ASPETTI ETIO-PATOGENETICI, DIAGNOSTICI E TERAPEUTICI DELLA SCLEROSI MULTIPLA: LO STATO DELL'ARTE E I PREVEDIBILI SVILUPPI

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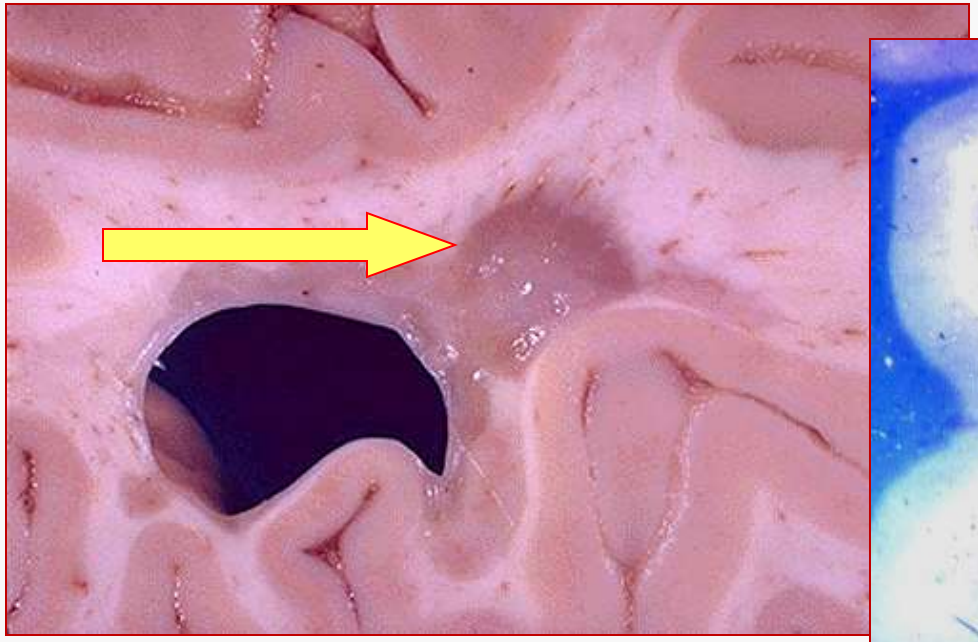
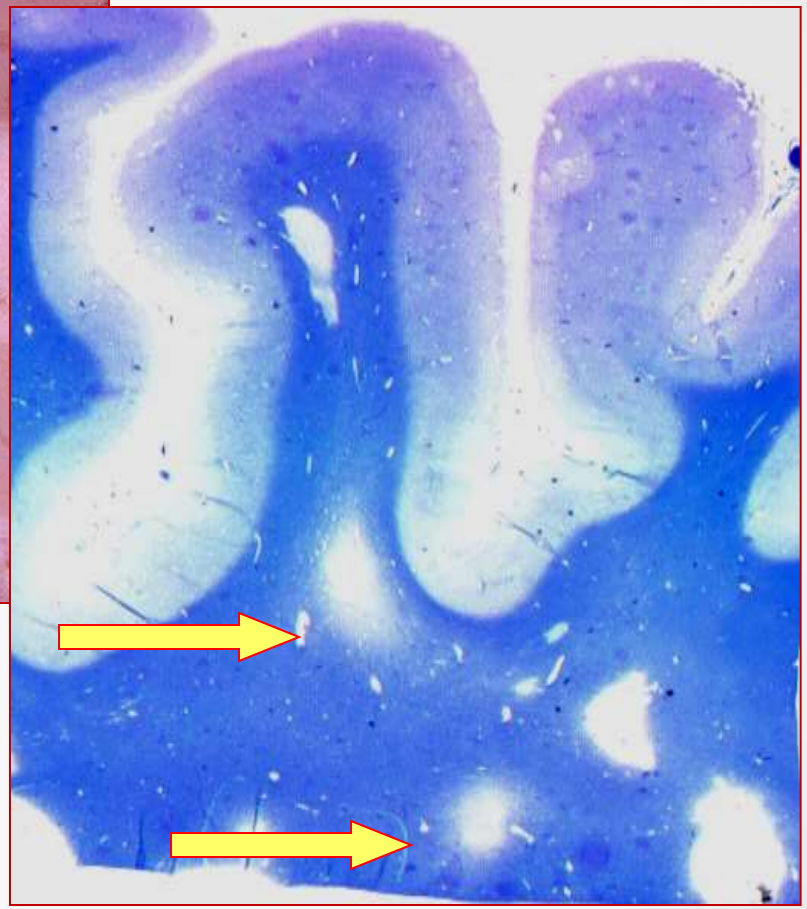
Dpt Scienze Mediche e Sanità Pubblica
Università di Cagliari

MULTIPLE SCLEROSIS



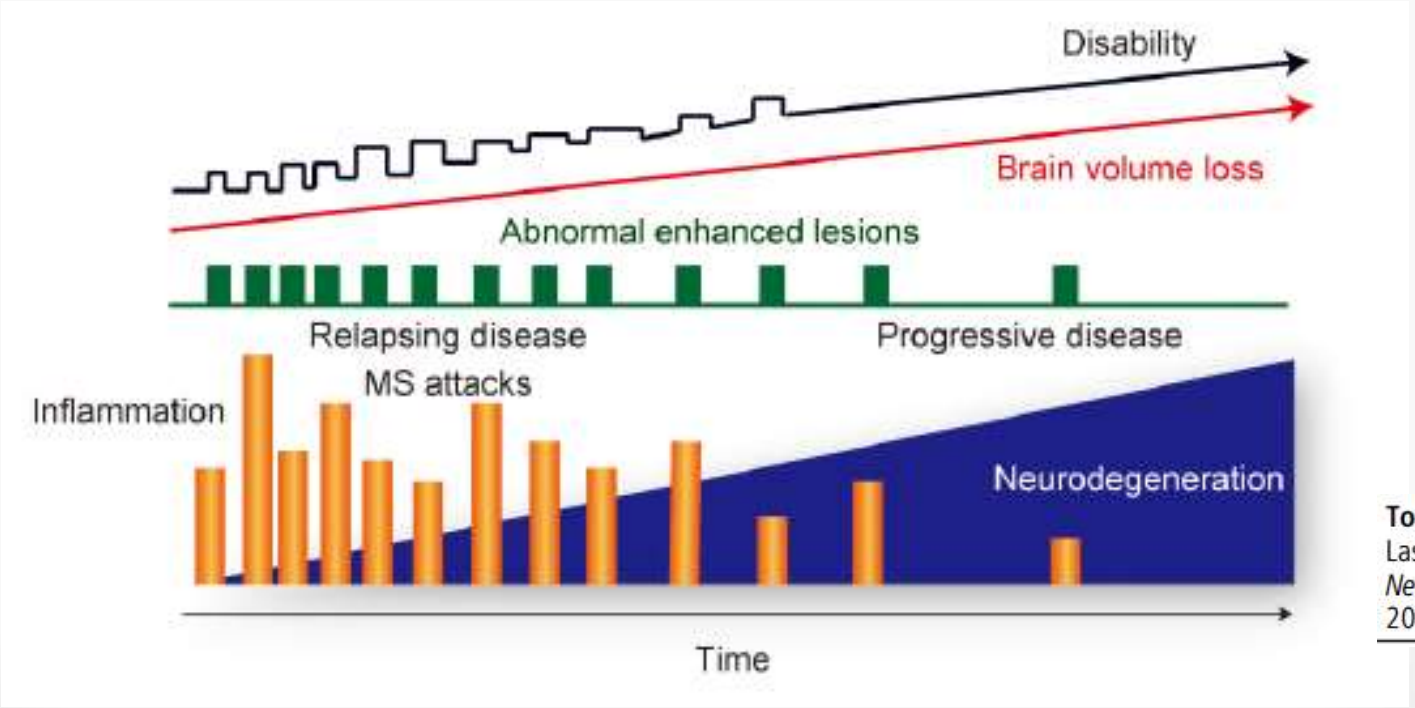
DEMYELINATING PLAQUES



MYELIN STAIN

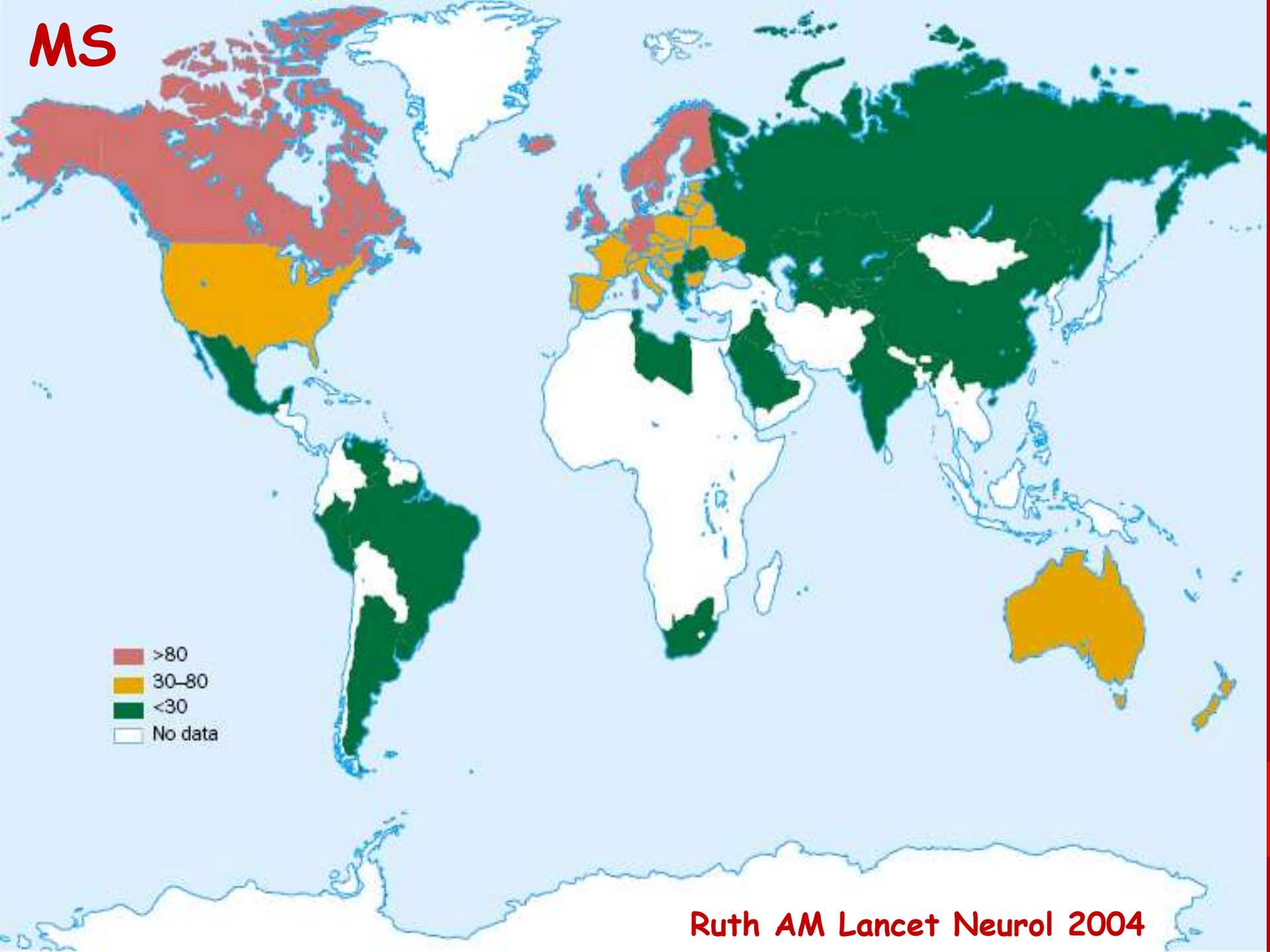
MULTIPLE SCLEROSIS FEATURES

- Autoimmune disease of CNS; a two stages disease: inflammation and neurodegeneration
- 4,000,000 people affected worldwide
- Women:men 2:1
- Age of disease onset: 20-30 ys (young adulthood)
- Neurological impairments: blindness, loss of sensation, lack of coordination, incontinence, paralysis
- Relapsing-remitting (80%); chronic progressive (10%); benign (10%)



To cite: Kawachi I, Lassmann H. *J Neurol Neurosurg Psychiatry* 2017;**88**:137–145.

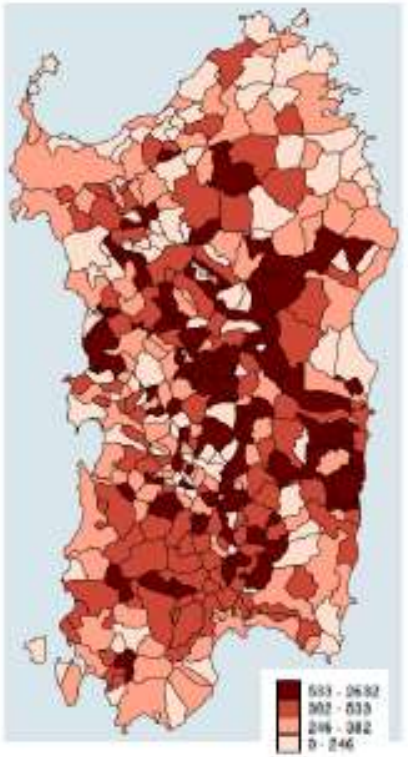
MS

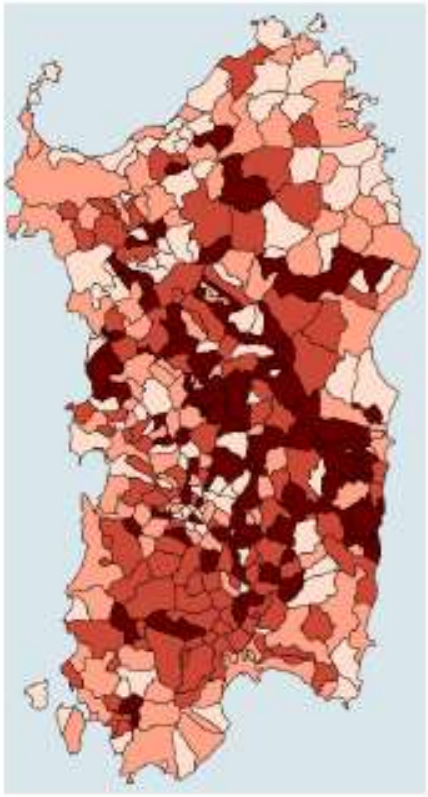


Ruth AM Lancet Neurol 2004

MS Prevalence rate (Pop rif ITA-ISTAT 2015) x 100,000

Asl di residenza	N	Tasso grezzo	Tasso adj età/genere	CI 95%		F		M	
						Tasso grezzo	Tasso adj età	Tasso grezzo	Tasso adj età
ASL 1 SS	334715	317	307	288	325	448.5	433.4	178.9	172.5
ASL 2 OT	159950	260	248	224	271	384.0	360.5	138.2	127.9
ASL 3 NU	158413	471	472	439	506	629.3	632.2	307.0	302.7
ASL 4 OG	57642	488	488	432	545	660.9	660.8	309.4	306.5
ASL 5 OR	162643	362	359	330	388	517.5	512.6	200.2	195.2
ASL 6 VS	100141	423	417	377	456	582.7	572.6	260.5	251.3
ASL 7 CI	127857	361	348	316	380	469.7	452.5	248.0	236.6
ASL 8 CA	561925	397	376	360	392	519.2	489.1	269.2	255.9
RAS	1663286	373	360	352	369	507.3	488.1	234.0	224.9





MS standarized ratio of prevalence rate (Pop rif Tuscany 2011; Bezzini D et al 2016)

Asl di residenza	Osservati	Attesi	SPR	CI 95%	
ASL 1 SS	1061	647	164	154	174
ASL 2 OT	415	307	135	122	149
ASL 3 NU	746	301	248	230	266
ASL 4 OG	281	109	257	228	289
ASL 5 OR	588	312	189	174	204
ASL 6 VS	424	192	220	200	242
ASL 7 CI	462	251	184	167	201
ASL 8 CA	2233	1096	204	195	212
RAS	6210	3217	193	188	198

RAS 2016

OPEN ACCESS Freely available online

PLoS one

Population Based Study of 12 Autoimmune Diseases in Sardinia, Italy: Prevalence and Comorbidity

