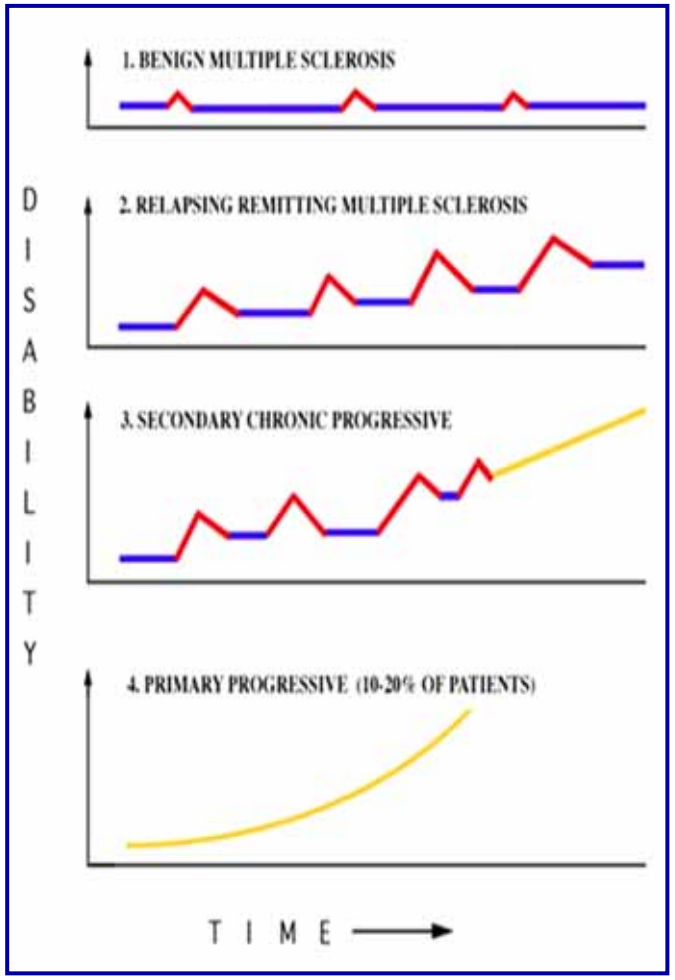
Multiple Sclerosis Pathology

- Introduction to MS
- Gross pathology of MS
- Cellular pathology
- Pathogenetic mechanisms

Prof R Reynolds 2011

MS SYMPTOMS & PATHOLOGY

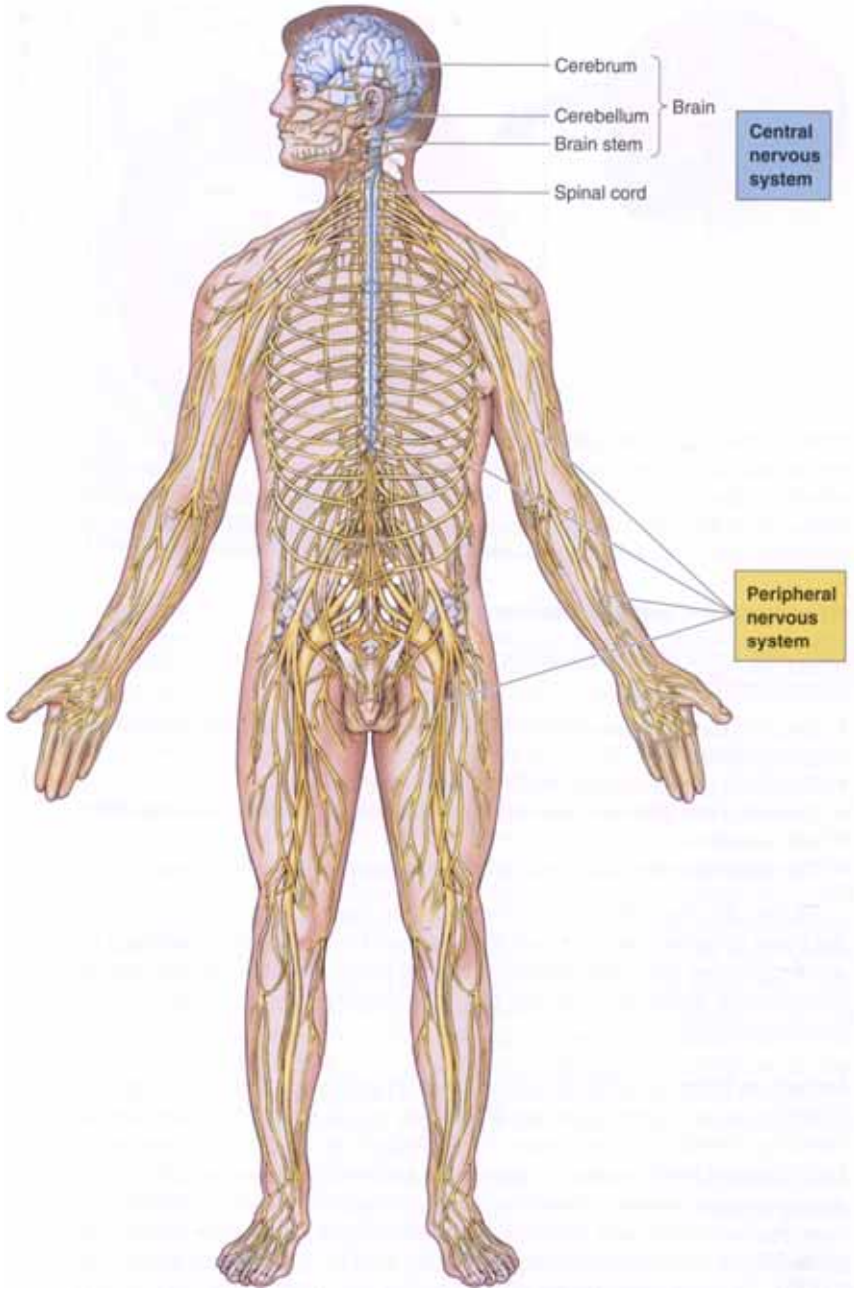
- MS is characterised by multiple episodes of the same or different neurological symptoms separated by periods of remission
- MS follows a very unpredictable and variable disease course from relatively benign forms to rapidly progressive forms.
- Although neurological recovery does occur during the early stages, the majority of MS cases develop chronic progressive symptoms eventually.



The central and peripheral nervous systems

CNS

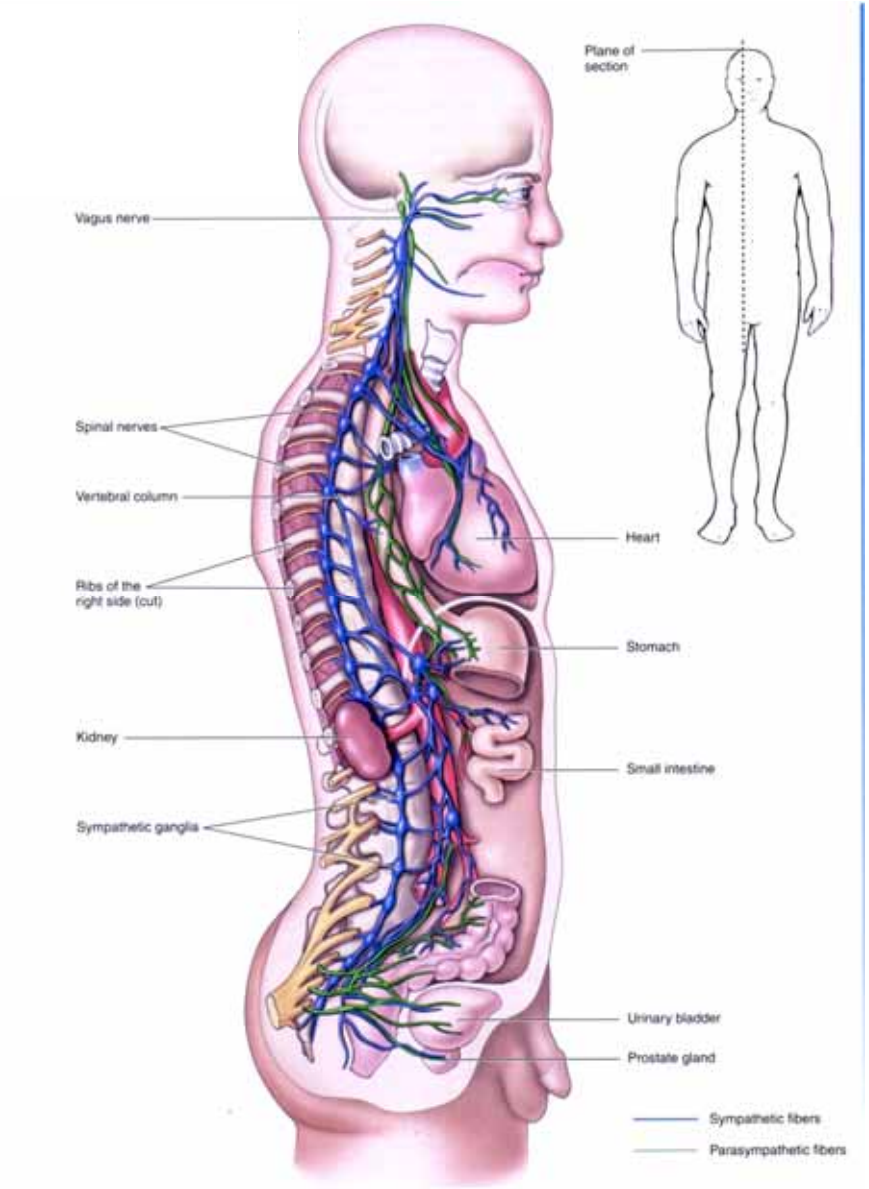
PNS



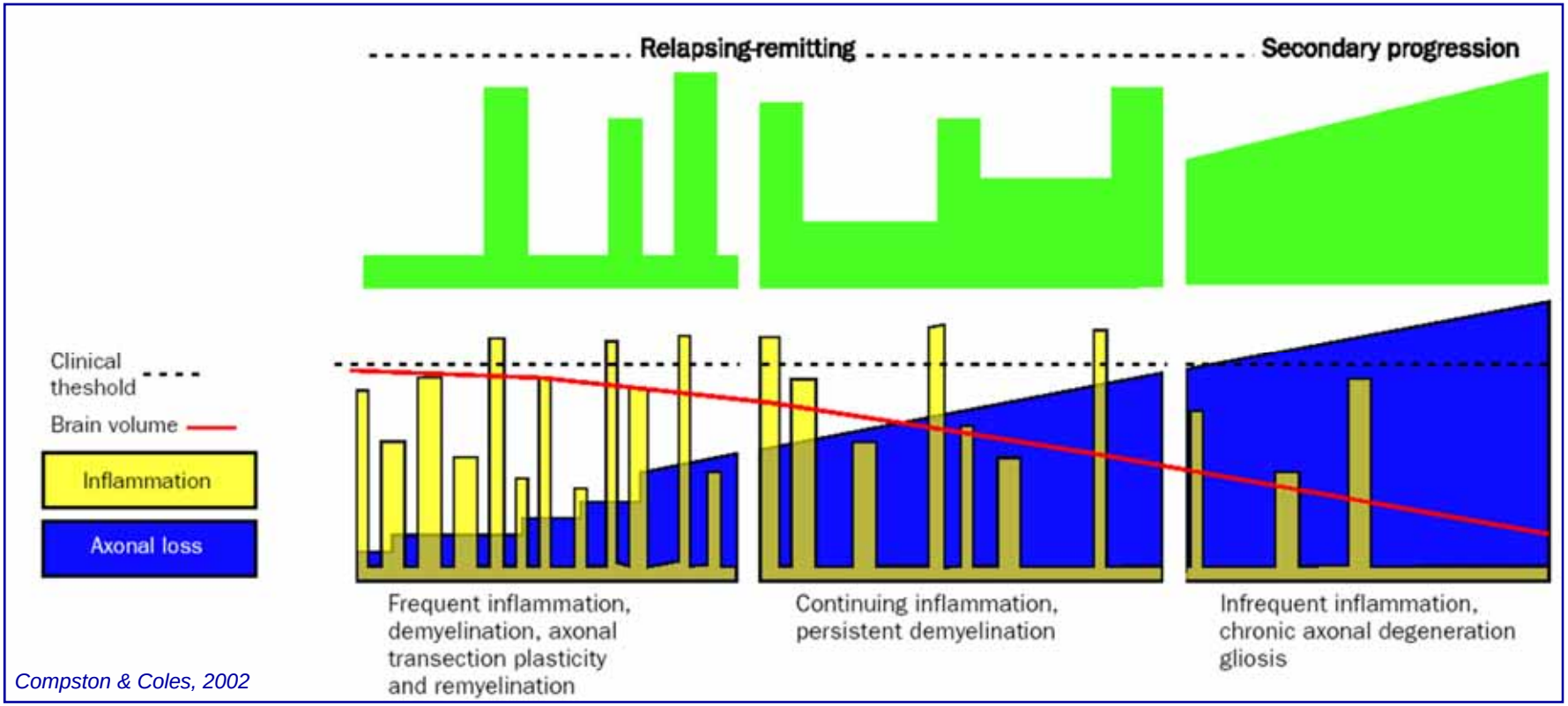
MS damages only the central nervous system

But other parts of the nervous system are affected

The autonomic nervous system



- Gut function
- Blood pressure
- Heart rate
- Kidney function
- Sweating
- Sexual function
- Bladder function

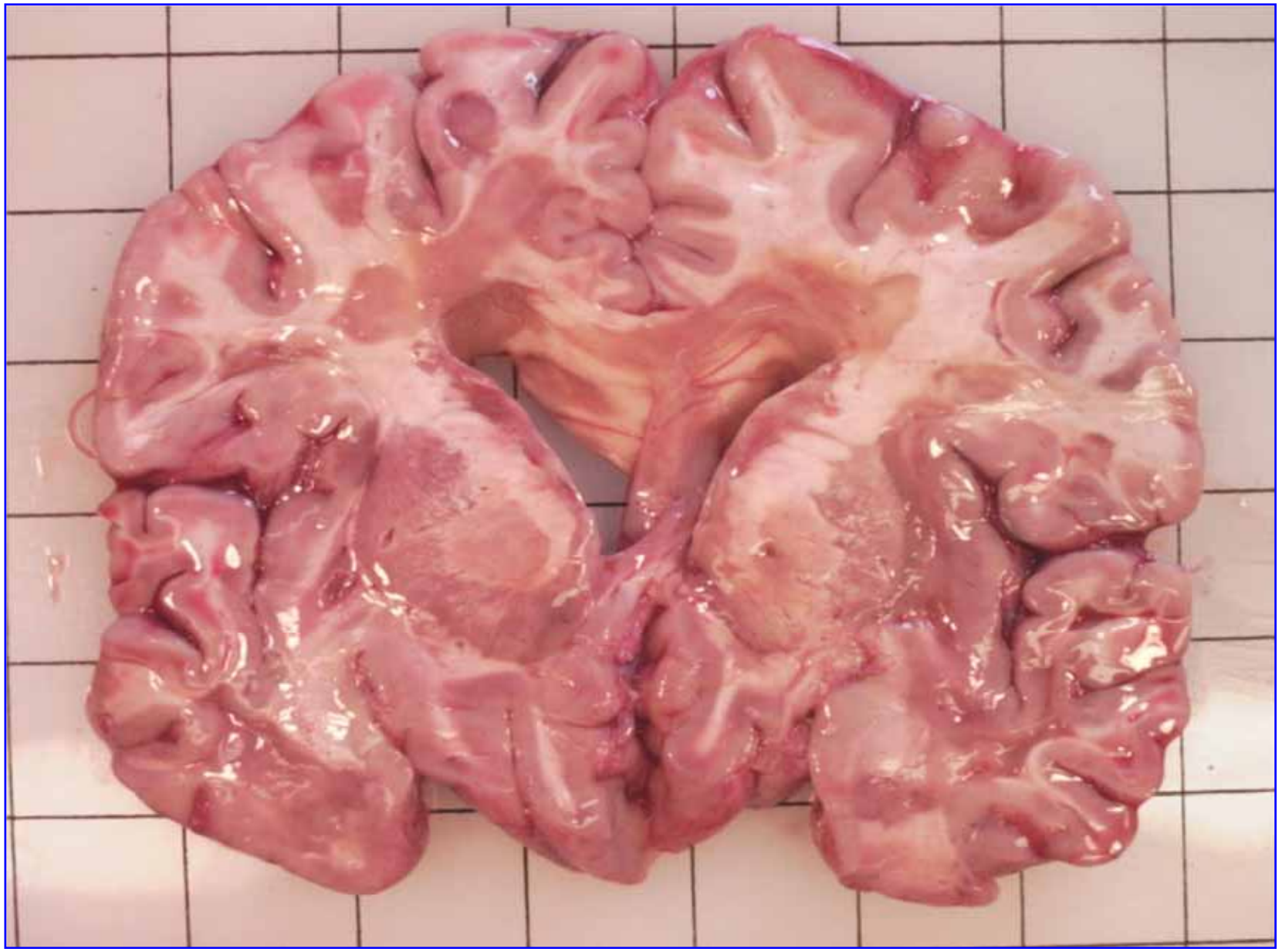


Compston & Coles, 2002

Clinico-pathological correlations in MS

- inflammatory foci without demyelination	- acute relapses
- primary demyelination	- acute & chronic
- grey matter demyelination	- progressive
- axonal loss in lesions	- progressive symptoms
- grey matter neuronal and axonal loss	- progressive motor, sensory and cognitive
- diffuse white matter changes	- fatigue?
- diffuse grey matter changes	- motor, sensory and cognitive symptoms. Fatigue?

What can we learn from post-mortem studies?



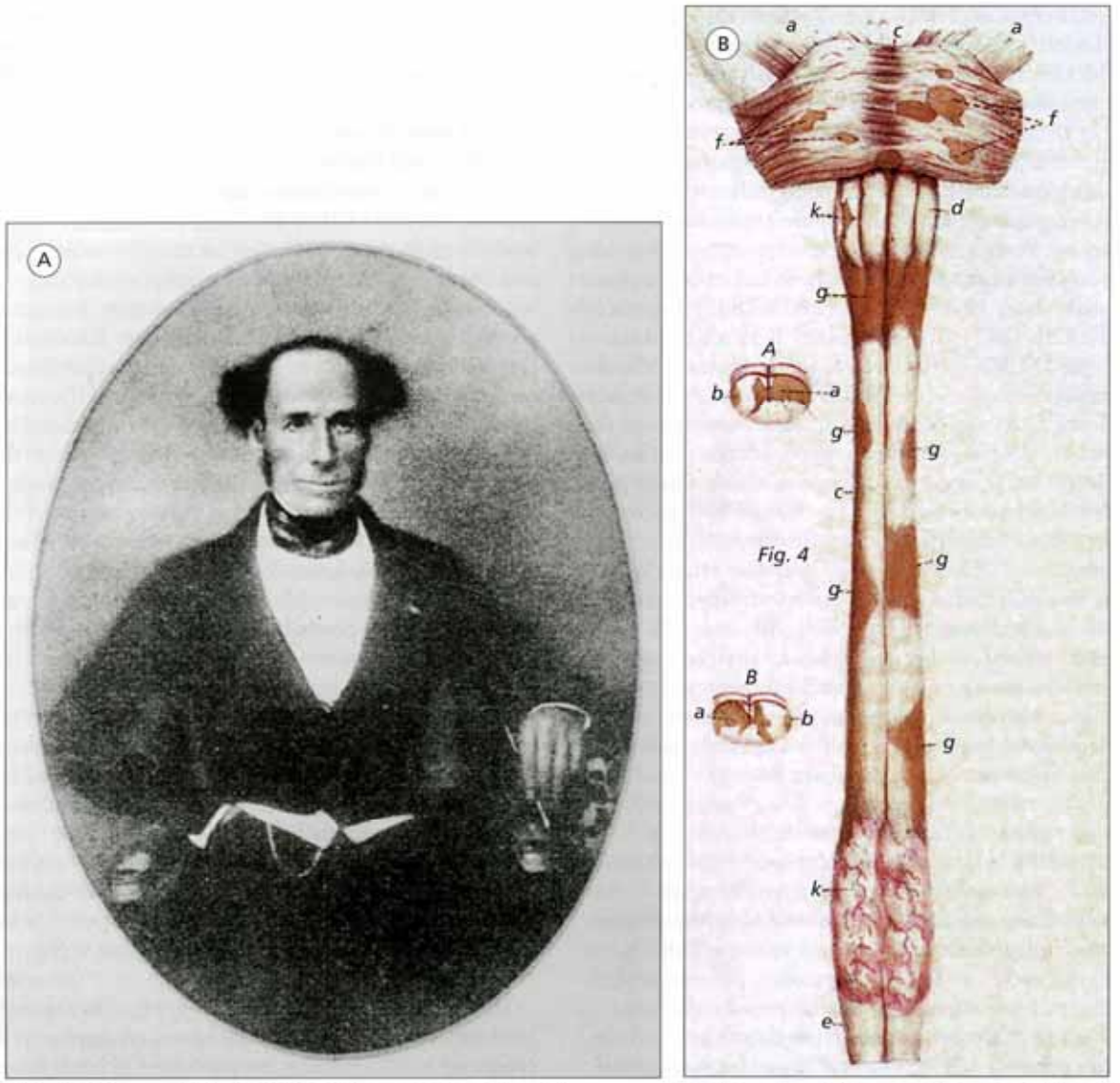
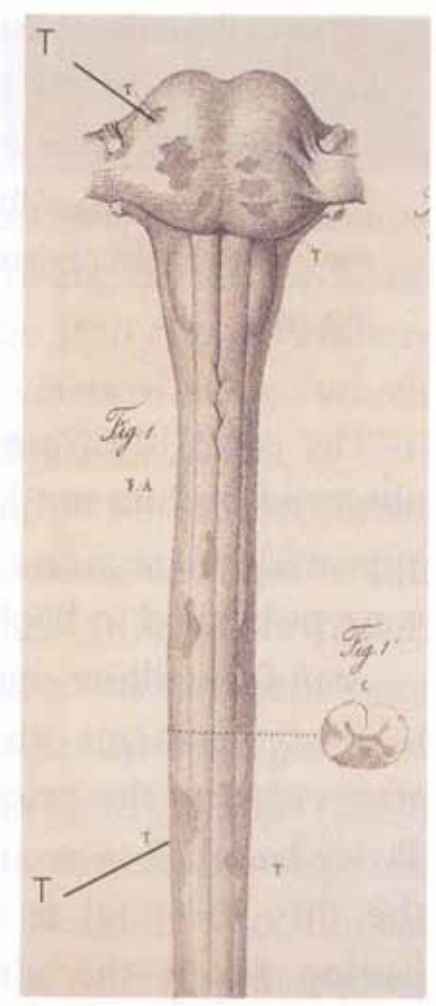
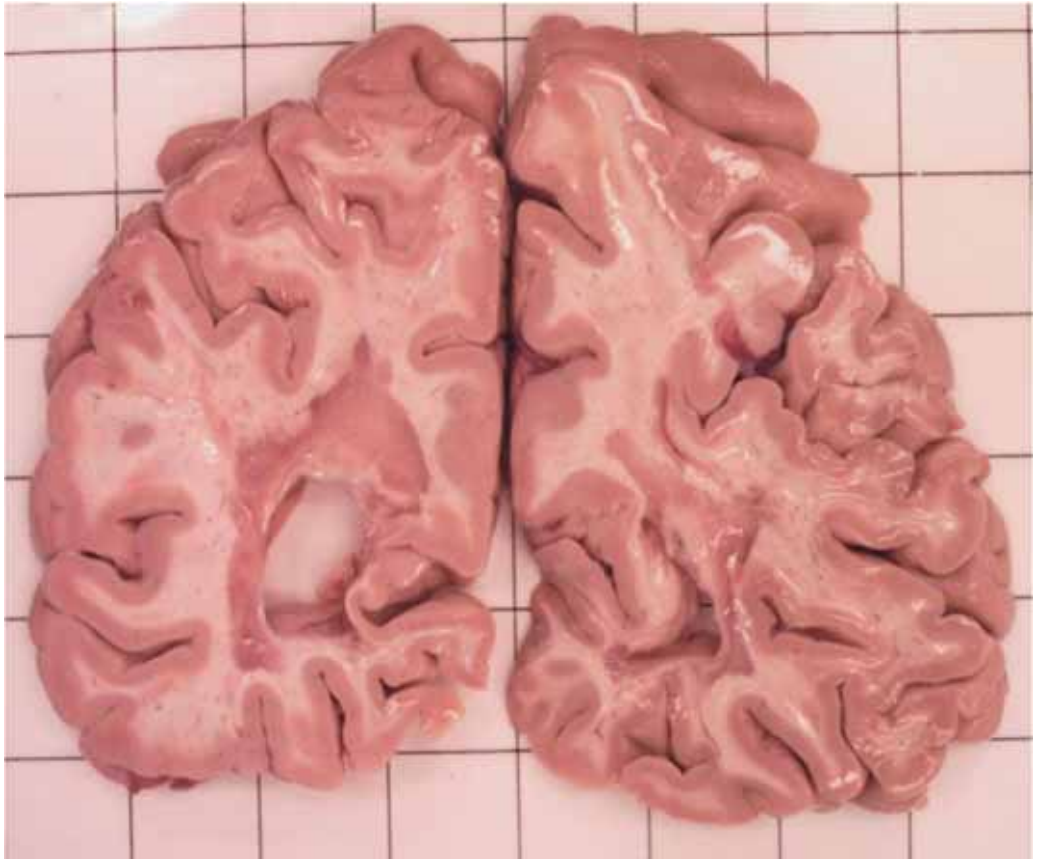


