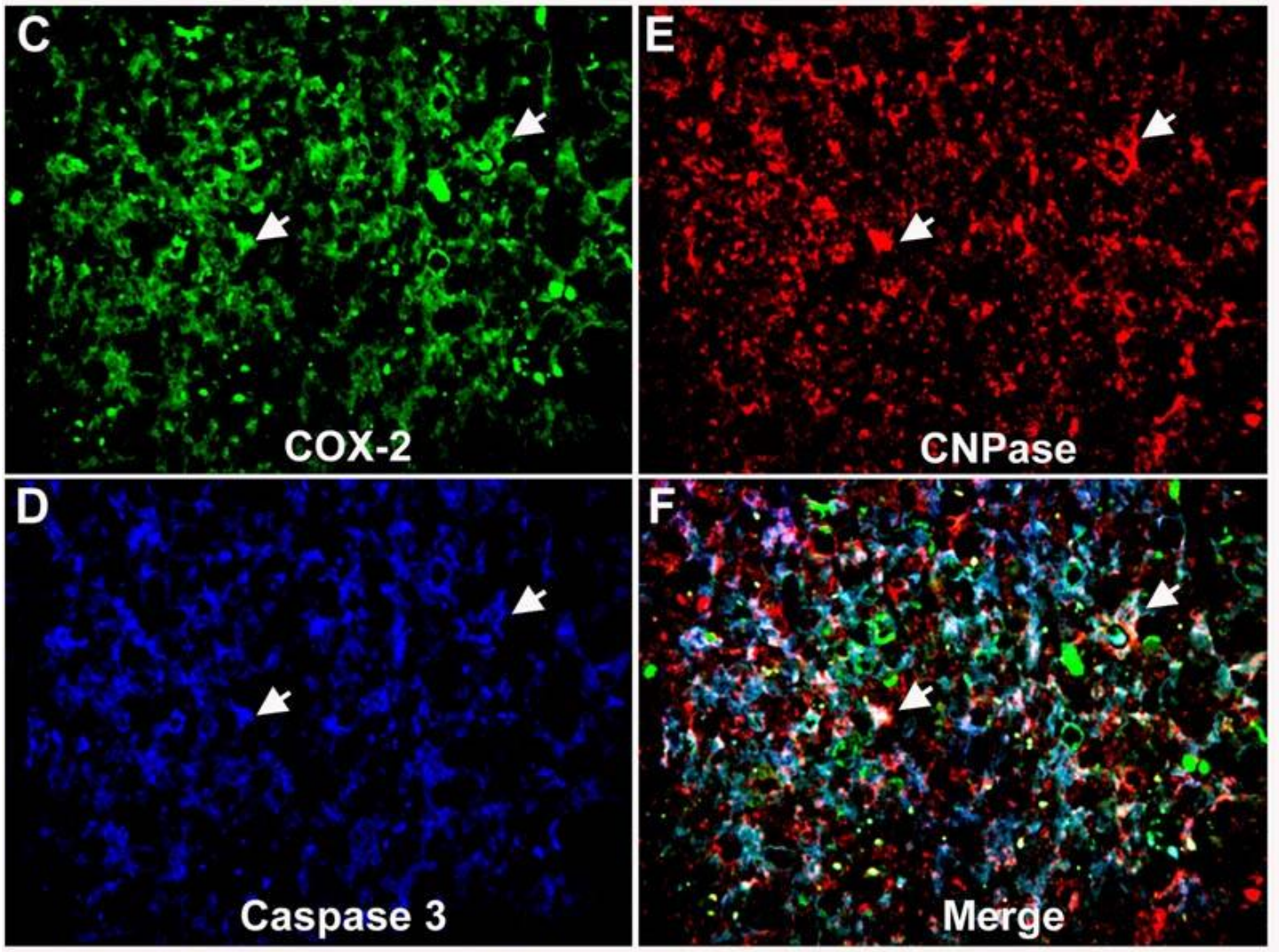
COX-2 (red) is expressed with iNOS (green) in the MS lesion



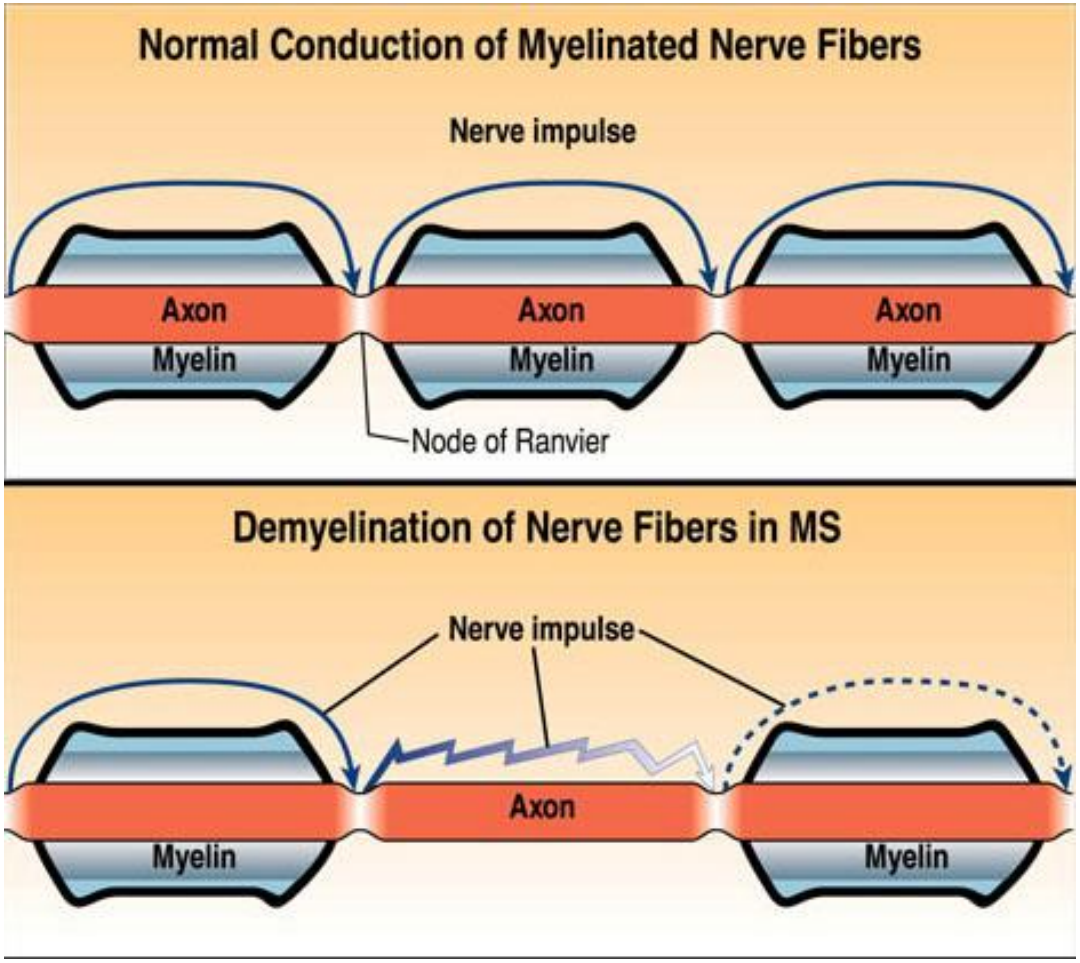
Oligodendrocyte Death and Demyelination



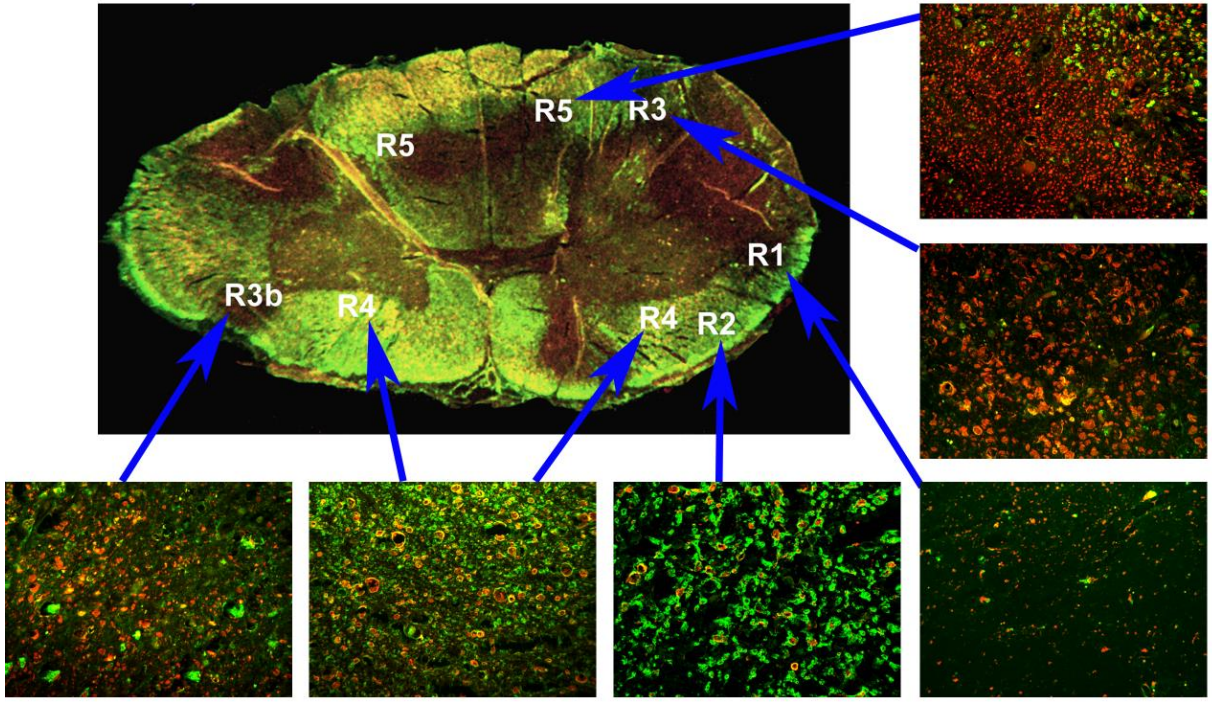
In-Vivo: Expression of COX-2 in Dying Oligodendrocytes MS Lesion



