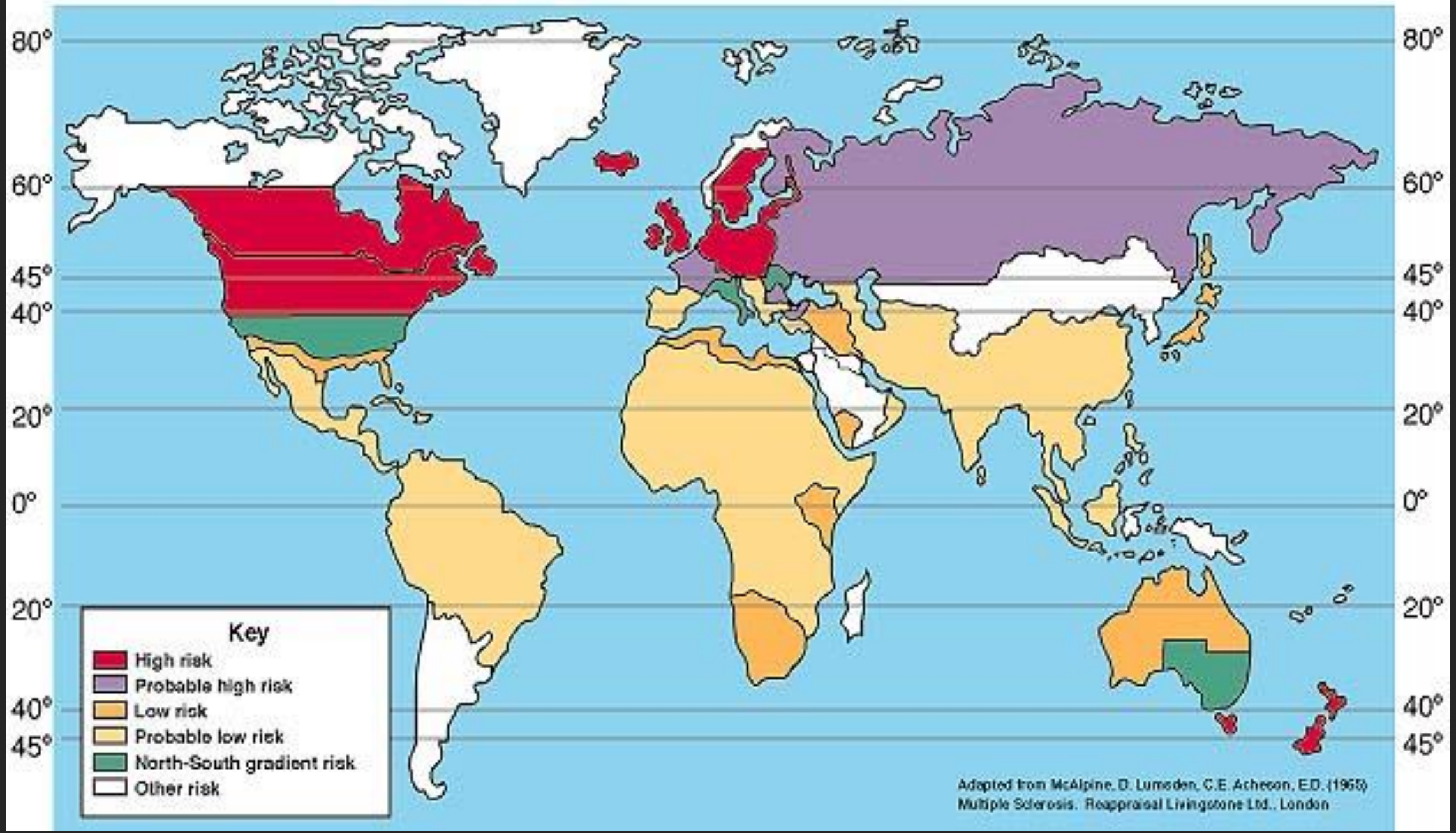
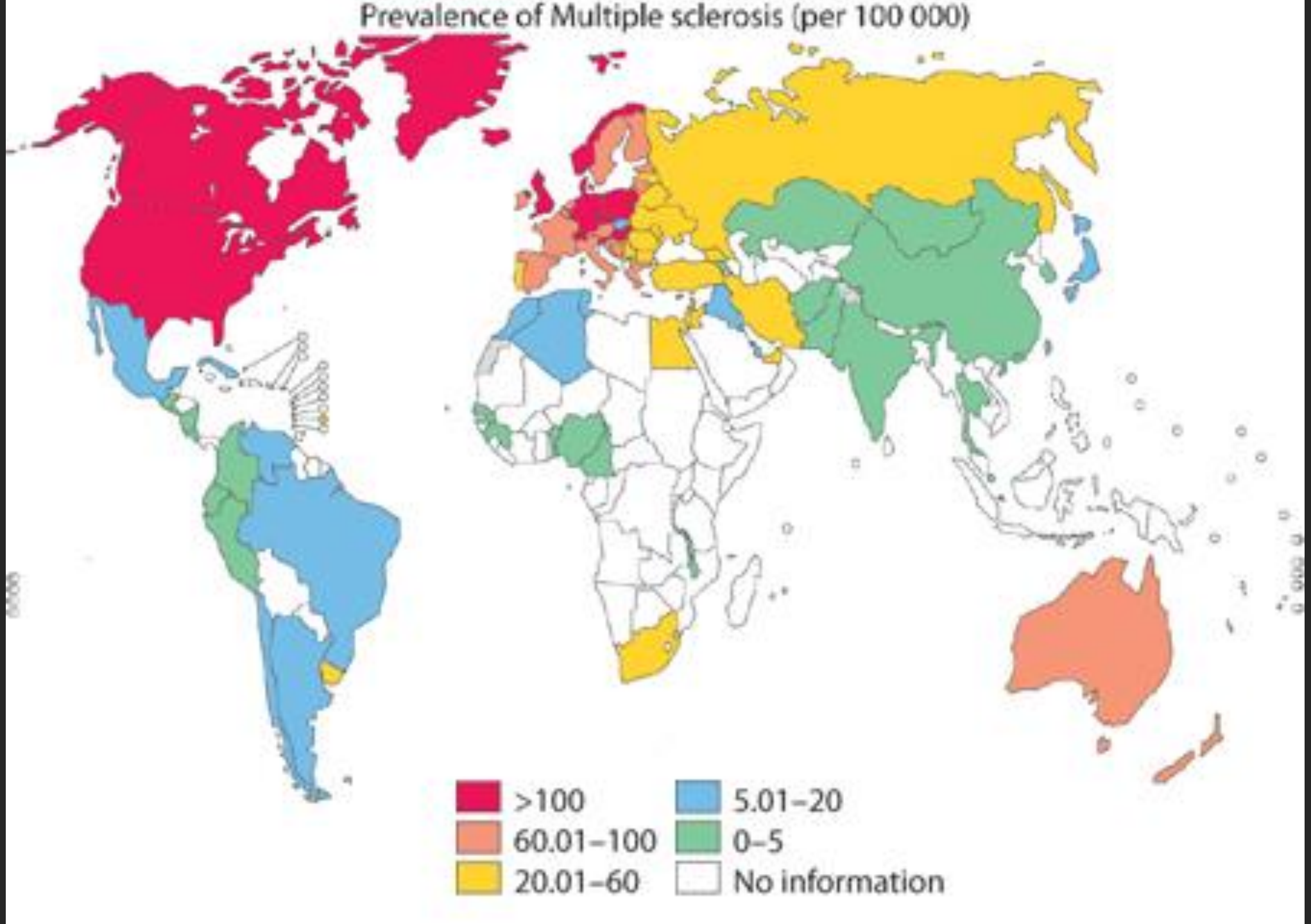
MULTIPLE SCLEROSIS - MS