Figure 1.3 (A) Robert Carswell (1793–1857). (B) *f*: Isolated points of the pons varolii of a yellowish-brown colour. *g*: Patches of the same kind on the spinal cord, all of them occupying the medullary substance, which was very hard, semitransparent and atrophied. The atrophy was more conspicuous in some points than in others and is particularly well seen in the figure at *h* where it affects the right olivary body. *k*: Softening of a portion of the cord. *A* and *B* represent transverse sections of the cord to show that the discoloration commences on the surface of the white and extends inwards to the grey substance. From Carswell (1838).

MS Pathology

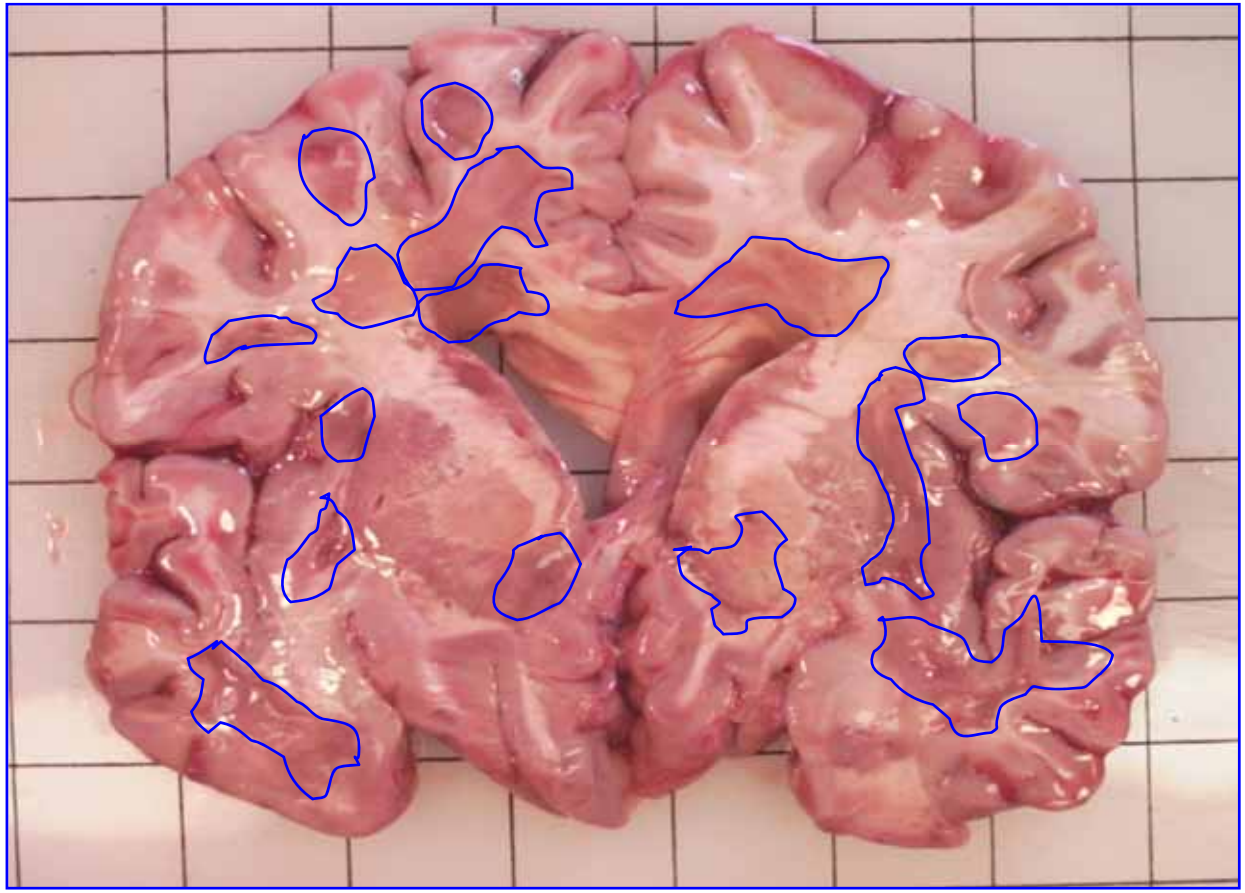


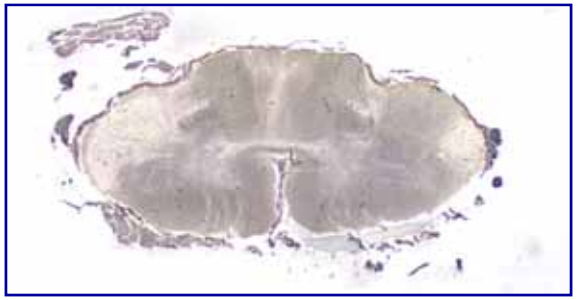
Cruveilhier (c1841)



The essential CNS lesion in MS is the demyelinated plaque which can be identified at post-mortem and can occur at any site where myelin sheaths are present.

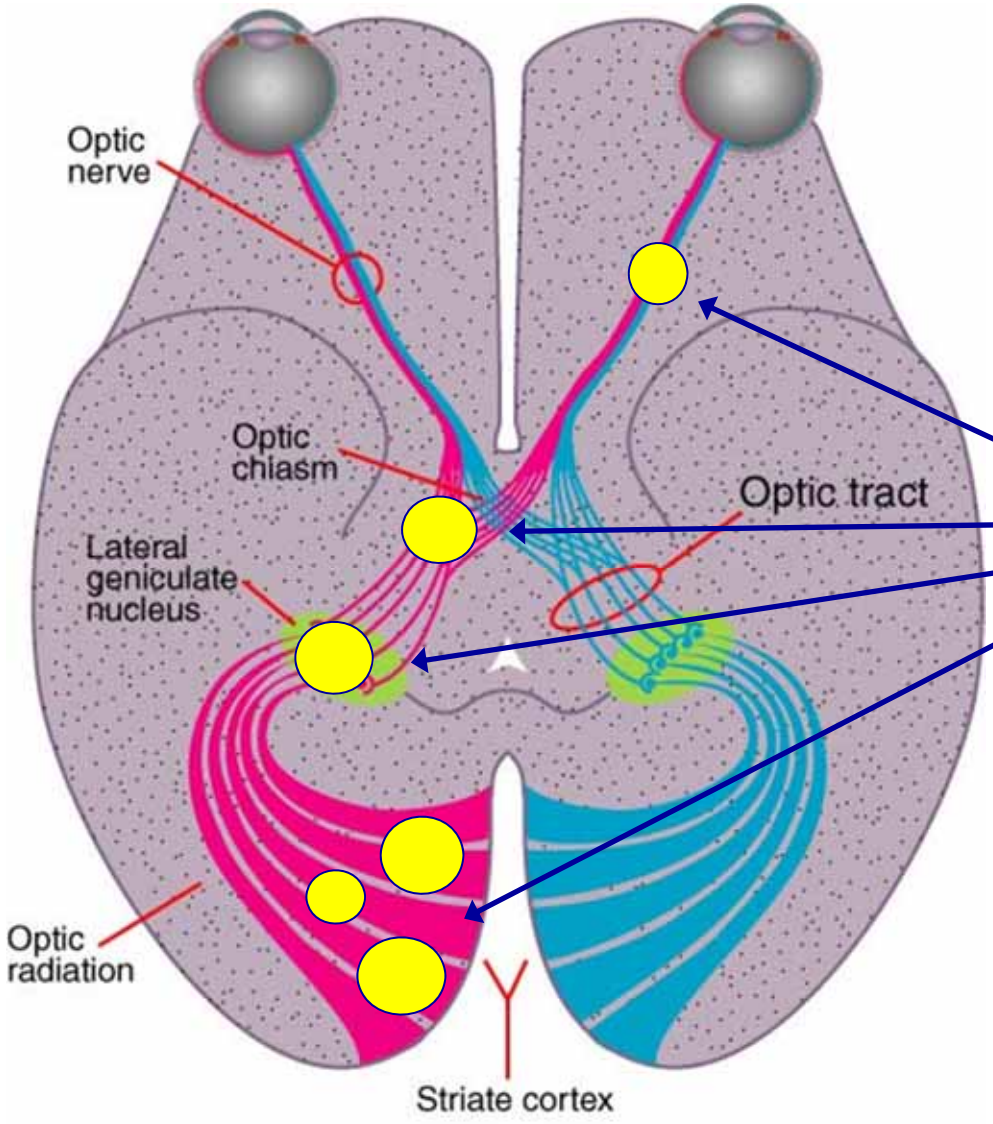
Damage can occur anywhere in the brain and spinal cord





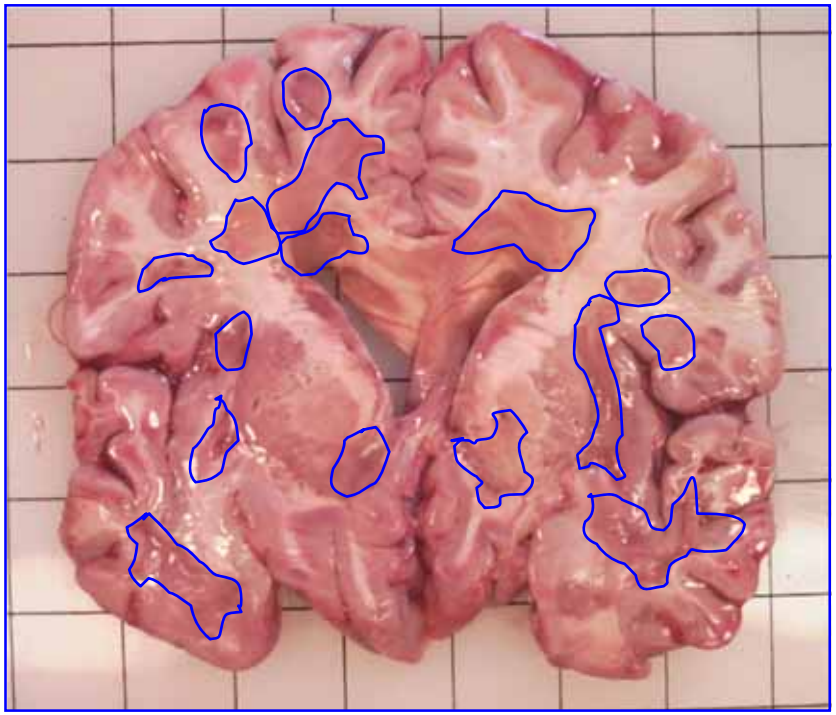
But it is difficult to ascribe every symptom to a particular lesion and not all lesions cause symptoms

A particular symptom could be caused by damage in different parts of a system

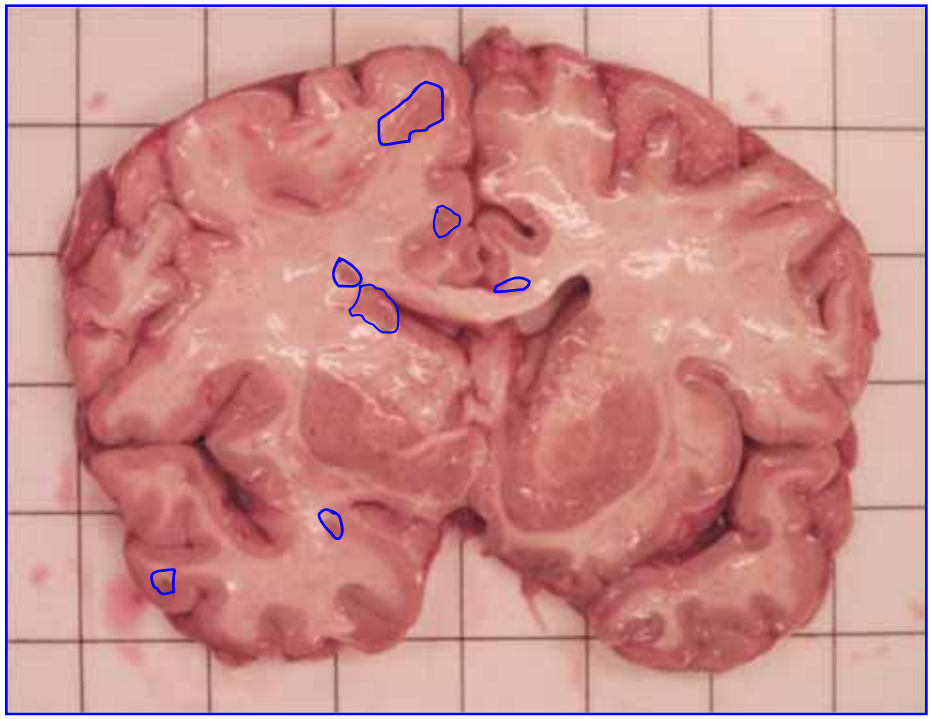


Why are symptoms so varied

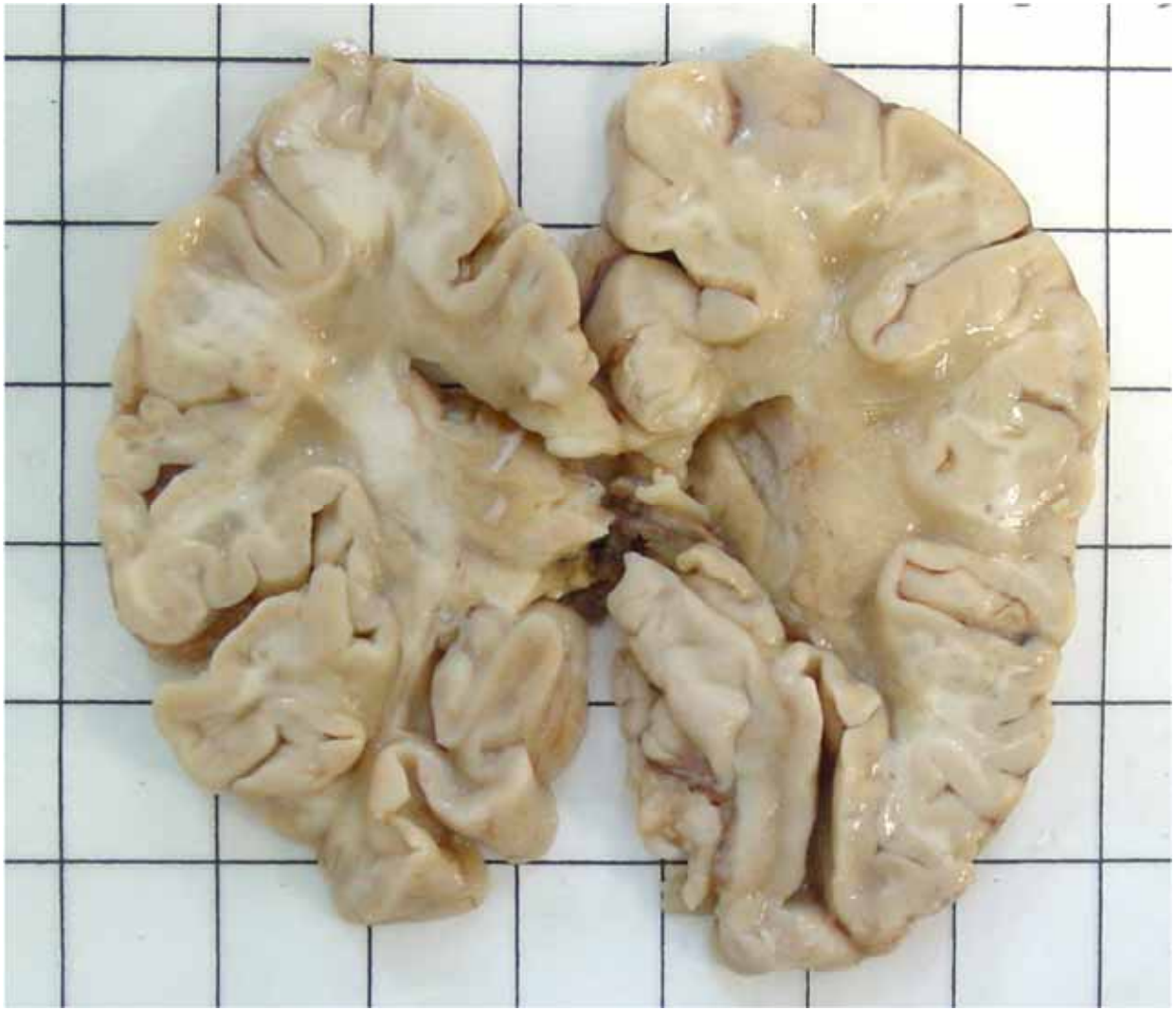
Because the amount and location of damage to the nervous system is different in each person with MS



Disease duration <20 years, age 44



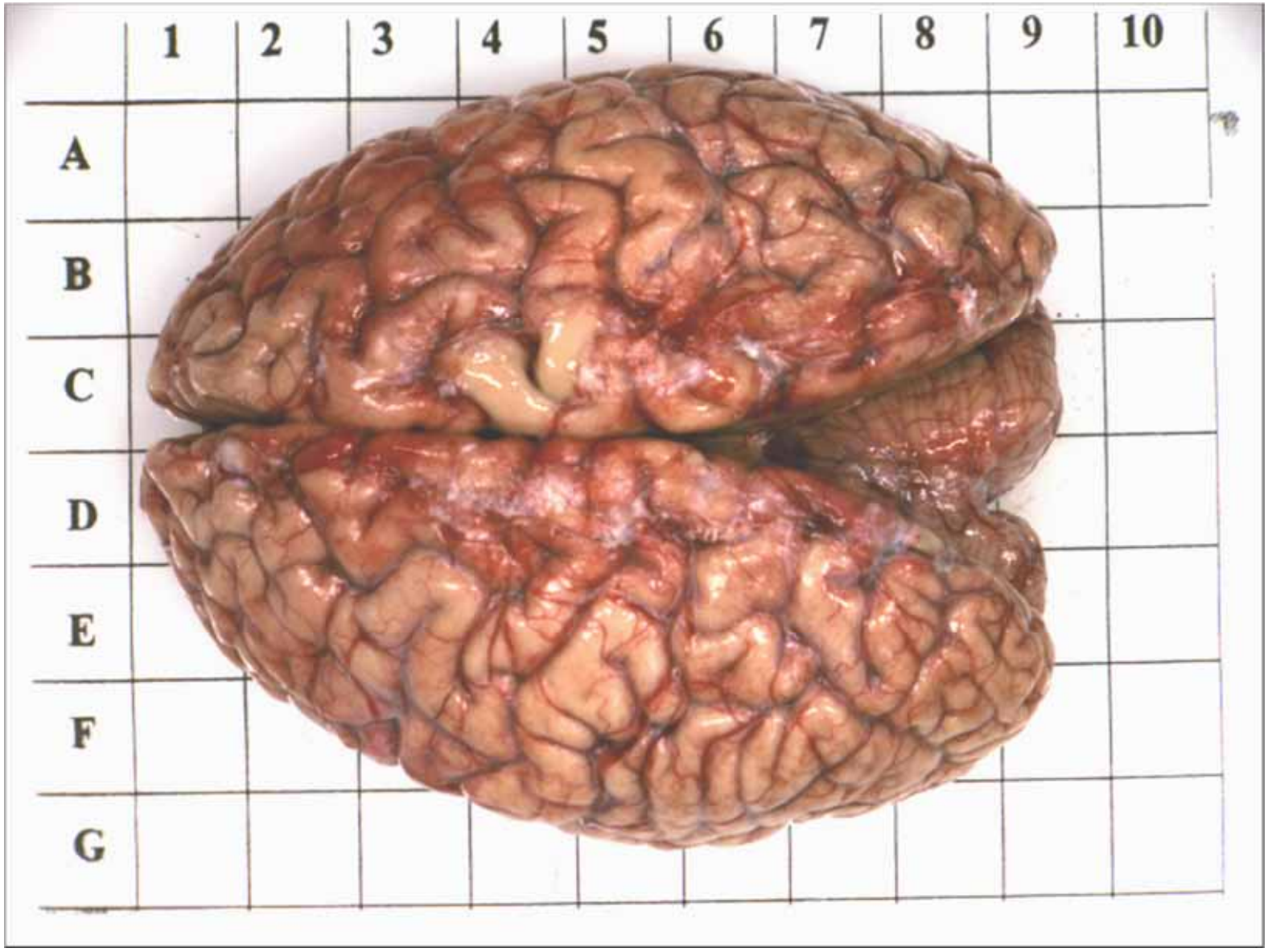
Disease duration 35 years, age 71



Acute inflammation in very aggressive MS. Note the multiple large plaques, some of which are quite poorly defined