Effects of Demyelination



Wide Range of Pathology in MS Cervical Cord



Fluorochrome colors

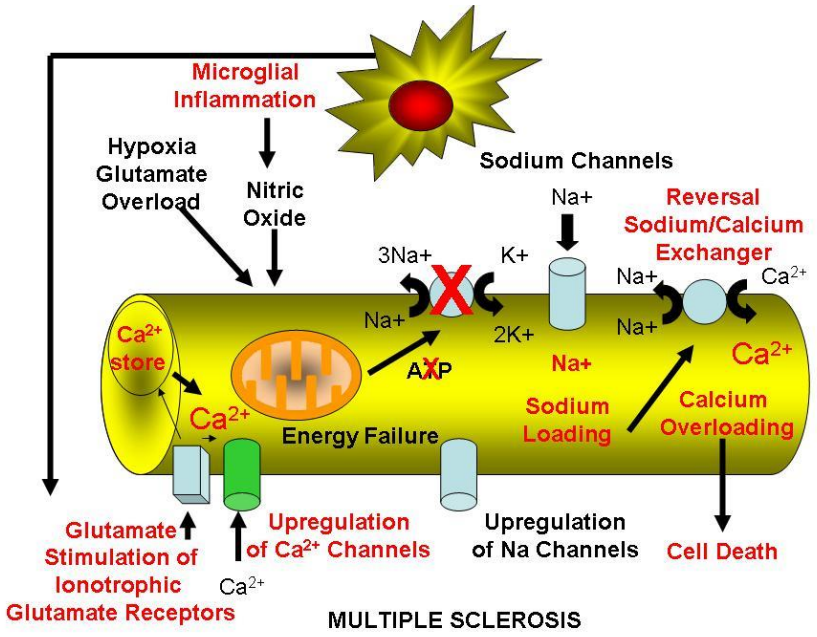
Red Neurofilament [light, medium & heavy chain]

Green Myelin Basic Protein [intact molecule]

Yellow Co-labeling of both neurofilament and MBP {red + green}

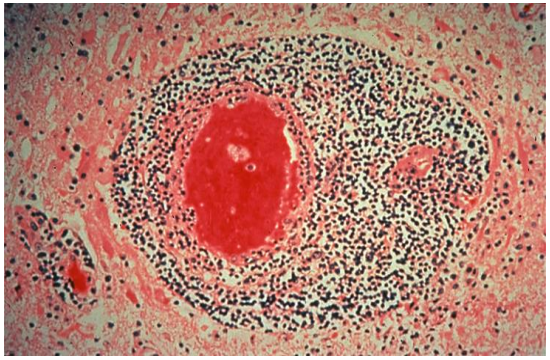
	Lens
R 1:Loss of both axons & Myelin	20X
R 2:Loss of axons, relative myelin preservation	40X
R 3:Loss of Myelin, relative axon preservation	20X
R 3b:Loss of Myelin, relative axon preservation {mixed area showing partial myelin degradation}	40X
R 4:relative NAWM	20X
R 5:Transitional areas of partial loss of axons/myelin	20X

Consequences of Demyelination*



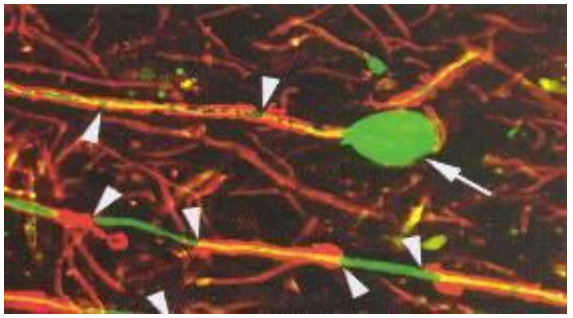
Histological Hallmarks of Multiple Sclerosis

Inflammation



Demyelination

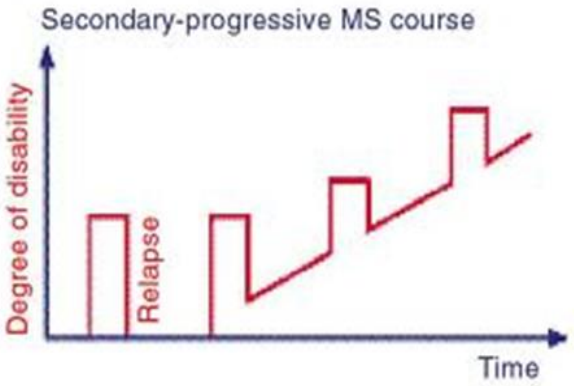
Axonal Damage



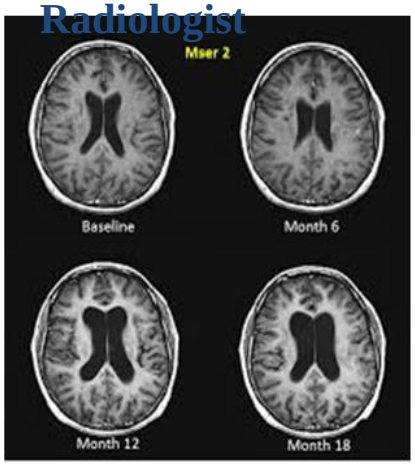
Courtesy of Dr. Bruce Trapp

What is Progressive MS?