(disseminated sclerosis)

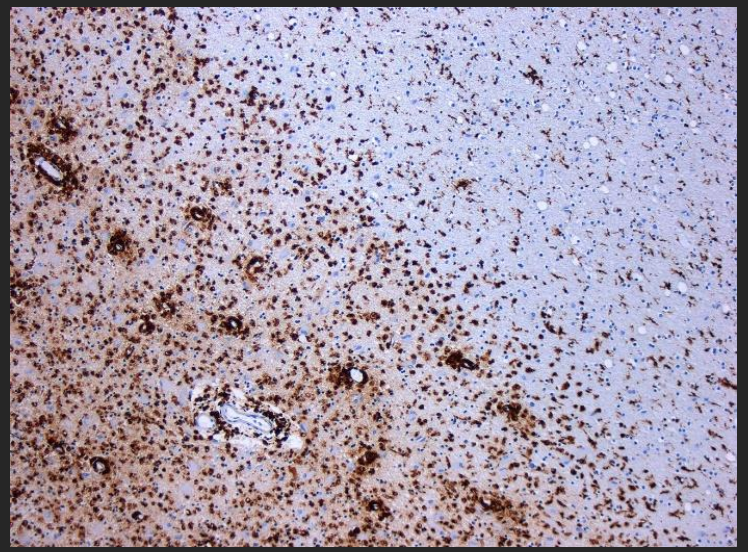
World Distribution of Multiple Sclerosis