Gross Pathology of MS

- Inflammation
- Demyelination
- Axonal loss
- Neurodegeneration
- Atrophy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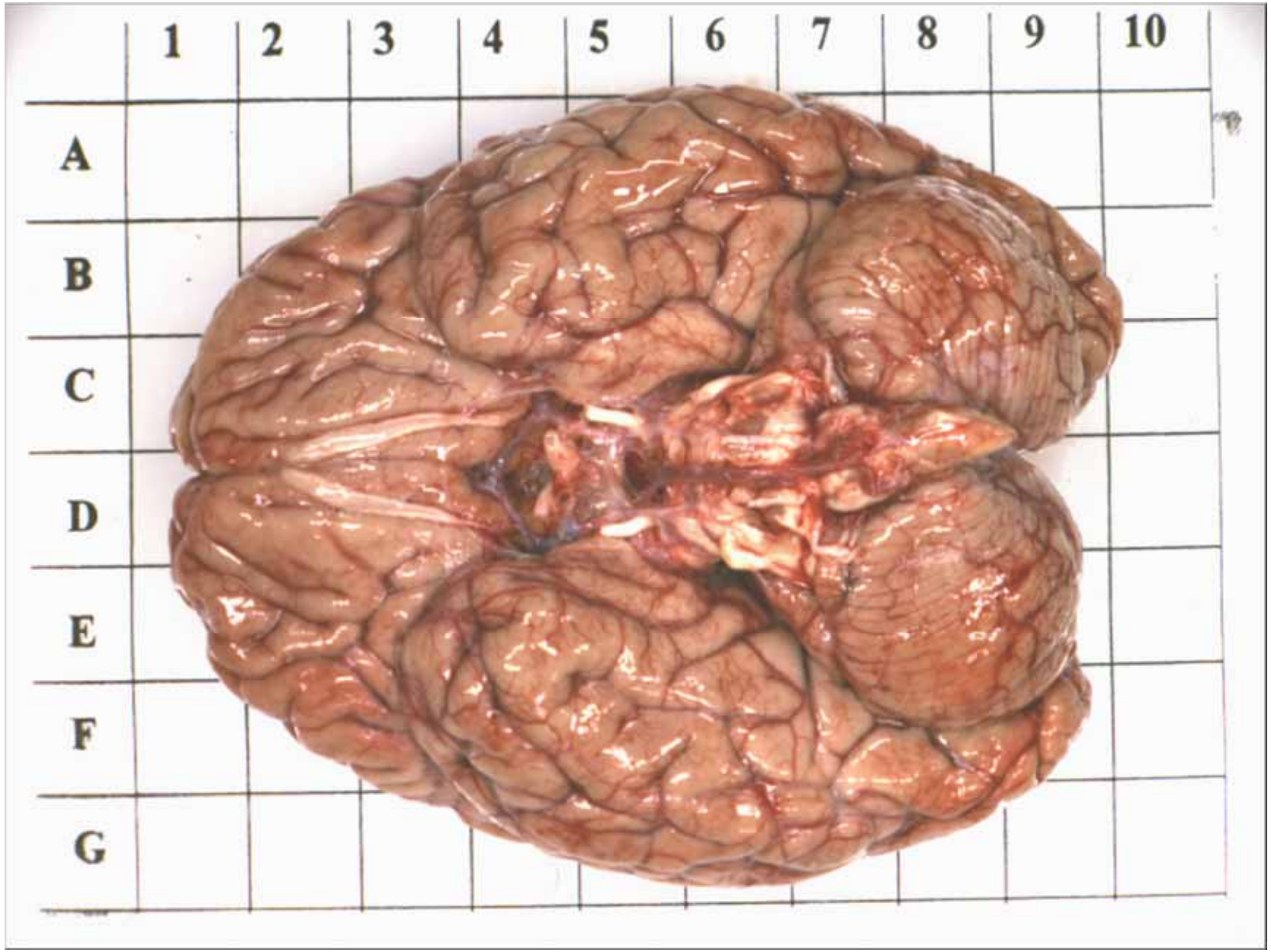
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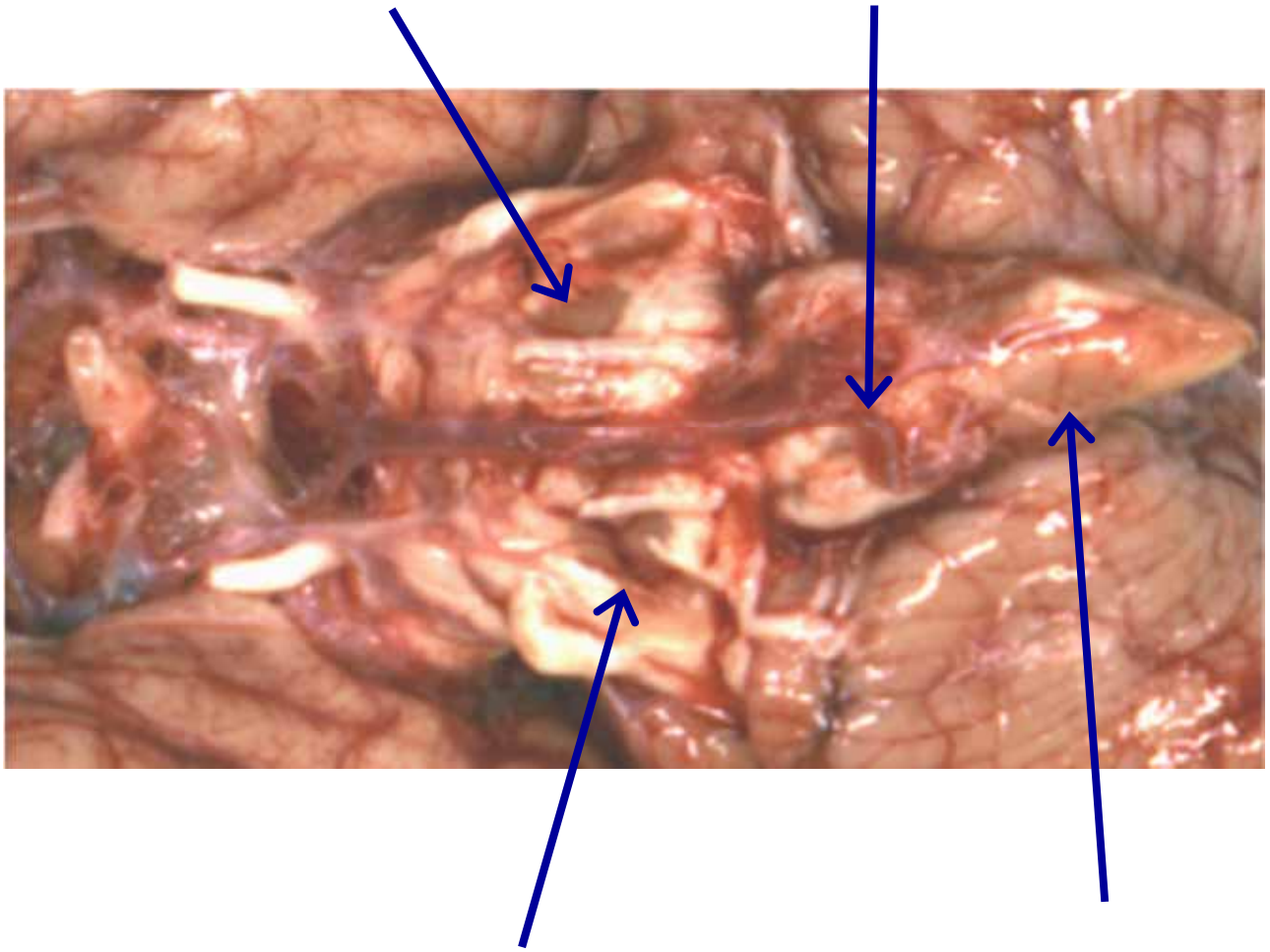
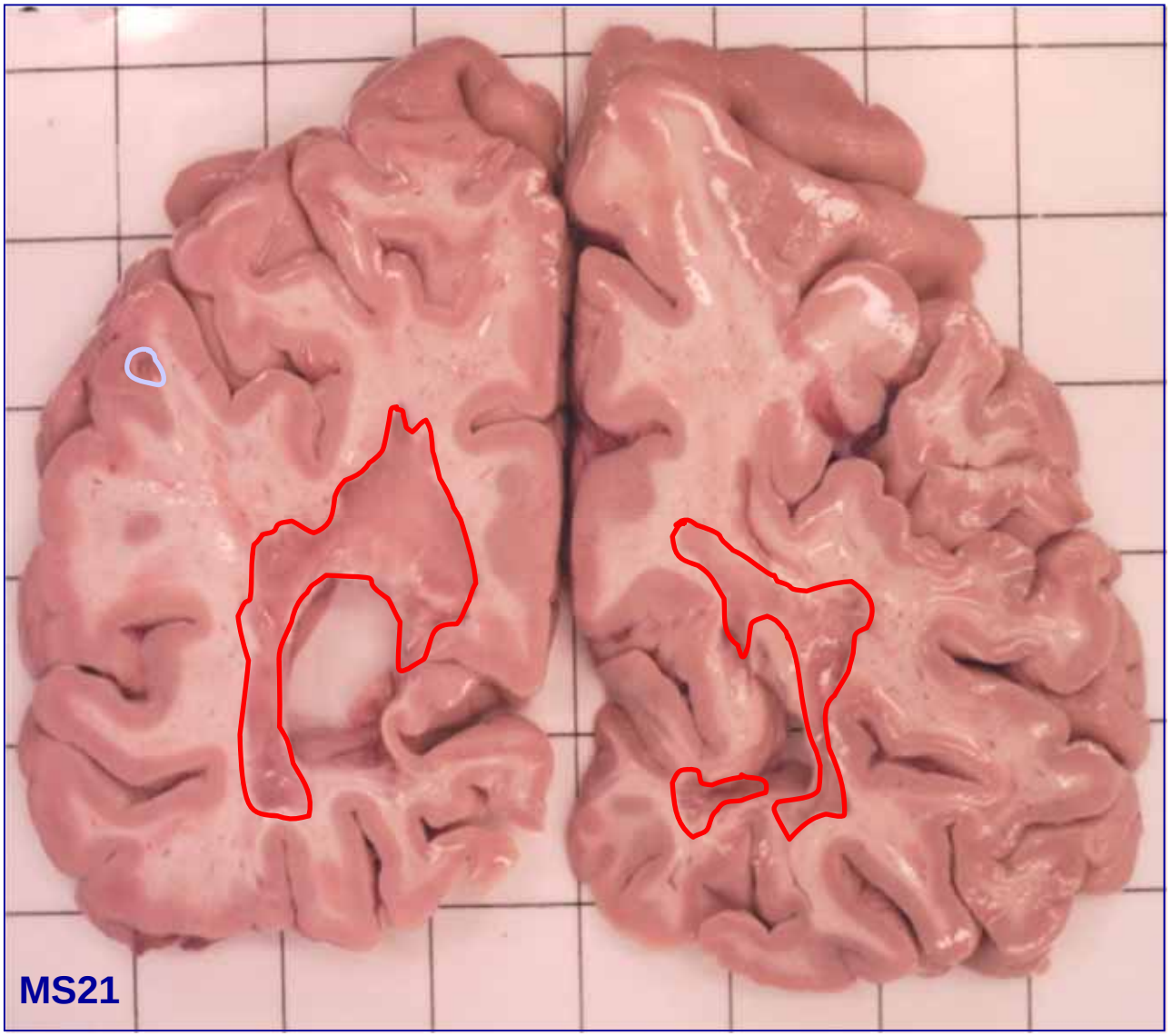
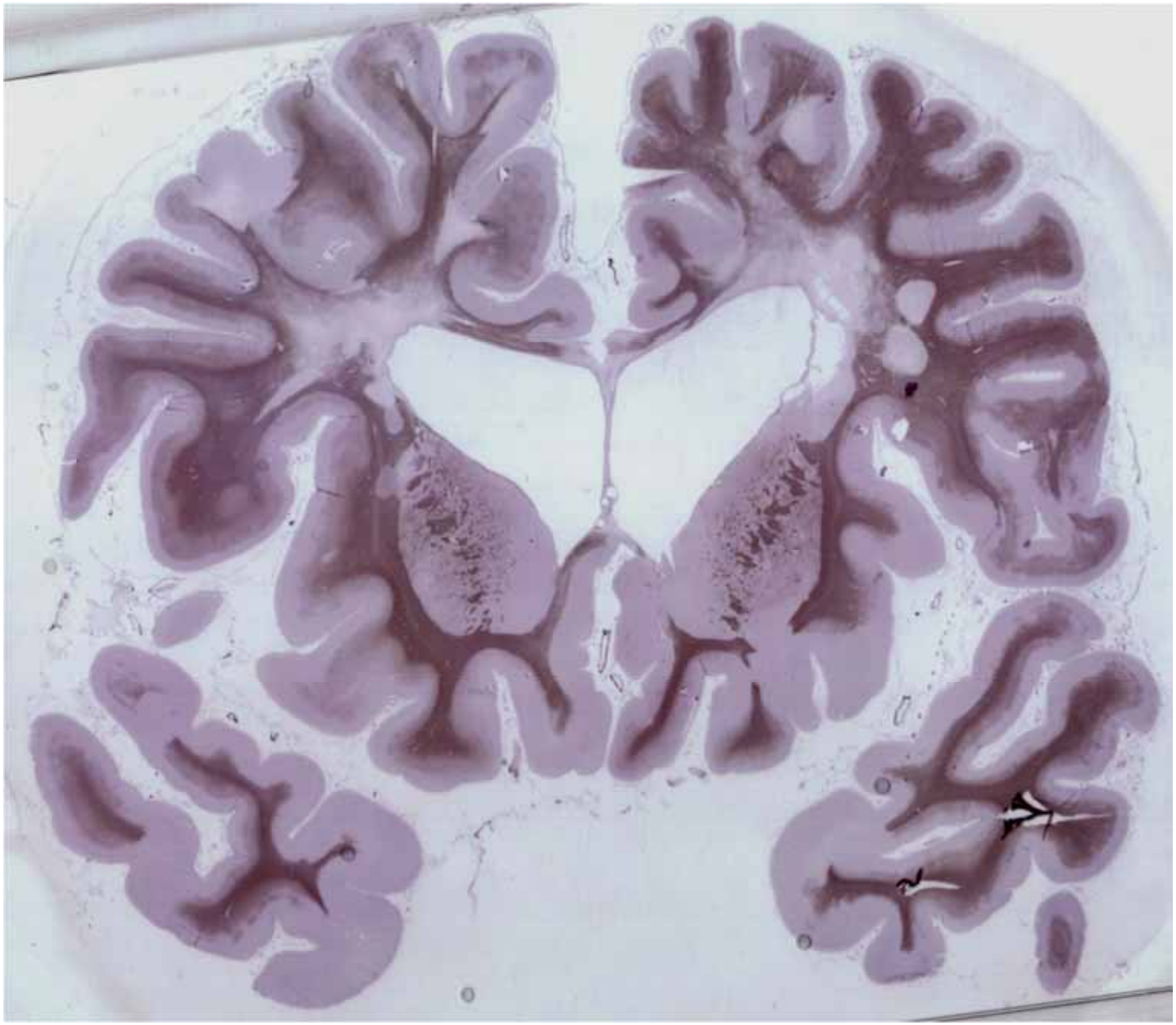
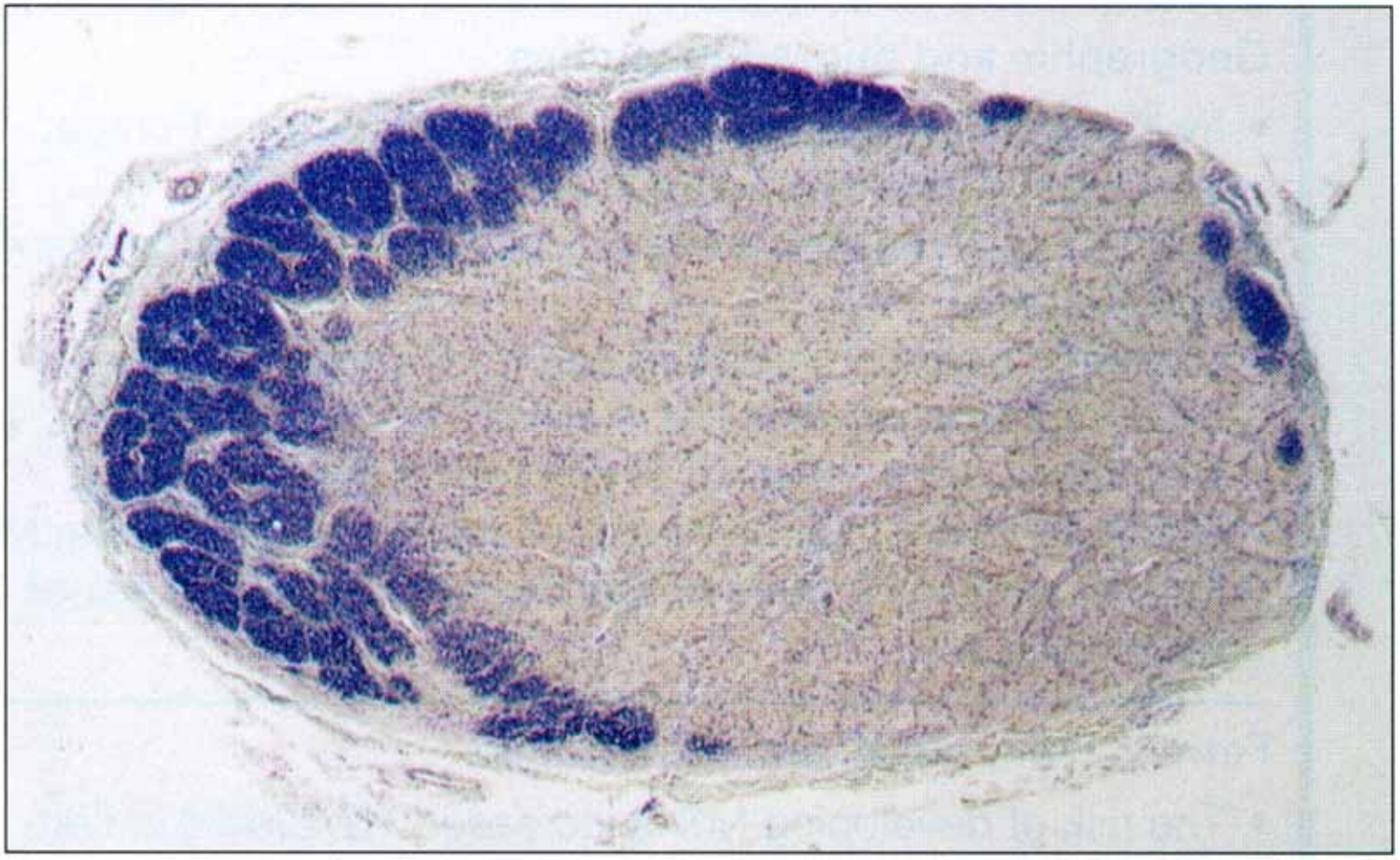