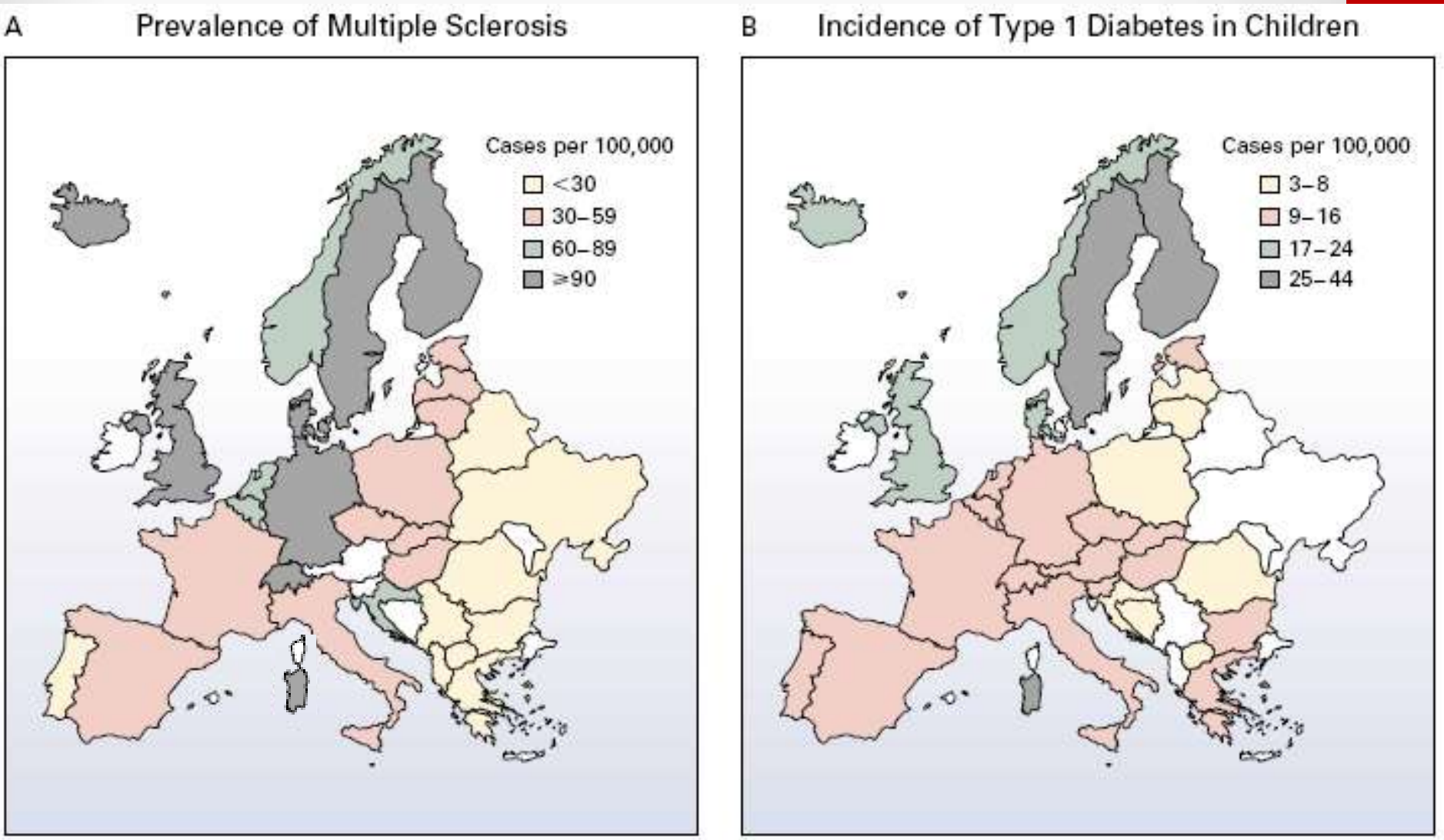
Claudia Sardu[1]*, Eleonora Cocco[2], Alessandra Mereu[1], Roberta Massa[1], Alessandro Cuccu[1], Maria Giovanna Marrosu[2], Paolo Contu[1]

Table 1. Absolute frequencies of people with zero, one, or more than one autoimmune diseases.

	Number of autoimmune diseases		
	0	1	>1
TOTAL SAMPLE (N = 25885)	24,585	1,243	57
WOMEN (N = 14167)	13,186	934	47
MEN (N = 11718)	11,399	309	10

Table 2. Prevalence of each autoimmune disease per 100000 people.

	Prevalence per 10^5	95% C.I.
Autoimmune thyroiditis	2,619	2426–2824
Psoriasis/psoriatic arthritis	939	824–1065
Rheumatoid arthritis	552	466–651
Type 1 diabetes	464	384–554
Multiple sclerosis	224	170–290
Ulcerative colitis	124	85–175
Celiac disease	124	85–175
Systemic lupus erythematosus	81	50–124
Myasthenia gravis	35	16–66
Systemic sclerosis	35	16–66
Sjogren's syndrome	31	13–61
Crohn's disease	15	4–40



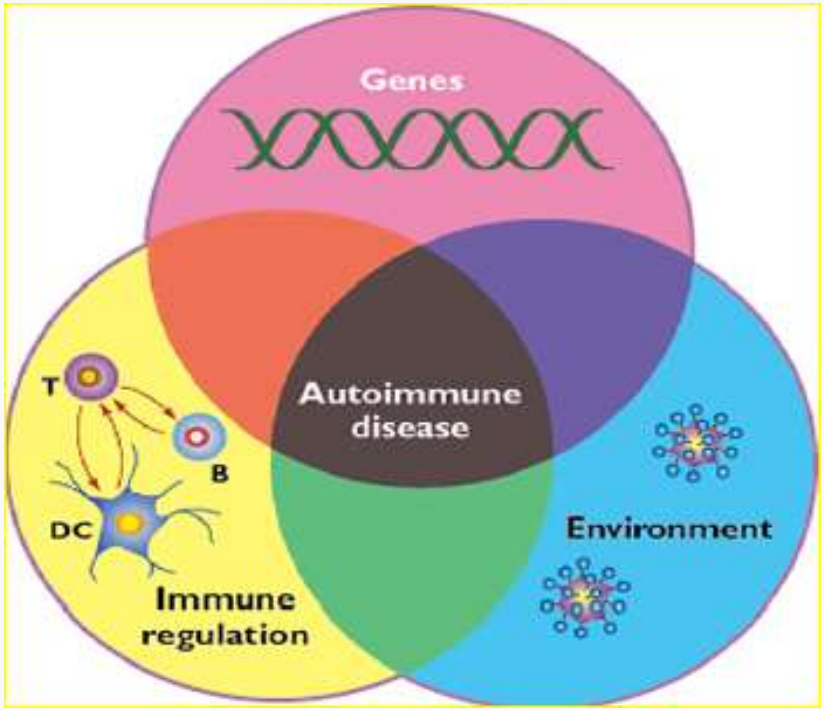
Bach JF NEJM 2002

Patients with multiple sclerosis and risk of type 1 diabetes mellitus in Sardinia, Italy: a cohort study

Maria Giovanna Marrosu, Eleonora Cocco, Marina Lai, Gabriella Spinicci, Maria Paola Pischedda, Paolo Contu

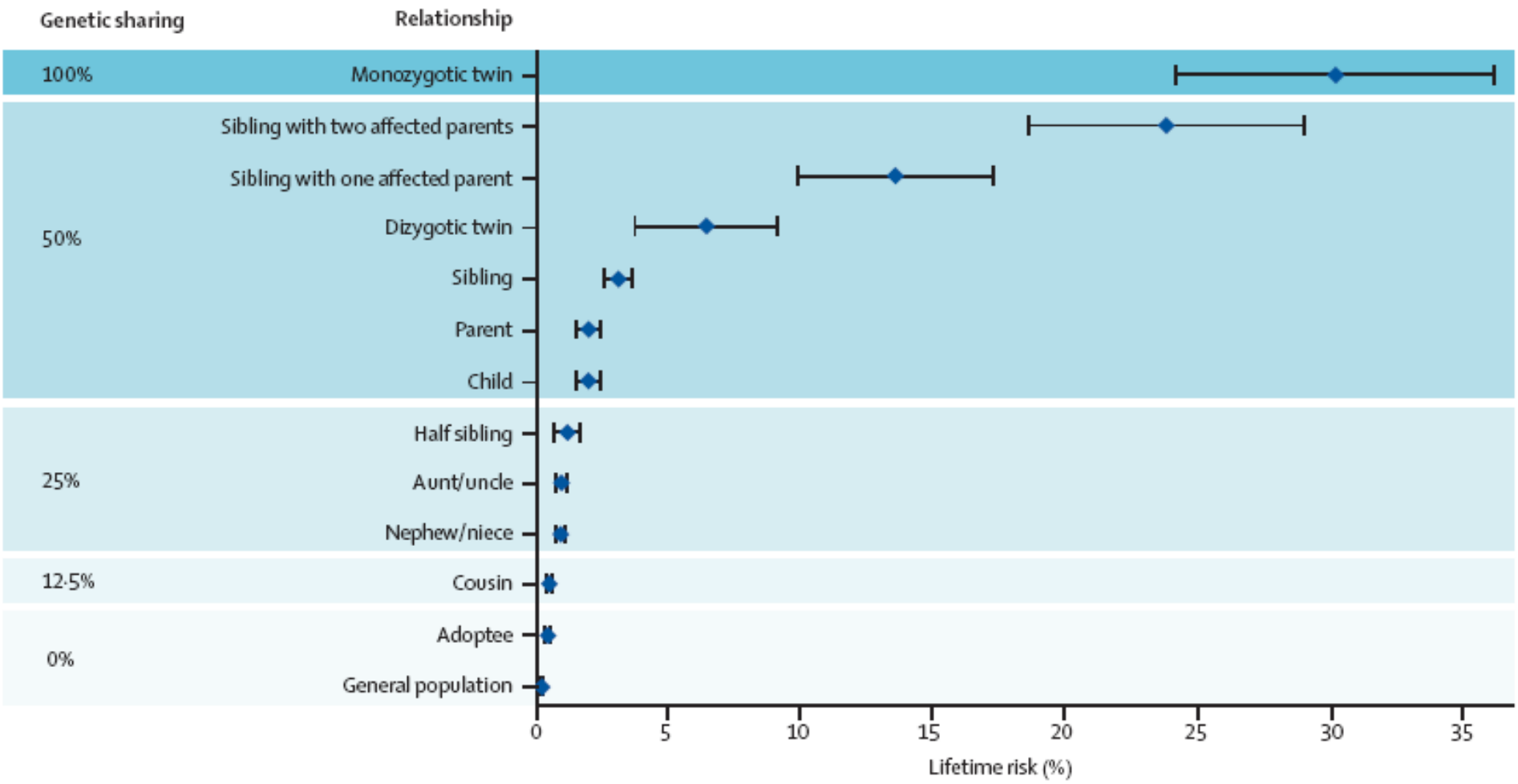
Lancet 2002; 359: 1461–65

MS is a multifactoriol disorder



Contribution:

1. Genes
2. Environment
3. Interaction Genes/environment



Compston A and Coles A The Lancet 2008

Quante varianti di suscettibilita' agiscono nella predisposizione alla SM

- Ipotesi della malattia comune/varianti comuni:

20-100 alleli comuni che determinano un rischio modesto sono sufficienti

- Modello delle multiple varianti rare:

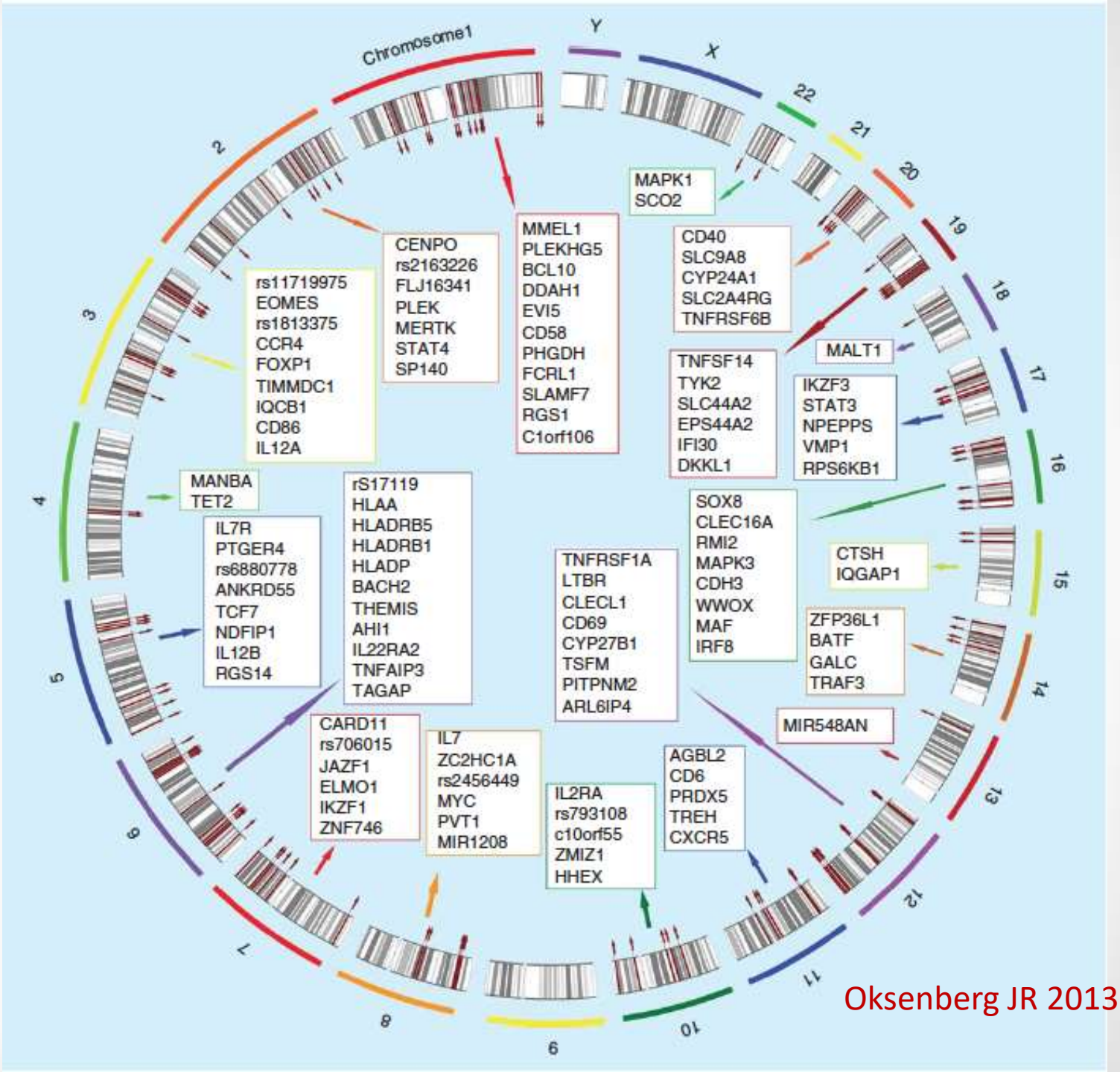
numerosissime (centinaia/migliaia) sono necessarie

POSSIBILE SCENARIO

✓Circa 100 varianti comuni con una bassa penetranza possono giustificare la maggior parte della suscettibilità genetica alla SM

✓Una piccola proporzione di malattia e' determinata da varianti rare ma con una penetranza maggiore.

Yang and al., 2005; Sawcer S 2008



Oksenberg JR 2013

Eureka!!