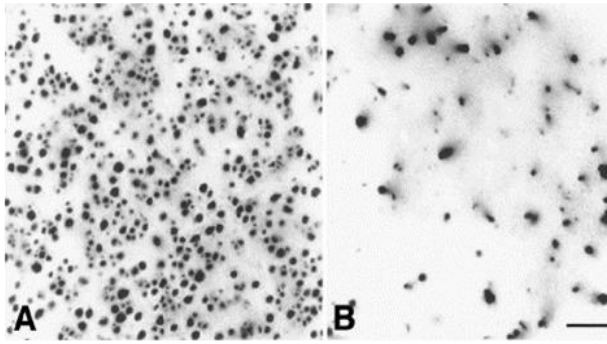
Neurologist



Radiologist



Pathologist



Physiatrist

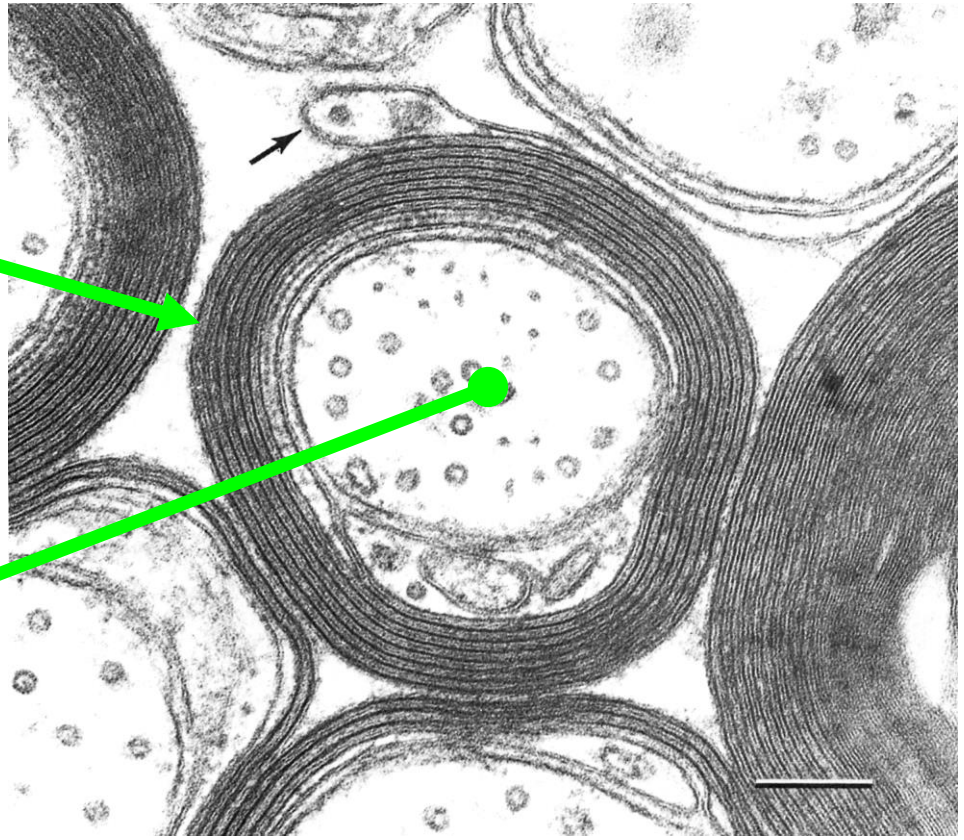
Person with MS

myelinated axon

myelinated axon

Myelin

Axon



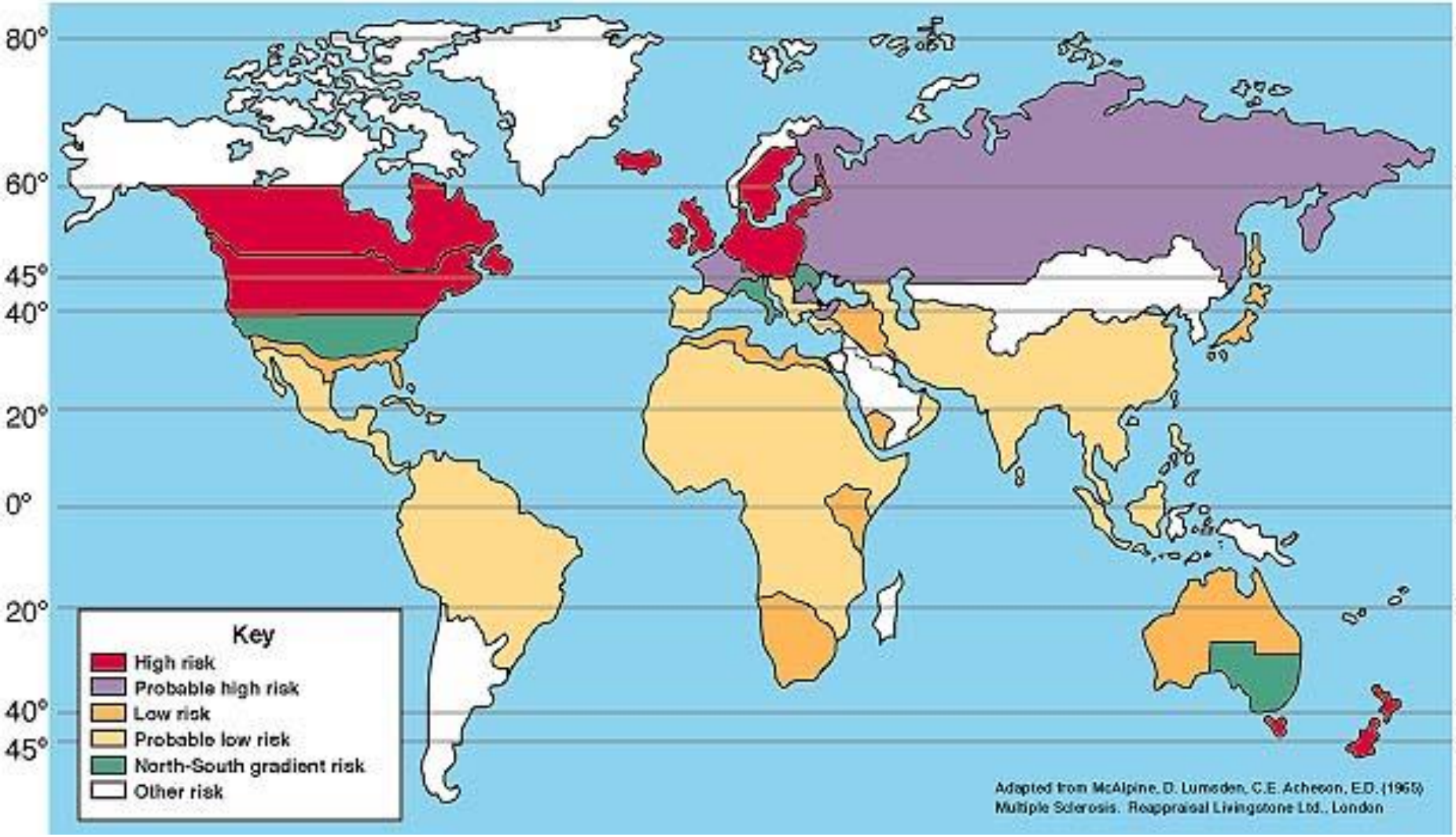
Remyelination

- Limited Capacity in CNS
- Thin Myelin
- Short Segments

Heterogeneity in MS

- Disease Course: RR,2P,PP,B,M,CIS
- Gender: F/M=3:1; Progression M>F
- Neuropathology: 4 subtypes & Acute
- Immunogenetic: DR2/OCB+ & DR4/OCB-
- ON: Better Prognosis
- MRI: Inflammation and Injury
- Remyelination: 20% Good, 80% Poor

World Distribution of Multiple Sclerosis



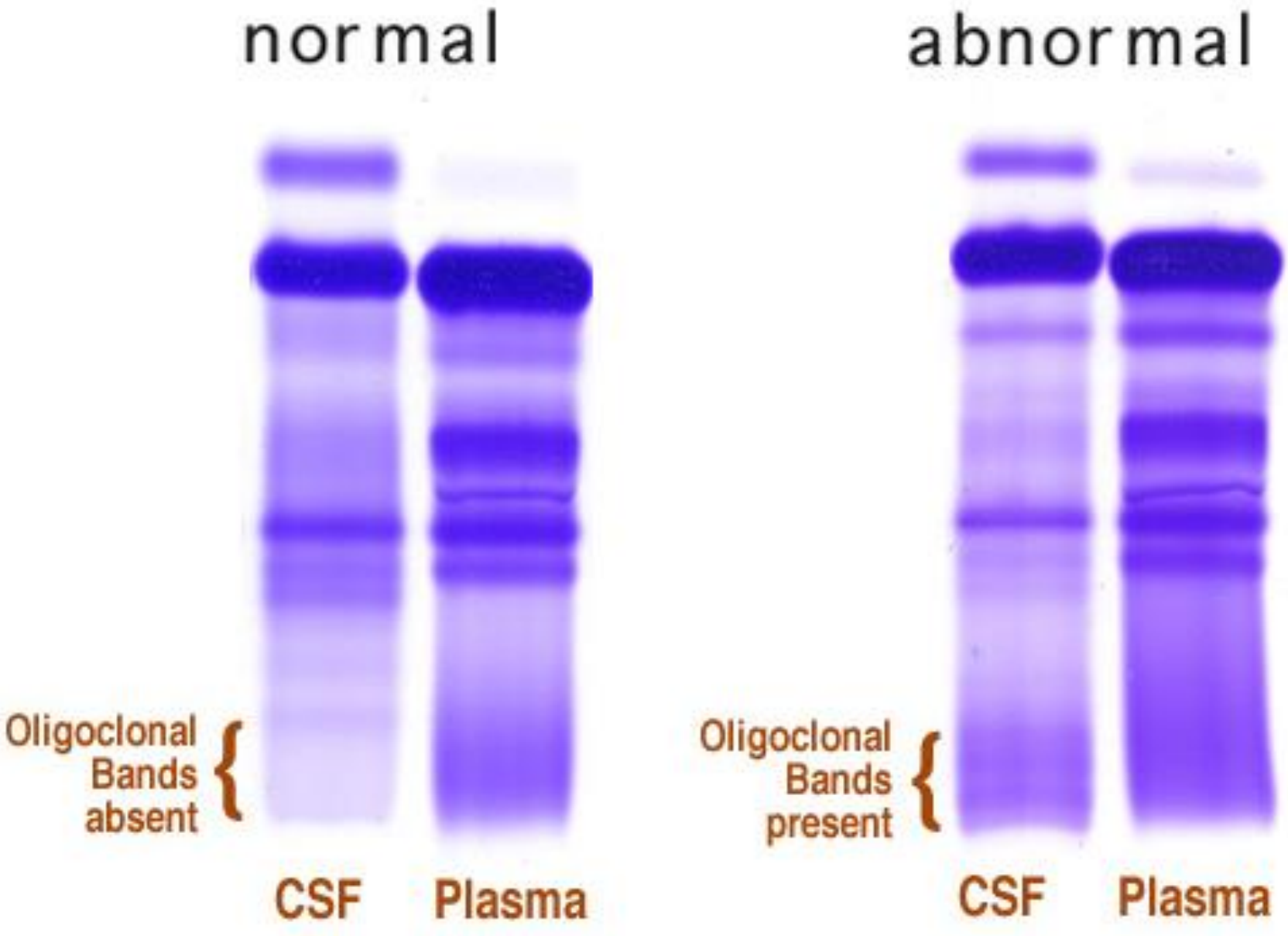
Disease Modifying Factors

- Vitamin D Deficiency May Increase Risk
- Smoking Produces Increased Disease
- Infections Precipitate Relapses
- Obesity
- Air Quality
- Alcohol

Diagnosis

- History
- Neurologic Examination
- MRI: Brain, Spinal Cord, Optic Nerves
- Cerebrospinal Fluid
- Evoked Potentials
- Bladder Testing
- Neuropsychological