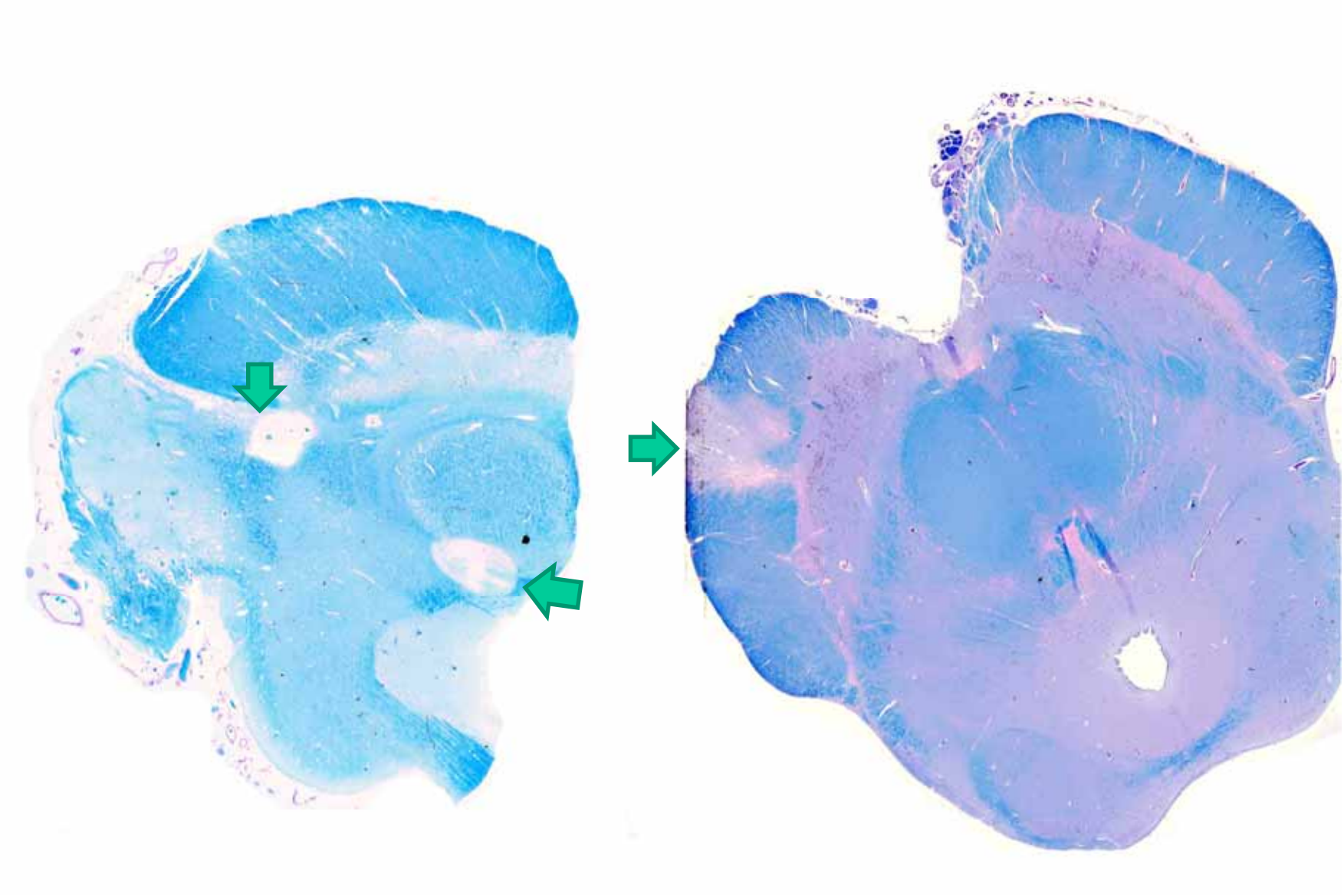


Extensive lesions often follow the lateral ventricles

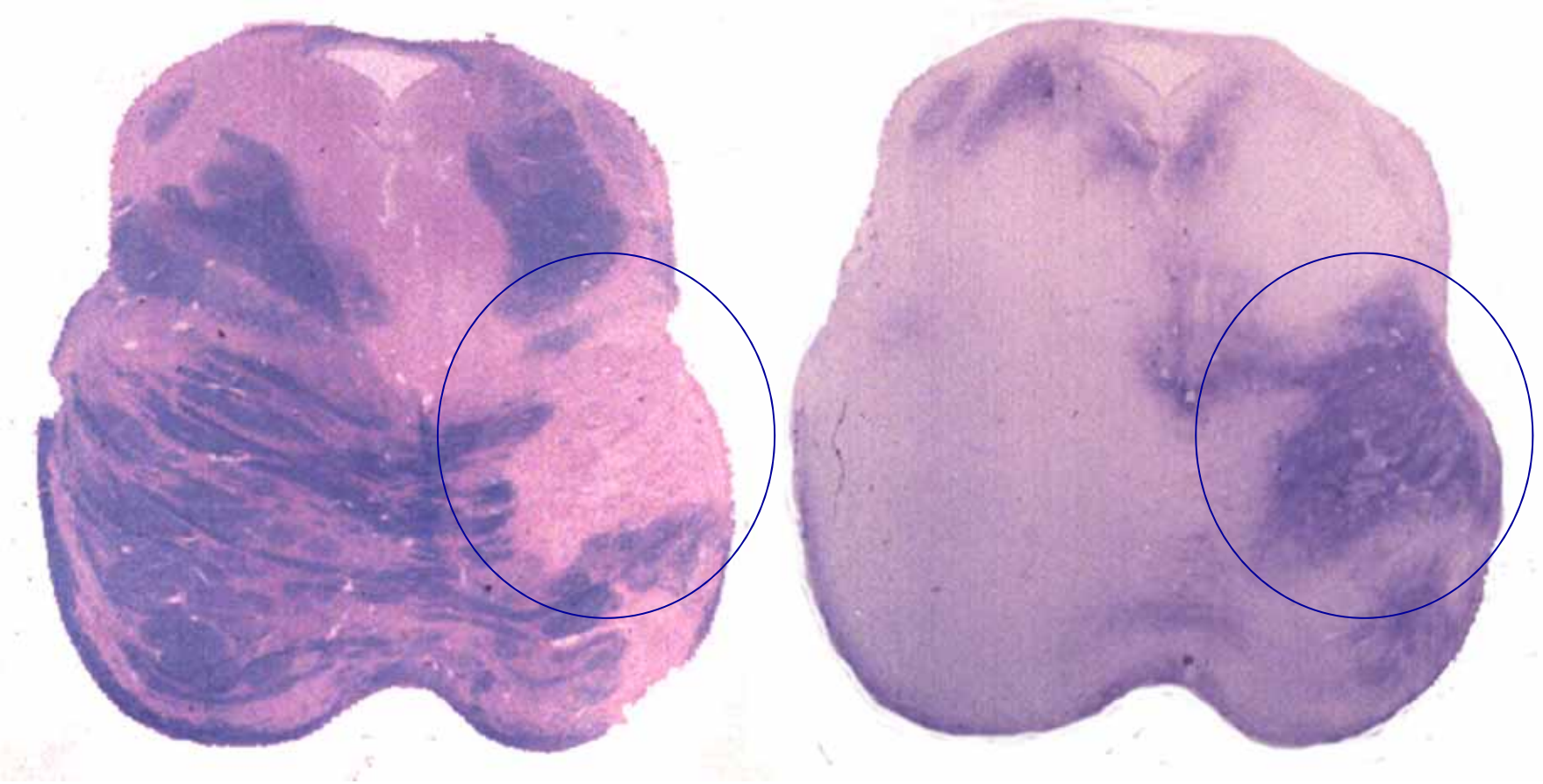




Optic nerve in MS. Transverse section through optic nerve in which only a peripheral crescent of myelin can still be stained



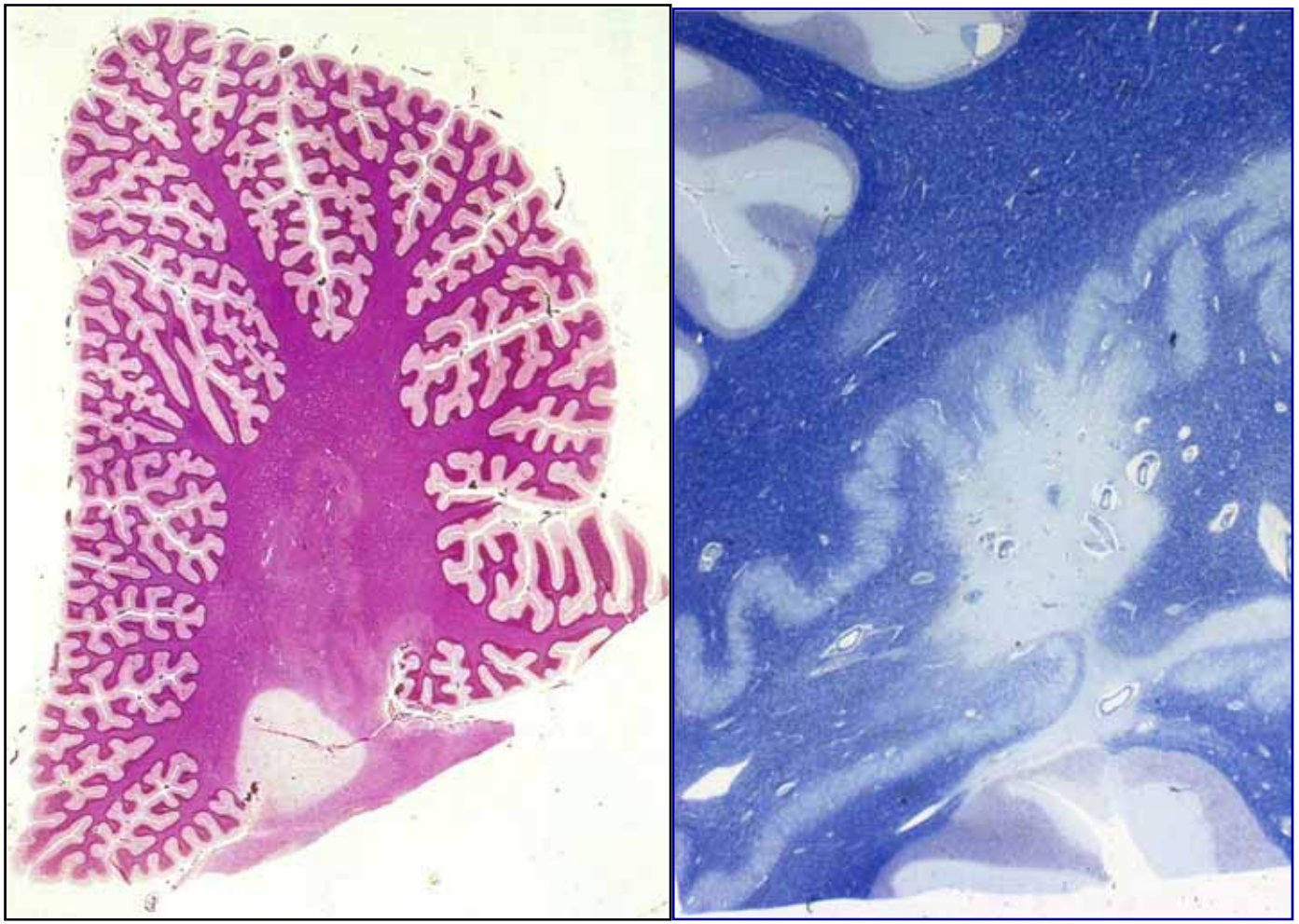
Midbrain. Lesions are common in the substantial nigra and at many levels of the pyramidal tracts



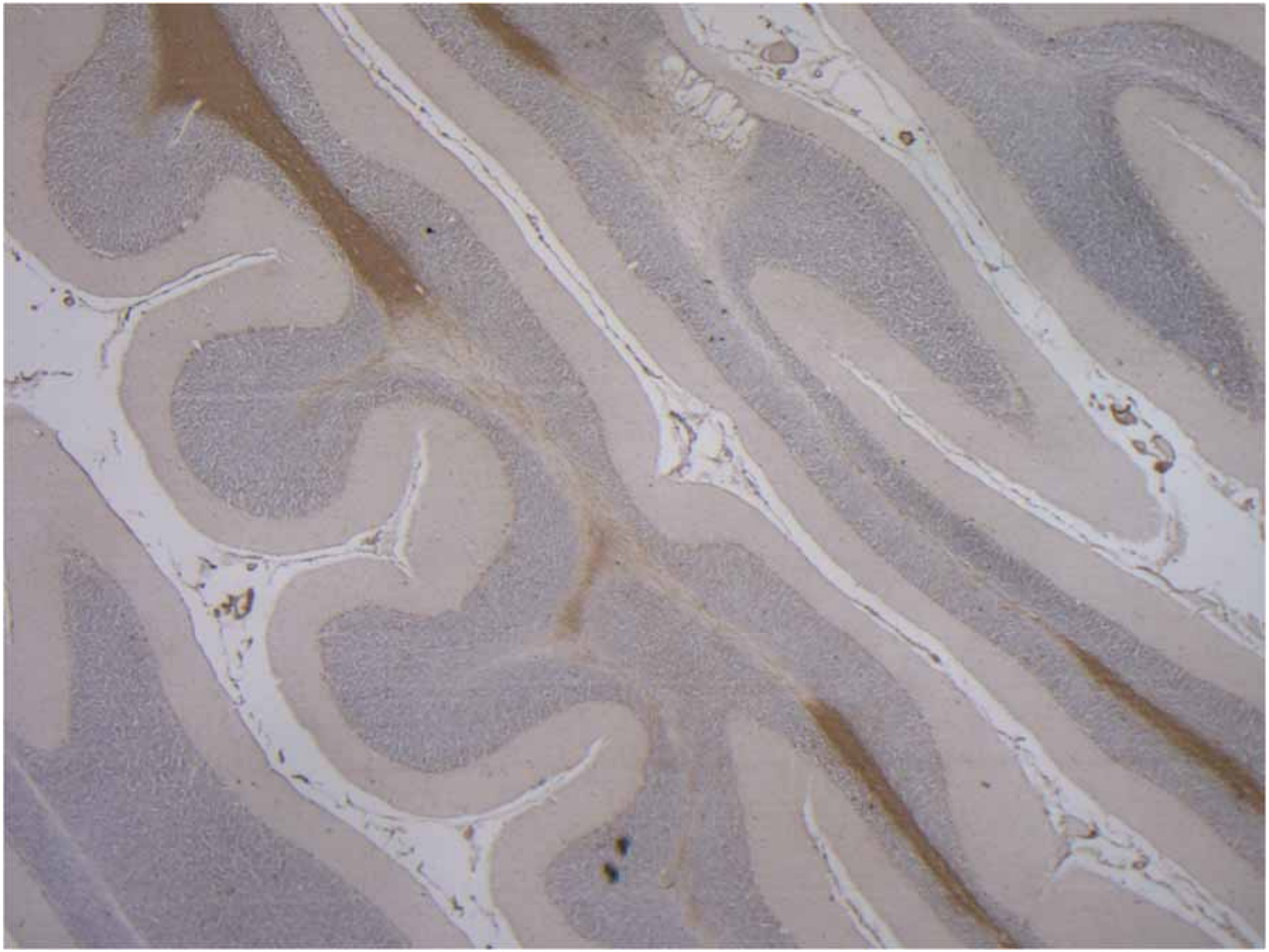
Luxol-fast blue/PAS

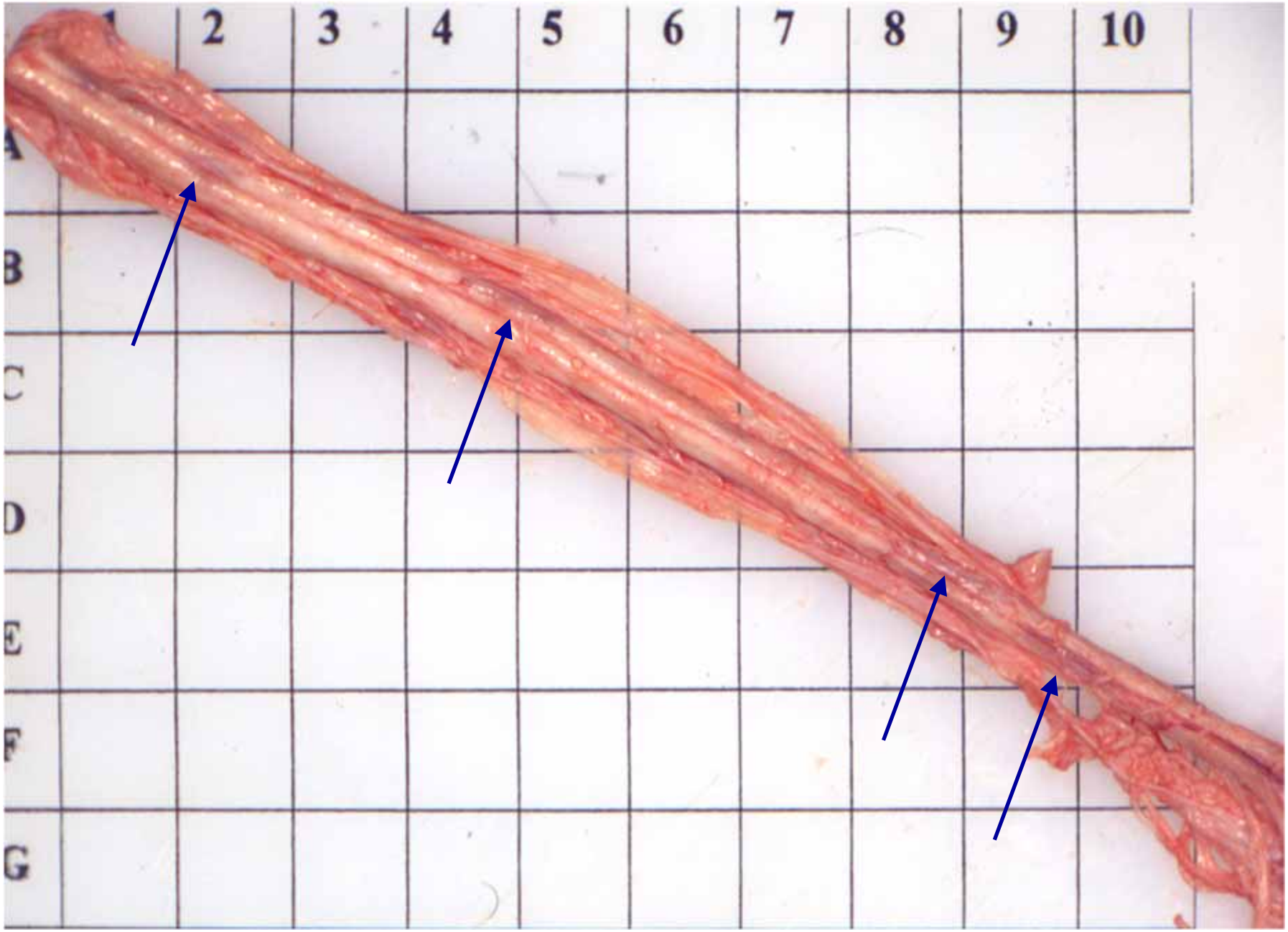
Holzer

Brainstem. Lesions are common in the pons and are likely to have major clinical significance



Lesions in the deep cerebellar white matter, nuclei and peduncles

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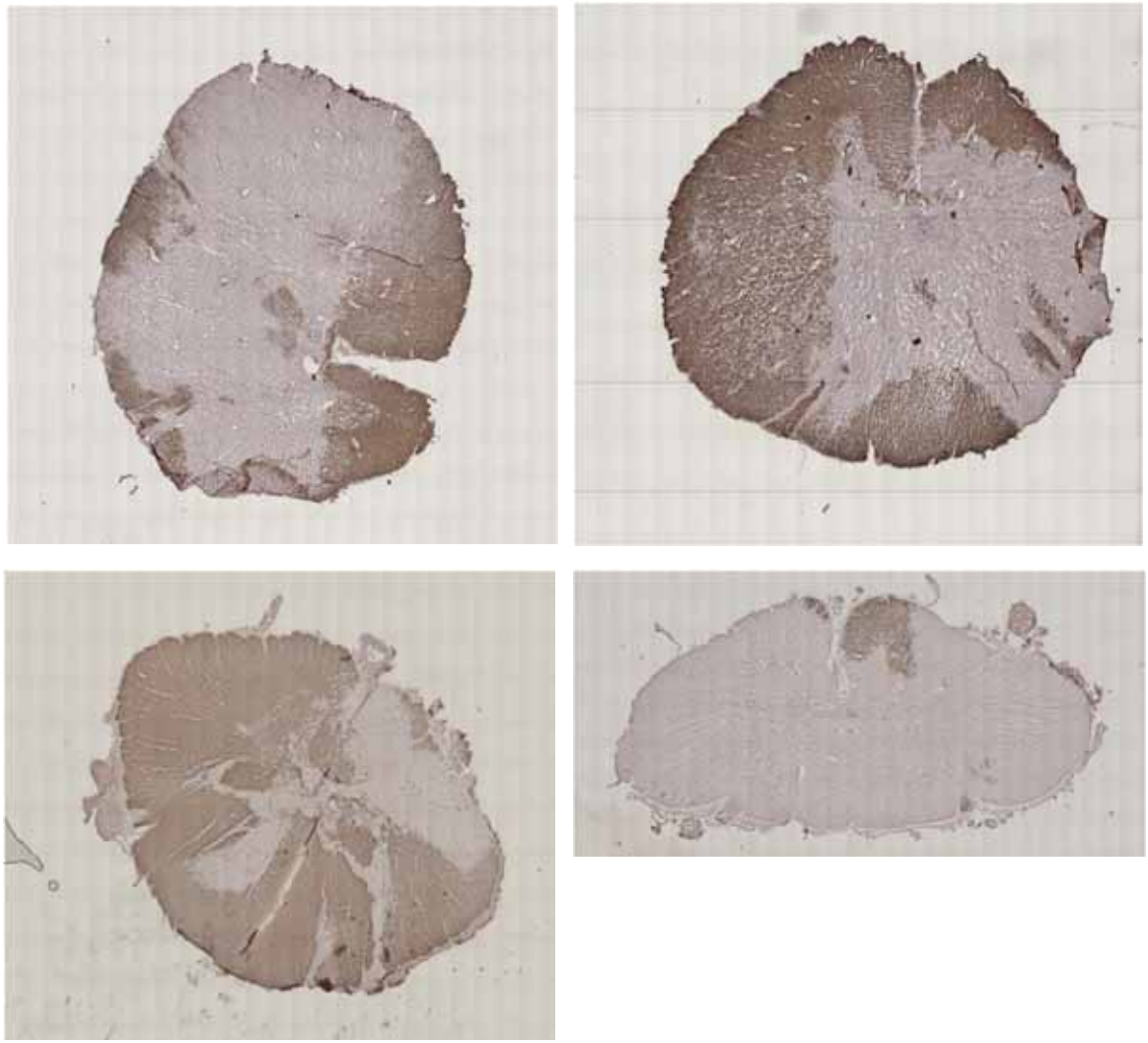
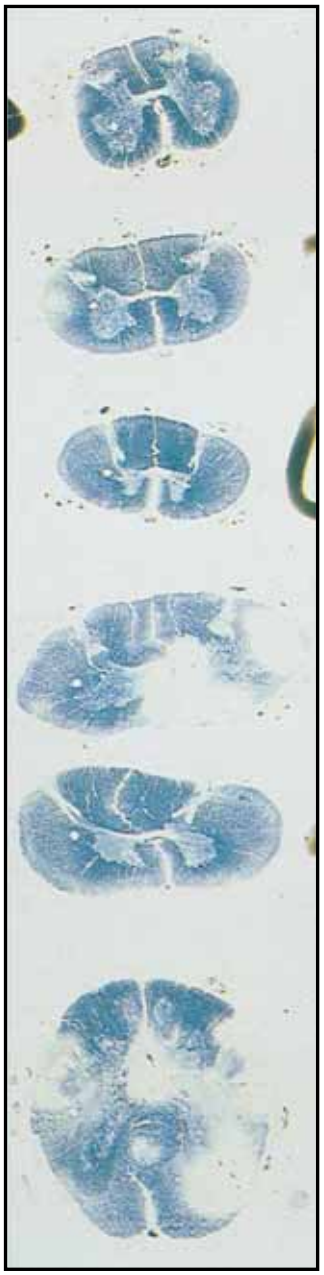
Spinal Cord Pathology