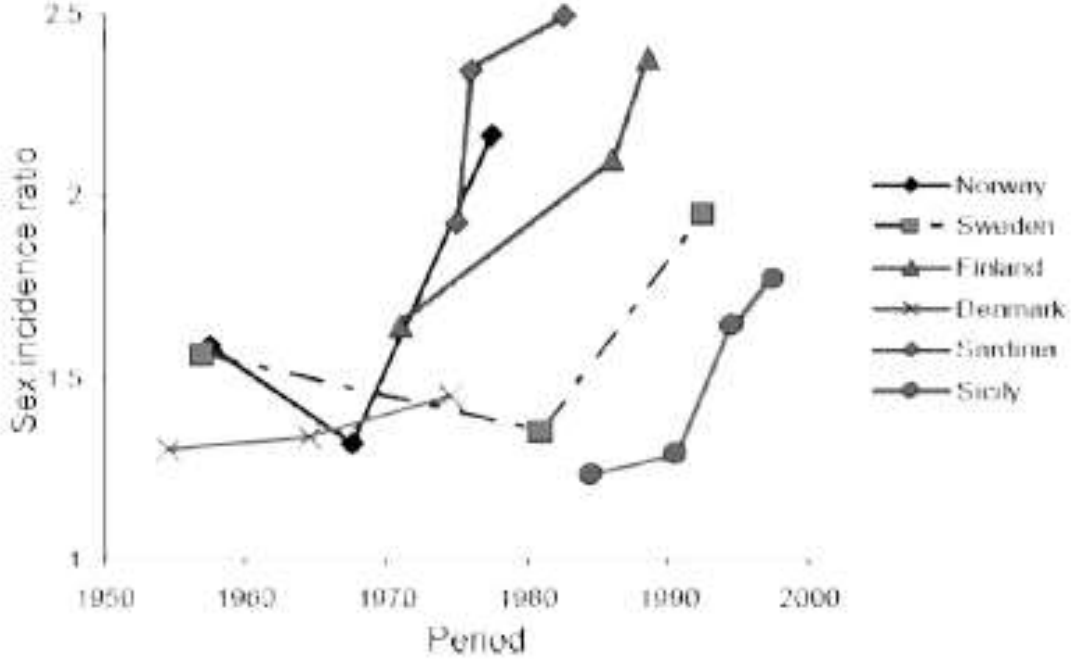
Ho scoperto il gene che ci fa pensare che tutto sia determinato da geni

Temporal trends in the incidence of multiple sclerosis

A systematic review

Alvaro Alonso, MD
Miguel A. Hernán, MD

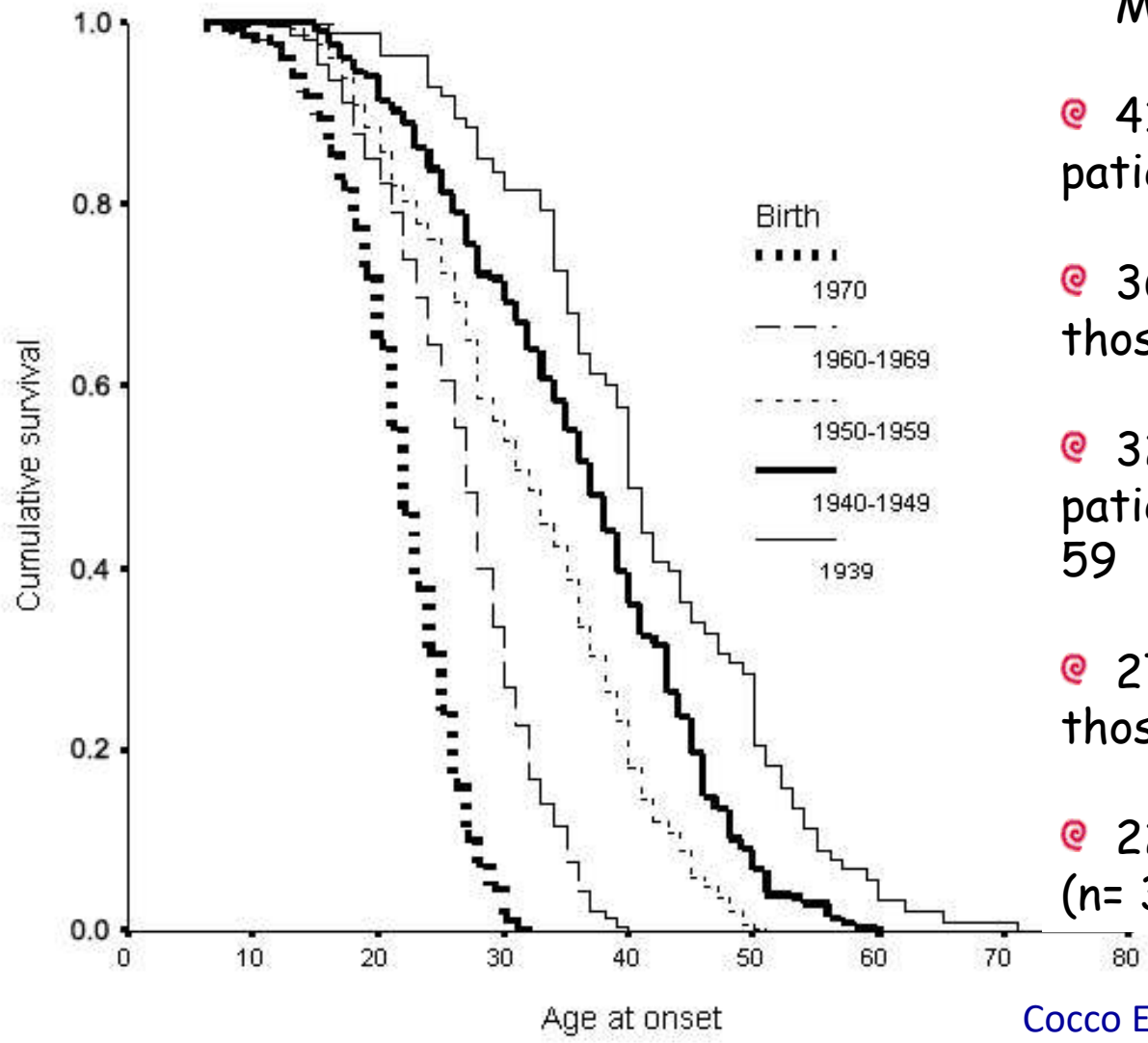
Neurology® 2008;71:129-135



Sex (female-to-male) incidence rate ratio of multiple sclerosis by study year and region

ANTICIPATION OF AGE AT ONSET:

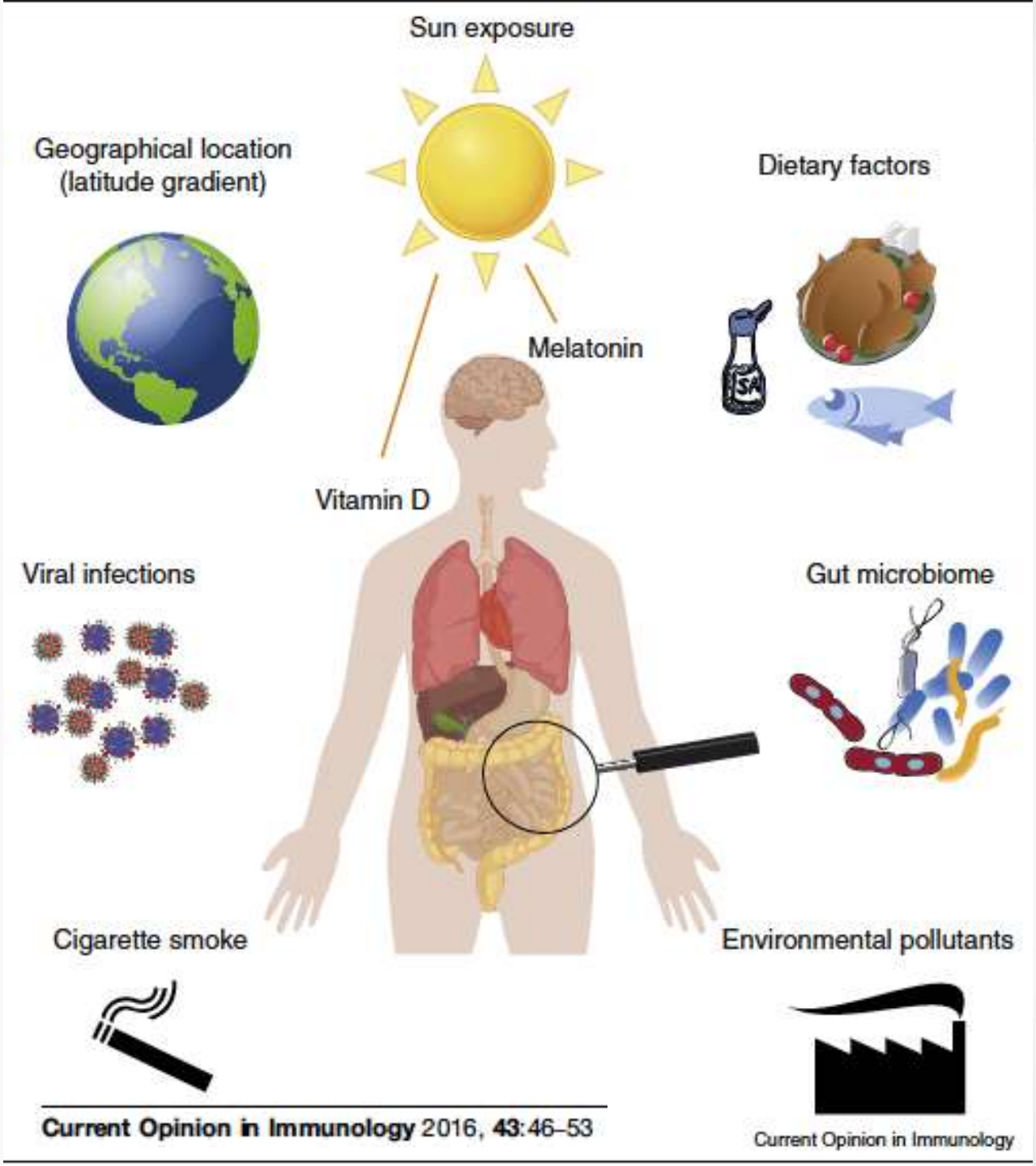
Survival analysis of 1500 Sardinian patients showed a progressively earlier age-at-onset (log rank t
778,27, p< 0.0001) moving from the oldest to the most recent decade of birth.



Mean age at onset was :

- 41 years (95% CI 39-44) in patients (n= 88) born in 1913-39
- 36 years (95% CI 35-37) in those (n= 209) born in 1940-49
- 32 years (95% CI 31-33) in patients (n= 352) born in 1950-59
- 27 years (95% CI 26-27) in those (n= 487) born in 1960-69
- 22 (95% CI 21-22) in patients (n= 347) born from 1970 on.

Cocco E et al Neurology 2004



Current Opinion in Immunology 2016, **43**:46–53

RESEARCH ARTICLE

Is Geo-Environmental Exposure a Risk Factor for Multiple Sclerosis? A Population-Based Cross-Sectional Study in South-Western Sardinia

Maria Cristina Monti[1☯]*, Davide Guido[1☯], Cristina Montomoli[1], Claudia Sardu[2], Alessandro Sanna[3], Salvatore Pretti[3], Lorena Lorefice[2], Maria Giovanna Marrosu[4], Paolo Valera[3‡], Eleonora Cocco[2‡]

PLOS ONE | DOI:10.1371/journal.pone.0163313 September 26, 2016

Association of *Mycobacterium avium* subsp. *paratuberculosis* with Multiple Sclerosis in Sardinian Patients

Davide Cossu[1], Eleonora Cocco[2], Daniela Paccagnini[1], Speranza Masala[1], Niyaz Ahmed[3,4], Jessica Frau[2], Maria Giovanna Marrosu[2], Leonardo A. Sechi[1]*

PLoS ONE 6(4): e18482.

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Mycobacterium avium subsp. paratuberculosis and multiple sclerosis in Sardinian patients: epidemiology and clinical features

Multiple Sclerosis Journal
19(11) 1437–1442

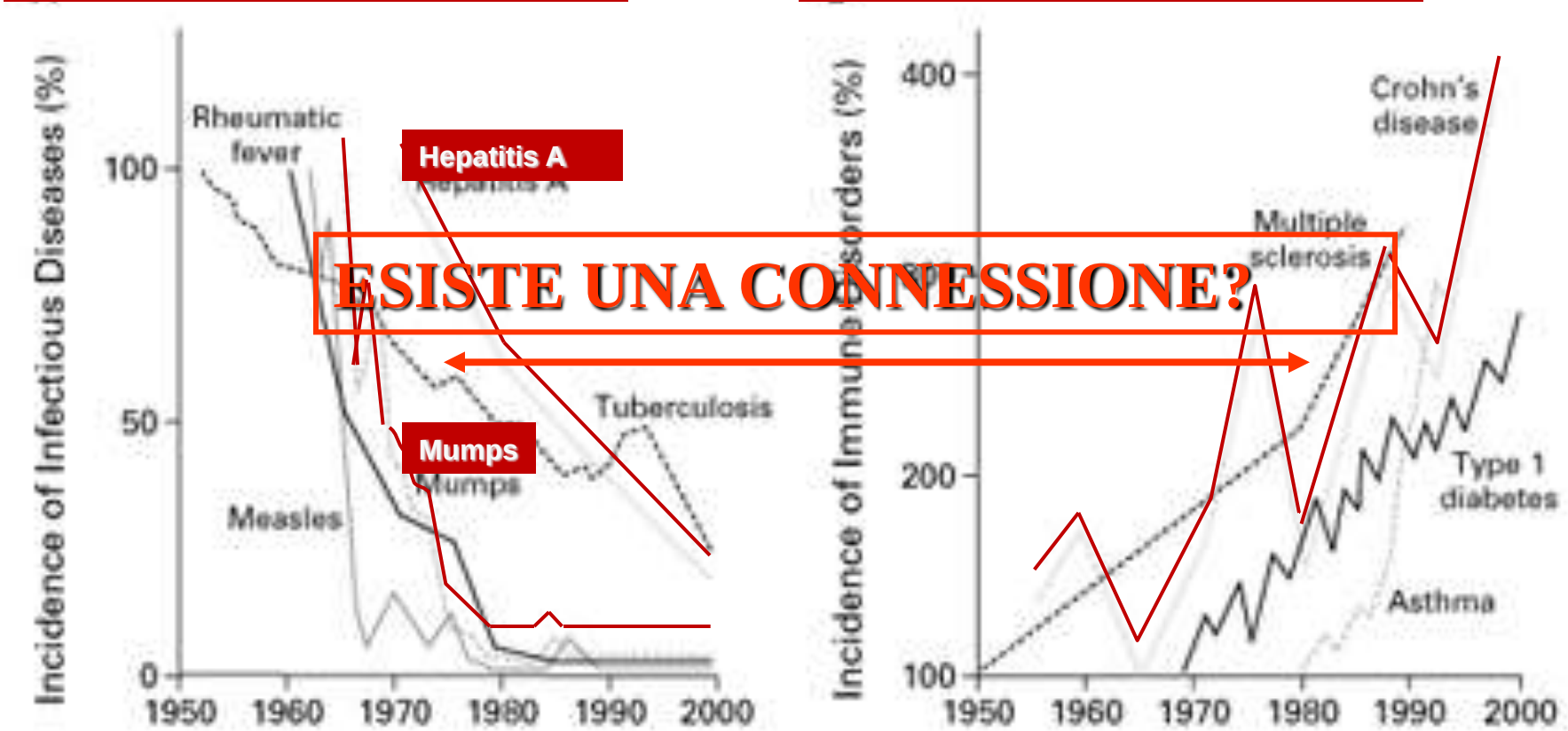
DOI: 10.1177/1352458513477926
msj.sagepub.com
SAGE

J Frau[1], D Cossu[2], G Coghe[1], L Lorefice[1], G Fenu[1], M Melis[1], D Paccagnini[2], C Sardu[3], MR Murru[1], S Tranquilli[1], MG Marrosu[1], LA Sechi[2] and E Cocco[1]

Table 1. Presence of anti-MAP2694 antibodies and/or MAPDNA in MS patients and HCs.