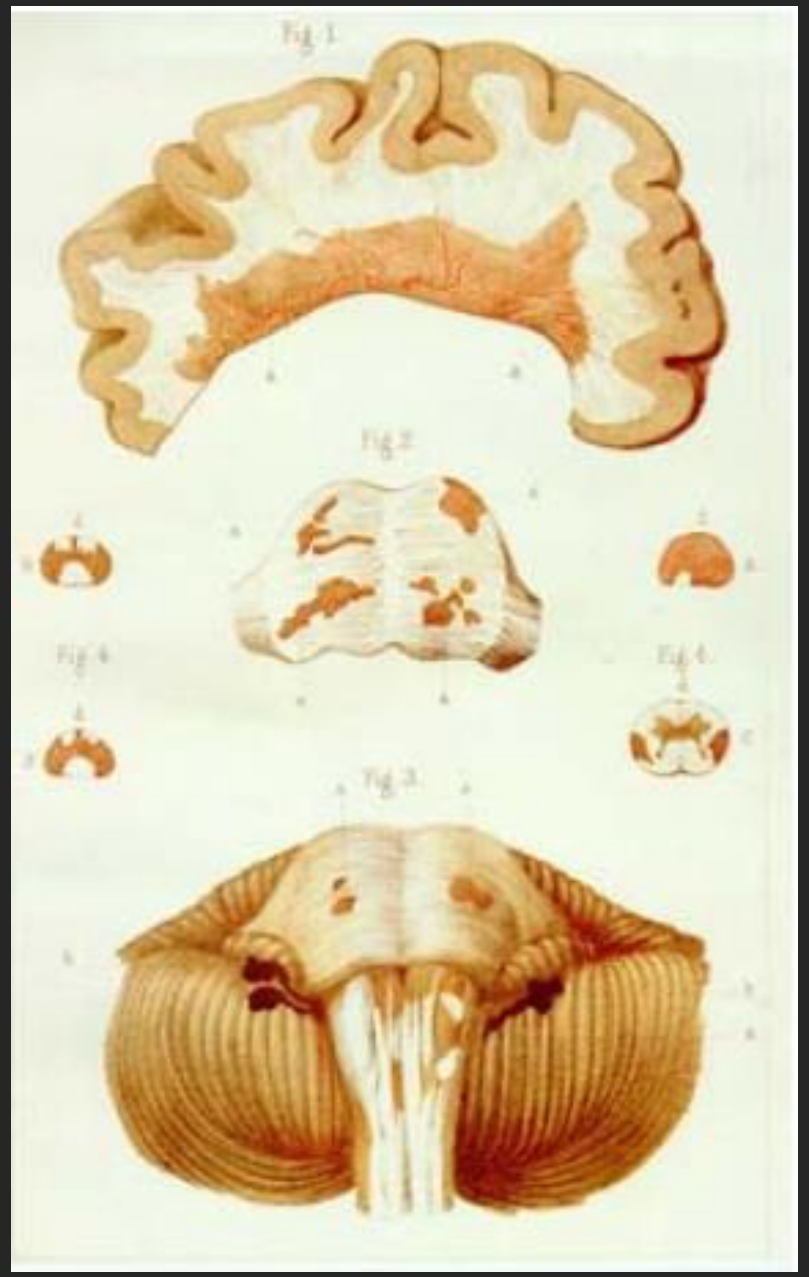

Prevalence of Multiple sclerosis (per 100 000)
>100
60.01–100
20.01–60
5.01–20
0–5
No information

Jean-Martin Charcot

1825-1893



Macrofage in the demyelination of MS



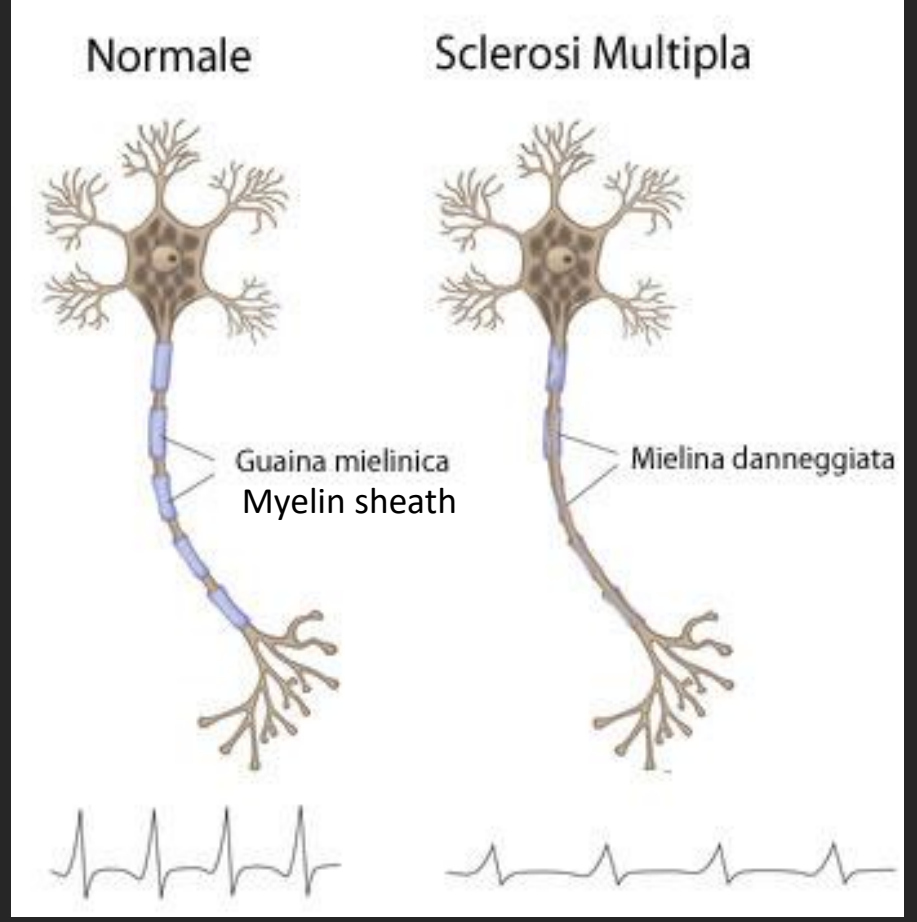
MULTIPLE SCLEROSIS ORIGIN

autoimmune disease: demyelination

infections, genes, inflammation, environment

young adults (women)

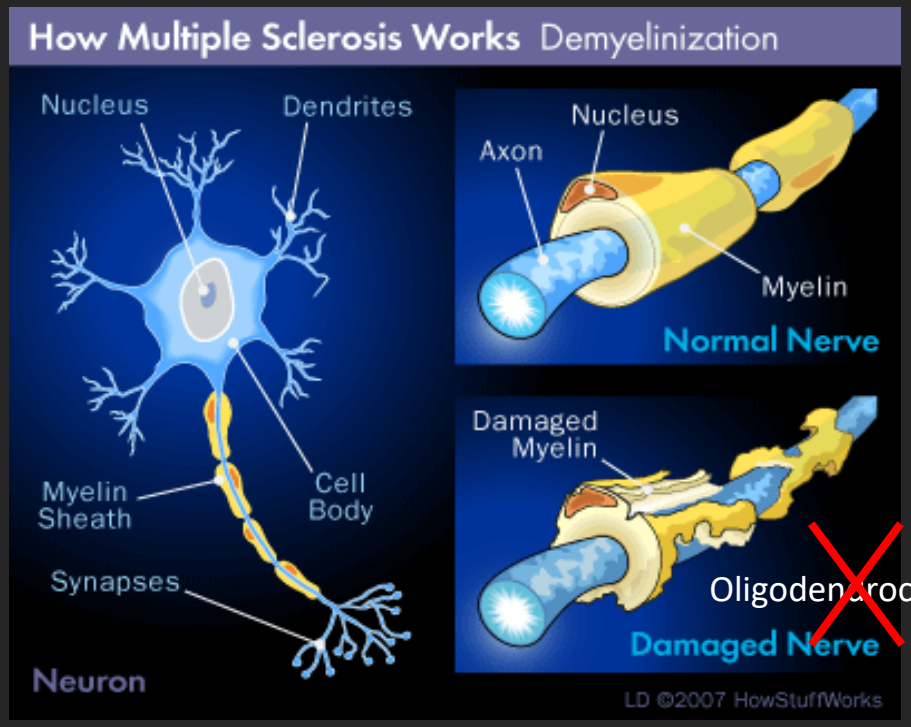
prognosis (subtype of disease)