- chronic MS plaque on posterior surface of thoracic spinal cord

- spinal cord lesions often appear shrunken due to loss of axons as well as myelin sheaths





S1

L3

T6

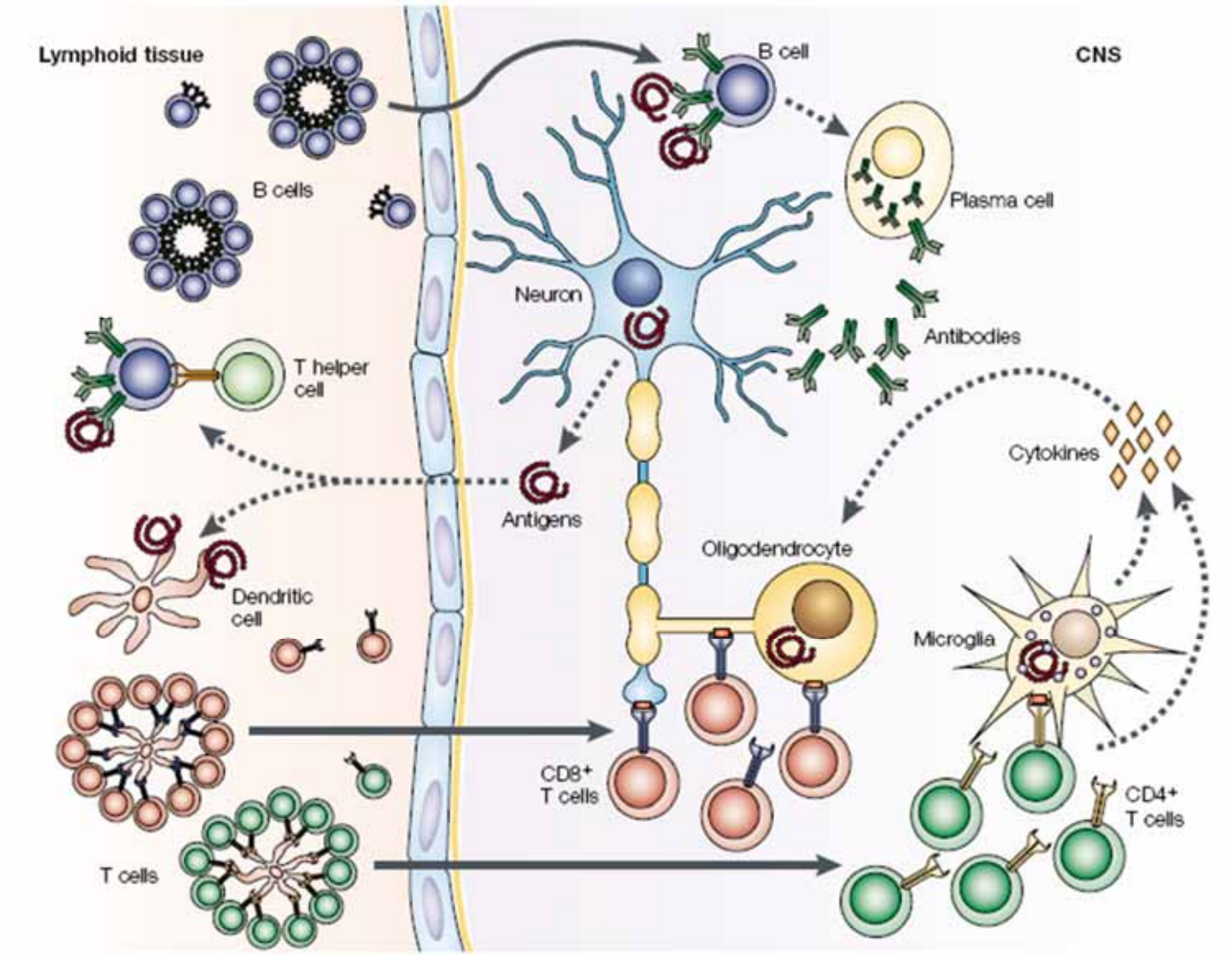
C7

C4

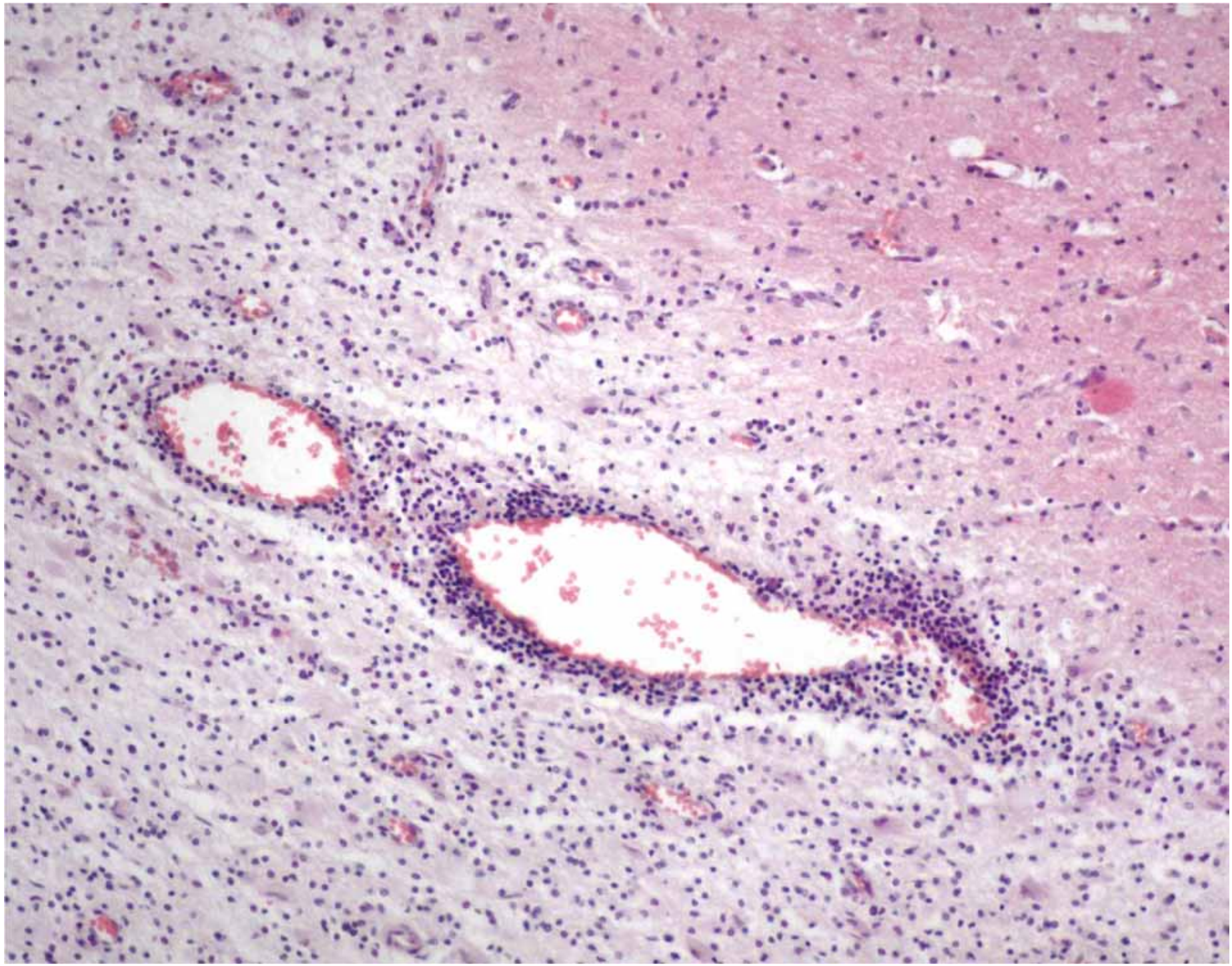
MED

Lesions are often found at multiple levels of the cord but do not follow any particular pattern

Inflammation and MS



Hemmer et al, 2002



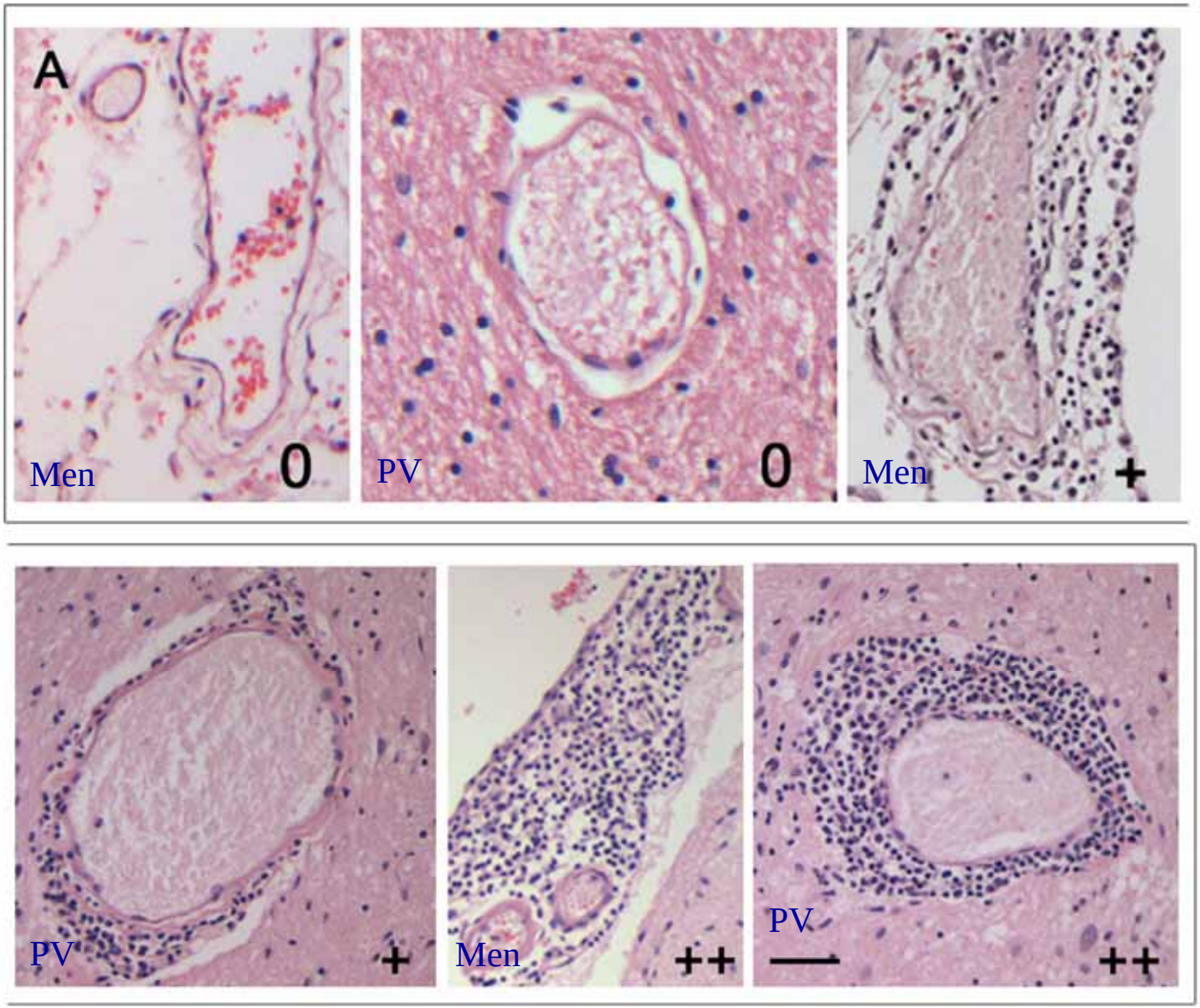

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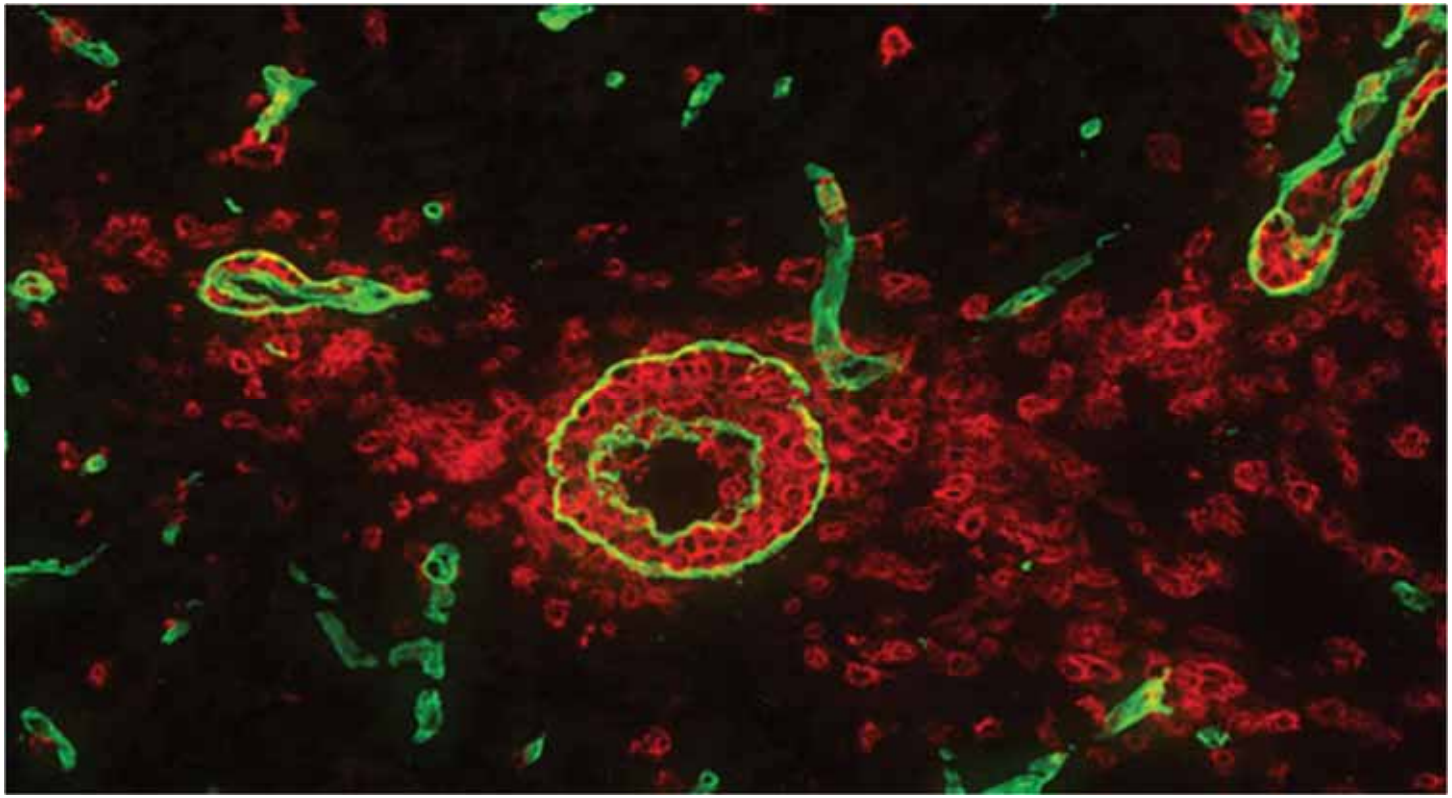
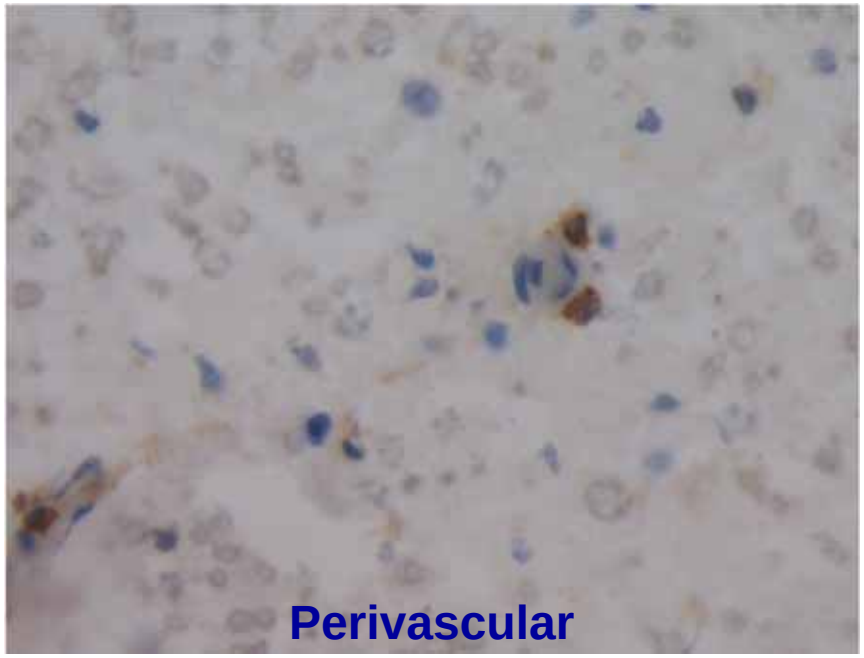
Figure 1 Brain section showing laminin in the basement membranes (green)

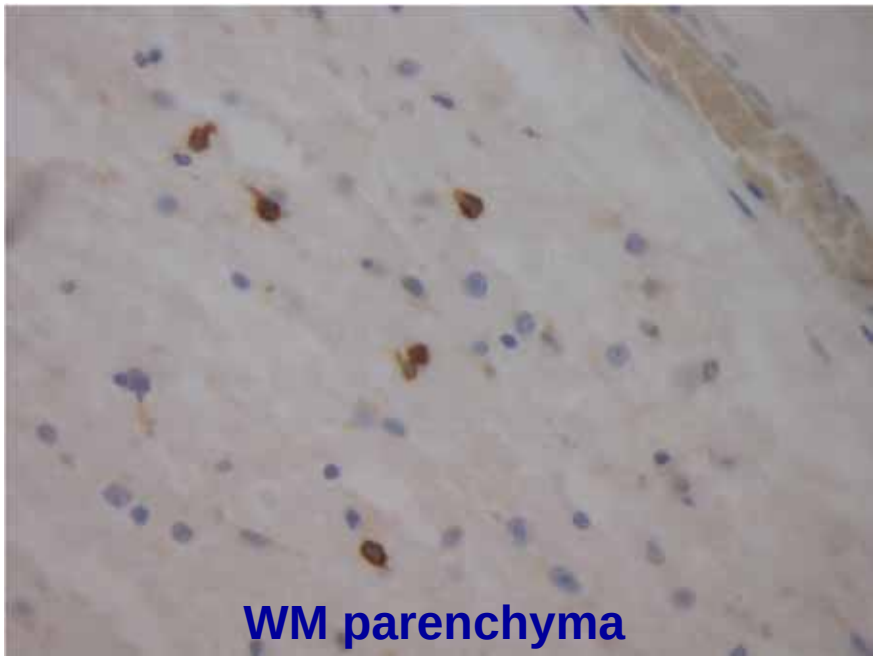


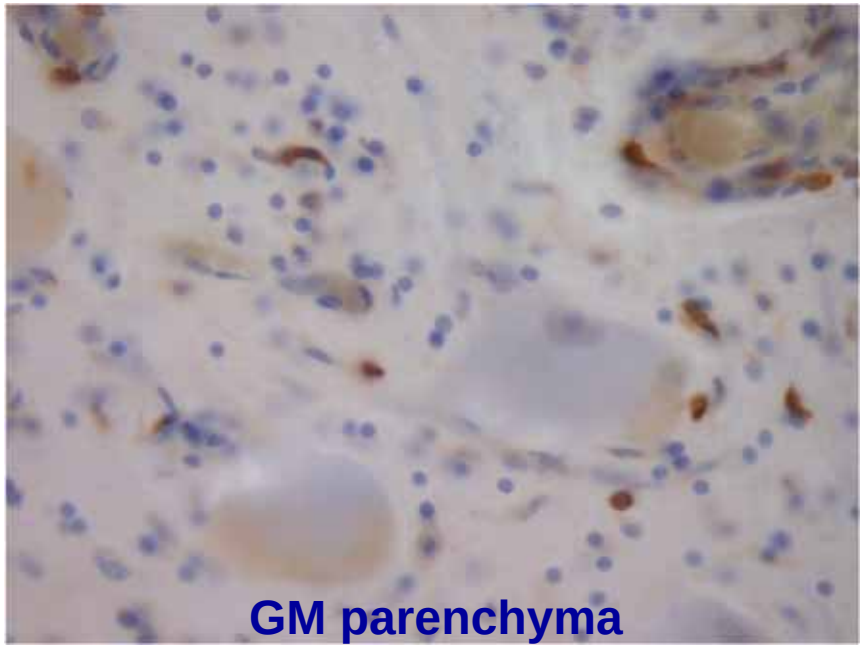
Kathryn Senior (2009) Laminins control T-cell entry into the CNS
Nat. Rev. Neurol. doi:10.1038/nrneurol.2009.76