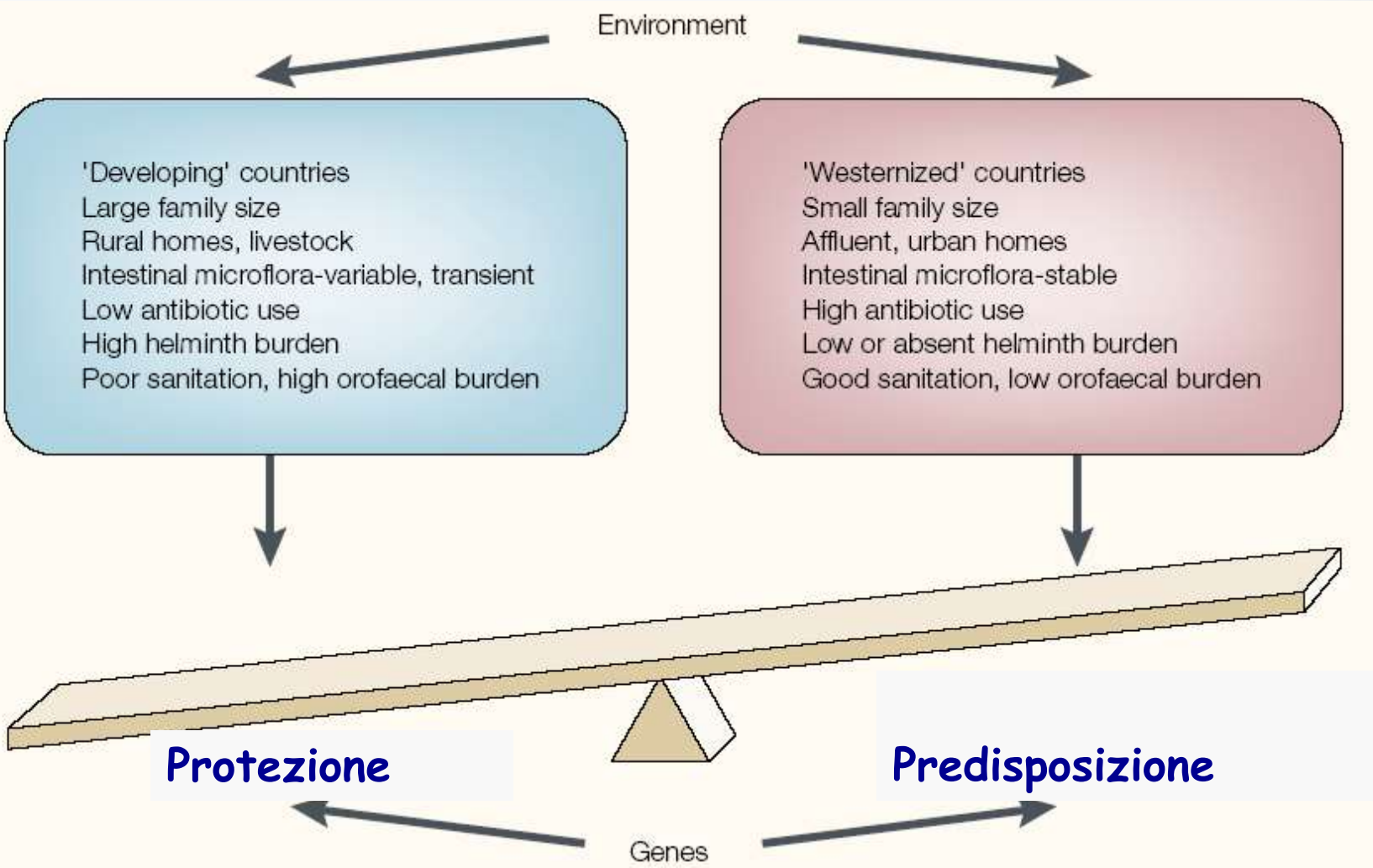
Test z	Patients	HCs	
MAP2694	123 (33.7%)	10 (3.8%)	$p = 2.59 \times 10^{-23}$
MAPDNA	68 (15.5%)	6 (2.3%)	$p = 1.14 \times 10^{-11}$
MAP2694 and MAPDNA	20 (4.5%)	0	$p = 4.68 \times 10^{-6}$

Ipotesi Igienica: Cambiamento proporzionale nell'incidenza delle classiche malattie infettive e delle malattie immuni,
Dal 1950 al 2000, US



Bach JF et al. *NEJM*, 2002

FATTORI ETIOLOGICI: GENI E AMBIENTE



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 27, 2017 VOL. 376 NO. 17

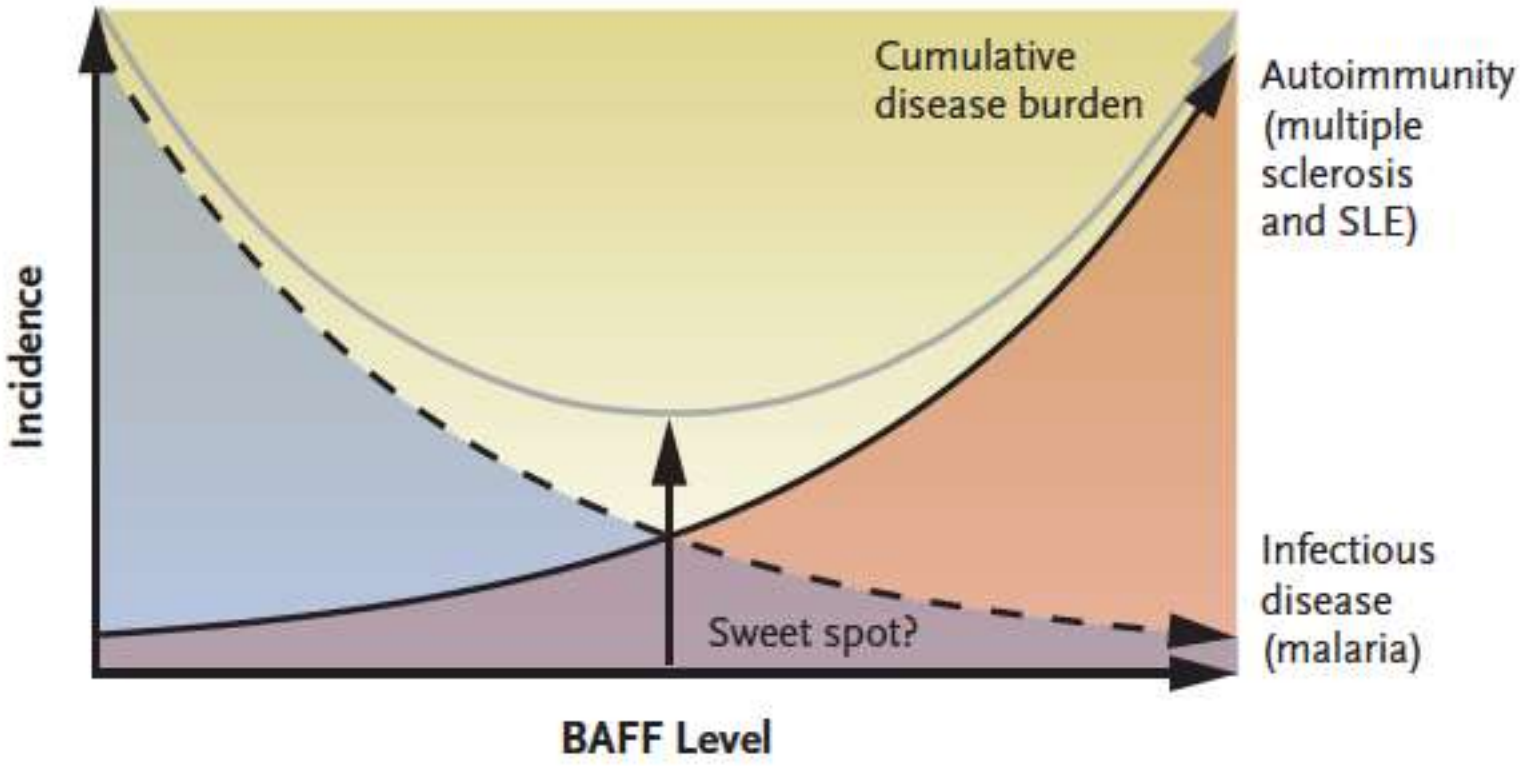
Overexpression of the Cytokine BAFF and Autoimmunity Risk

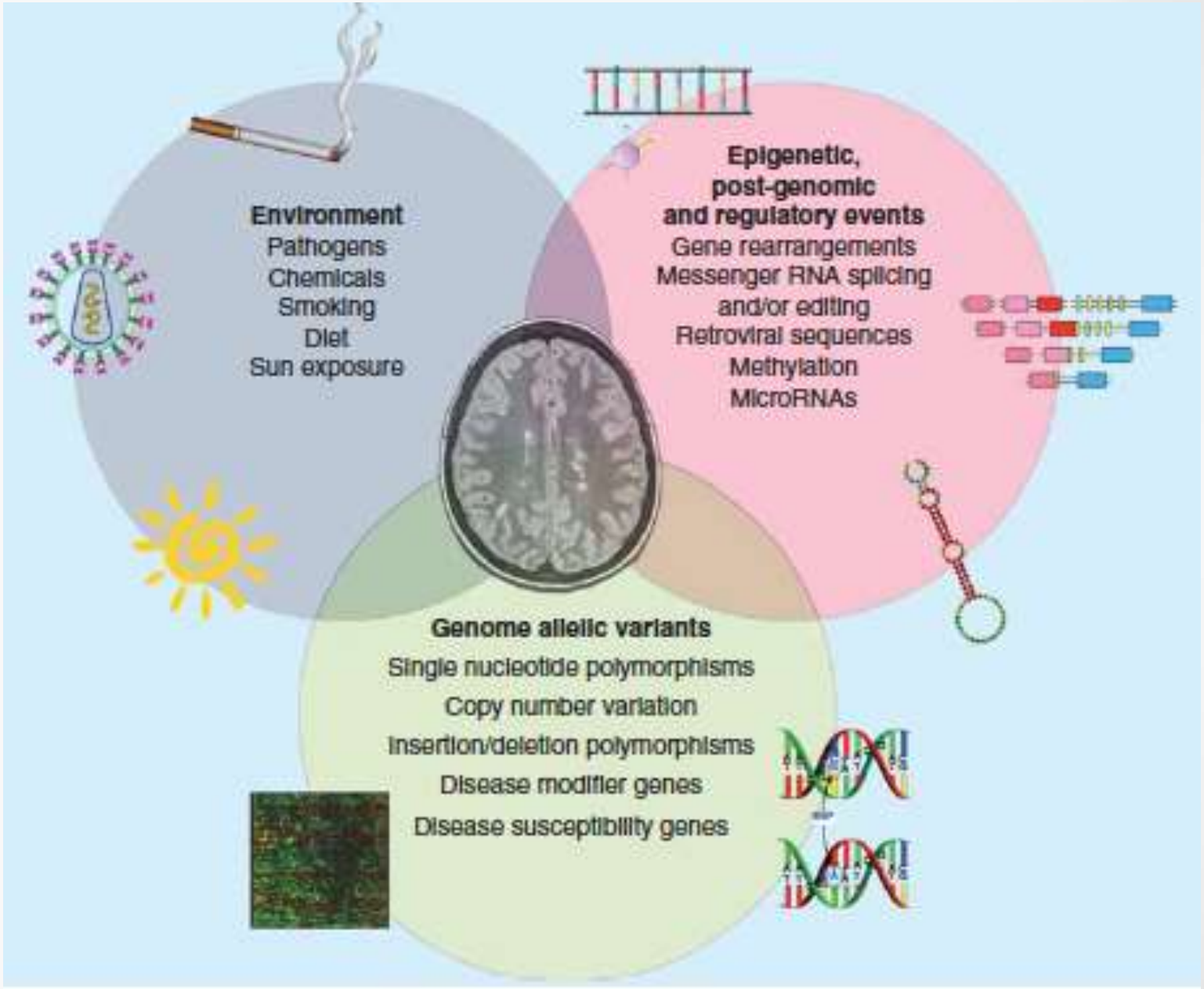
M. Steri, V. Orrù, M.L. Idda, M. Pitzalis, M. Pala, I. Zara, C. Sidore, V. Faà, M. Floris, M. Deiana, I. Asunis, E. Porcu, A. Mulas, M.G. Piras, M. Lobina, S. Lai, M. Marongiu, V. Serra, M. Marongiu, G. Sole, F. Busonero, A. Maschio, R. Cusano, G. Cuccuru, F. Deidda, F. Poddie, G. Farina, M. Dei, F. Virdis, S. Olla, M.A. Satta, M. Pani, A. Delitala, E. Cocco, J. Frau, G. Coghe, L. Lorefice, G. Fenu, P. Ferrigno, M. Ban, N. Barizzone, M. Leone, F.R. Guerini, M. Piga, D. Firinu, I. Kockum, I. Lima Bomfim, T. Olsson, L. Alfredsson, A. Suarez, P.E. Carreira, M.J. Castillo-Palma, J.H. Marcus, M. Congia, A. Angius, M. Melis, A. Gonzalez, M.E.A. Riquelme, B.M. da Silva, M. Marchini, M.G. Danieli, S. Del Giacco, A. Mathieu, A. Pani, S.B. Montgomery, G. Rosati,* J. Hillert, S. Sawcer, S. D'Alfonso, J.A. Todd, J. Novembre, G.R. Abecasis, M.B. Whalen, M.G. Marrosu, A. Meloni, S. Sanna, M. Gorospe, D. Schlessinger, E. Fiorillo, M. Zoledziewska, and F. Cucca

A BAFFling Association between Malaria Resistance and the Risk of Multiple Sclerosis

Thomas Korn, M.D., and Mohamed Oukka, Ph.D.

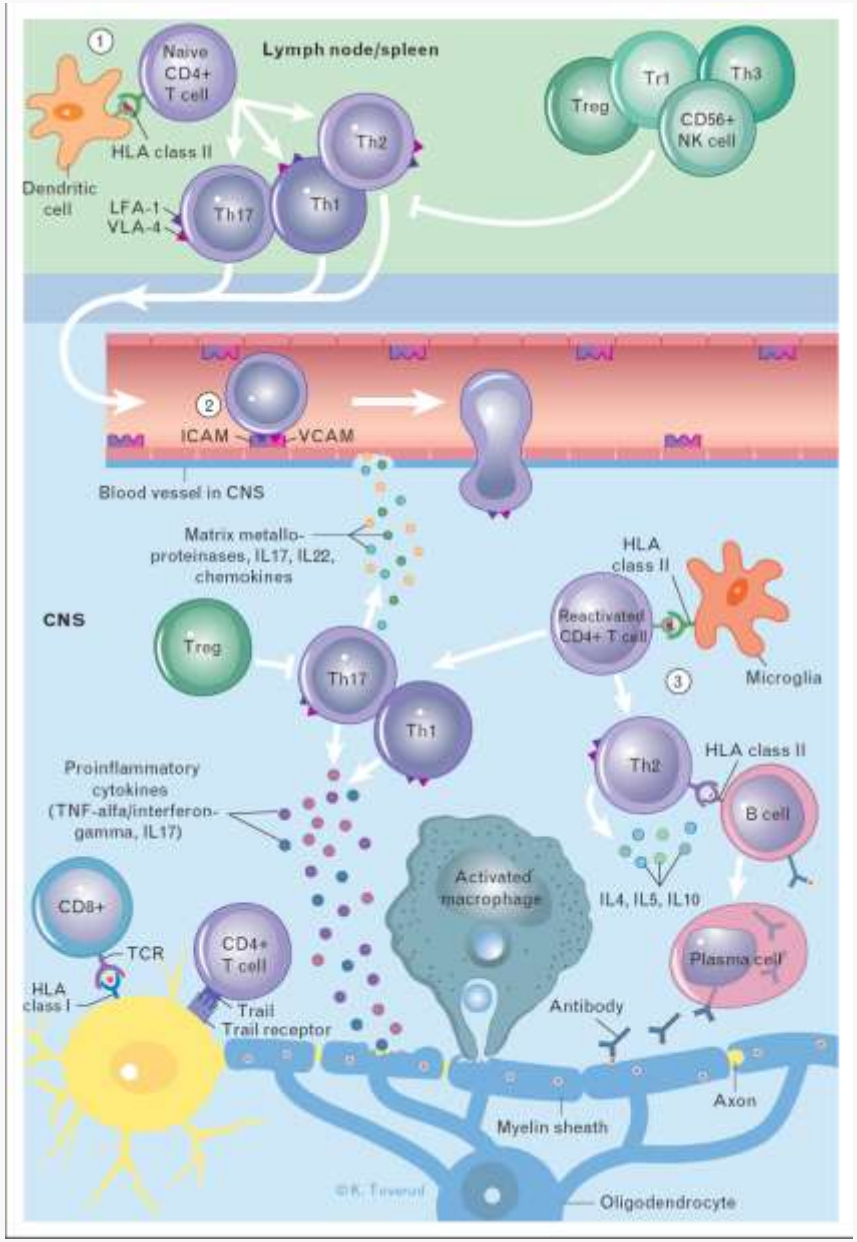
N ENGL J MED 376;17 NEJM.ORG APRIL 27, 2017