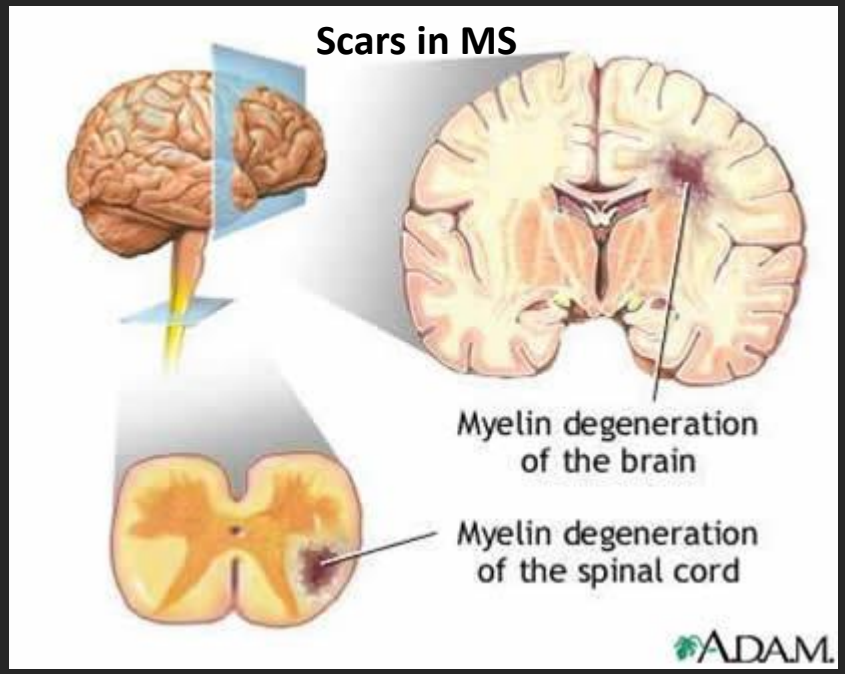
impediment communication between neurons (scars)

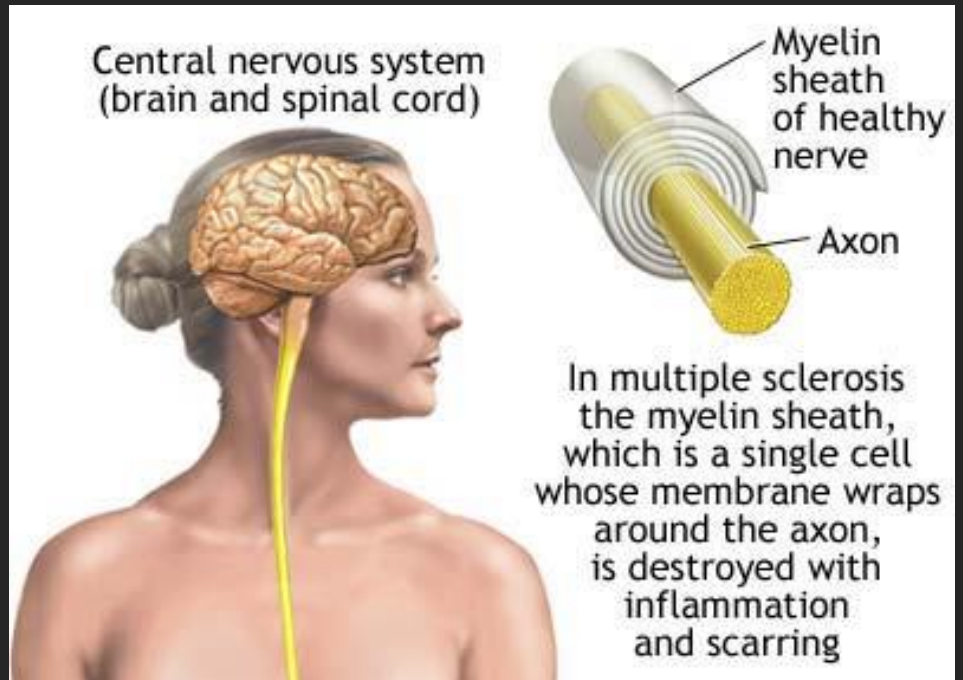
symptoms (sensitivity, muscle weakness, ataxia, dysarthria, dysphagia, vision problems)