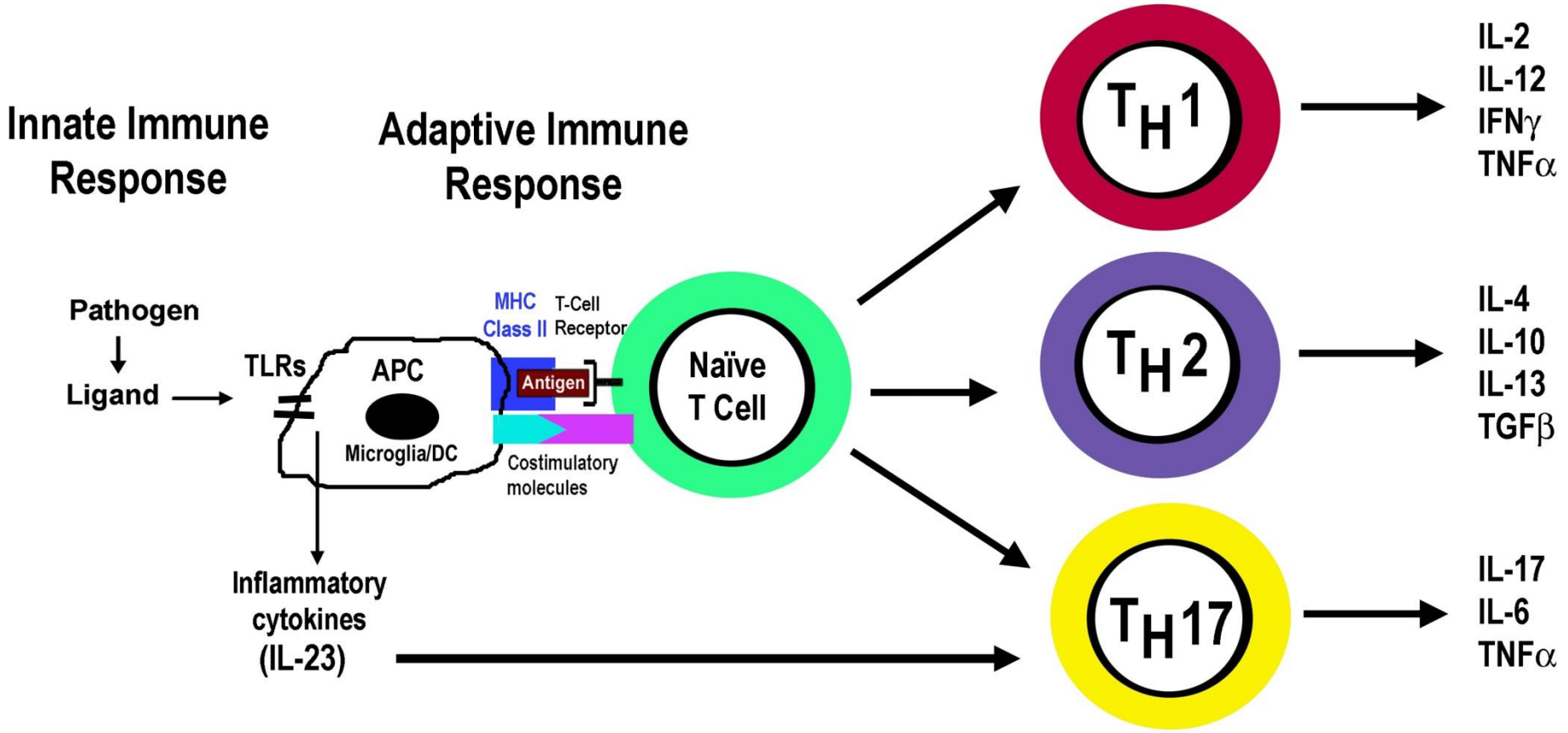
Oligoclonal Bands in CSF



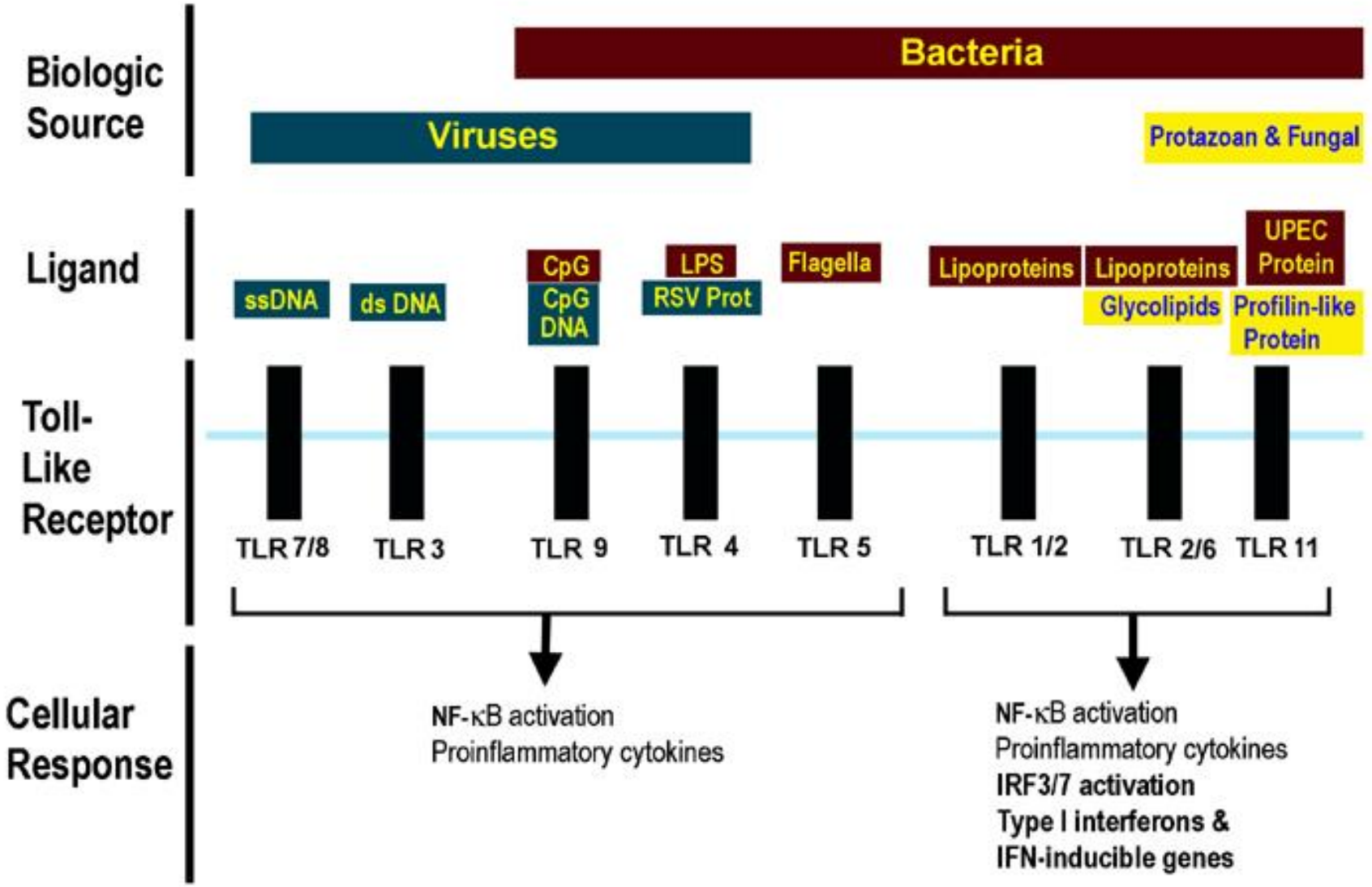
Infections & MS

- Infections Stimulate Relapses
- Potential Induction of MS via Molecular Mimicry
- Latent Viral Infection & Reactivation
- Non Specific Stimulation of Inflammatory Response
- Toll Receptor Stimulation Activates Th17 Population
- Super Antigenic Stimulation of T Cells Through Receptor Subtypes
- Viral Encoded Cytokine Homologs Alter Immune Responses

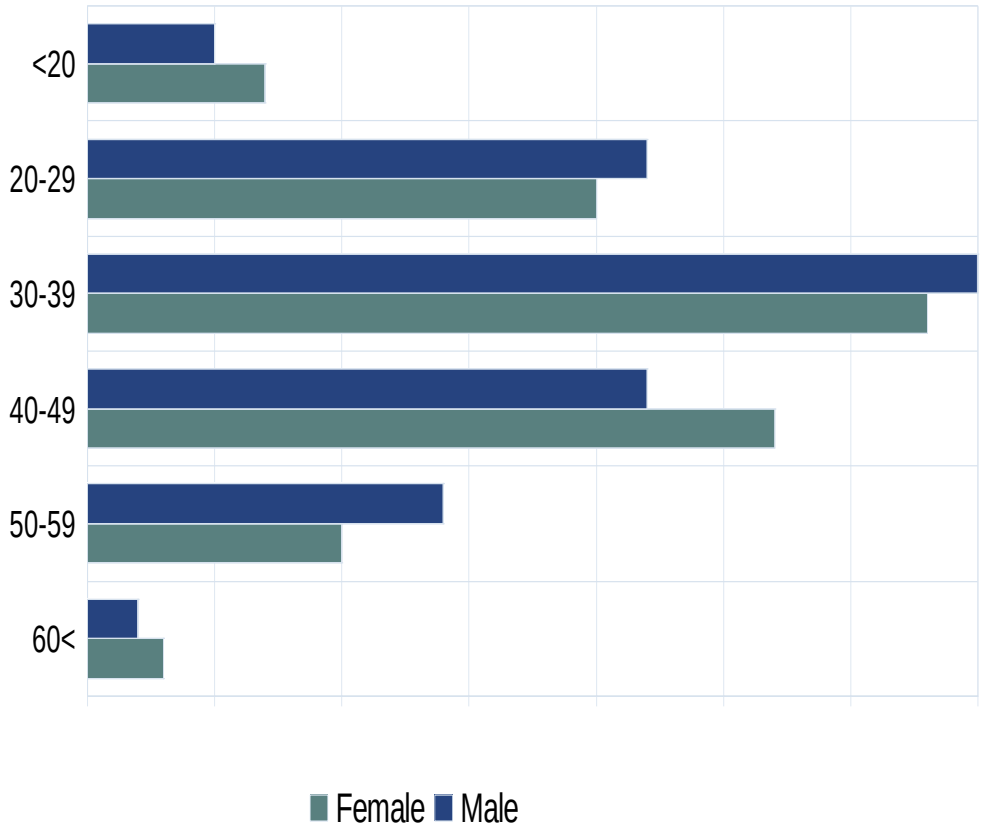
Immune Response: Pathways to Autoimmunity