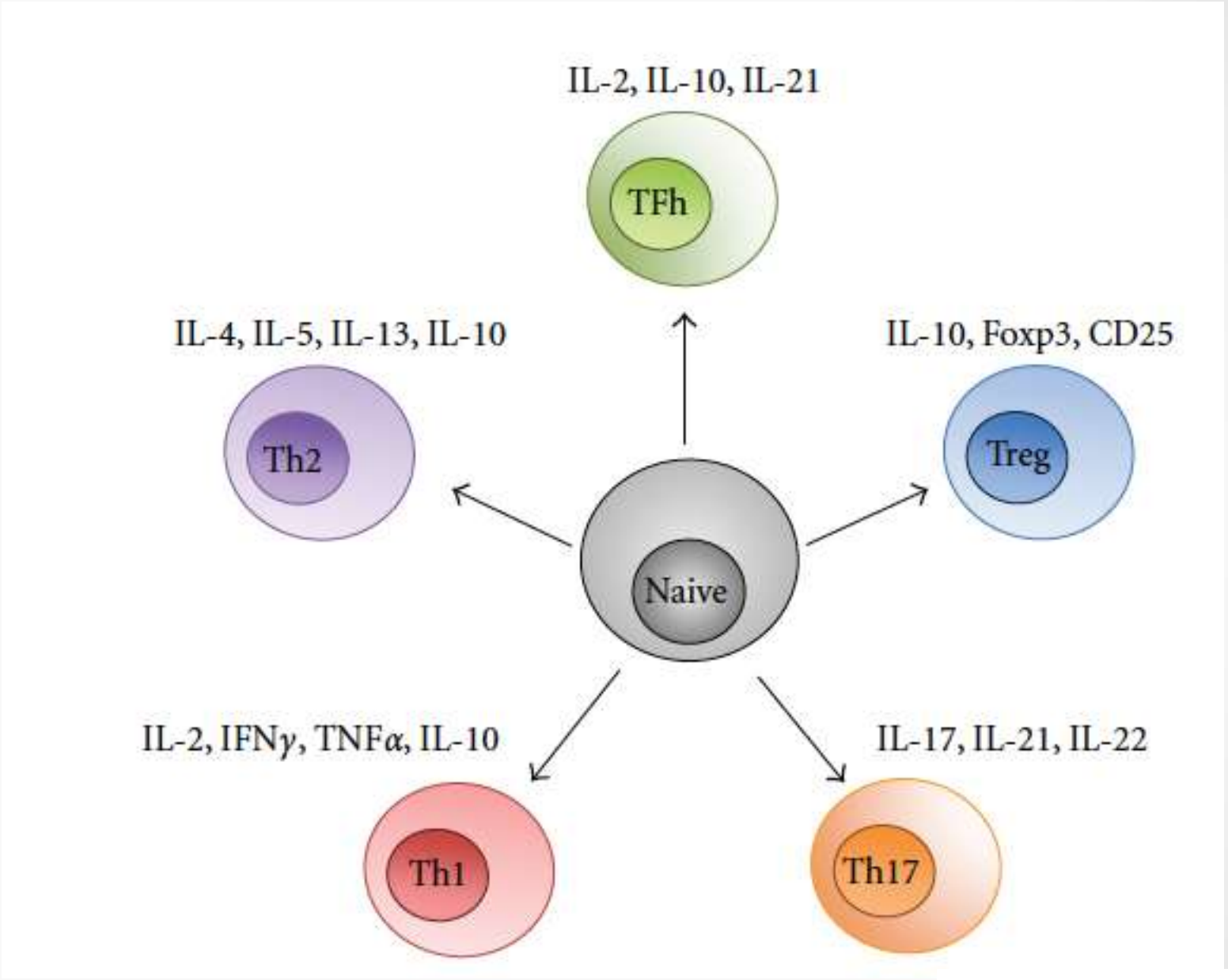


Oksenberg JR 2013

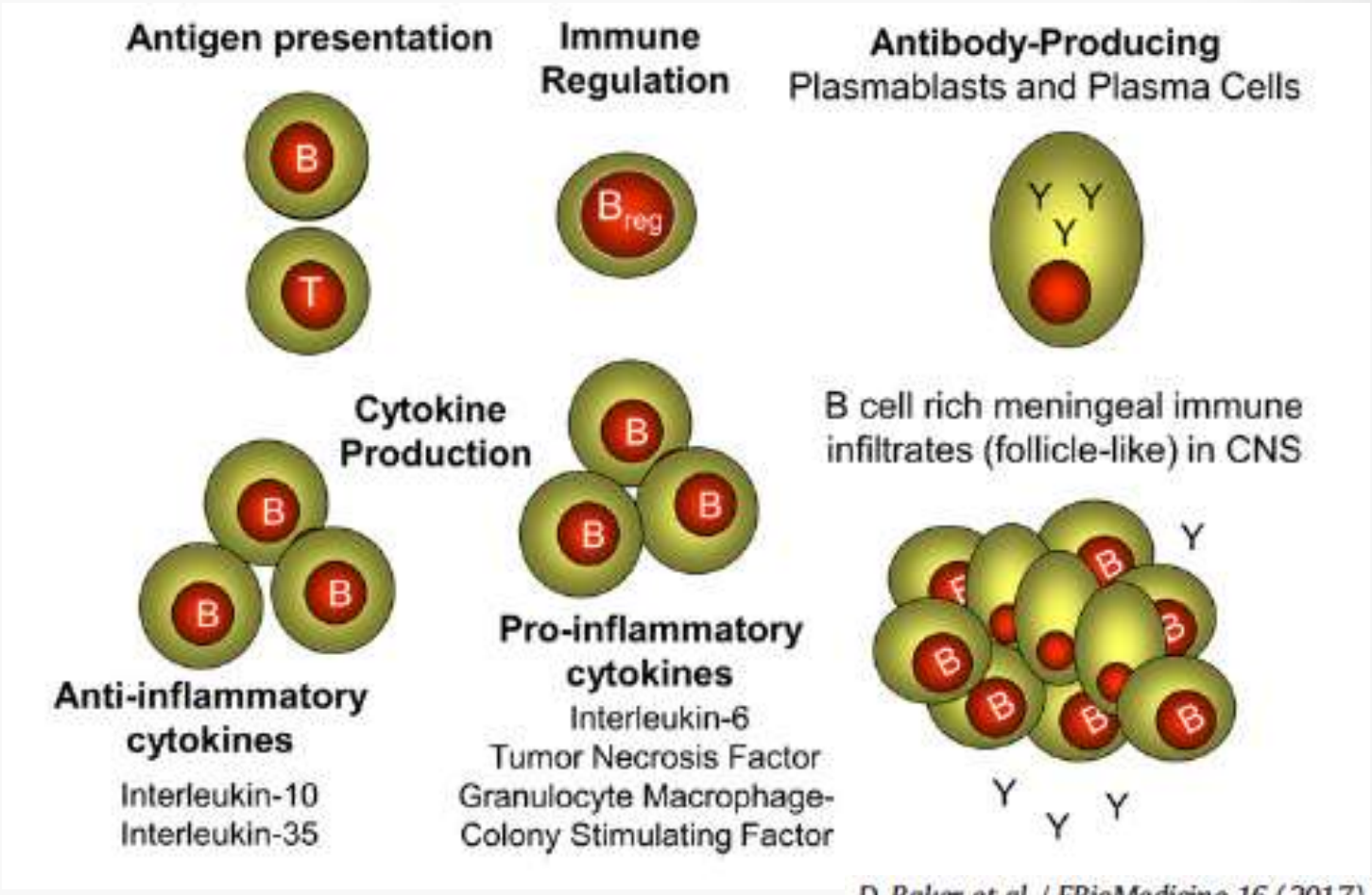
La SM è una malattia autoimmune



Holmoy T 2008



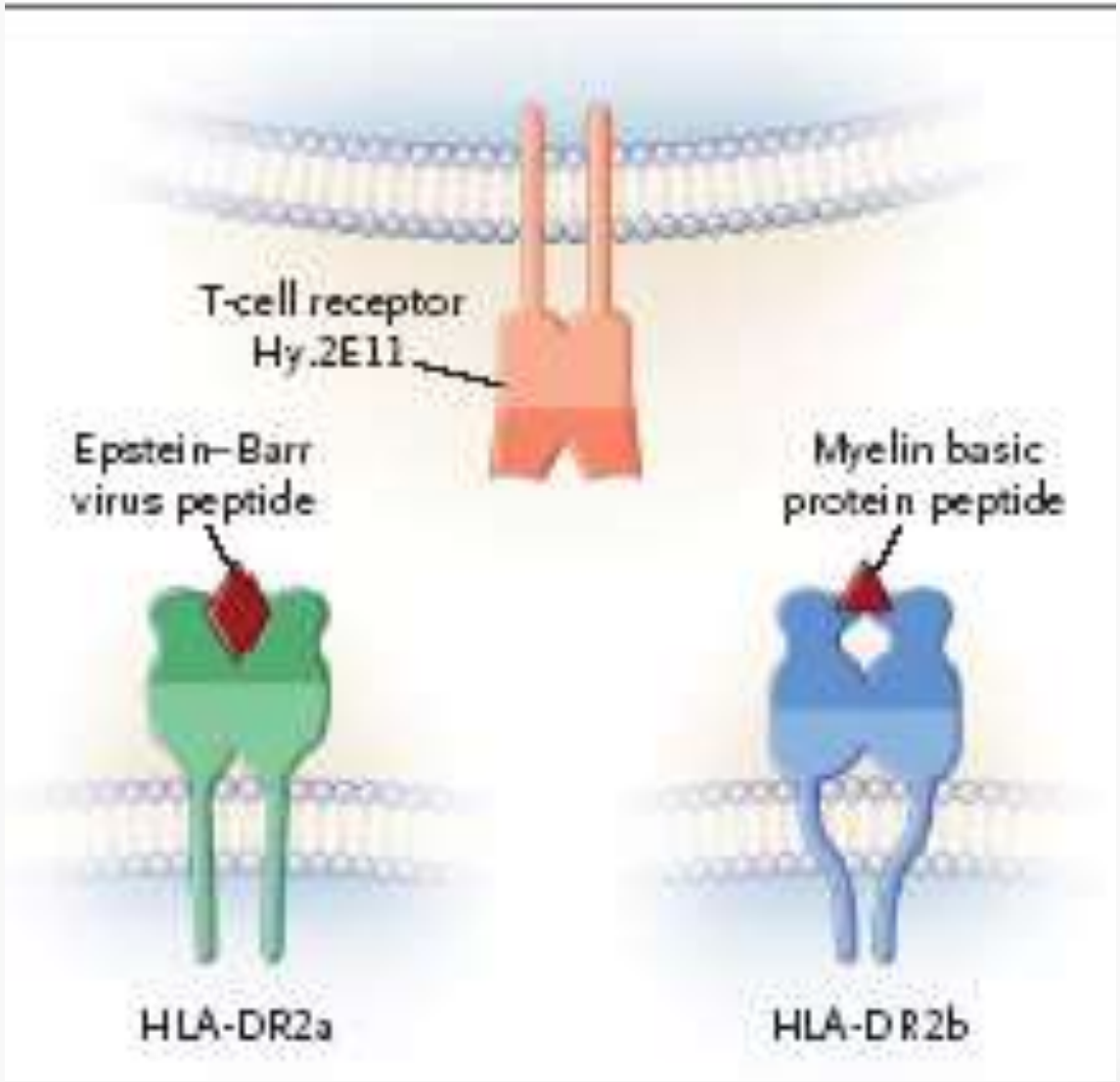
Wootla et al 2012



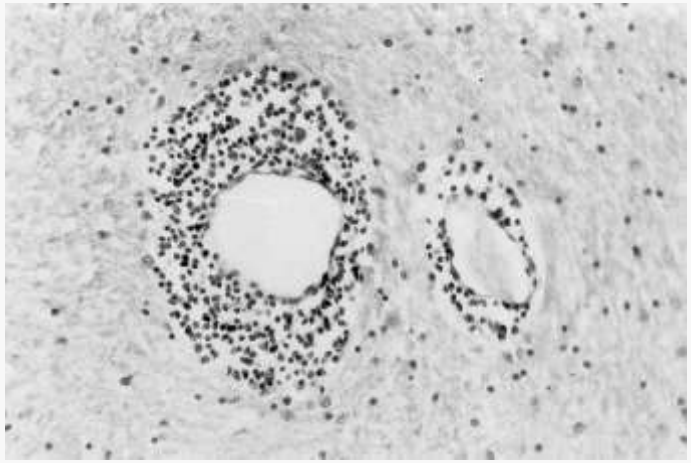
D. Baker et al. / EBioMedicine 16 (2017) 41–50

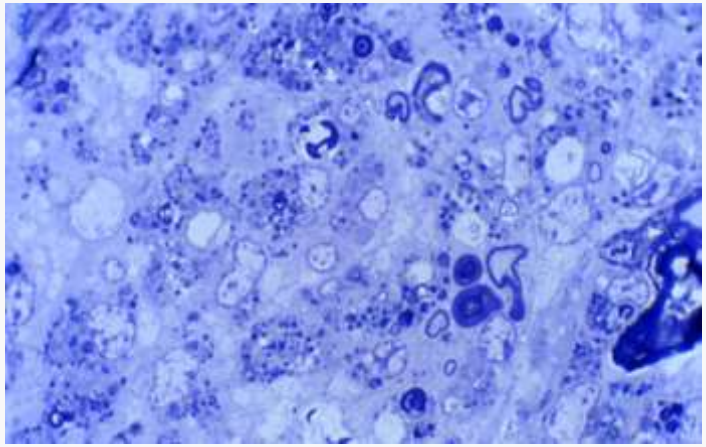
Molecular Mimicry in Multiple Sclerosis

Hartmut Wekerle, M.D., and Reinhard Hohlfeld, M.D.



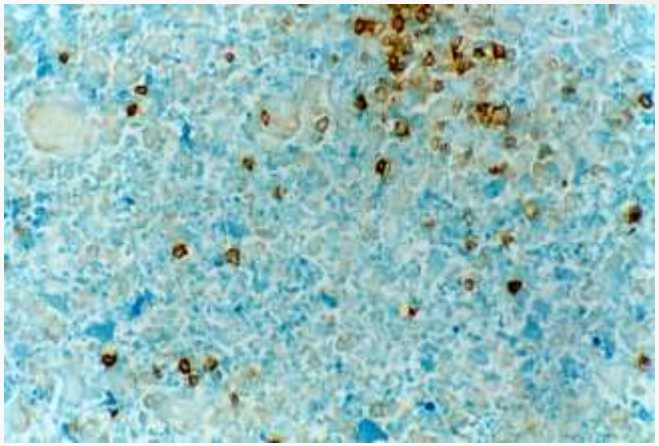
Infiltrato infiammatorio perivasale in in una lesione

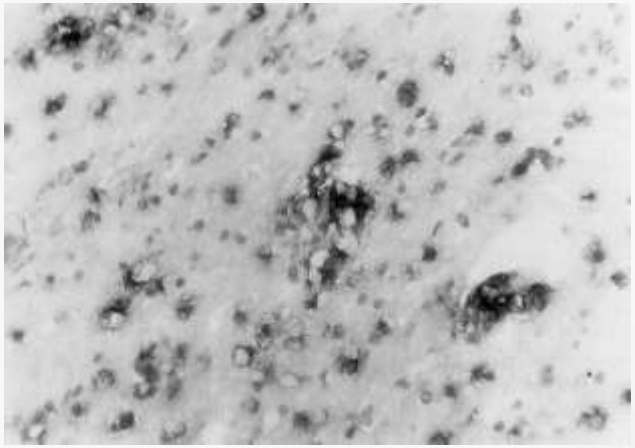




Diffusa infiltrazione macrofagica/microgliale in una placca precoce attiva

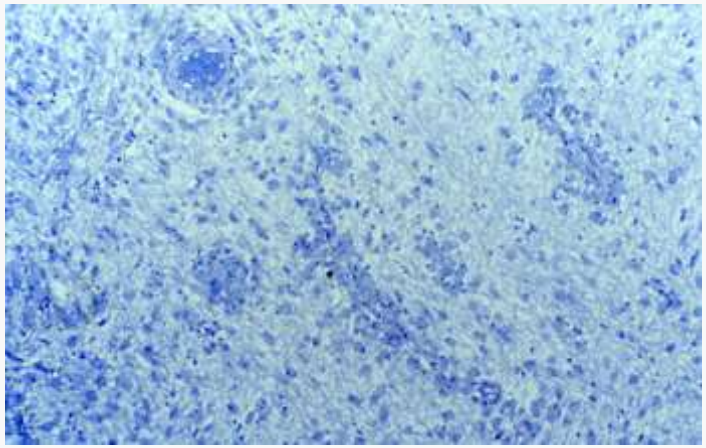
Infiltrato infiammatorio di linfociti T CD4



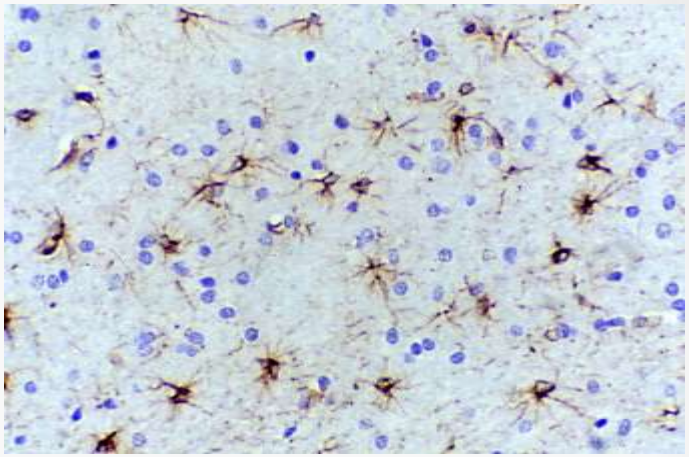


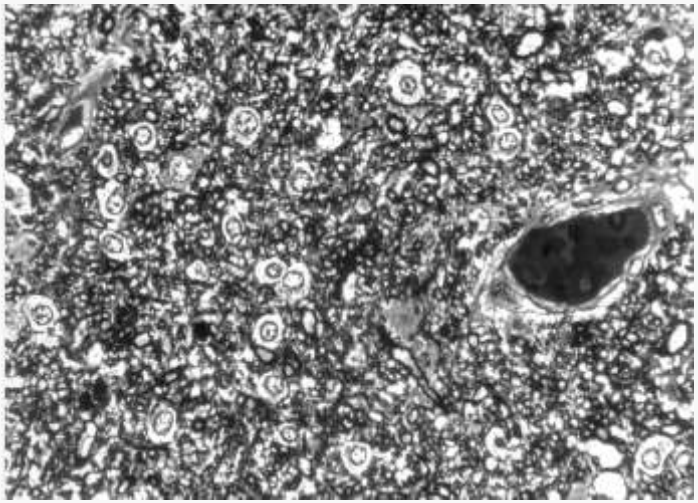
Macrofagi HLA-DR positivi in una placca attiva precoce