↑cholesterol, ↓vitamin D



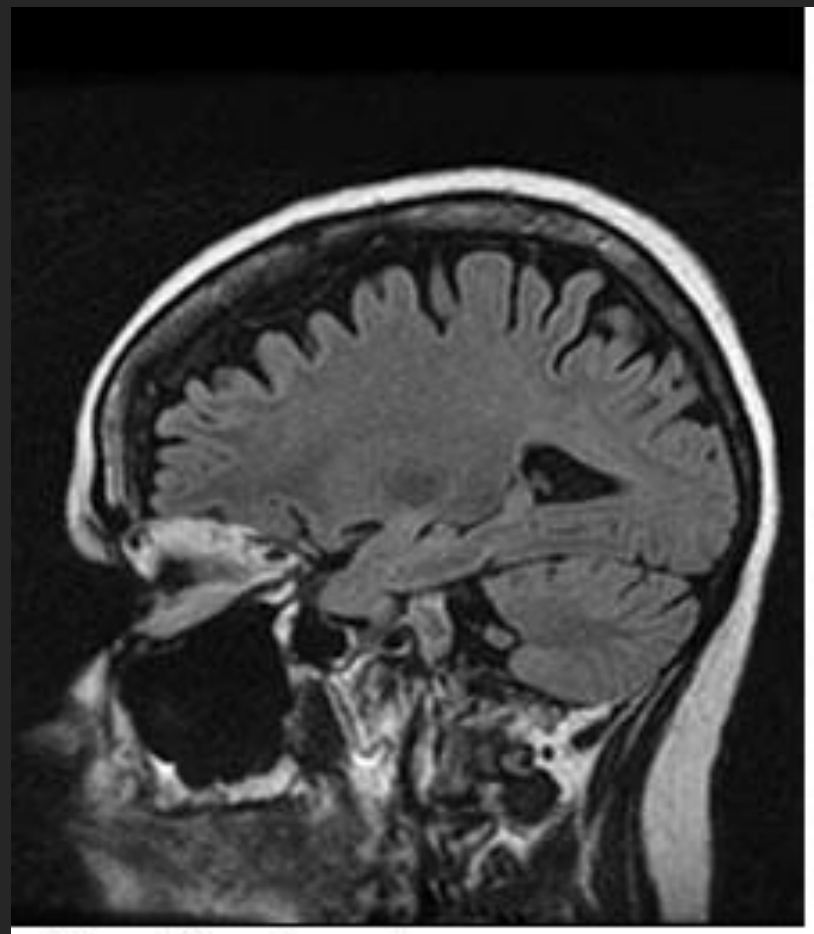
Oligodendrocytes



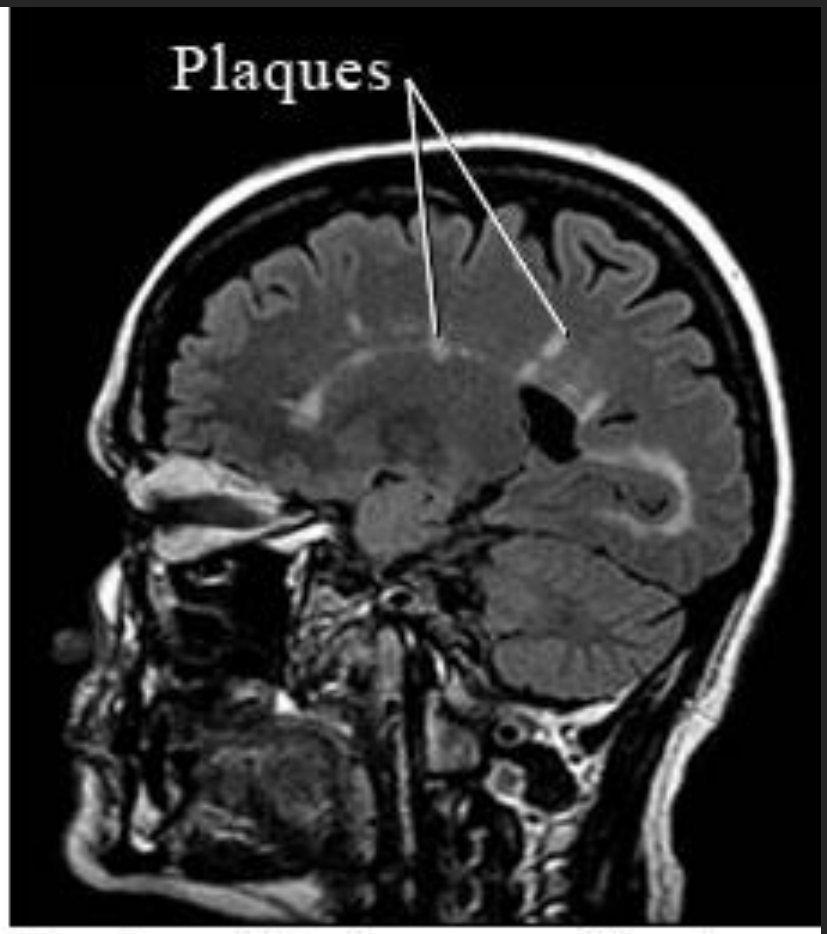


- Relapsing-Remitting MS (RRMS)
- Secondary-Progressive MS (SPMS)
- Primary-Progressive MS (PPMS)
- Progressive-Relapsing MS (PRMS)