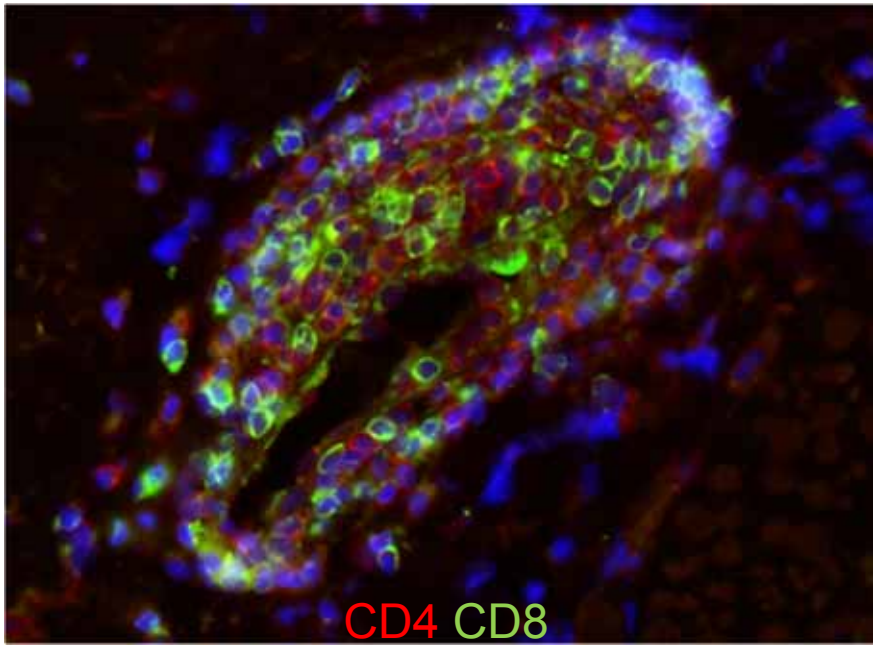
nature REVIEWS NEUROLOGY

CD4+ T-cells

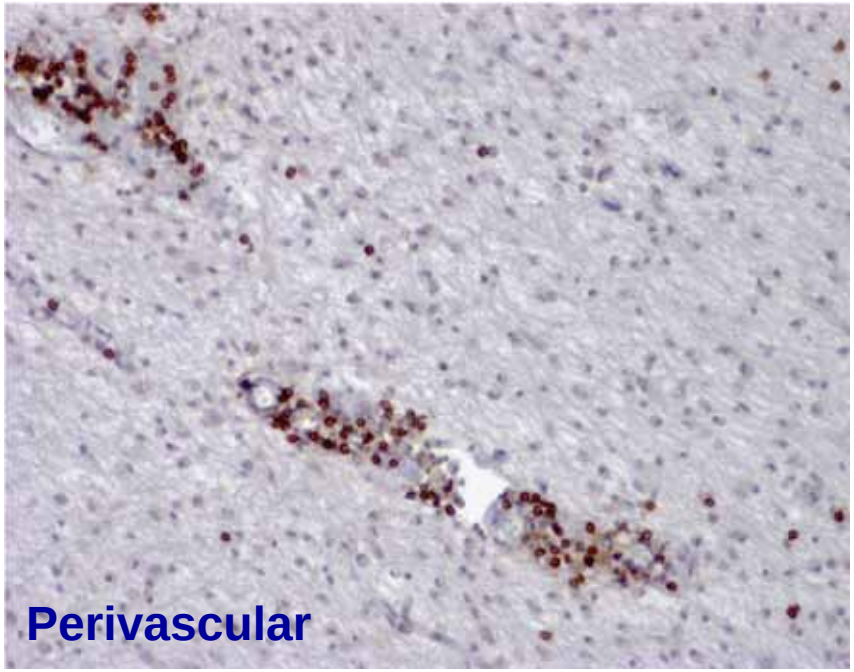


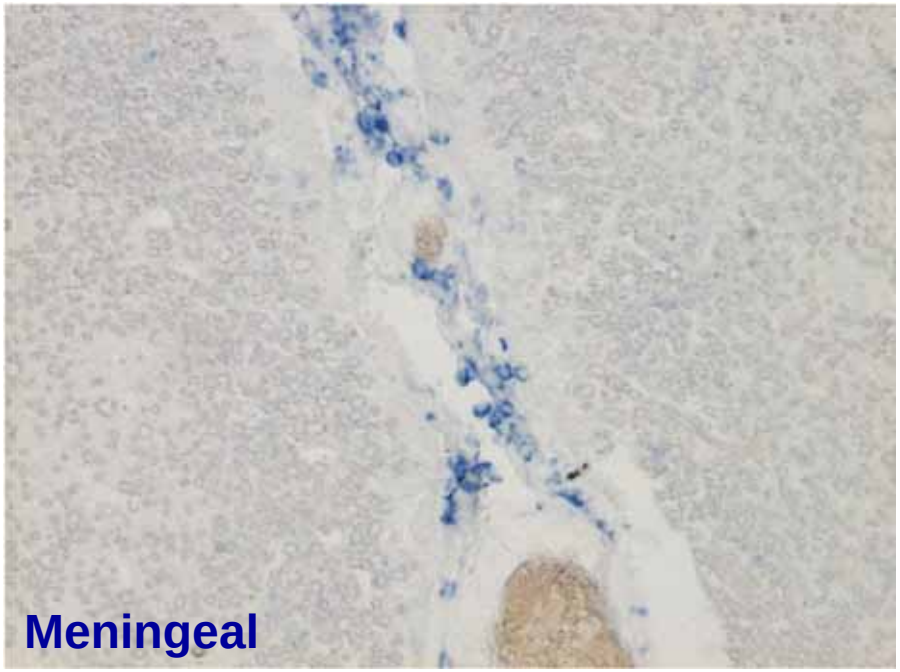


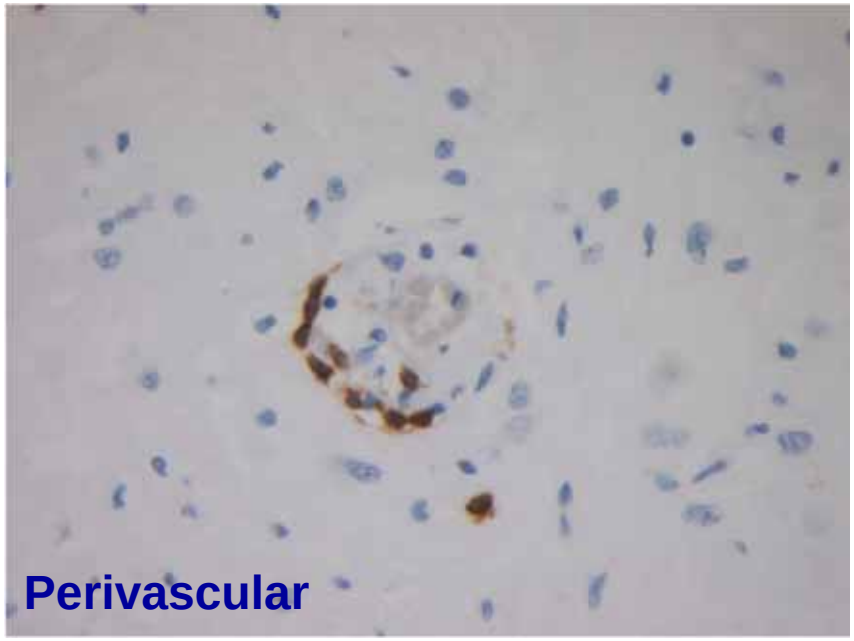


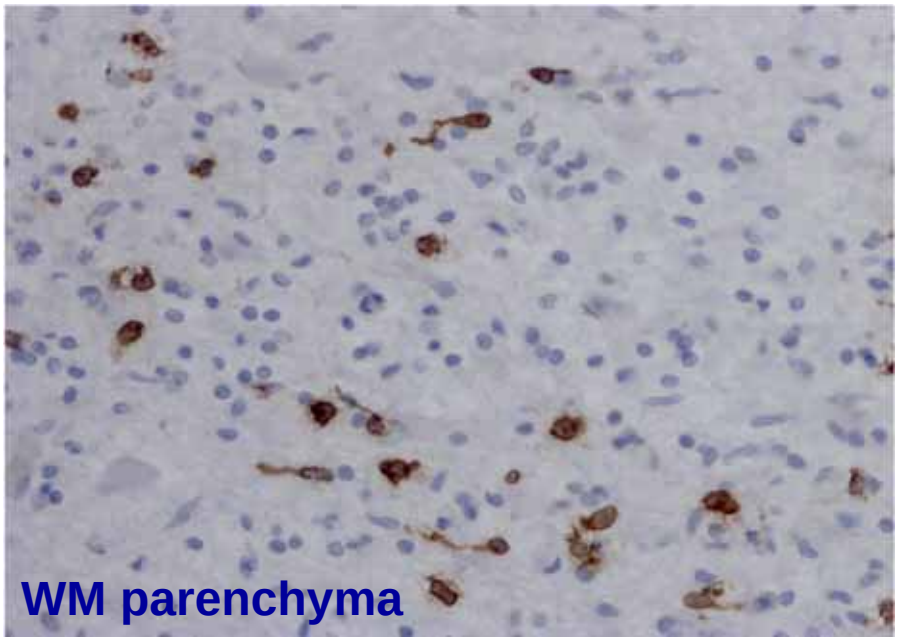


CD8+ T-cells

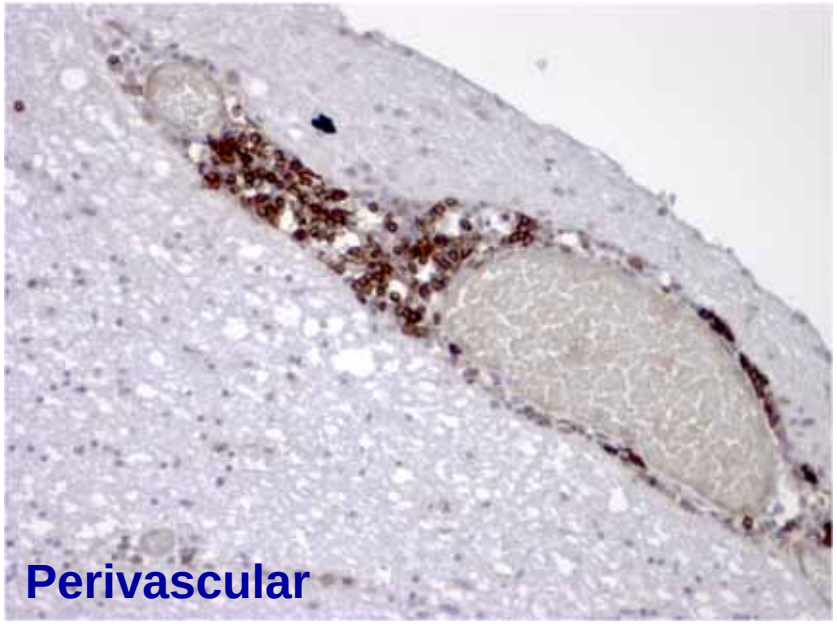


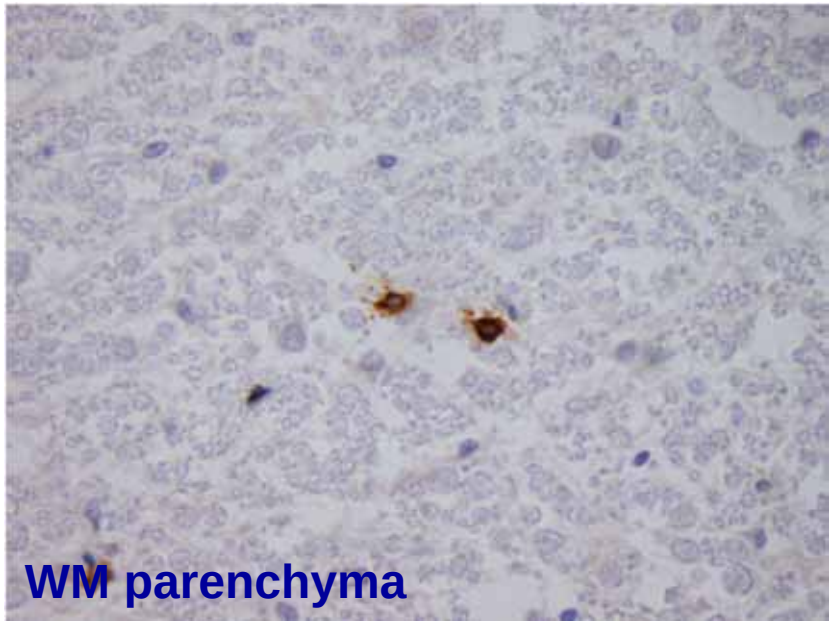


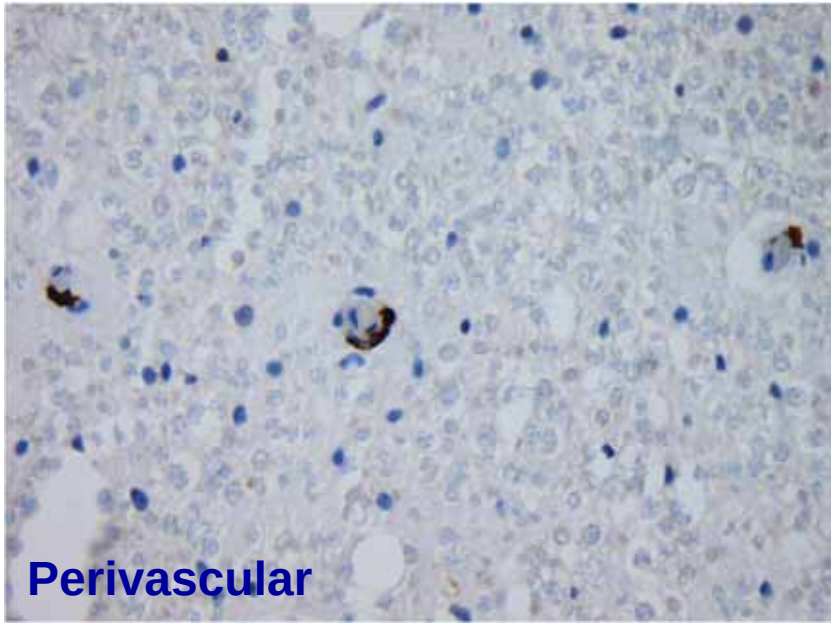


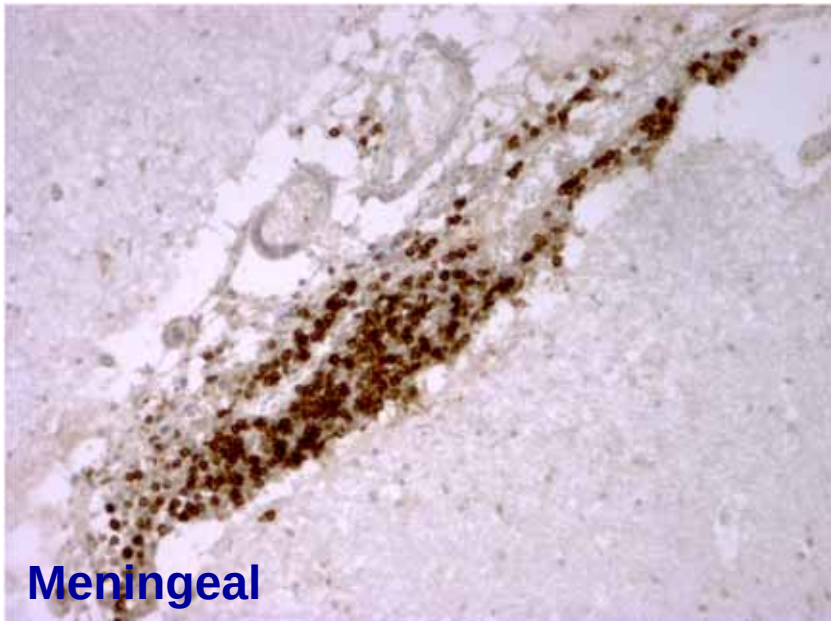


CD20+ T-cells and plasma cells

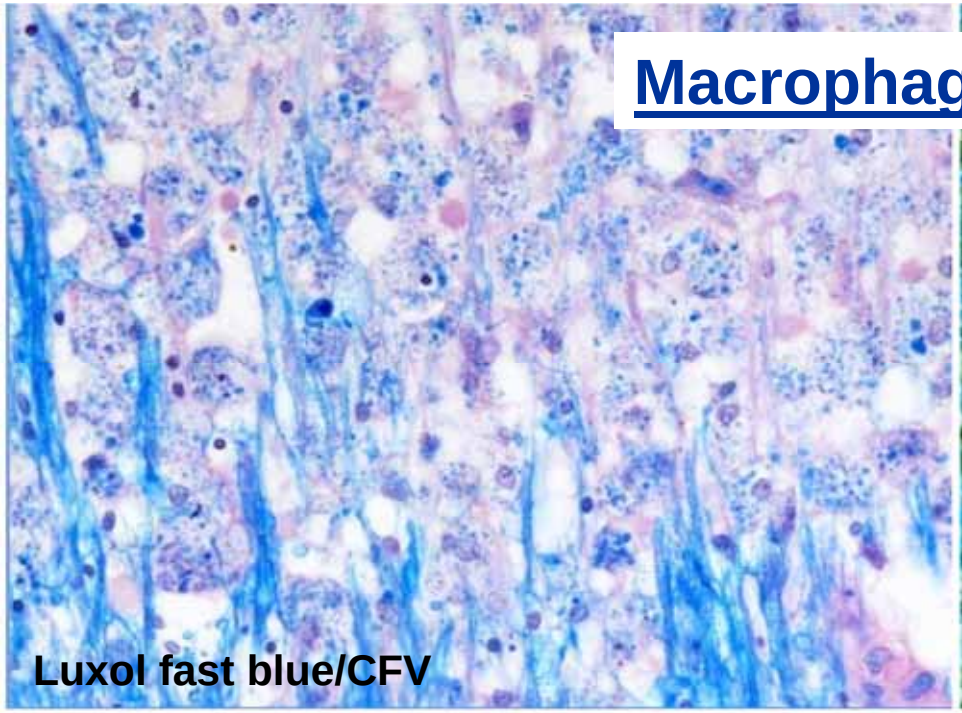


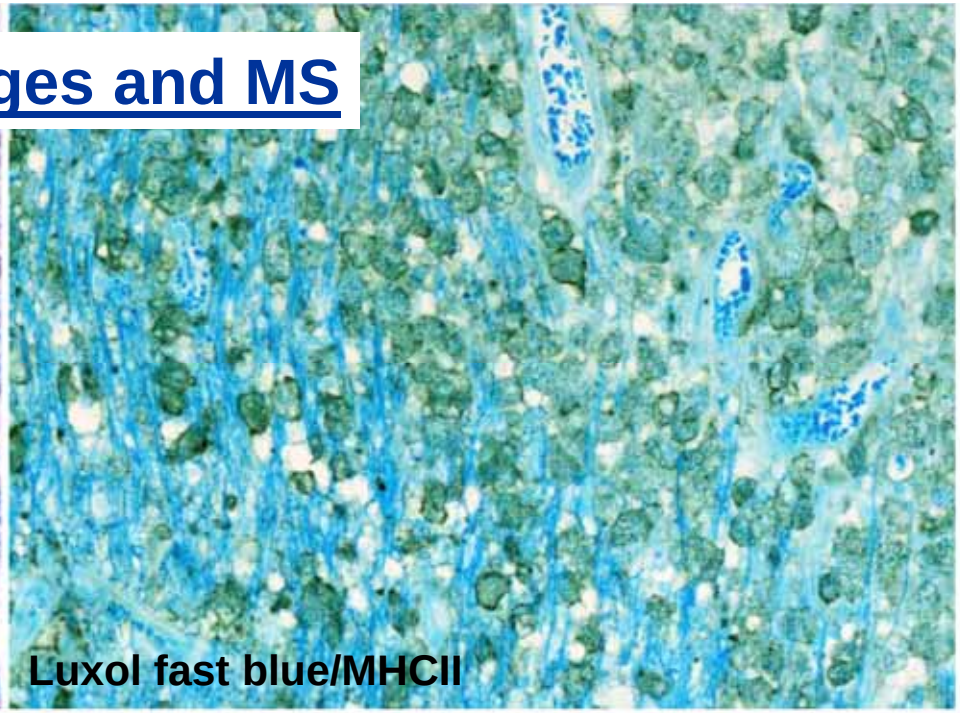


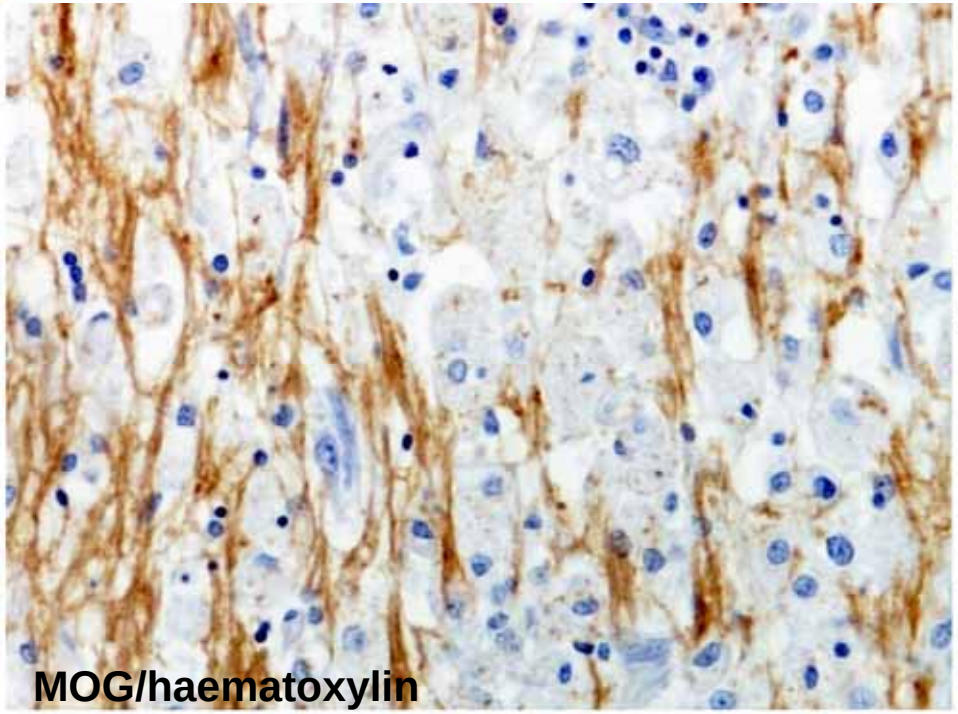


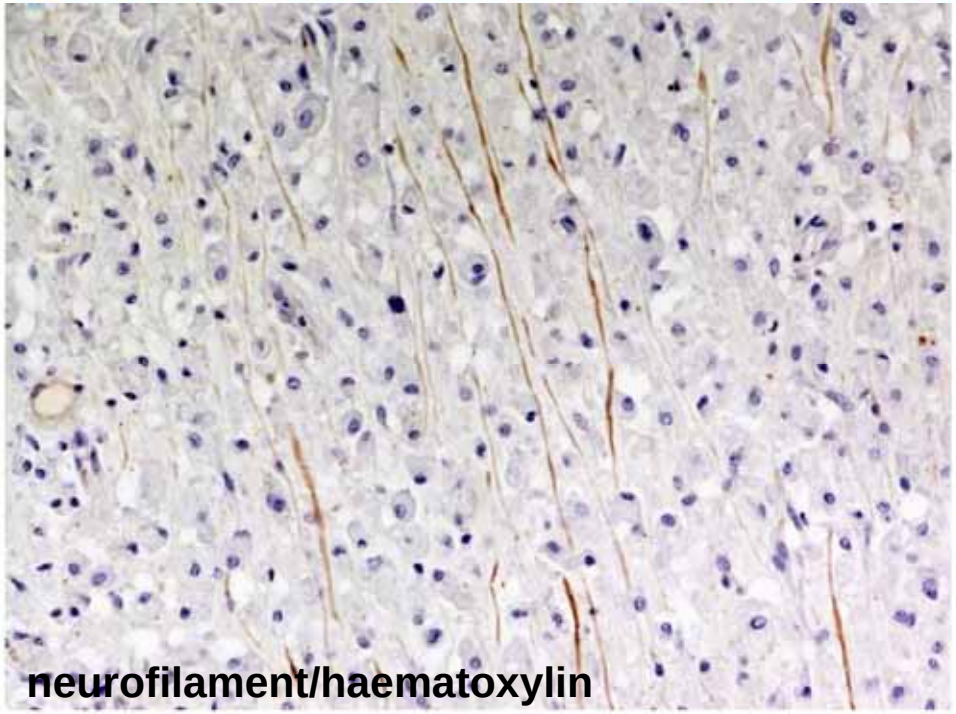


Macrophages and MS

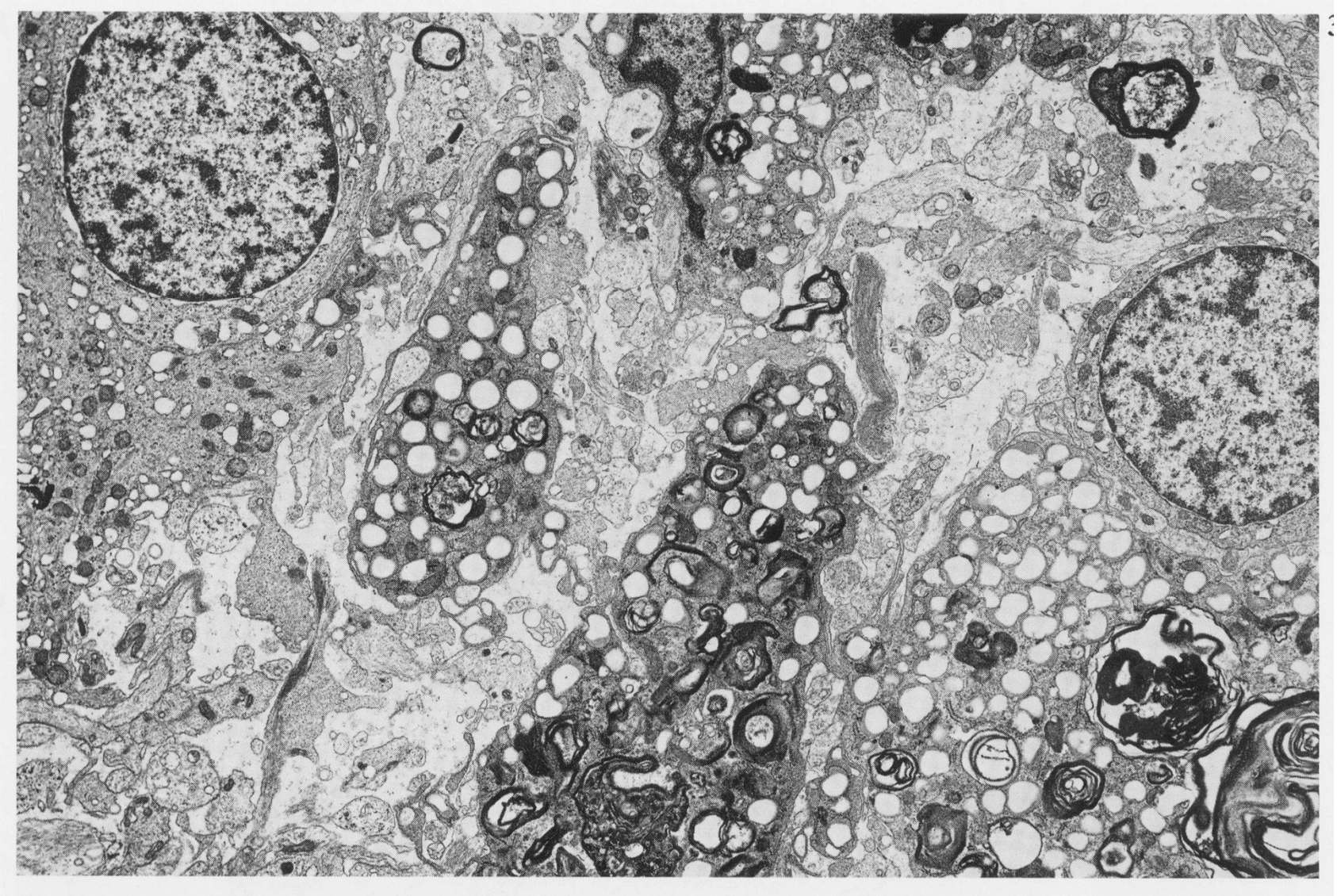






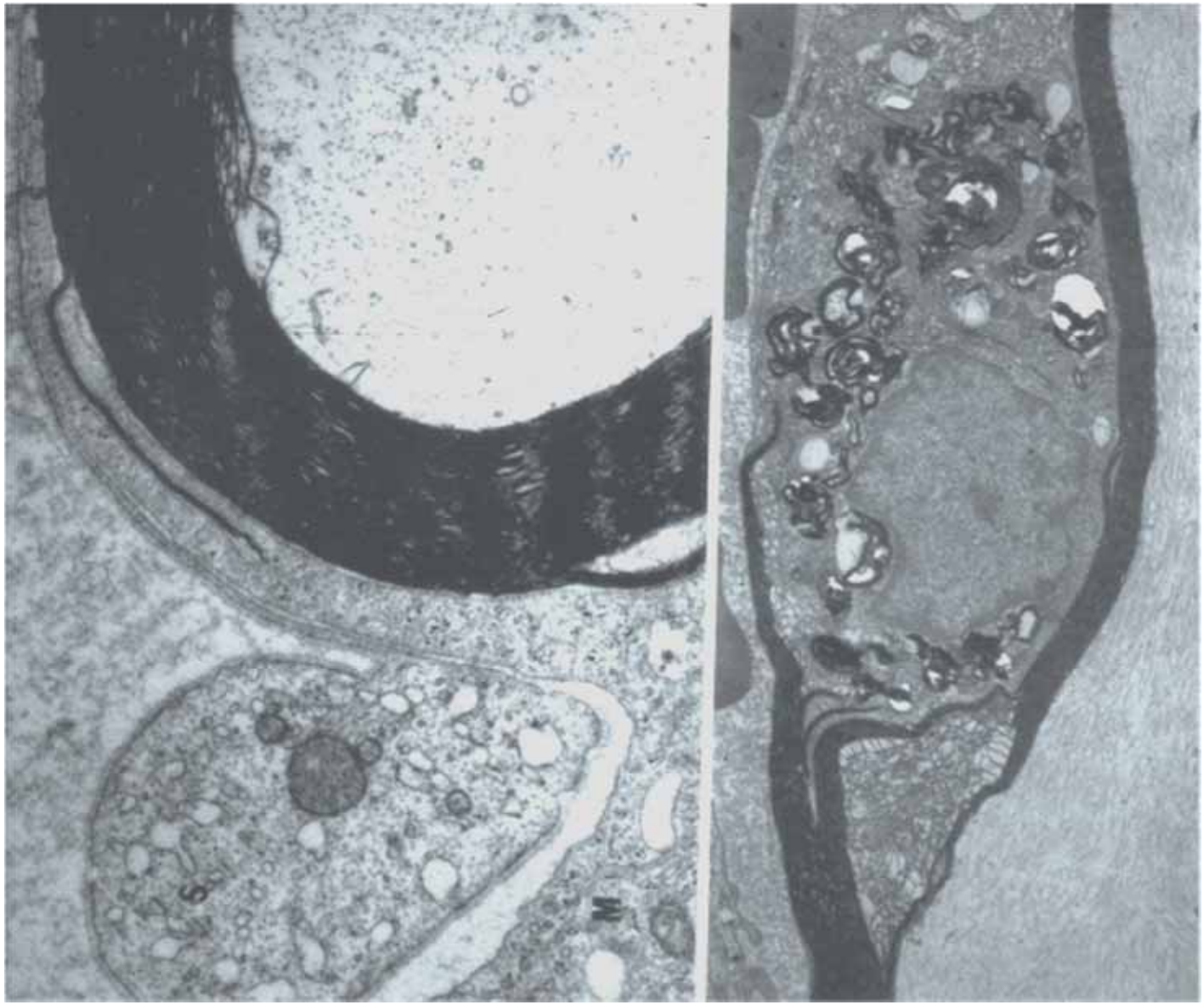


Macrophages and MS



Foamy macrophages at the electron microscopic level showing inclusions containing myelin debris

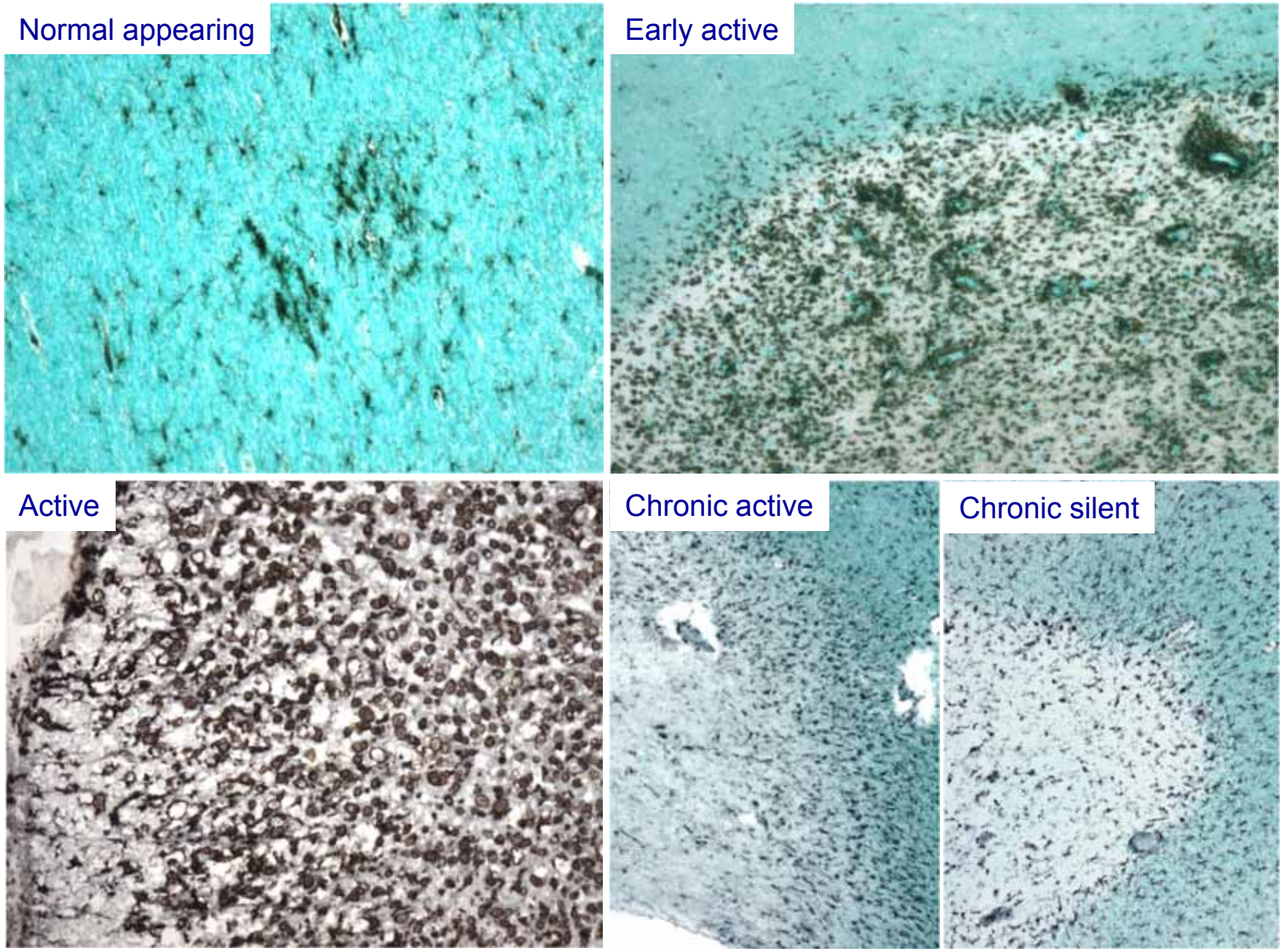
Macrophages and MS



Lesion stages

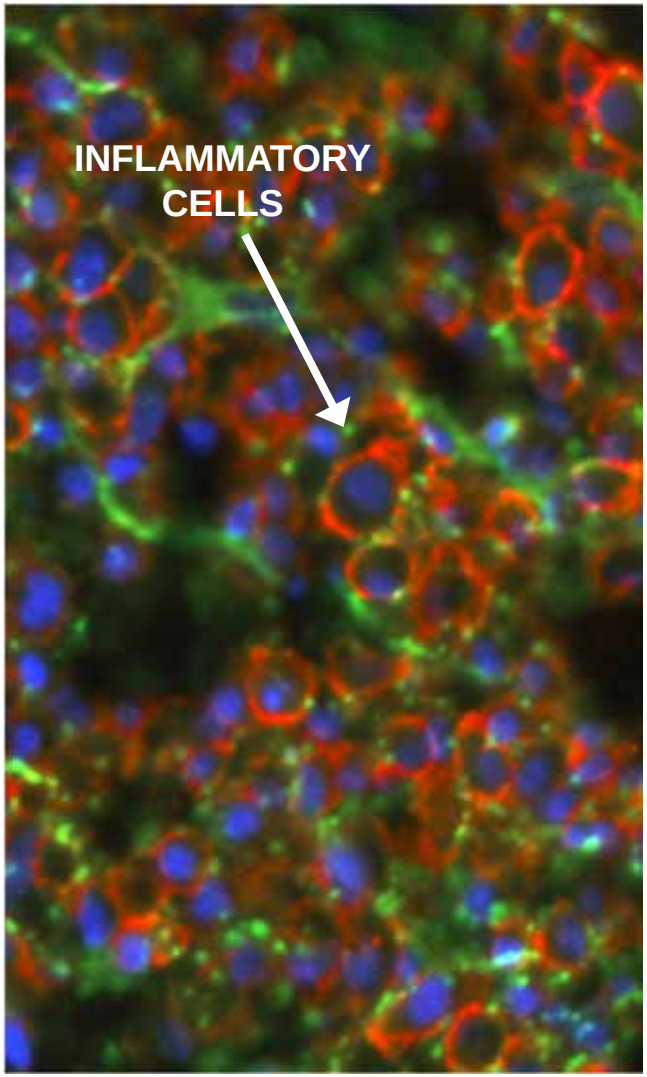