Placca cronica attiva, con infiammazione perivascolare e gliosi diffusa

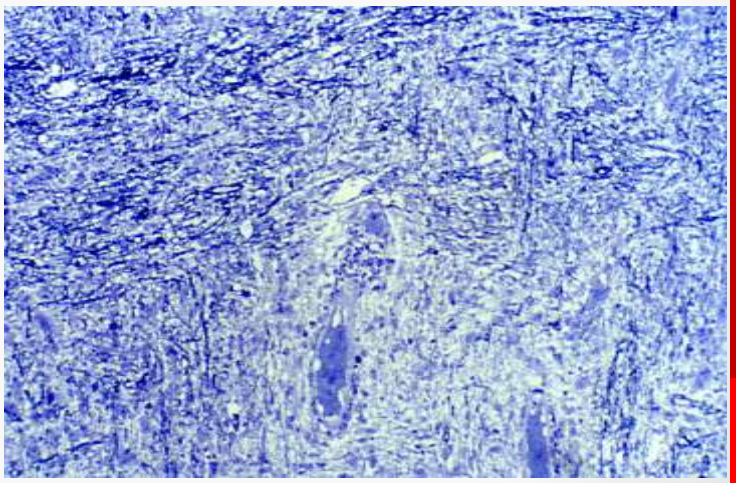


Gliosi in una placca di demielinizzazione

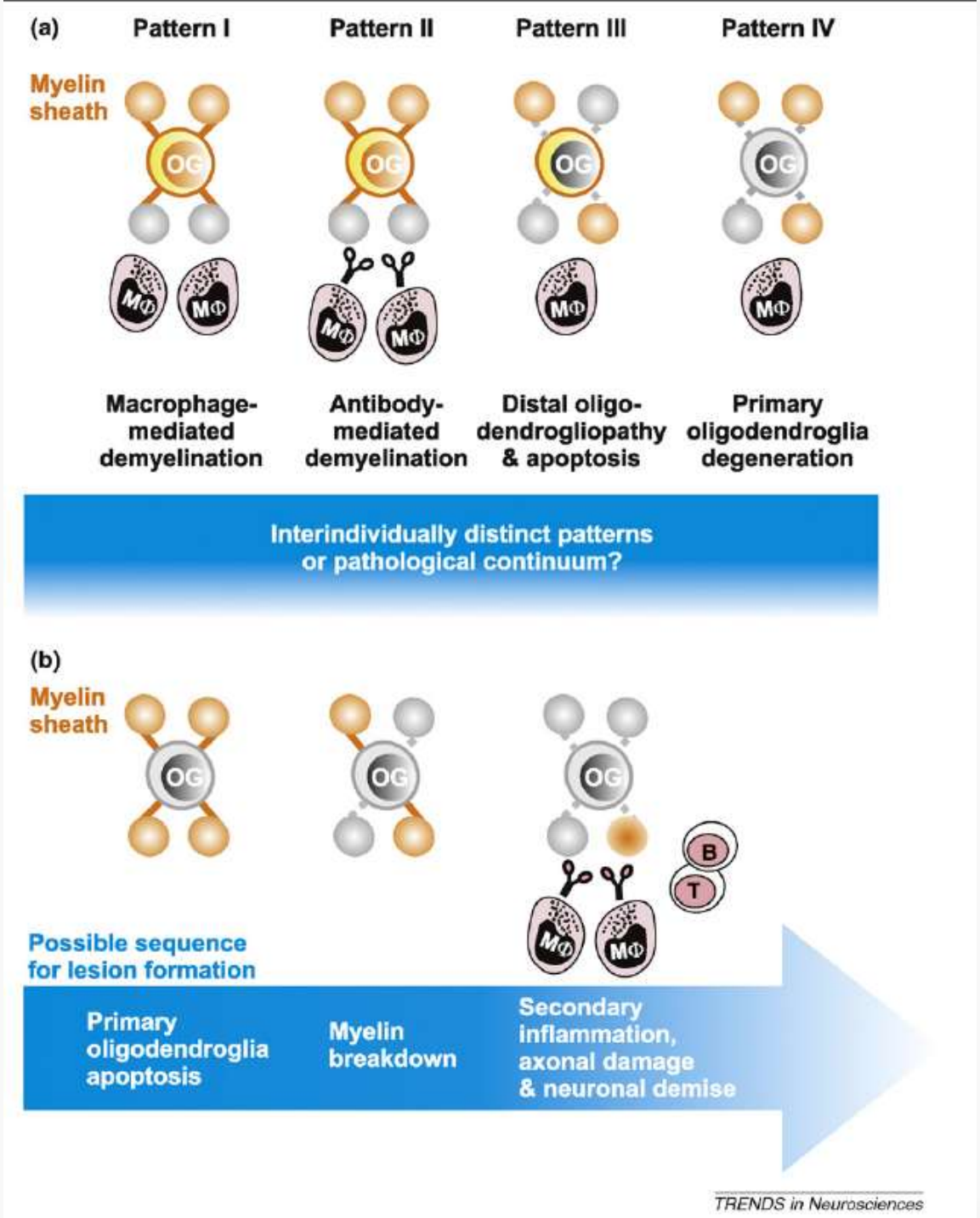




Oligodendrociti in una placca di demielinizzazione



Placca ombra: rimielinizzazione diffusa



Aktas O et al 2010

In apparenza normale…

- Normal-appearing white matter has been defined pathologically as macroscopically normal white matter that is microscopically normally myelinated and at least 1 cm away from a plaque's edge.
- This matter has to be differentiated from diffusely abnormal or dirty-appearing white matter, which includes areas of diffuse myelin pallor with ill-defi ned borders.
- Nowadays, diffuse pathology in the MS brain might be a more appropriate definition than focal lesional pathology.
- Only 27.8% of the specimens of this matter were microscopically normal. The major histological abnormalities included gliosis, demyelination, small round cell infiltration, and the presence of macrophages.

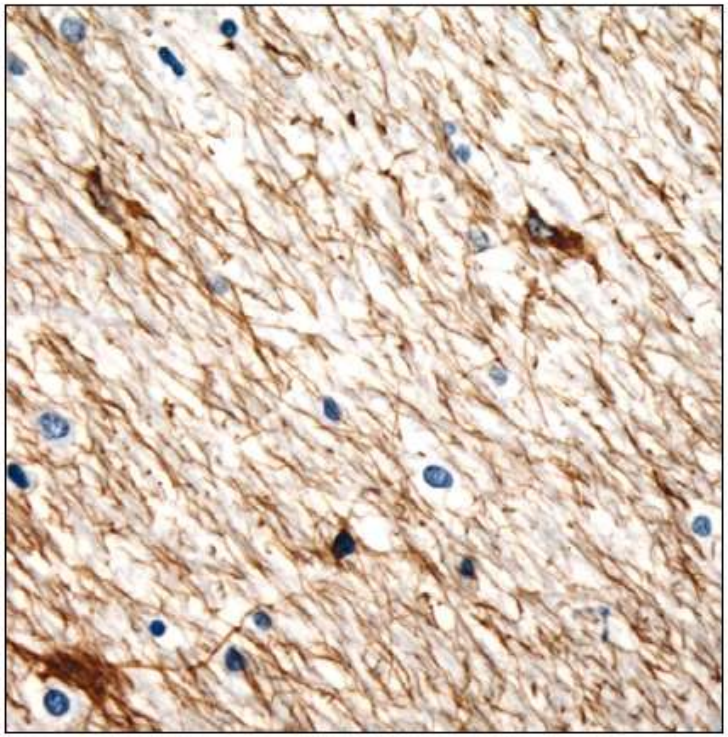


Figure 2: **Immunocytochemistry for glial fibrillary acidic protein**
Reactive astrocytes and fibre gliosis are present in normal-appearing white matter seen at the autopsy of a patient with multiple sclerosis.

Filippi et al 2014

Grey matter pathology in multiple sclerosis

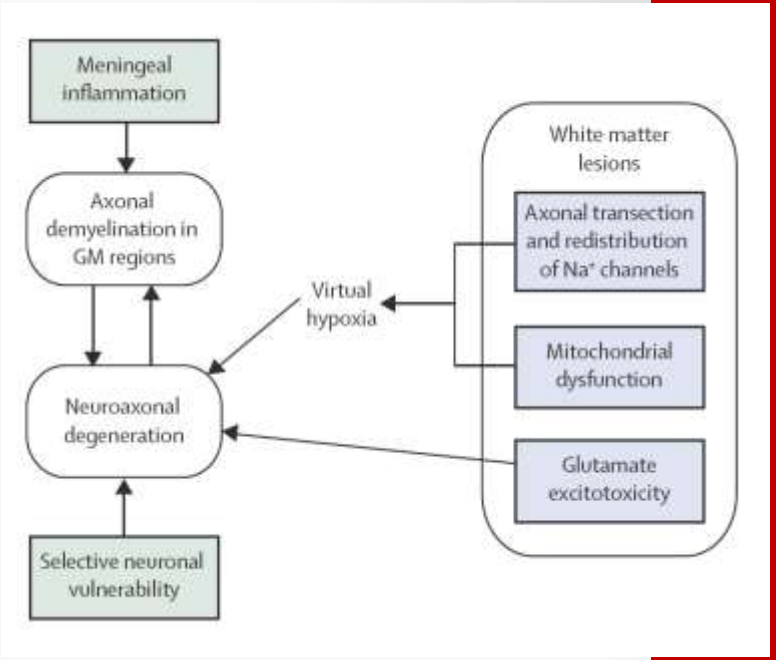
Jeroen J G Geurts, Frederik Barkhof

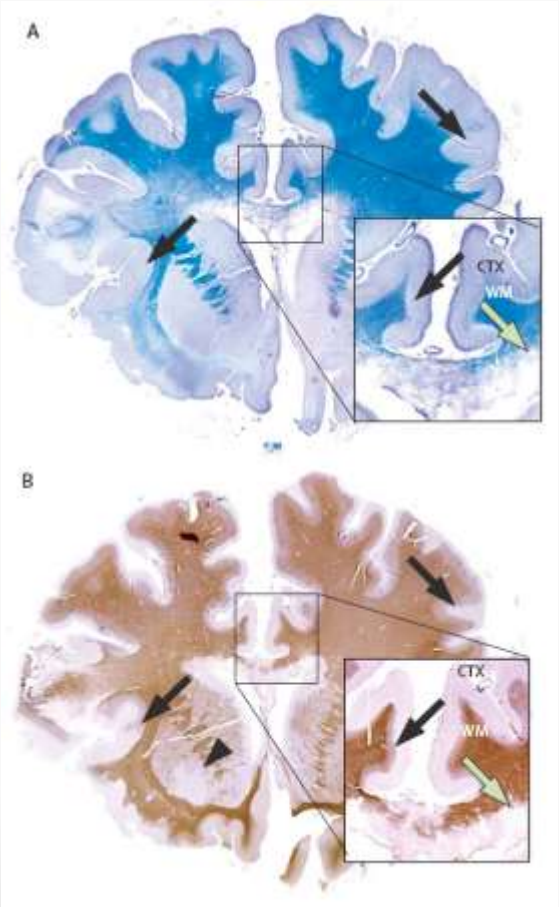
Multiple sclerosis (MS) has been classically regarded as a white matter disease. However, recent histopathological studies have convincingly shown that grey matter regions are also heavily affected. Grey matter damage starts early in the disease and substantially affects clinico-cognitive functioning. Detection of cortical grey matter lesions by use of standard MRI techniques has proved challenging, and more advanced techniques are needed. At present, the causes of grey matter damage are unclear. We review several exciting new hypotheses on grey matter pathogenesis, including meningeal inflammation as a cause of subpial cortical damage, but also selective vulnerability of neuronal subpopulations, growth factor dysregulation, glutamate excitotoxicity, mitochondrial abnormalities, and the "use-it-and-lose-it" principle. These hypotheses remain to be validated over the coming years, and could substantially affect our current views on MS pathogenesis.

Lancet Neurol 2008; 7: 841–51

Department of Radiology (J J G Geurts PhD, F Barkhof MD) and Department of Pathology (J J G Geurts), VU University Medical Centre, Amsterdam, Netherlands