Multiple Sclerosis

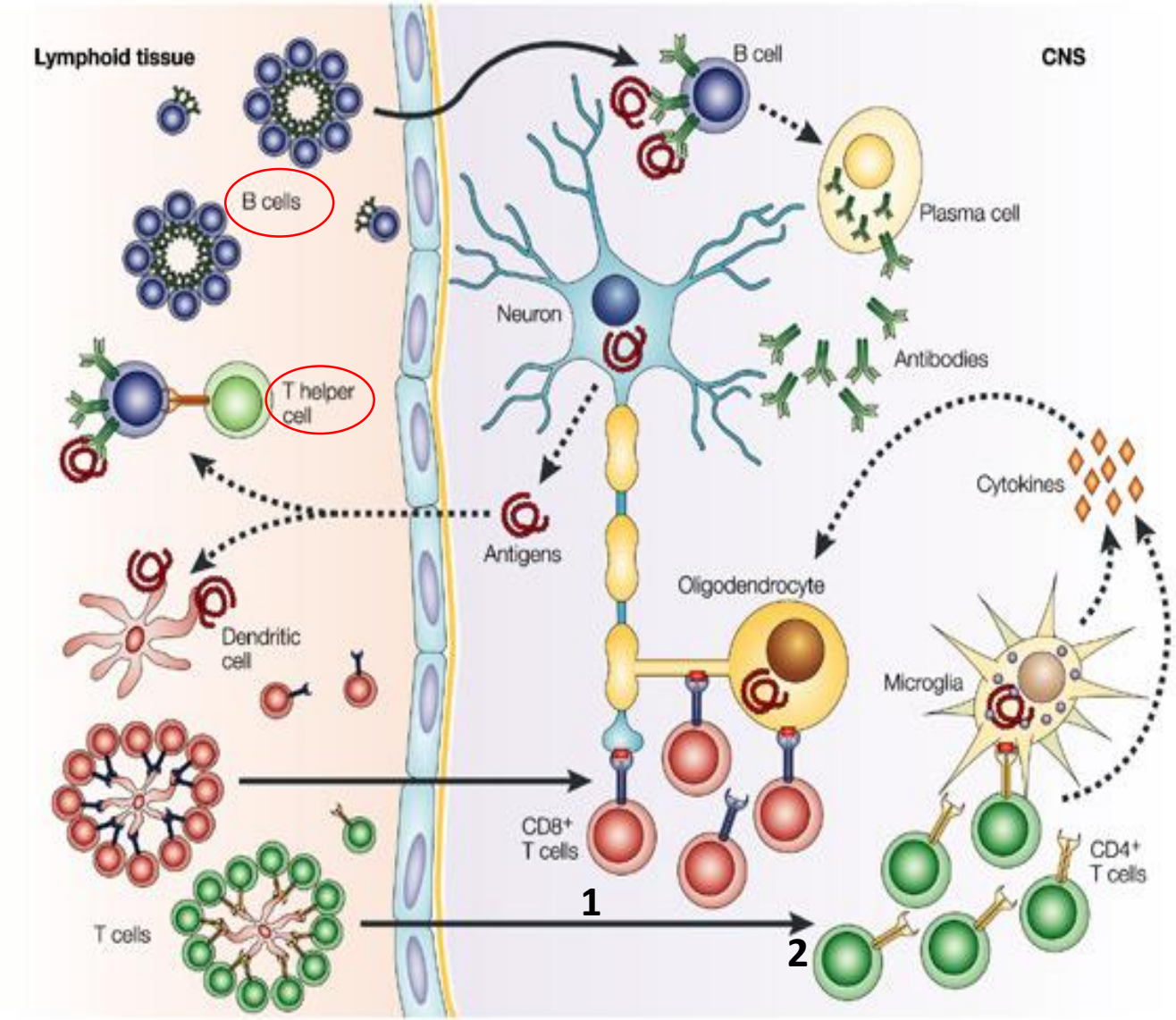


Healthy brain



Brain with damage (lesions or plaques) caused by MS

BEE (infections or virus)



T cells attack myelin

They enter the CNS through BEE made permeable by infections or viruses

Increase Th1 CD4 (interferon gamma, TNF)

Decreased Th2 CD4 (cytokines, IL4, 5, 13)
Th17 CD4 (IL 17)

THERAPY

Receding and remitting forms; progressive; secondarily progressive

Corticosteroids: methylprednisolone (acute attack)

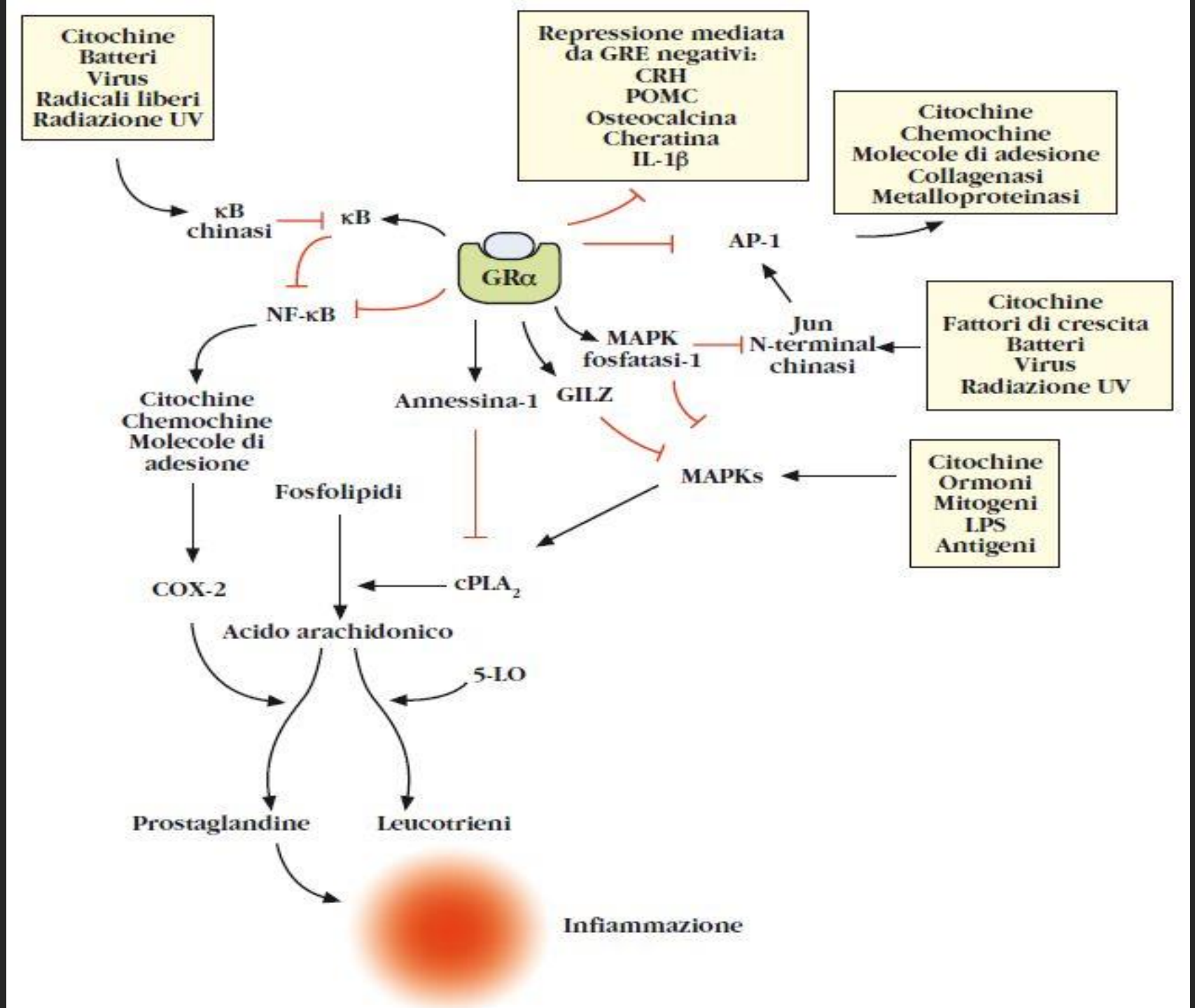
Interferon beta (i.m. or s.c.)