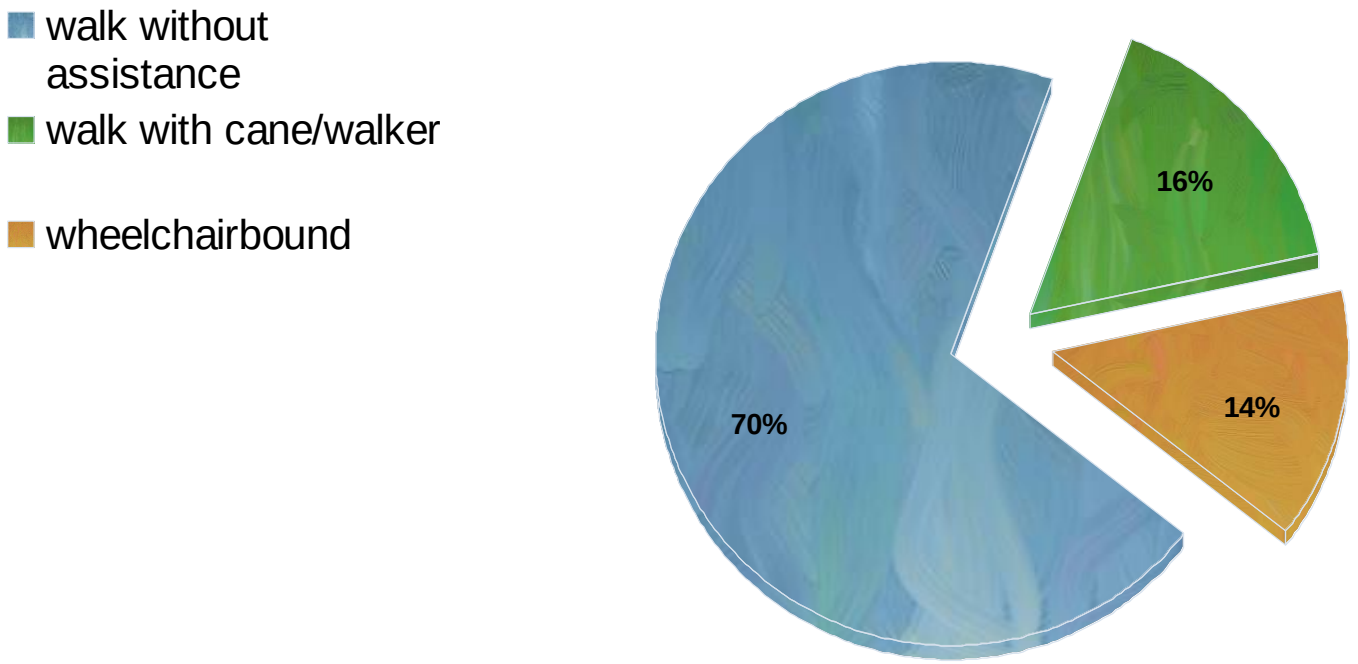
Why Infections Cause Relapses I



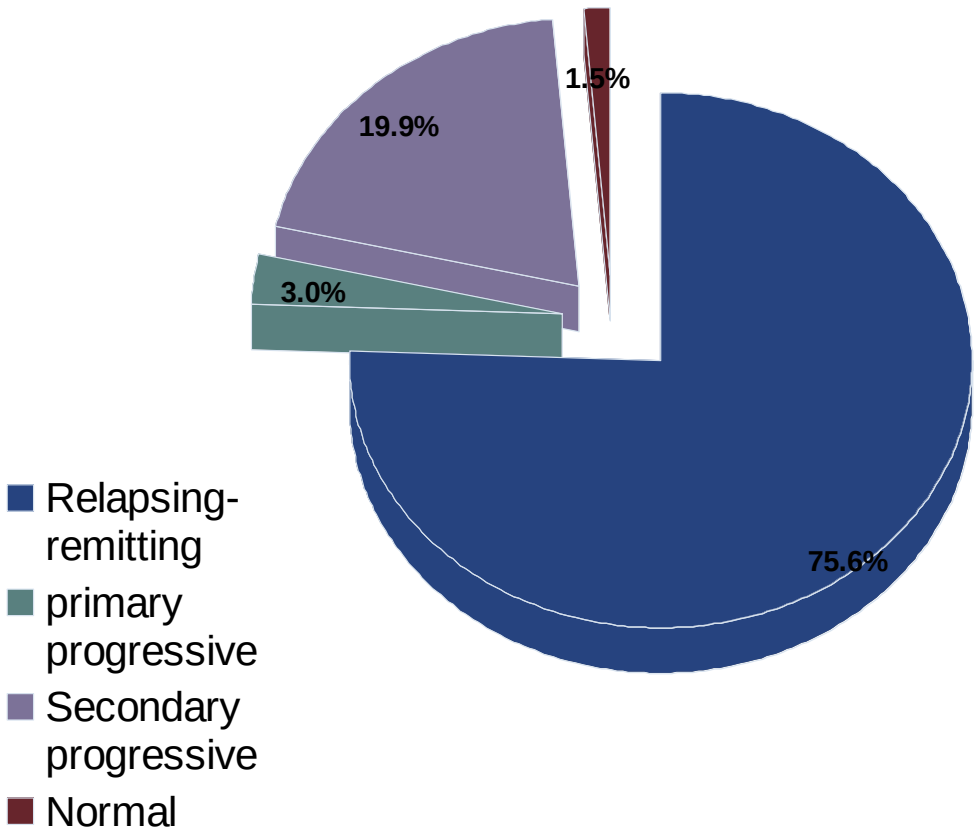
IMSP: Comparison of Male & Female Age At Diagnosis