Correspondence to: J J G Geurts, VU University Medical Centre, Department

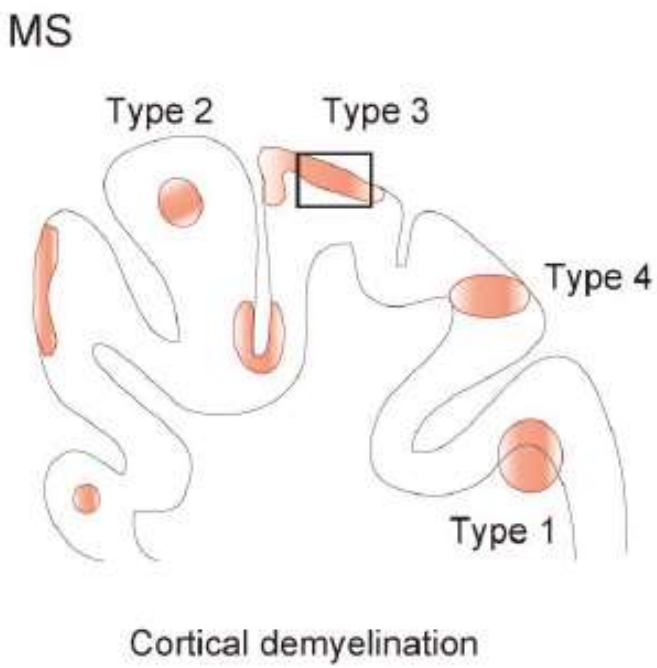


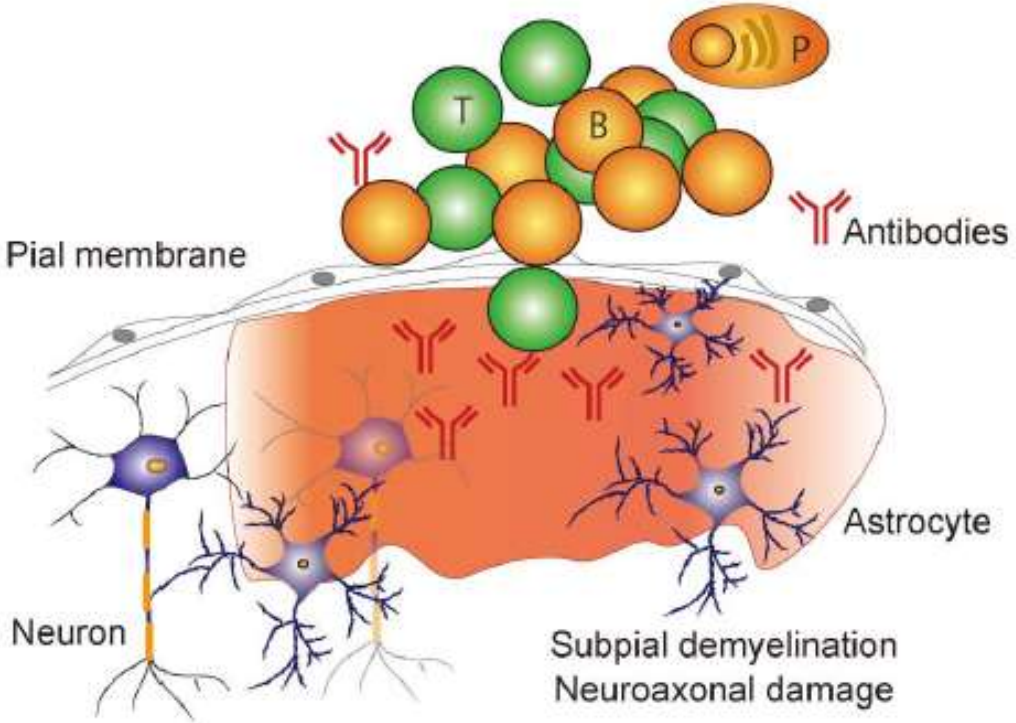


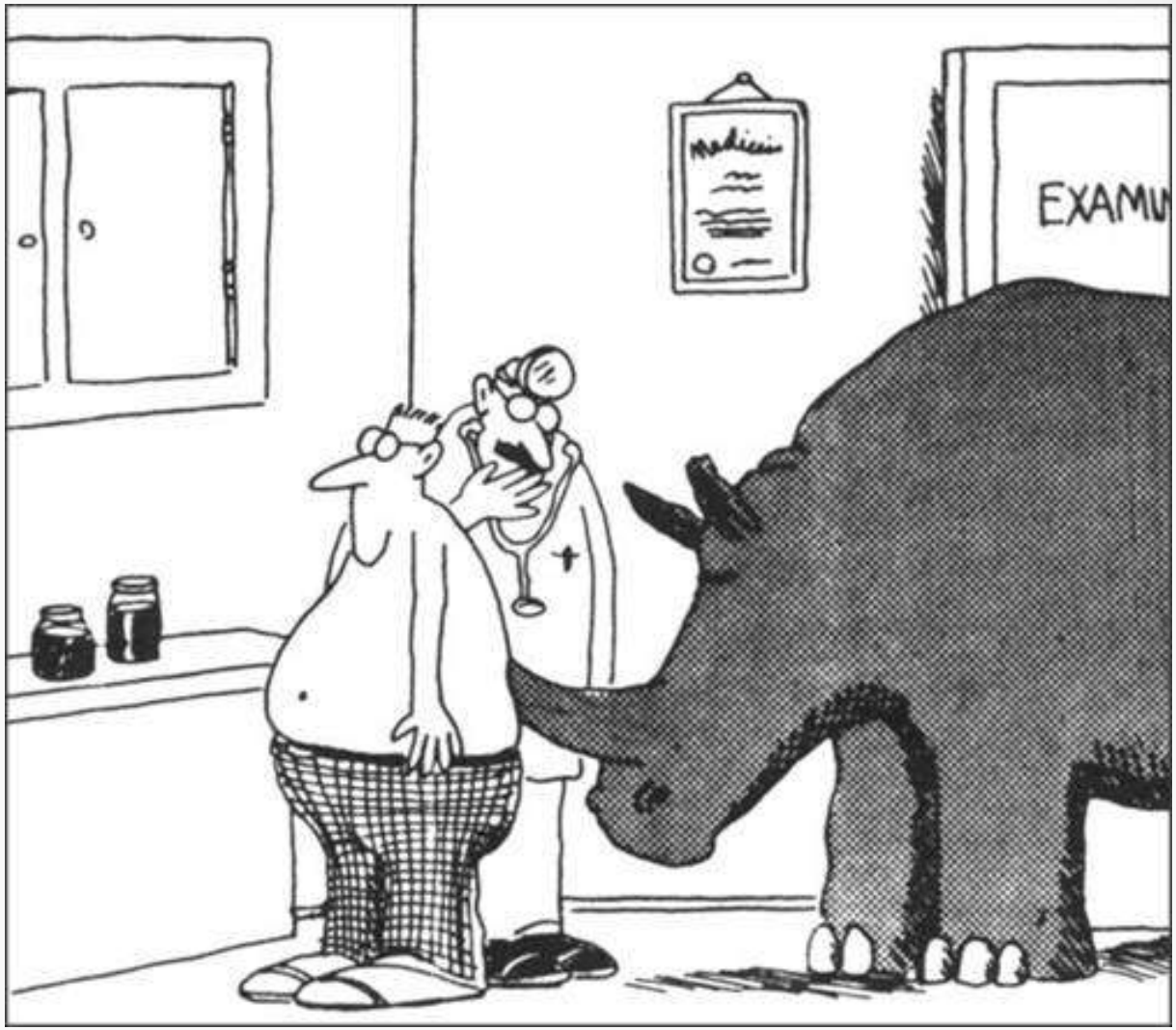
Lesioni corticali

- ✓ Sono presenti e comuni in tutte le fasi di malattia (anche precoci)
- ✓ Sono altamente infiammattorie
- ✓ Possono rappresentare il substrato sia di sintomi specifici (cognitivi e epilessia) sia di disabilità fisica interessante altri sistemi funzionali

To cite: Kawachi I, Lassmann H. *J Neurol Neurosurg Psychiatry* 2017;**88**:137–145.







"Aspetti un attimo, Signor Pistis… Forse non è un calcolo renale dopo tutto"

The New England Journal of Medicine

AXONAL TRANSECTION IN THE LESIONS OF MULTIPLE SCLEROSIS

Bruce D. Trapp, Ph.D., John Peterson, B.S., Richard M. Ransohoff, M.D., Richard Rudick, M.D., Sverre Mork, M.D., Ph.D., and Lars Bo, M.D.

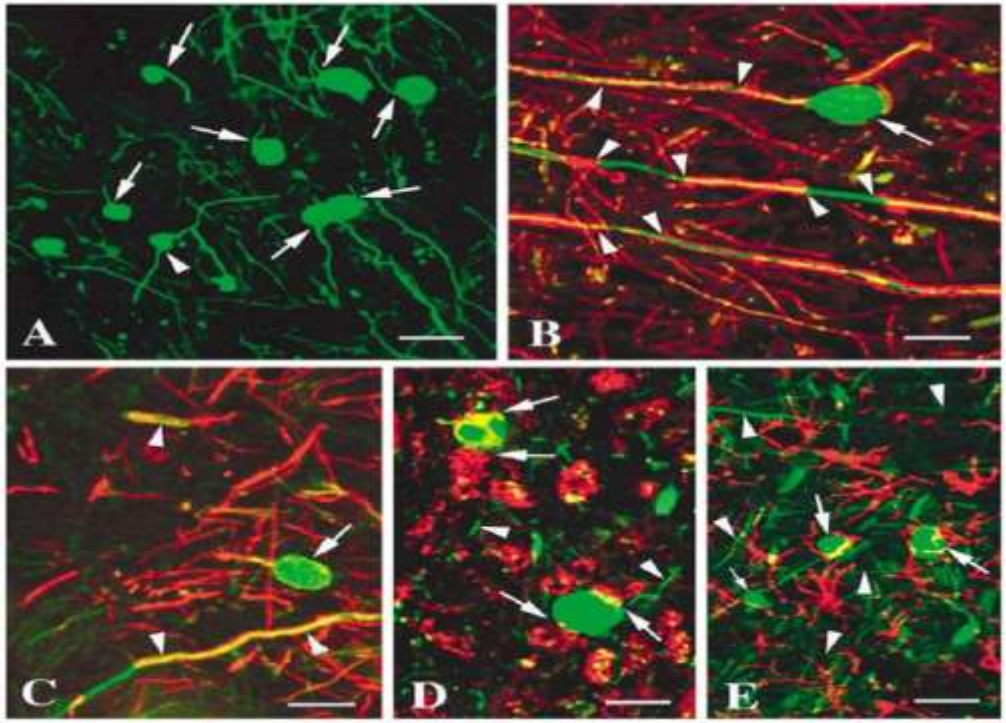
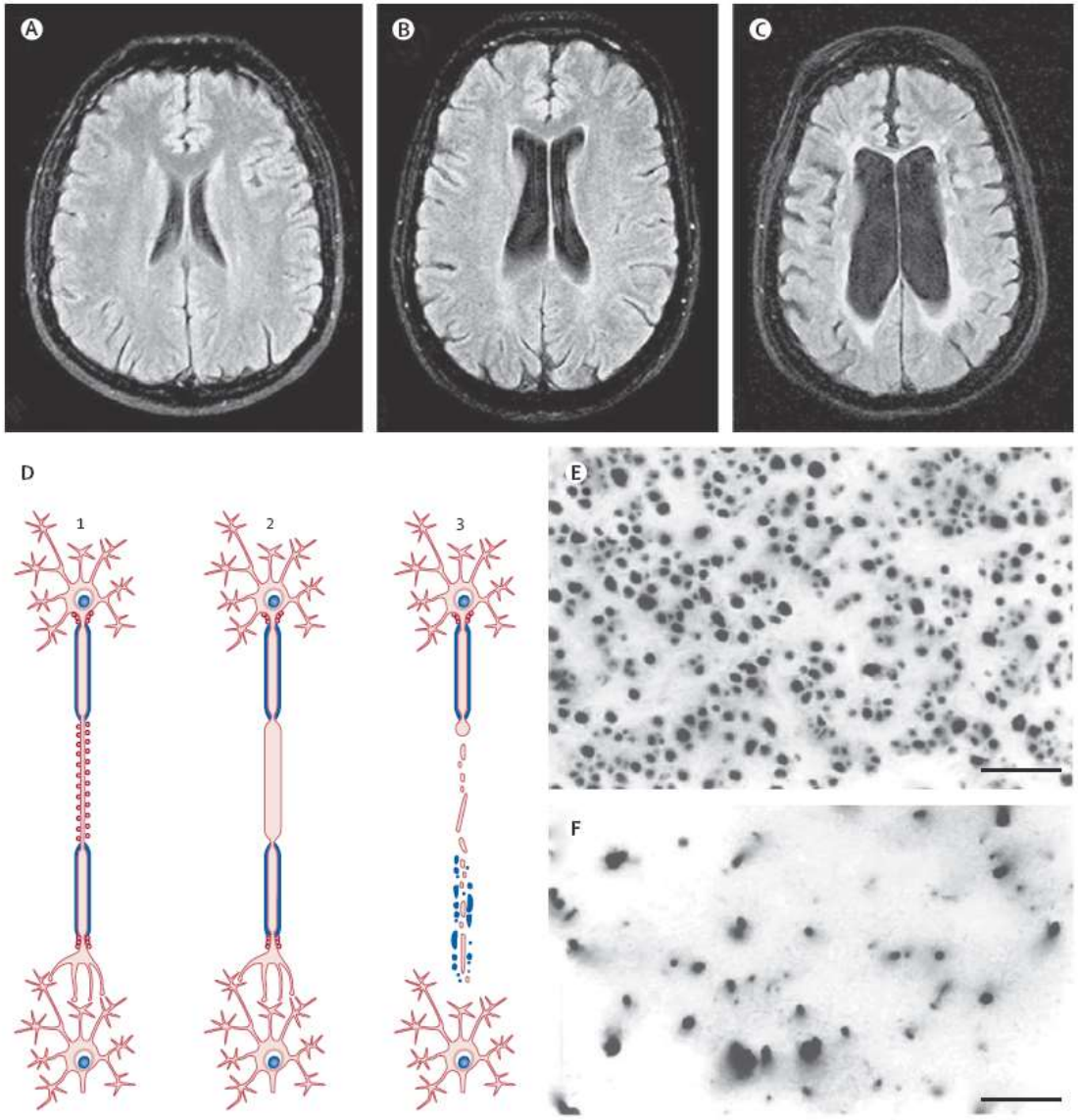


Figure 3. Confocal Microscopical Images of Axonal Changes in Multiple-Sclerosis Lesions.

Visualizzazione di ovoidi dell'assone all'estremità terminale degli assoni sezionati tramite microscopia confocale in encefali di pazienti SM con durata di malattia dalle 2 sett ai 27 aa

"axonal transection" è abbondante nelle fasi precoci di malattia e la densità correla con l'infiammazione

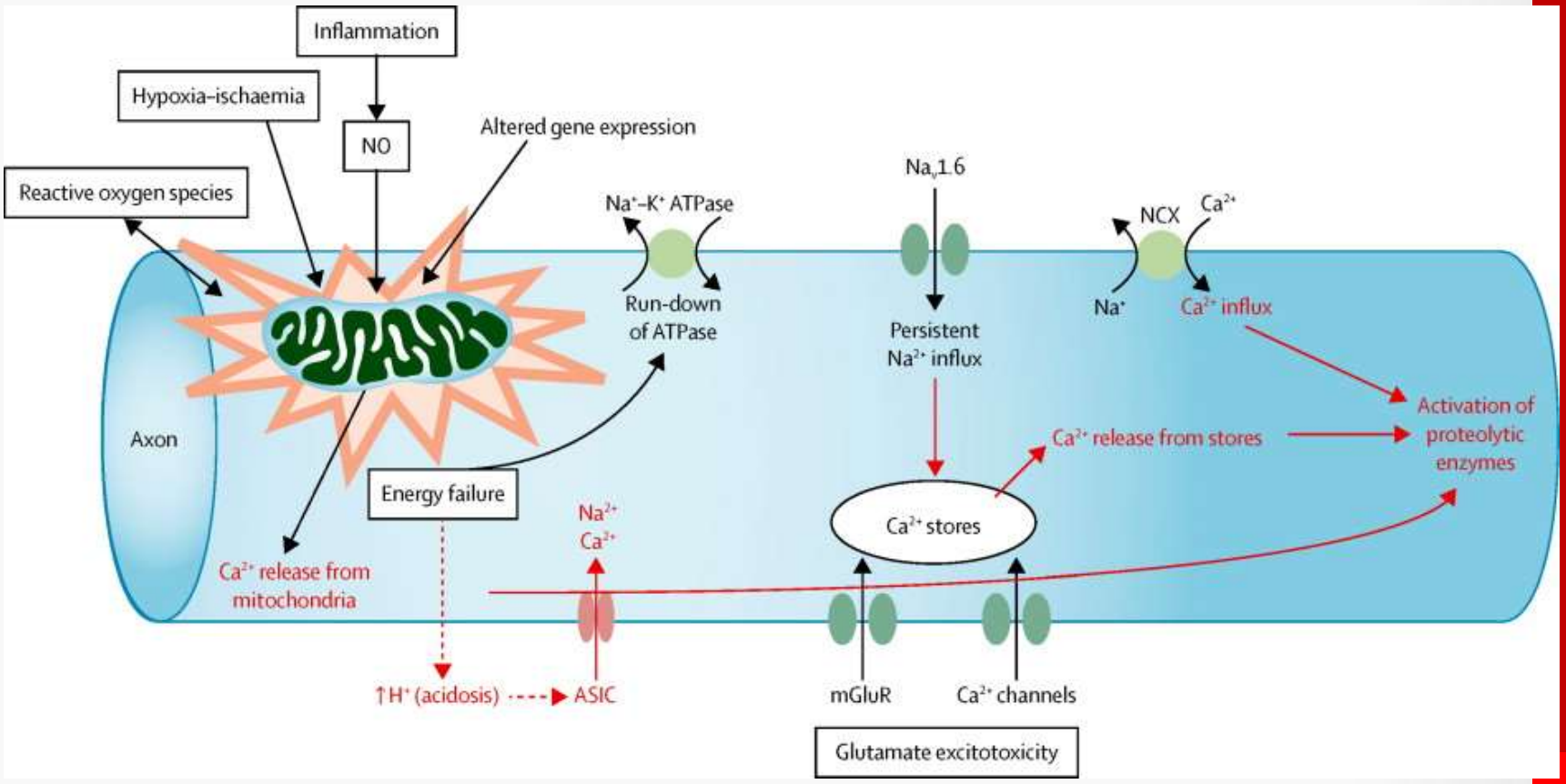
Chronically demyelinated axons degenerate due to loss of myelin trophic support and alterations in the chronic lesion microenvironment



- La perdita assonale (o neuronale) è considerata il maggior determinate dell'accumulo di disabilità permanente.
- Può avvenire sia nella nuove lesioni infiammatorie che nelle lesioni croniche
- Documentata riduzione del numero di assoni anche al di fuori delle lesioni.