Glatiramer (s.c), immunomodulator; Mitoxantrone, immunosuppressant

Natalizumab (i.v.), monoclonal antibody (prevents Immune System infiltration in the CNS, blocks adhesion molecules)

Cannabinoids (dronabinol), acts on symptoms: spasticity and pain

Corticosteroids



Inhibition

Stimolation

glucocorticoid-induced leucine zipper (GILZ)

Interferon production

- From cells of the immune system and tissue cells in response to external agents such as viruses, bacteria, parasites, cancer cells

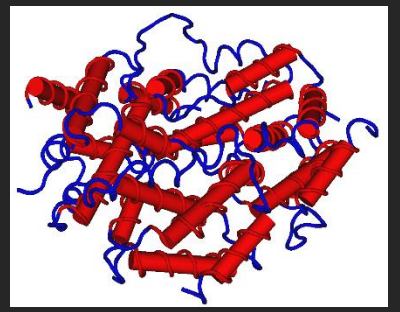
Interferon functions

Interferon effects:

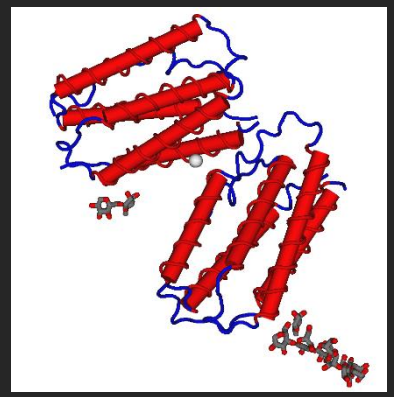
- inhibits the replication of viruses within infected cells
- prevents viral spread to other cells
- strengthen the activity of the cells responsible for immune defenses, such as T lymphocytes and macrophages
- inhibits the growth of some cancer cells

Interferons mechanism:

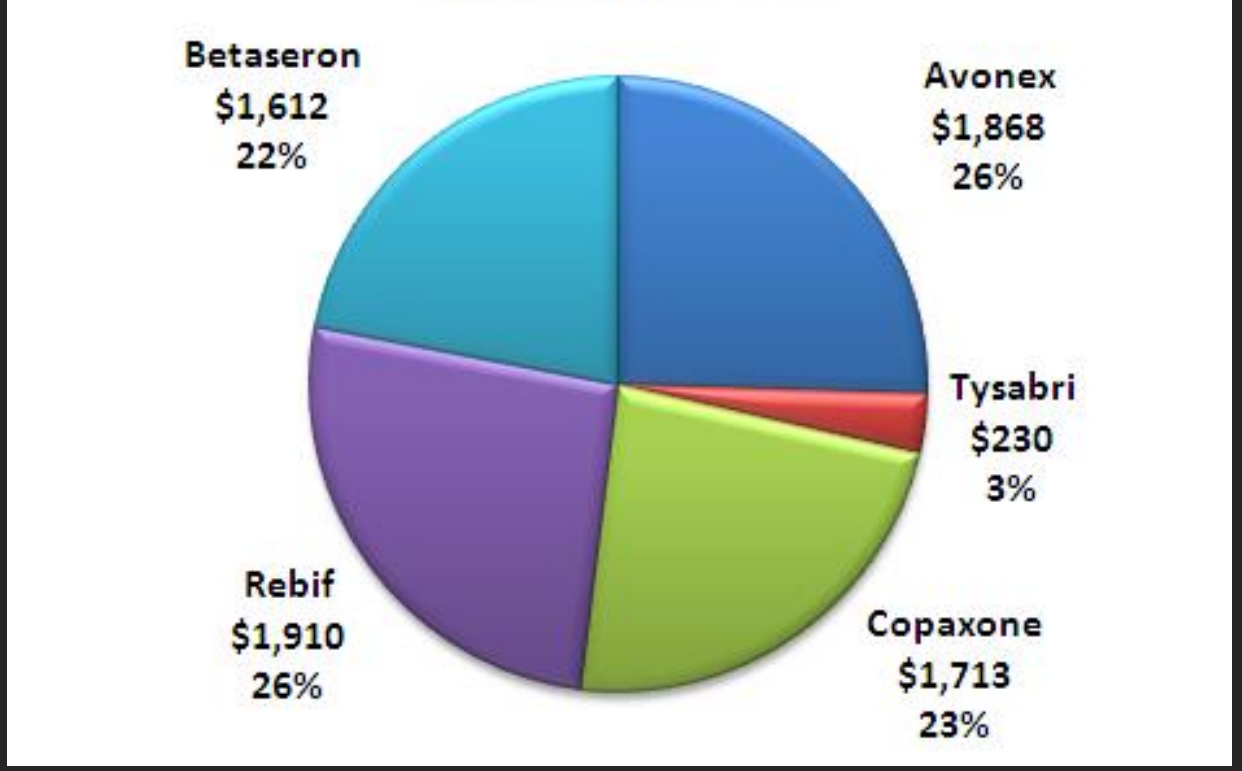
- they bind to the cell membrane and stimulate the production of antiviral enzymes
- the virus that attacks an interferon-activated cell cannot multiply due to antiviral enzymes
- stopping or attenuating the infection