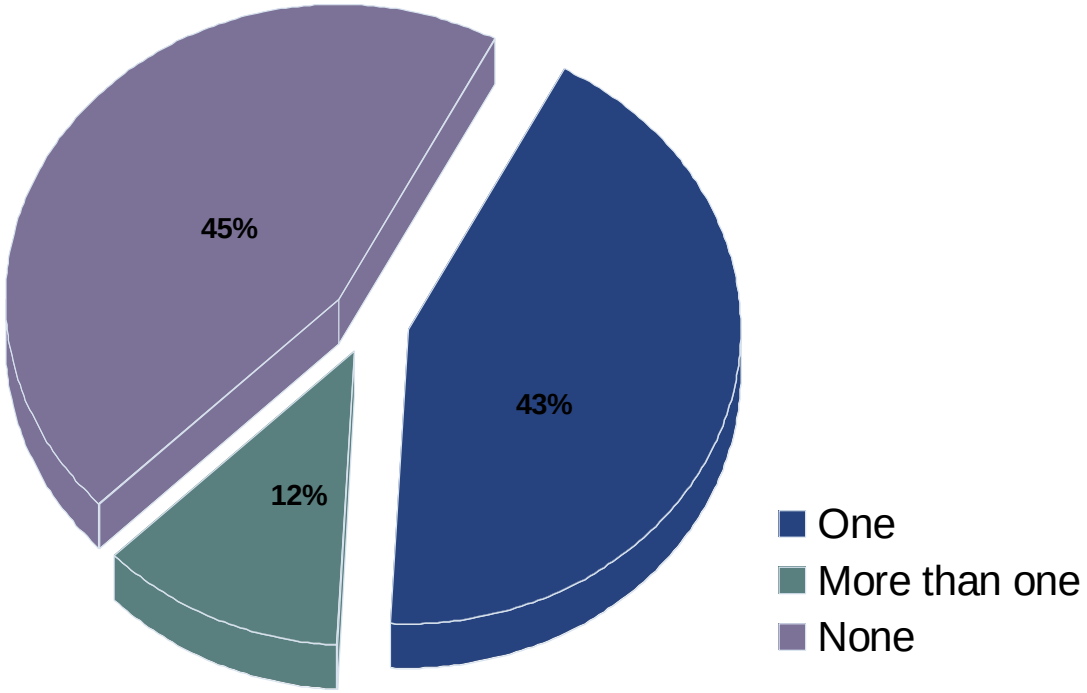
Ambulation Status



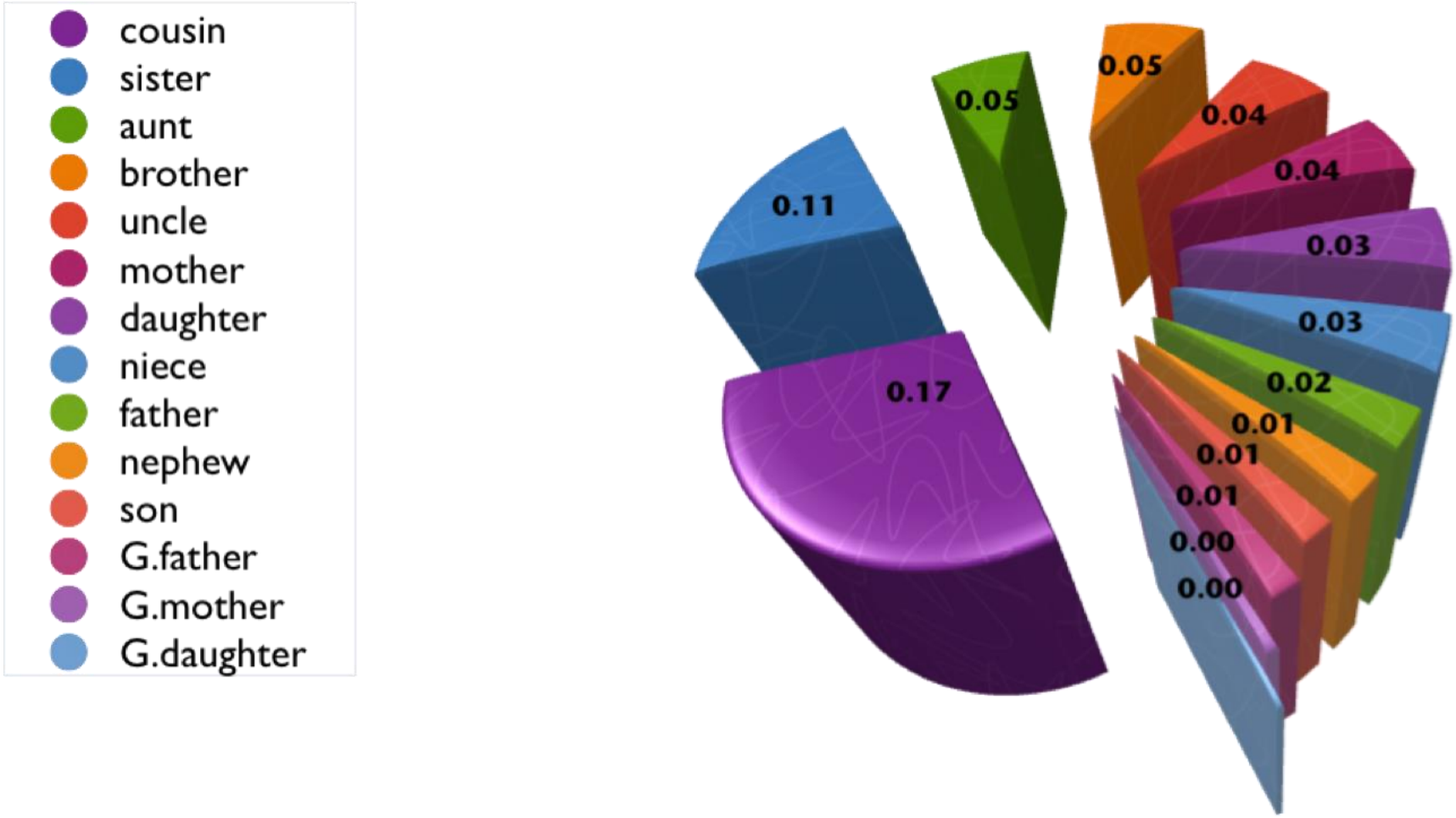
Disease Course



IMSP: Family Members With Multiple Sclerosis

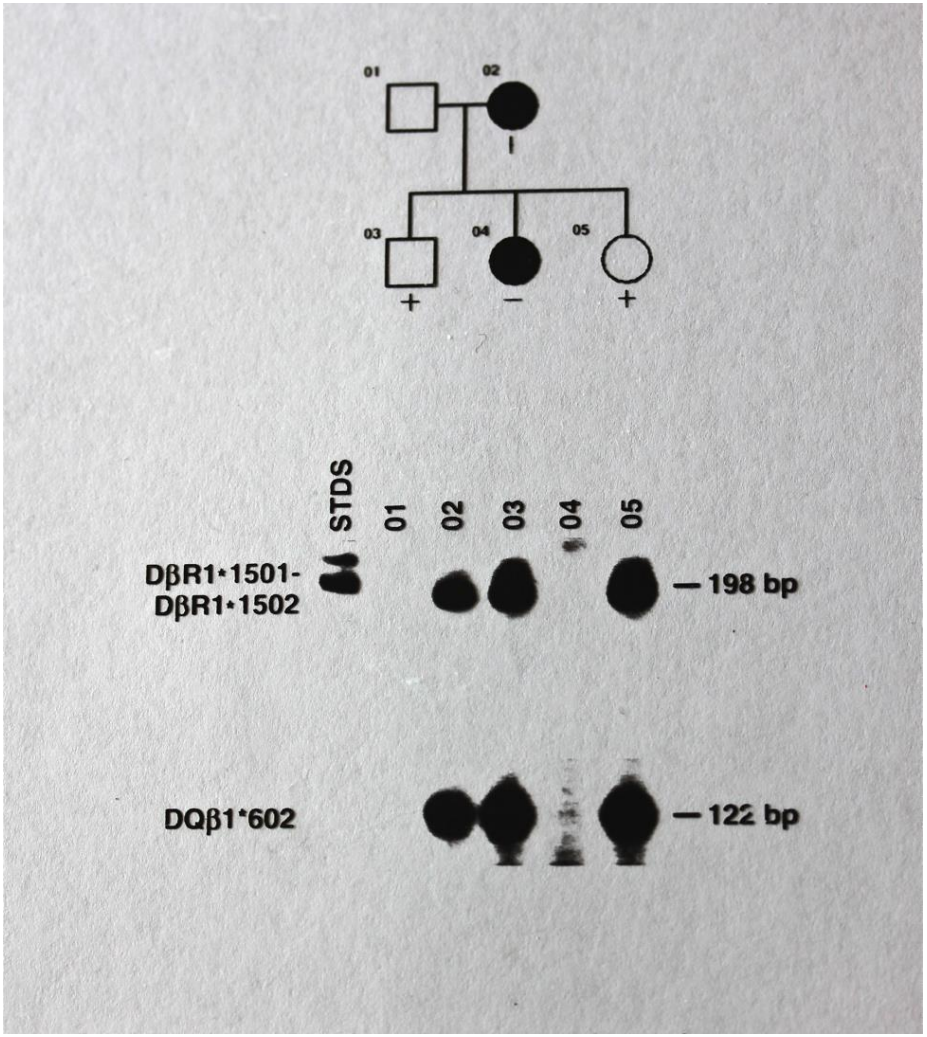


IMSP Family Members with Multiple Sclerosis



Genetic Susceptibility In Multiple Sclerosis

- Concordance Monozygotic Twins 30%
- Concordance Dizygotic Twins 5%
- Risk In First Degree Relatives 5%
- Greater Than 200 Genes Identified
- Genes Involved In Immune Response
- IL-2R alpha Gene Shared with DM 1
- Non-Associated Genes: MBP, MOG, PLP, OMG, TCRs, TNF, iNOS, APOE4
- DR2 Haplotype
  - 50% MS Patients
  - 70% Familial MS
  - 10% 0f Genetic Risk
  - Neither Necessary or Sufficient



Importance of Pediatric MS

- Critical to Diagnose and Treat
- Critical to Understanding the Cause
- NMSS Sponsored Pediatric Centers of Excellence
- Time to Diagnosis Greatly Reduced
- Time to Treatment Greatly Reduced
- Utilization of Immunomodulatory & Immunosuppressive Rx for Ped MS
- USNPMSC Evolution to Research Network
- International Pediatric MS Study Group

United States Network of PEDIATRIC MULTIPLE SCLEROSIS Centers

Network and Affiliate Centers

NPMSC Network Centers

- **Center for Pediatric-Onset Demyelinating Disease**
  - University of Alabama at Birmingham Center
  - Principal Investigator(s): Jayne Ness, MD, PhD
- **UCSF Regional Pediatric MS Center**
  - Principal Investigator(s): Emmanuelle Waubant, MD, PhD and Jennifer Graves, MD, PhD
- **Pediatric Multiple Sclerosis Center**
  - Loma Linda University Children's Hospital
  - Principal Investigator(s); Gregory Aaen, MD
- **Partners Pediatric MS Center**
  - Massachusetts General Hospital for Children
  - Principal Investigator(s): Tanuja Chitnis, MD
- **Pediatric MS and Related Disorders Program**
  - Boston Children's Hospital
  - Principal Investigator(s): Mark Gorman, MD and Leslie Benson, MD
- **Mayo Clinic Pediatric MS Center**
  - Principal Investigator(s): Moses Rodriguez, MD and Jen-Mendelt Tillema, MD
- **Pediatric MS Center of Jacobs Neurological Institute**
  - Principal Investigator(s): Bianca Weinstock-Guttman, MD
- **Lourie Center for Pediatric MS**
  - Stony Brook University Hospital
  - Principal Investigator(s): Lauren Krupp, MD and Anita Belman, MD
- **The Blue Bird Circle Clinic for Multiple Sclerosis**
  - Texas Children's Hospital
  - Principal Investigator(s): Timothy Lotze, MD
- **Rocky Mountain MS Center**
  - University of Colorado at Denver
  - Principal Investigator(s): Teri Schreiner, MD
- **Washington University Pediatric MS and Demyelinating Diseases Center**
  - Principal Investigator(s): Soe Mar, MD
- **Mellen Center for Multiple Sclerosis**
  - Cleveland Clinic
  - Principal Investigator(s): Mary Rensel, MD and Manikum Moodley, MD

NPMSC Affiliate Centers

- **Lurie Children's Hospital of Chicago**
  - Principal Investigator(s): Jennifer Rubin, MD
- **The Children's Hospital of Philadelphia**
  - Principal Investigator(s): Amy Waldman, MD
- **University of Texas Southwestern**
  - Principal Investigator(s): Benjamin Greenberg, MD
- **Primary Children's Hospital**
  - Principal Investigator(s): Meghan Candee, MD and Mateo Paz Soldan, MD
- **Children's National Medical Center**
  - Principal Investigator(s): Adeline Vanderver, MD

United States Network of PEDIATRIC MULTIPLE SCLEROSIS Centers

Data Collected in the PeMSDD

Demographics Worksheet

- Date of Birth
- Gender
- Race/Ethnicity
- Weight at Birth
- Delivery
- Breastfeeding/Formula
- Special Services
- School Attendance
- Residence
- Tobacco smoke exposure
- Living Situation
- Mother's Date of Birth
- Mother's Race/Ethnicity
- Mother Education Level
- Mother Occupation
- Father's Date of Birth
- Father's Race/Ethnicity
- Father Education Level
- Father Occupation
- Siblings
- Vaccinations
- Child and Family History of Disease

History of Disease Worksheet

- Disease Modifying Therapies
- Corticosteroids
- Infectious Disease History
- Blood Tests
- CSF Tests
- Vision Testing
- MRI Scans
- Neuropsychological Testing
- Material/Tissue Collection