Trapp B 2009

Danno e perdita assonale



Filippi et al 2014

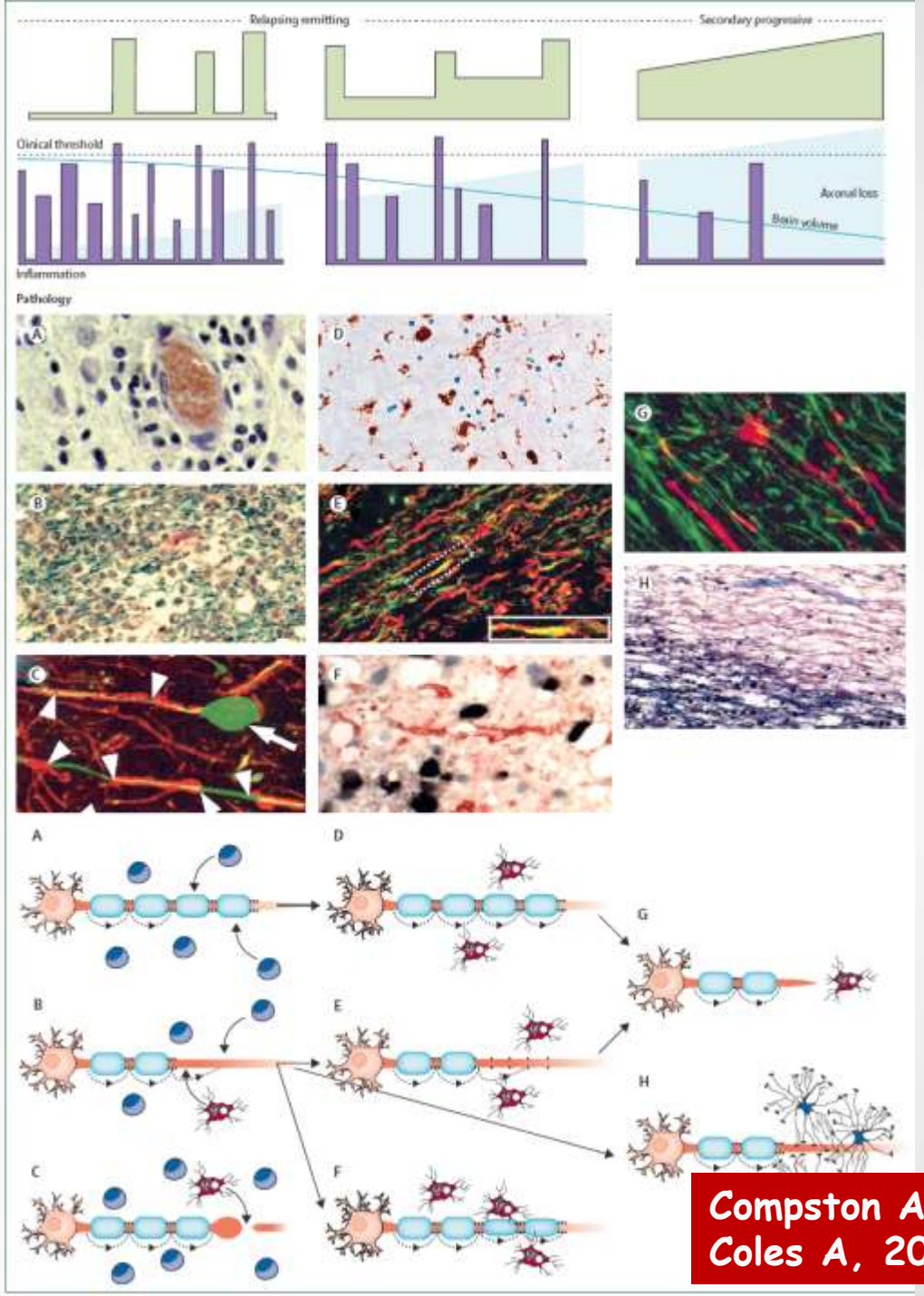
RIDONDANZA DEL SISTEMA NERVOSO CENTRALE

…..l'esame delle fibre retiniche del nervo ottico a livello del disco ottico hanno rilevato che più del 50% di tessuto nervoso deve andare perso prima che un deficit visivo diventi evidente……

Quigley and Addicks 1982

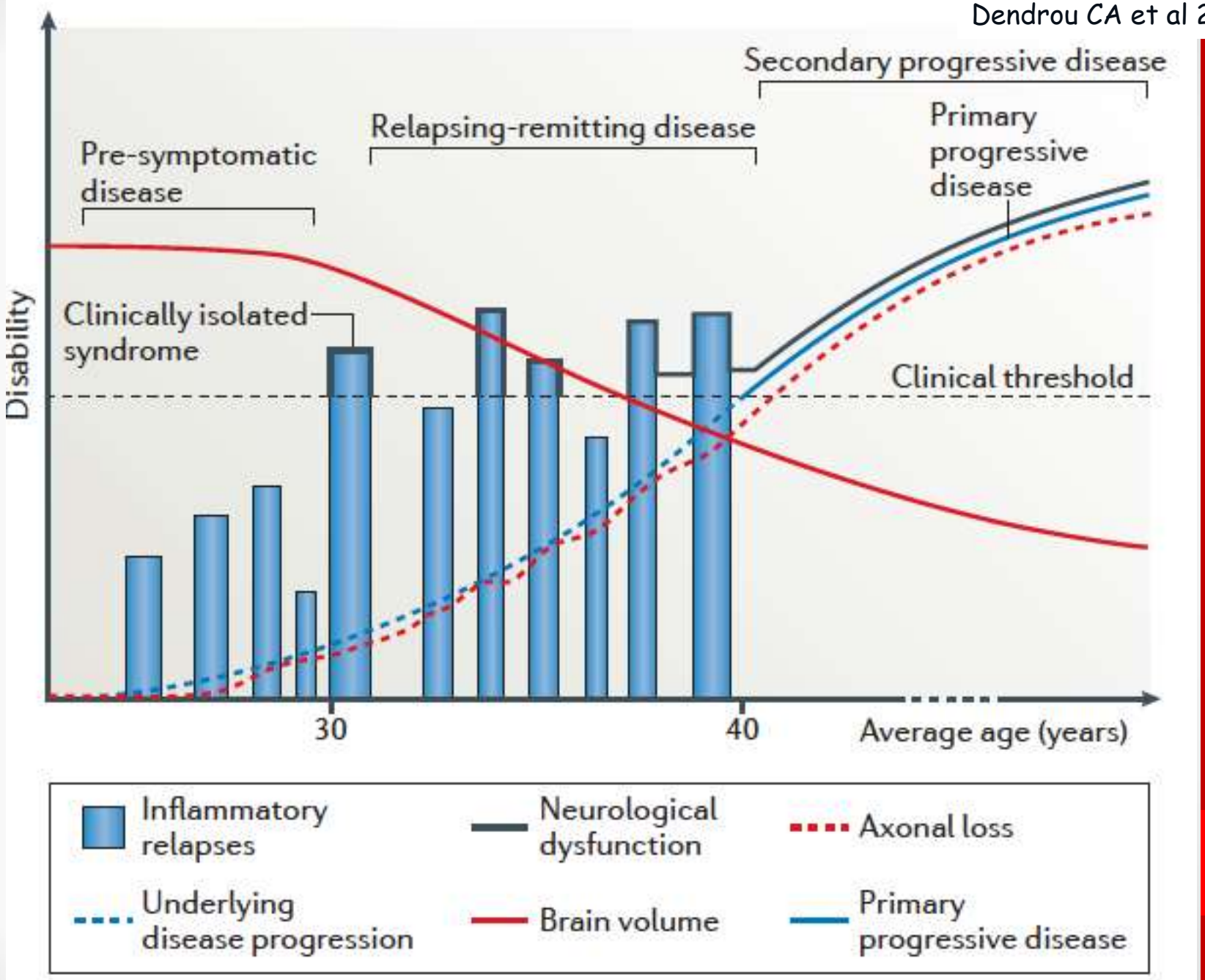
PATOGENESI

- ✓ Infiammazione
- ✓ Demielinizzazione
- ✓ Danno assonale
- ✓ Proliferazione gliale

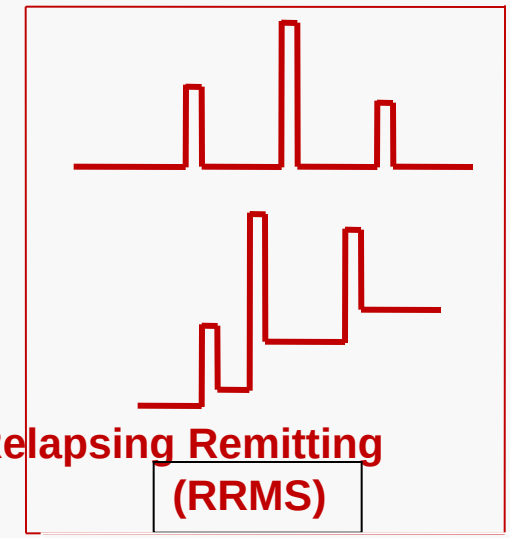


Compston A & Coles A, 2008

Dendrou CA et al 2015



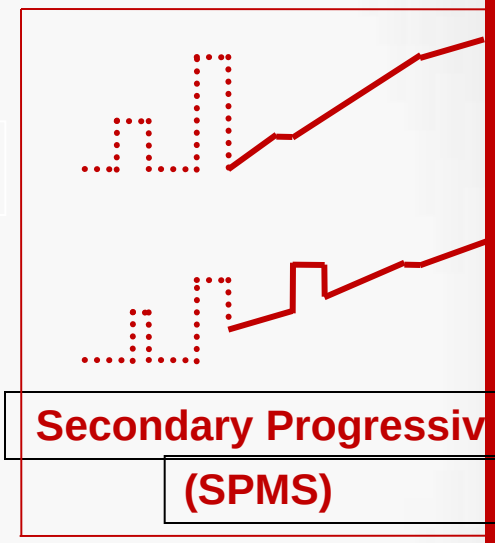
DECORSO CLINICO; SCLEROSI MULTIPLA



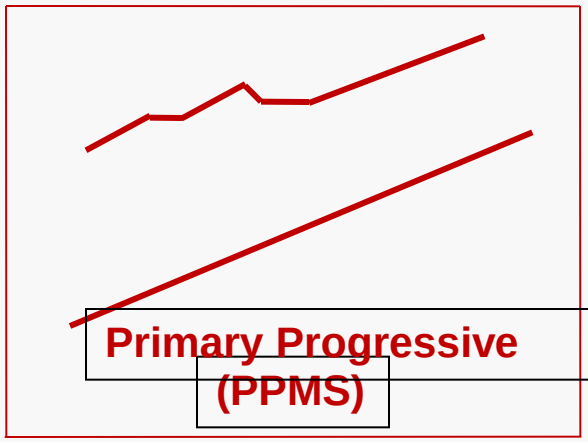
Relapsing Remitting
(RRMS)

Initial Course for
80 – 85%

90% Convert



Secondary Progressiv
(SPMS)



Primary Progressive
(PPMS)

Initial Course
for 10 – 15%

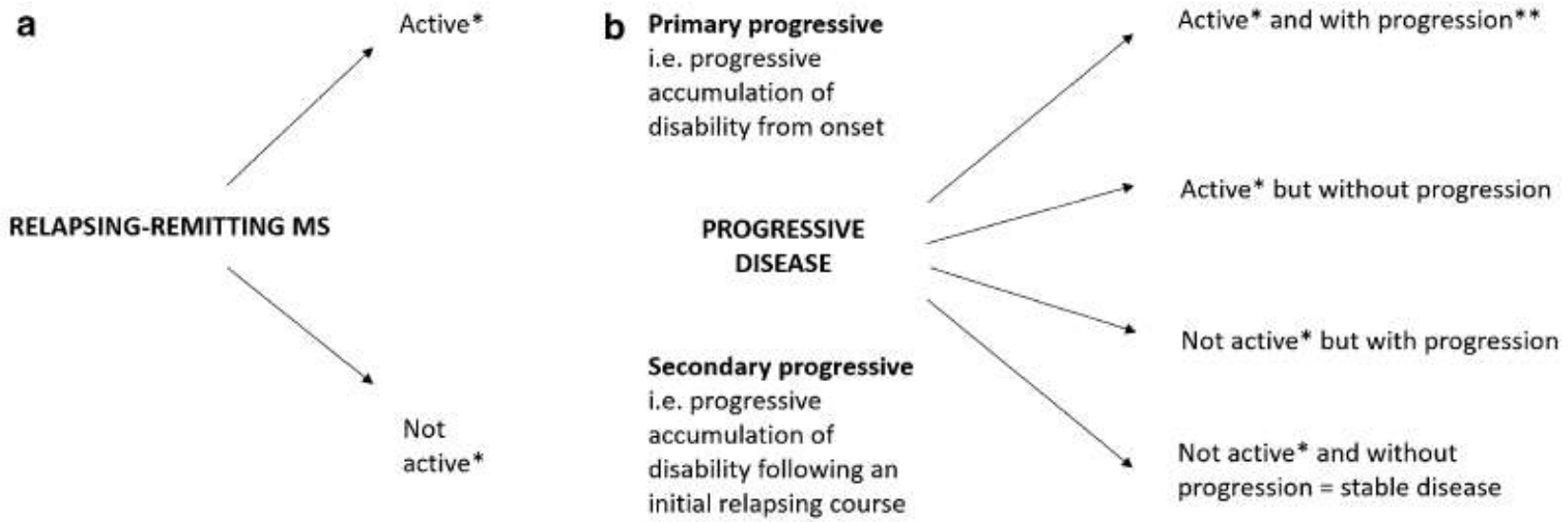


Fig. 1 Adapted from the 2013 multiple sclerosis phenotype descriptions by Lublin et al. [15] for **a** relapsing-remitting disease and **b** progressive disease. *Activity determined by clinical relapses assessed at least annually and/or MRI activity (contrast-enhancing lesions; new and unequivocally enlarging T2 lesions). **Progression measured by clinical evaluation, assessed at least annually

McCarthy et al 2016

Panel 1: Typical presentations of relapsing-remitting multiple sclerosis and selected atypical or red flag presentations that are more suggestive of an alternative diagnosis

Typical presentations

- Acute unilateral optic neuritis
- Double vision due to an internuclear ophthalmoplegia or sixth nerve palsy*
- Facial sensory loss or trigeminal neuralgia*
- Cerebellar ataxia and nystagmus
- Partial myelopathy
- Sensory symptoms in a CNS pattern
- Lhermitte's symptom
- Asymmetric limb weakness
- Urge incontinence or erectile dysfunction

Atypical or red flag presentations

- Bilateral optic neuritis or unilateral optic neuritis with a poor visual recovery
- Complete gaze palsy or fluctuating ophthalmoparesis
- Intractable nausea, vomiting, or hiccups
- Complete transverse myelopathy with bilateral motor and sensory involvement
- Encephalopathy
- Subacute cognitive decline
- Headache or meningism
- Isolated fatigue or asthenia
- Constitutional symptoms

*In a young adult (<40 years of age).

Brownlee et al 2016

Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

ANN NEUROL 2011;69:292–302

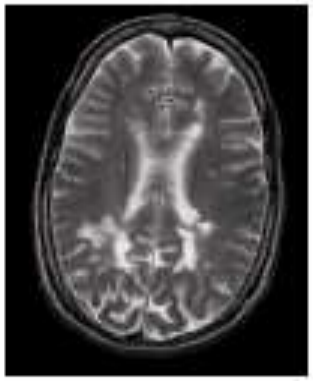
RICERCA DELLA:

DISSEMINAZIONE NEL TEMPO E NELLO SPAZIO

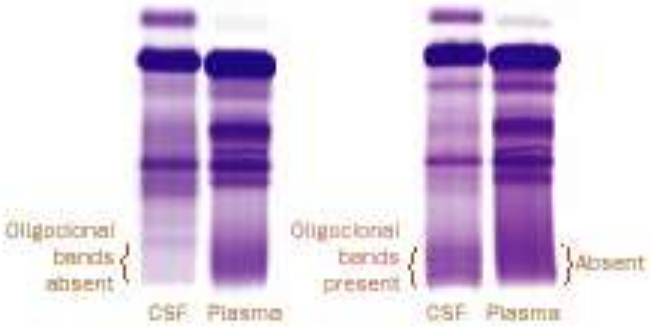
One or more episodes?	First clinical episode	Subsequent clinical episode	Paraclinical data
Two	1 site affected	Different sites affected	Not required
	1 site affected	Same site affected	Lesions disseminated in space on MRI (if CSF positive, MRI criteria less rigorous)
One	≥2 sites affected	None	Lesions disseminated in time on MRI
	1 site affected	None	Lesions disseminated in space on MRI (if CSF positive, MRI criteria less rigorous) **AND** Lesions disseminated in time on MRI
Progressive from onset	Insidious progression suggestive of multiple sclerosis	None	Positive CSF **AND** Lesions disseminated in space on MRI (if VEP abnormal, MRI criteria less rigorous) **AND** Lesions disseminated in time on MRI **OR** continued progression for 1 year

Investigations

MRI scan



CSF



VEP

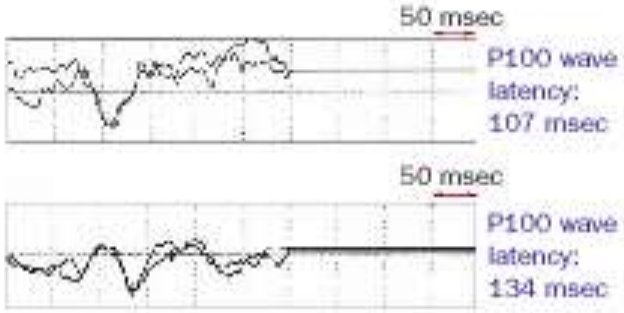


Figure 2: **Criteria for diagnosis of multiple sclerosis**