- ***Acute active*: macrophages throughout the lesion with synchronous myelin destruction.**
- ***Chronic active*: numerous macrophages at expanding plaque edge; centre contains few cells.**
- ***Chronic inactive*: hypocellular plaques with no macrophages and no ongoing demyelination.**
- ***Shadow Plaque:* represent remyelinated lesions with thin myelin sheaths.**
- ***Destructive plaques*: destruction of axons, oligos, astros and myelin loss - Marburg type MS and Devic's disease.**

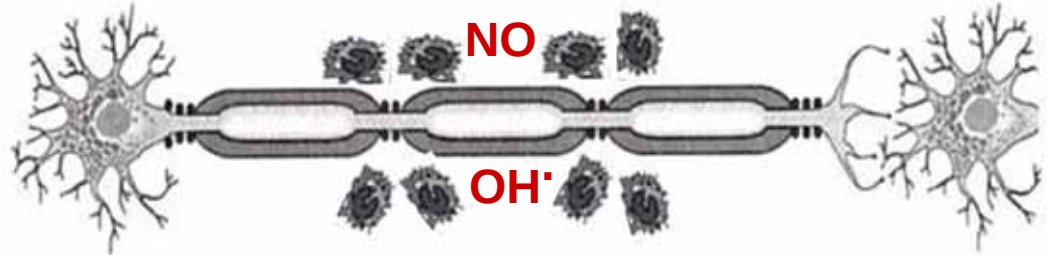
STAGES OF MS LESION FORMATION



All stages can be seen at any one time point in the MS brain and spinal cord

Inflammation produces transient symptoms



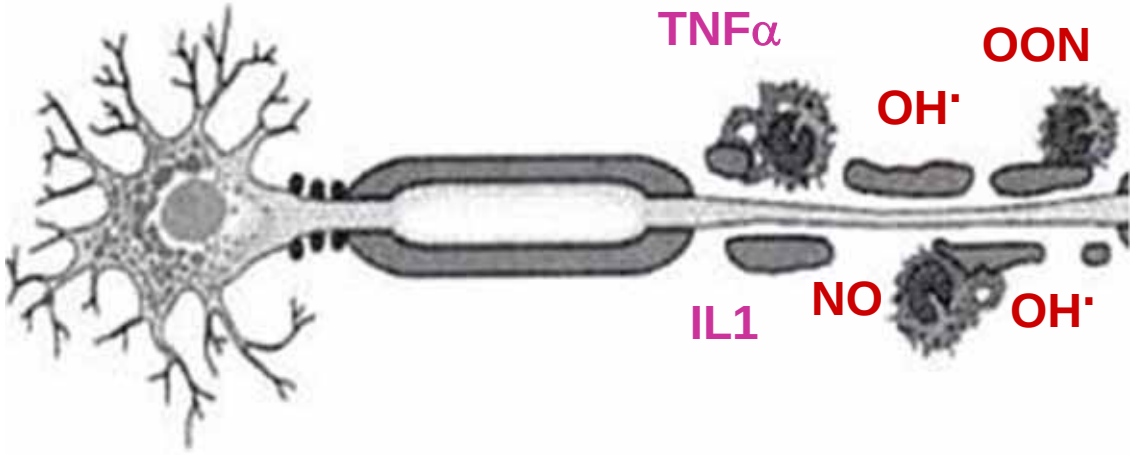


Inflammatory cells release free radicals and cytotoxic mediators

reversible block of electrical signals

+

demyelination

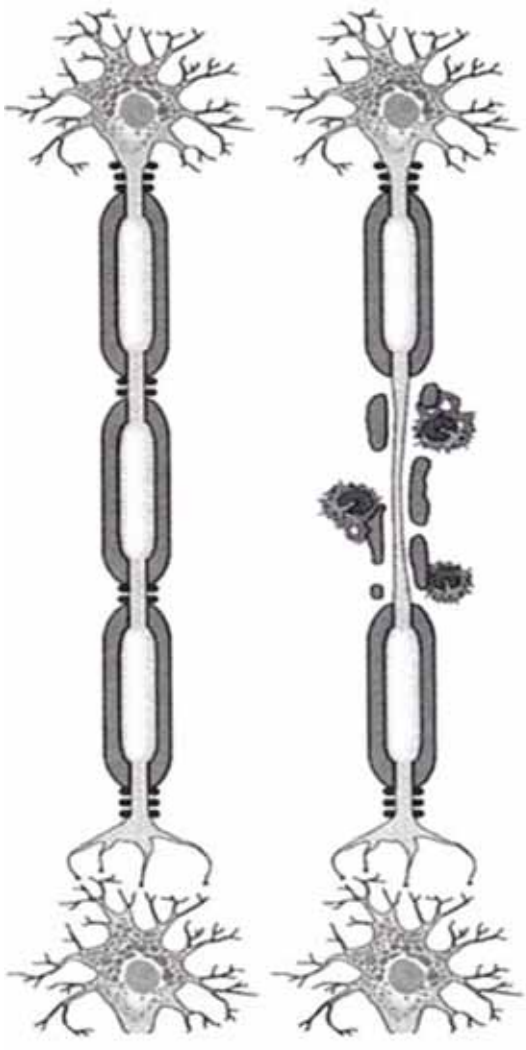


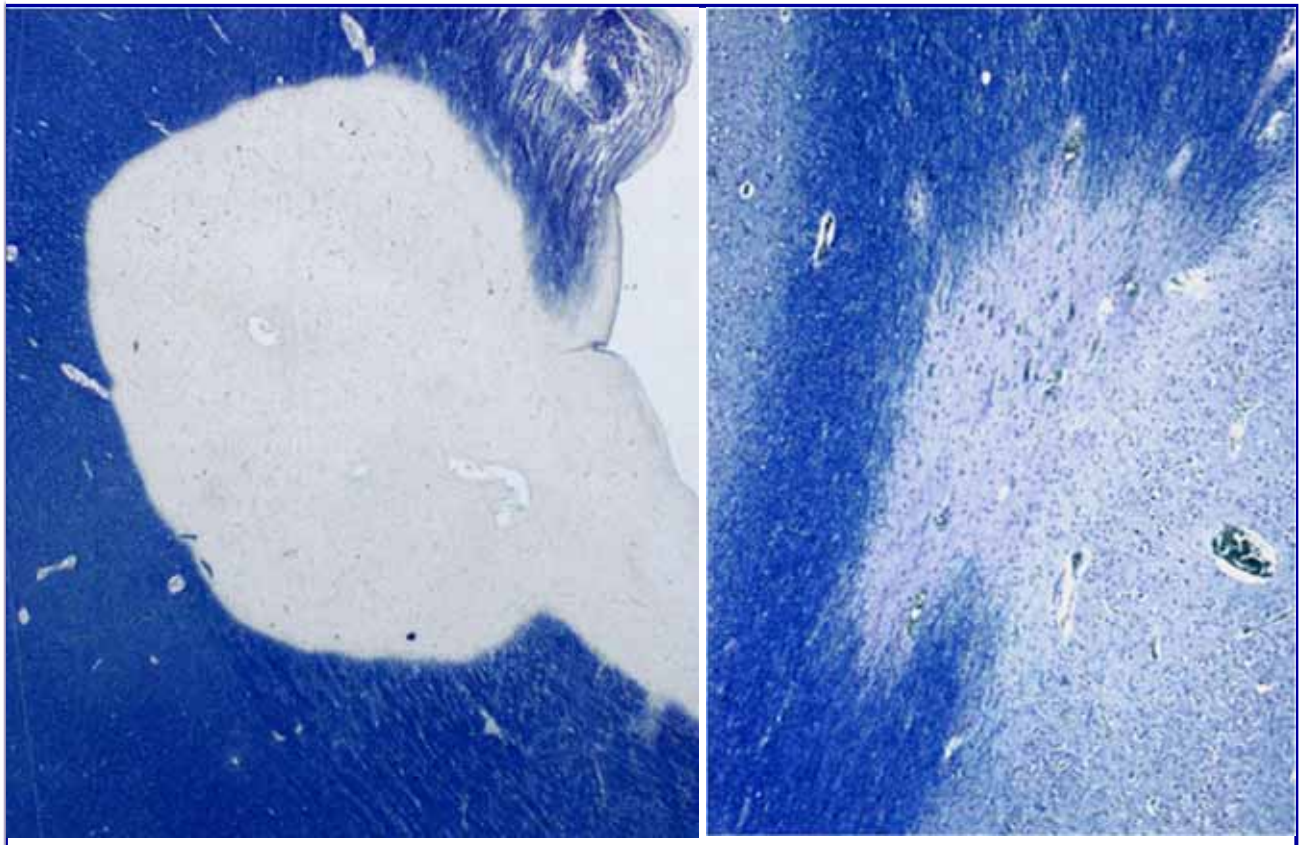
Immunomodulatory treatments aim to stop these effects