Visit Record

- Height and Weight
- Grade Level
- Symptomatic and Other Medications
- Diagnosis
- Tanner Stage
- Menstrual Periods
- Skin Color
- Neurostatus EDSS Test
- SDMT Test

Event Record

- Event Onset
- Hospitalization for Event
- Clinical Antecedent
- Localization of Clinical Event
- Event Severity
- Diagnosis

Network Description and Patient Population

The US Network of Pediatric Multiple Sclerosis Centers: Development, Progress, and Next Steps, Casper C, Rose J, Roalstad S et al Child Neurology 2015

Characterstics of Children and Adolescents with Multiple Sclerosis. Belman et al & USNPMSC: Pediatrics 2016

RESEARCH MISSION

To uncover the key pathogenic mechanisms underlying MS and improve outcome through the study of pediatric MS

The pediatric MS Network will advance our understanding of MS disease processes by leveraging the unique features of an adult disease when clinically presenting in children and adolescents

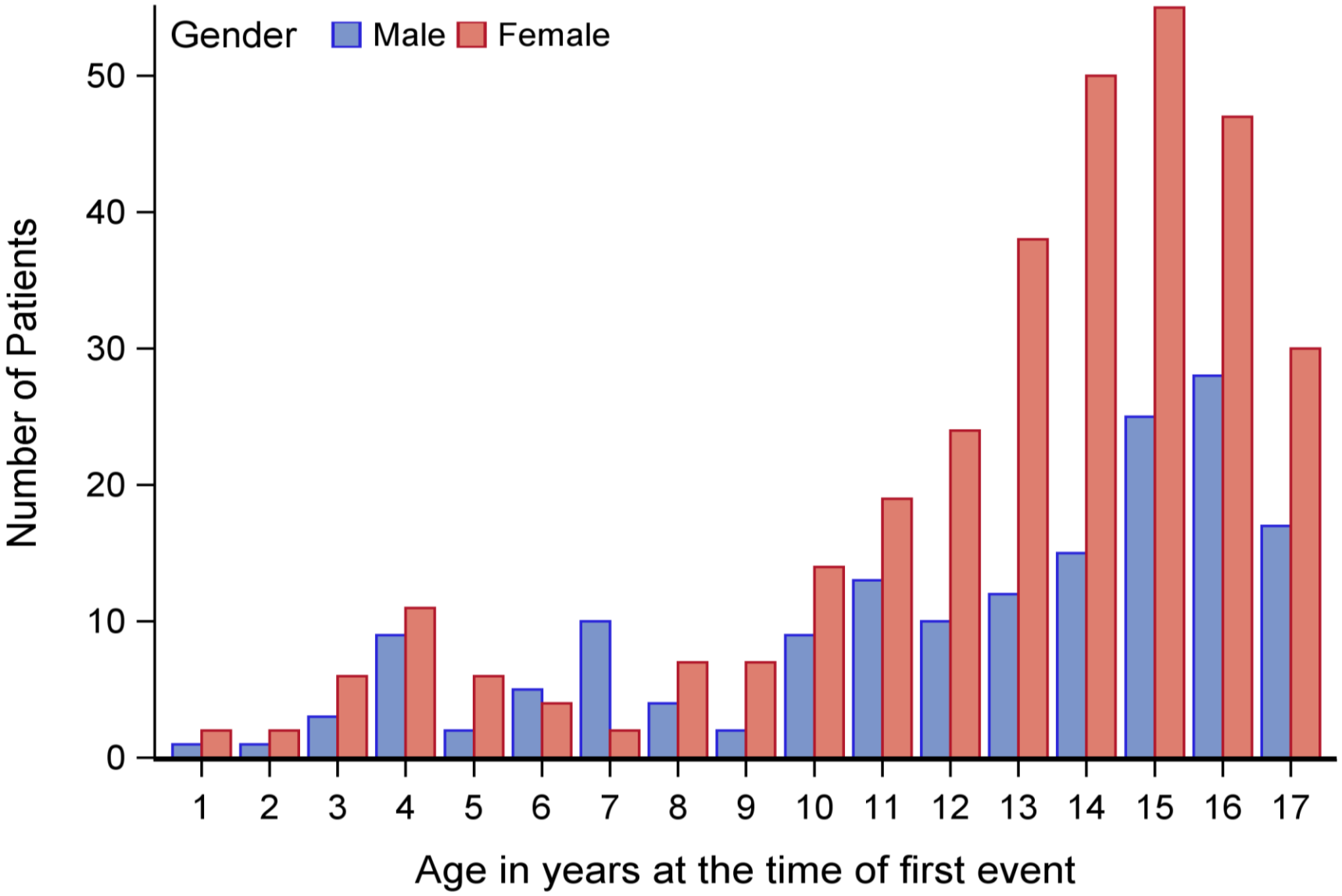
USNPMSC Ongoing Funded Research

Study	Center	Funding/Priority
Genes and Environment (MS)	UCSF and Network	NIH RO1/RP#1
Registry	Network/DCAC	NMSS/RP#s1,2,3 & 4
Gut Microbiome	UCSF and Network	NMSS/RP#1
MRI in NMO SPECTRUM	MGH and Network	Guthy-Jackson Charitable Foundation/RP#1
Fingolimod Trial	Network Centers	Pharma/RP#4
HCDPR PT & Family Views	MGH and Network	NMSS/RP#4
Cognition In Ped MS	NYU and Network	NMSS/RP#2
Dietary Factors	UCSF and Network	NMSS/RP#1

Pediatric MS Demographics

Characteristic	Overall N (490)
Age at time of first event:	
Mean (SD) [Min-Max]	13.2 (3.87) [1.6 - 18.0]
Male: Mean (SD) [Min-Max]	12.8 (4.16) [1.8 - 17.9]
Female: Mean (SD) [Min-Max]	13.4 (3.70) [1.6 - 18.0]
Age < 10 years at first event	84 (17.1%)
Age < 11 years at first event	107 (21.8%)
Age < 12 years at first event	139 (28.4%)
Gender	
Male	166 (33.9%)
Female	324 (66.1%)

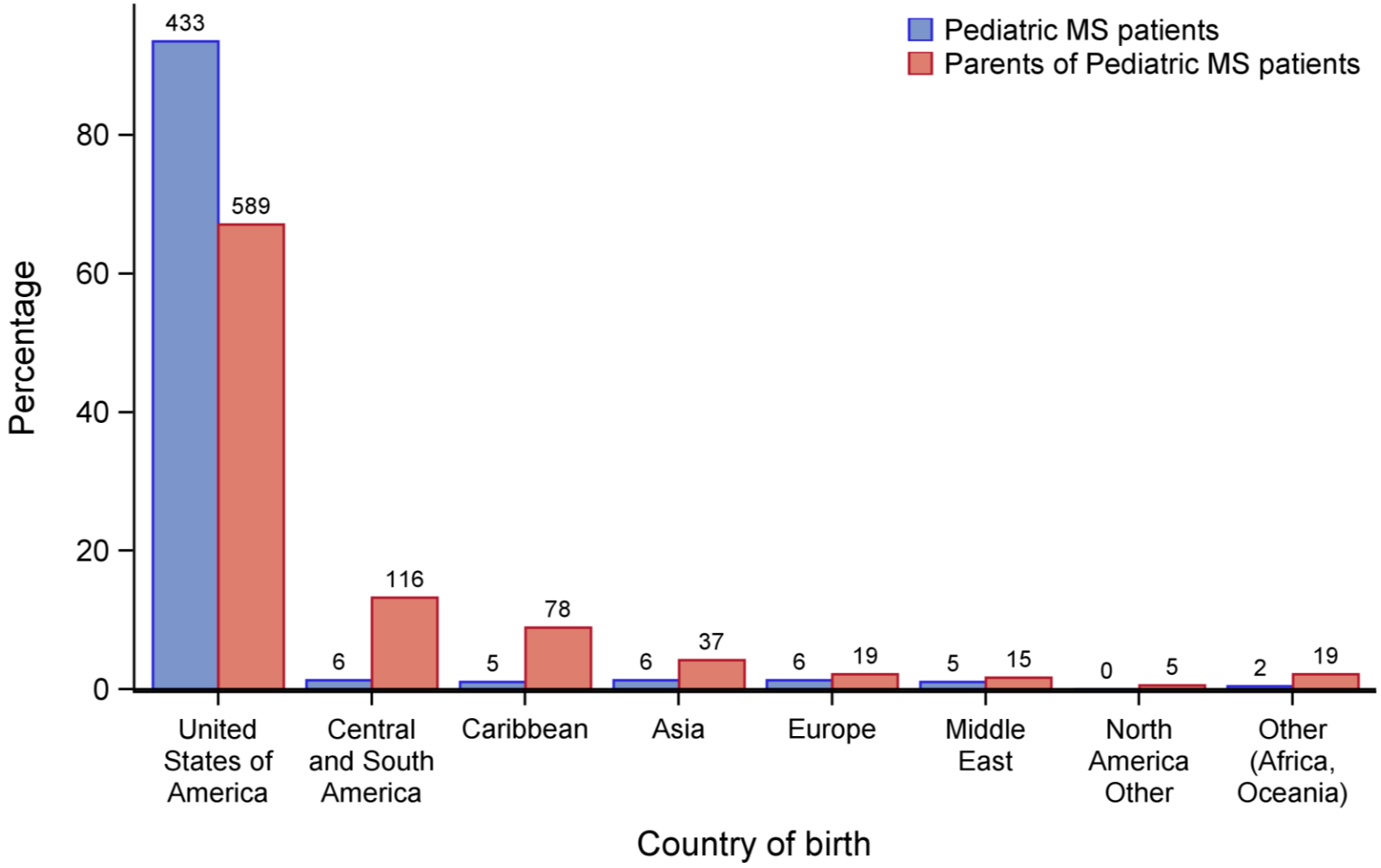
Gender and Age of Onset



Pediatric MS Race and Ethnicity

Characteristic	Overall Number (490)
Race	
White	303 (**67.0%**)
Black/African-American	93 (**20.6%**)
American Indian/Alaskan Native	8 (**1.8%**)
Asian	17 (**3.8%**)
Native Hawaiian or Pacific Islander	1 (**0.2%**)
Multiracial	30 (**6.6%**)
Ethnicity	
Hispanic or Latino	139 (**30.2%**)
Not Hispanic or Latino	321 (**69.8%**)