Human interferon-γ



Human interferon-β



1) Interferon beta 1a and 1b (Avonex <Rebif <Betasoren) (fever)
2) Natalizumab (Tysabri) (monoclonal antibody) immunomodulator (prevents system infiltration of immune system in the CNS, blocks adhesion molecules). Encephalopathy
3) Glatiramer (copaxone) (immunomodulator)
4) Corticosterone (only in the acute phase)
5) Mitoxantrone (immunosuppressant also used in cancer chemotherapy) more advanced stages
6) Teriflunomide Pyrimidine synthesis inhibitor, decrease inflammation, lower number of white blood cells in the CNS

Dalfamprine, Ampyra (K channel blocker)
Dimethyl fumarate (immunomodulator)
Fingolimod (prevent lymphocytes from getting into the CNS)
Mitoxantrone, Ocrevus (ocrelizumab) monoclonal antibody CD20-positive B cells

Cladribine is a nucleoside analogue of deoxyadenosine
Used as a second choice
The mechanism of action of cladribine, a tablet drug, consists of a **reduction in the number of lymphocytes** that feed the inflammation processes underlying the alterations of the nervous system that are characteristic of multiple sclerosis. Like other products recently introduced in clinical practice for the treatment of multiple sclerosis, cladribine is also used in other fields, such as hematology, for the treatment of some forms of leukemia

Table. Summary of Multiple Sclerosis Disease-Modifying Therapy Effects on B-Cell Immunity

Drug	Mechanism of Action for B Cells	Effect on Circulating B Cells	Vaccine Response
Interferon beta	Increased BAFF[5,6] Decreased expression of costimulatory molecules[10] Impaired antigen presentation[11,12] Increased anti-inflammatory cytokines (IL-10)[5,11,12] Inhibits proinflammatory cytokines (eg, IL-1β, IL-23)[12]	Increased total numbers[5,a] Relative increase in transitional cells[5] Relative decrease in class-switched memory cells[5]	Normal[13]
Glatiramer acetate	Decreased BAFF[14,b] Impaired antigen presentation[15,b] Increased anti-inflammatory cytokines (IL-4, IL-10)[14-16] Inhibits pro-inflammatory cytokines (eg, IL-17, IL-6, TNF-α, LT)[14,16]	Decreased total numbers[16,a] Relative increase in naive cells[16,a] Relative decrease in plasmablast and memory cells[16]	Impaired relative to healthy and interferon-treated controls (influenza)[13]
Fingolimod	Sequesters B cells in lymphoid tissue; impedes access to CNS Decreased expression of costimulatory molecules[17] Increased anti-inflammatory cytokines (IL-10)[17] Inhibits proinflammatory cytokines (eg, TNF-α)[17]	Decreased total numbers[17] Relative increase in naive cells[17] Relative decrease in newly produced B cells and memory cells[17,19]	Impaired relative to placebo treated, but seroprotection usually achieved[13,20]
Dimethyl fumarate	Unknown	Slight decrease in total numbers[22,23]	Unknown
Teriflunomide	Impairs proliferation of rapidly dividing cells Less infiltration into CNS[25,b]	Unknown	Generally intact; may be slightly diminished for some antigens[13]
Natalizumab	Impairs transmigration into CNS and other tissues	Increased total numbers[30,31] Increase in precursor, regulatory, marginal zone–like, and memory cells[32-35] Relative decrease in naive B cells[34]	Decrease in plasma IgG and IgM[36] Possibly impaired; data are conflicting[13]
Alemtuzumab	Increased BAFF[41] Temporary depletion of B cells with subsequent reconstitution; long-term depletion of T cells	Increase in newly produced cells (immediately after infusions) and mature naive cells[41] Relative decrease in memory cells[41]	Normal[13]
Mitoxantrone	Cytotoxic for rapidly dividing cells Increased anti-inflammatory cytokines (IL-10)[45] Inhibits proinflammatory cytokines (eg, LT, TNF-α)[45]	Decreased total numbers after infusions[44]	Impaired[13]
Rituximab or ocrelizumab	Long-term (months) depletion of CD19⁺ B cells specifically (circulation and CNS)[46] Increased anti-inflammatory cytokines (IL-10)[50] Inhibits proinflammatory cytokines (GM-CSF)[50]	Complete depletion of CD19⁺ cells Mature plasma cells spared	Impaired for recall antigen[13,c] Live viral vaccines contraindicated