Country of Birth: Ped MS Patients & Parents



CSF In Pediatric MS

	N	Age <12 yrs (N = 139)	N	Age ≥12 yrs (N = 351)	N	Overall (N = 490)	P-value
Cerebrospinal fluid profile							
First Event total white blood cell count: Mean (SD)	74	20.2 (35.73)	182	13.6 (17.96)	256	15.5 (24.57)	0.823[b]
First Event % Lymphocytes: Mean (SD)	54	**73.1 (23.28)**	143	**85.6 (20.88)**	197	82.2 (22.22)	**<.001[b]**
First Event % Neutrophils: Mean (SD)	24	**16.0 (14.24)**	34	**4.5 (7.86)**	58	9.3 (12.26)	**0.001[b]**
Any Elevated IgG Index	71	**28 (39%)**	147	**105 (71%)**	218	133 (61%)	**<.001[a]**
Any Positive test for OCBs	92	**47 (51%)**	217	**168 (77%)**	309	215 (70%)	**<.001[a]**

Summary of USNPMSC Demographics & Clinical Charatarestics

- Average Age Onset: 13
- Age Less Than 10: 17%
- Female to Male Ratio: 2:1
- Race: White 67% & African American 20%
- Ethnicity: 30% Latino/Hispanic
- Juvenile MS Differs From Adolescent MS: Antecedent Infection, Clinical Manifestations and CSF
- Wide Range of Immunotherapies Appear Effective (None are FDA Approved for Pediatric MS)

Genetic risk factors for pediatric-onset multiple sclerosis

FINDINGS

- Pediatric and adult MS share many genetic variants suggesting similar biological processes are present.
- MHC variants beyond HLA-DRB1*15:01 and HLA-A*02 are also associated with POMS
- Additional MHC class III risk variants in the MHC region associated with POMS were revealed after accounting for HLA-DRB1*15:01 and HLA-A*02.

Gianfrancesco Mult Scler. 2017

Contribution of dietary intake to relapse rate in early paediatric multiple sclerosis

219 CIS and MS Patients Under 18 Yrs

Validated Block Kids Food Screen

Each 10% Energy Intake Via Saturated Fat Increased Hazard of Relapse

(HR 3.37, $p<0.009$)

1 Cup equivalent of Vegetable Decreased Hazard of Relapse (HR .50, $p<0.024$)

These Results Are Considered Independent of Each Other

These Associations Persisted with Mutual Adjustment & Adjustment for Vitamin D

Azary J Neurol Neurosurg Psychiatry. 2017

Distinct effects of obesity and puberty on risk and age at onset of pediatric MS

- Higher BMI in early adolescence is a risk factor for MS in girls and boys

- Earlier age at sexual maturity contributes to earlier age at MS onset, particularly in association with obesity

Chitnis Ann Clin Transl Neurol. 2016

Evidence for a causal relationship between low vitamin D, high BMI, and pediatric-onset MS

- These Data support independent and causal effects of decreased vitamin D levels and increased BMI on susceptibility to Pediatric-Onset MS.

Gianfrancesco Neurology. 2017

Examining the contributions of environmental quality to pediatric multiple sclerosis

Study Design

- Pediatric MS cases and healthy controls were identified as part of an ongoing multicenter case-control study.

- Subjects' geographic locations were mapped by county centroid to compare to an Environmental Quality Index (EQI). The EQI examines 5 individual environmental components (air, land, water, social, built factors). Subjects' geographic locations were mapped by county centroid to compare to an

- A composite EQI score and individual scores were compared between cases and controls, stratified by median proximity to enrollment centers (residence <20 or ≥20 miles from the recruiting center), using logistic regression.

Mult Scler Relat Disord.

Examining the contributions of environmental quality to pediatric multiple sclerosis

Results

- Of the 287 MS cases and 445 controls, 46% and 49% respectively live in areas where the total EQI is the highest (worst environmental quality).
- Total EQI was not significantly associated with the odds for MS ($p = 0.90$ < 20 miles from center; $p = 0.43 \geq 20$ miles)
- Worsening Air Quality significantly impacted the odds for MS:
- Children living near a referral center (OR = 2.83; 95%CI 1.5, 5.4)
- Children who reside ≥ 20 miles from a referral center (OR = 1.61; 95%CI 1.2, 2.3)

Lavery Mult Scler Relat Disord. 2017

Pediatric & Adult MS Modifiable Risk: Adjustments

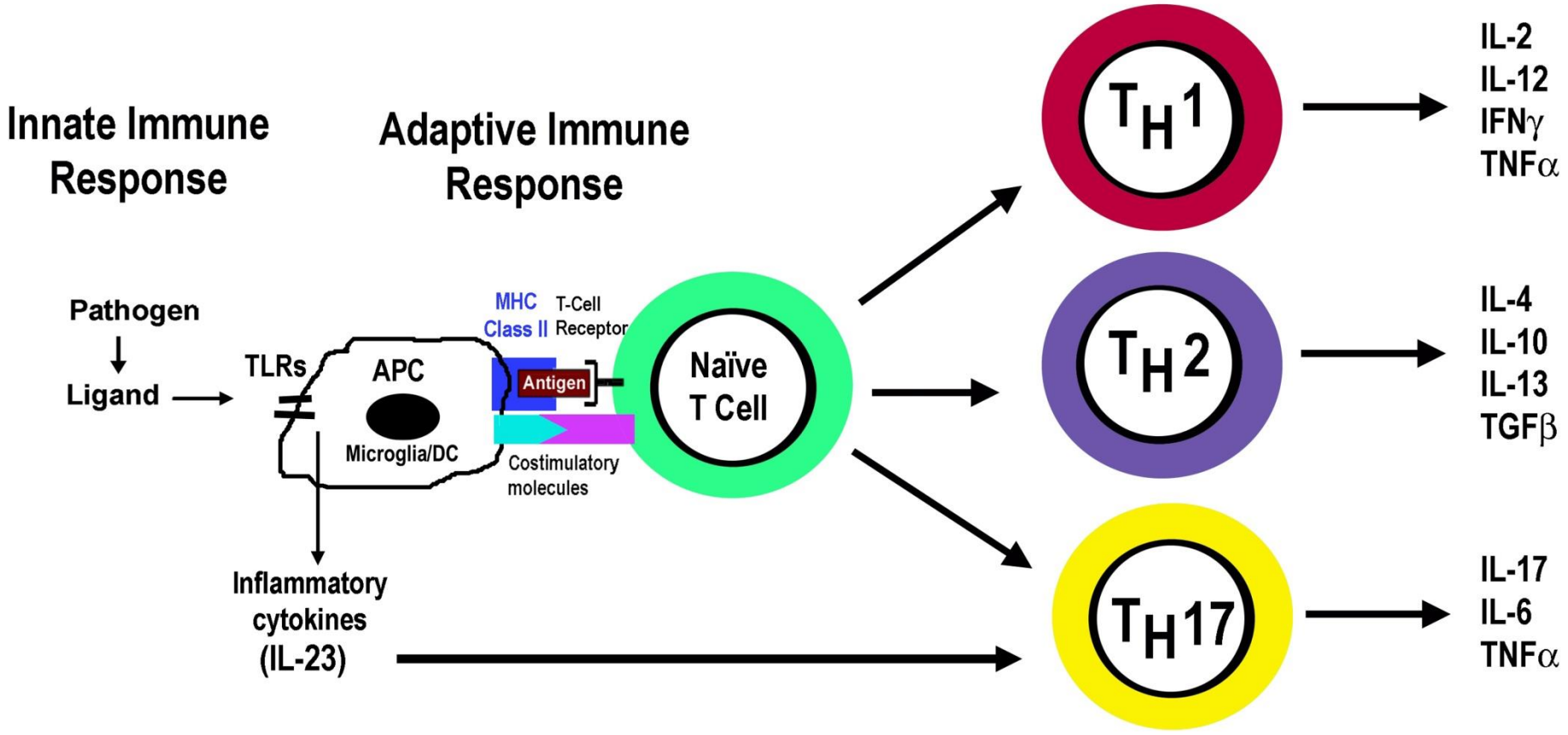
- Increase Vitamin D
- Decrease Saturated Fats
- Increase Intake of Vegetables
- Decrease Weight
- Decrease Air Pollution Exposure
- Increase Exercise

Pediatric MS Risk Factors Impact Immune Responses

Risk Factor Type	Inflam	Th1/Th17	Th1/Th2	Tcell Activation	TCR Subgroup Expansion	Vit D & Regulation of MHC
Environment Air Pollution	+			+		
Dietary Vit D BMI/Obesity Sat Fat	+	+		+		+
Endocrine Hormones			+			
Genetic MHC I MHC II MHC III TYK IL2Ra/CD25		+	+	+		+
Infectious Toll Receptor Super Ag Molec Mimic Cytokine (v) Microbiome		+		+	+	

Risk Factors Arising From Different Sources Promote Immune Activation—JR Hypothesis

Multiple Risk Factors Promote Autoimmunity



Risk Factors Arising From Different Sources Promote Immune Activation—JR Hypothesis

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