Inflammatory mechanisms of neuronal dysfunction

- release of free radicals by peripheral immune cells and activated microglia
  - Nitric oxide (NO), peroxynitrite (OON-), hydroxyl radicals (OH-)
- glutamate release by microglia resulting in excitotoxicity
- hypoxia
- cytotoxic cytokine release by immune cells and microglia
  - TNF, lymphotoxin, IL1β, interferon-γ

Demyelination in MS

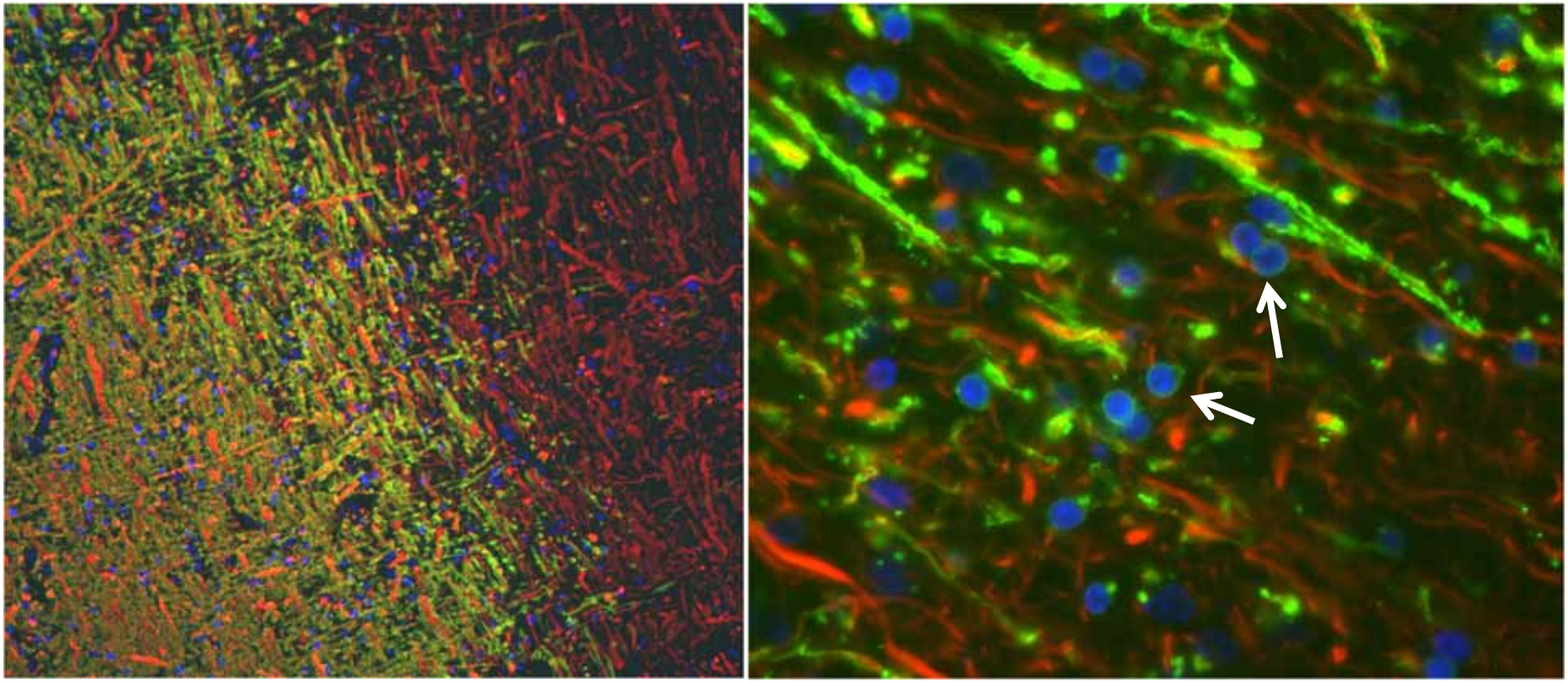




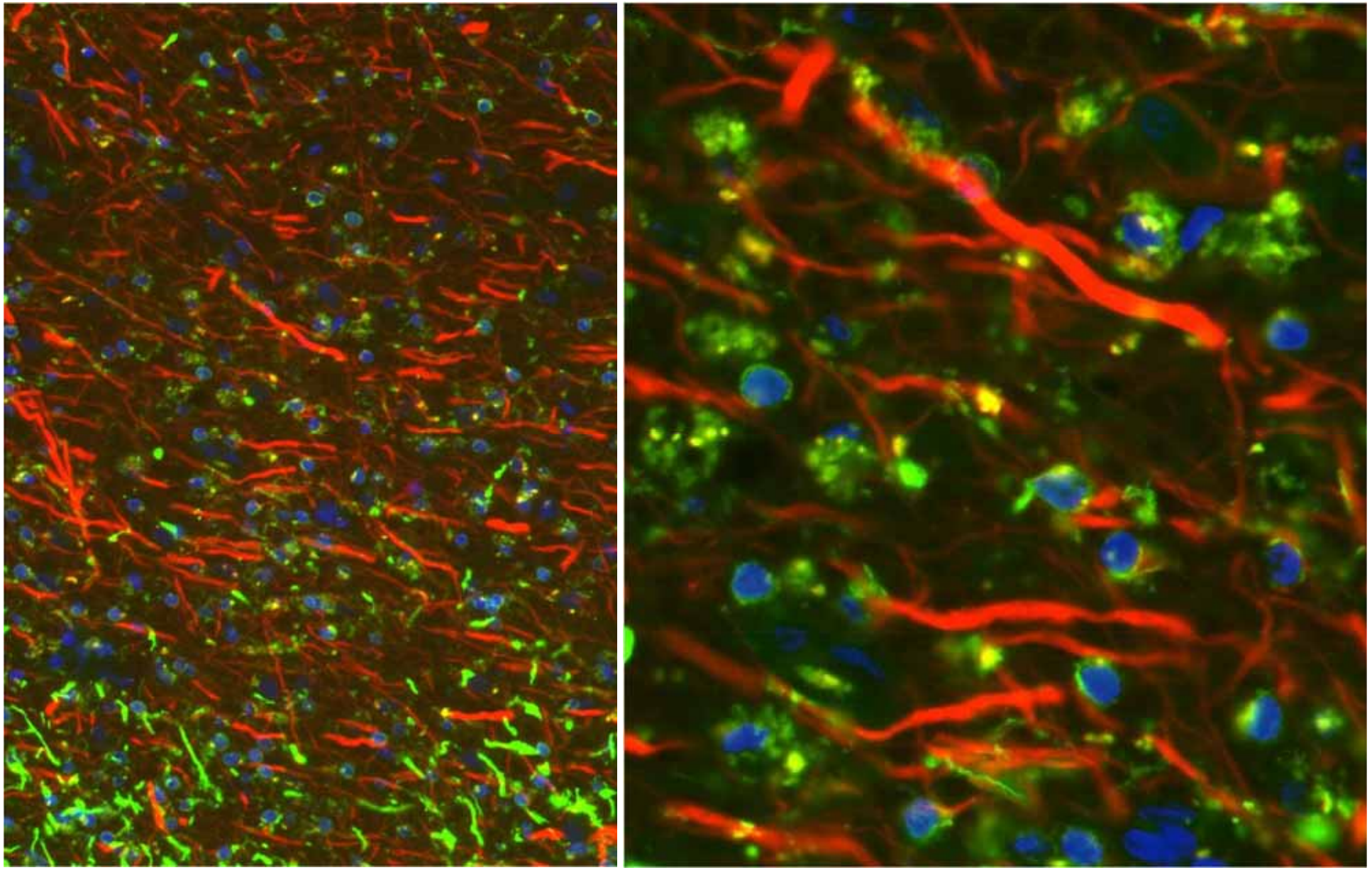
The borders of chronic silent lesions are usually well defined whereas the borders of active lesions are more ragged

Demyelination in MS

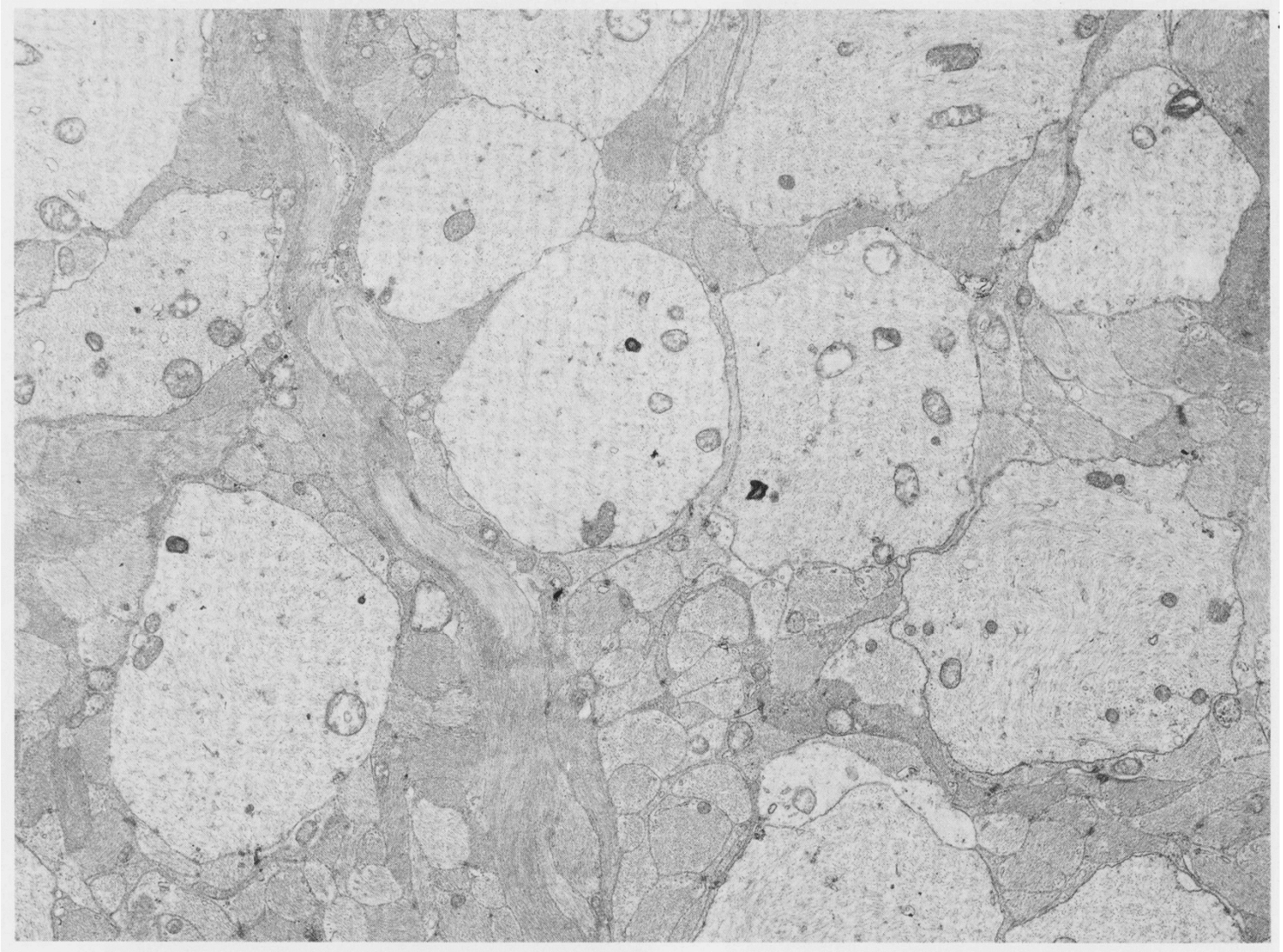
Oligodendrocytes in MS lesions



Oligodendrocytes are generally absent from the centre of chronic lesions although increased numbers are often seen at the lesion edge. MBP-expressing cells were found in large numbers at the edge of some MS lesions.

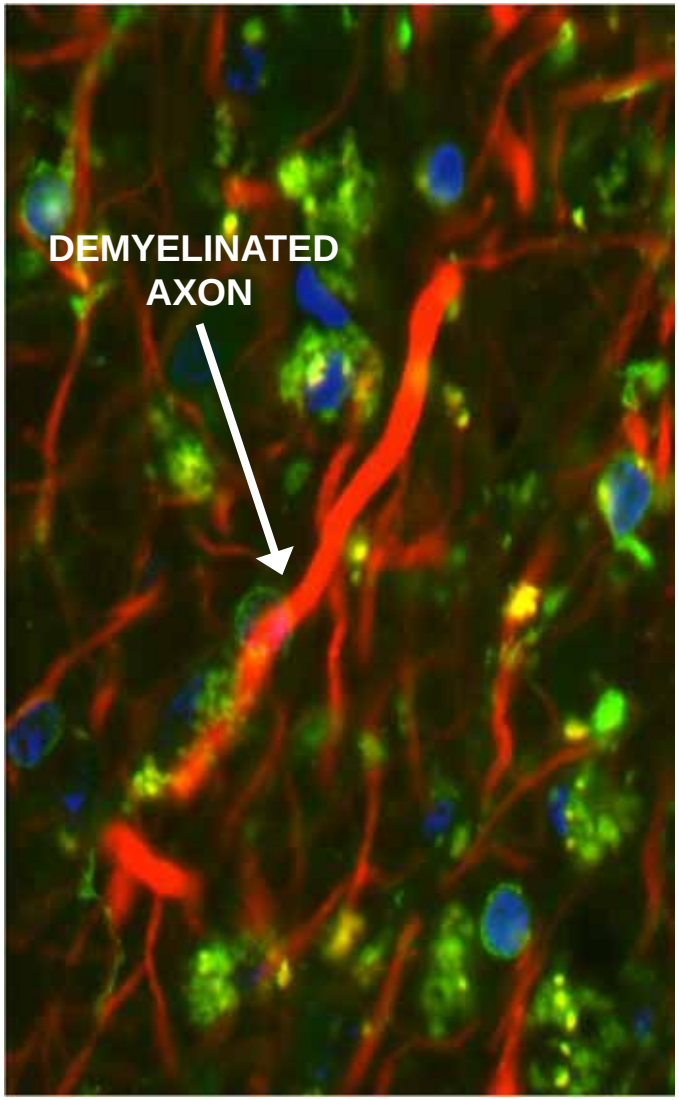


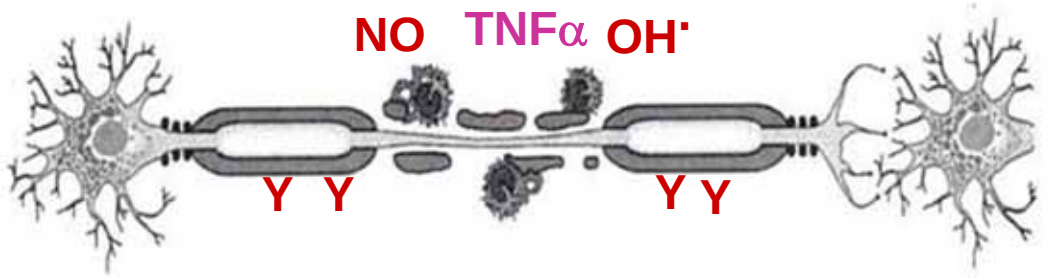
Demyelination in MS



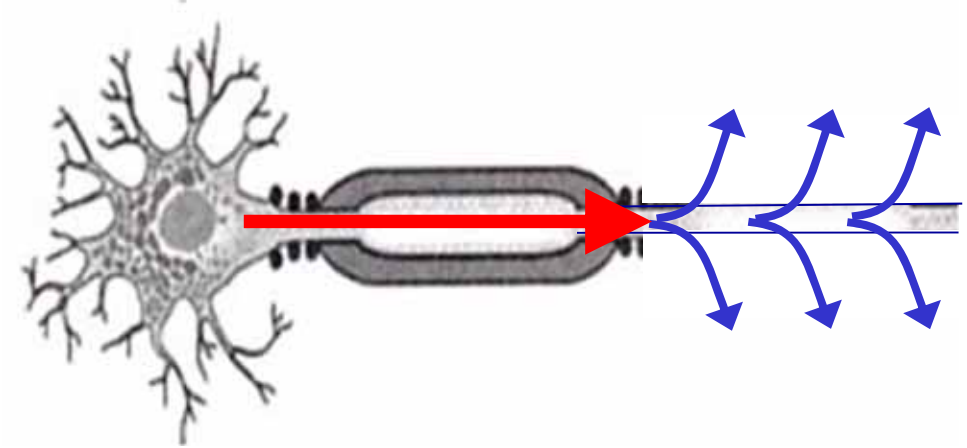
Bare axons surrounded by the fibrous processes of astrocytes in a chronic MS plaque

Demyelination can produce chronic symptoms



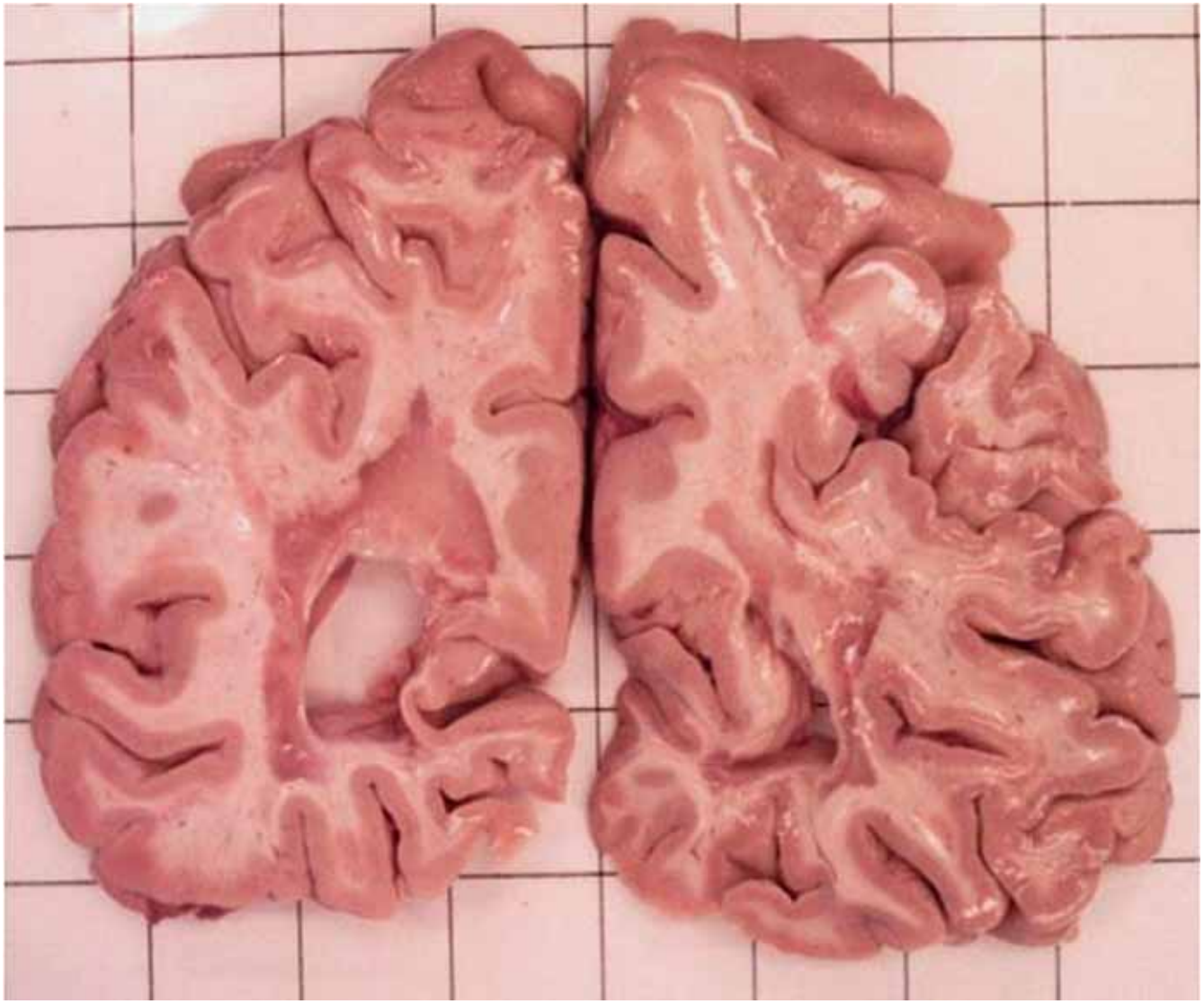


Inflammatory cells release antibodies and cytotoxic mediators that damage myelin



Without myelin electrical signals leak out and fade away and axons become more vulnerable to damage

A white matter lesion centric view of MS pathology



Clinico-pathological correlations in MS have focussed primarily on white matter inflammation and demyelination (based on MRI)

Lack of correlation between disease progression and inflammation/demyelination

- inflammation and demyelination are key features of MS visible on MRI

- MRI lesion load and rate of appearance of new lesions correlates poorly with clinical progression

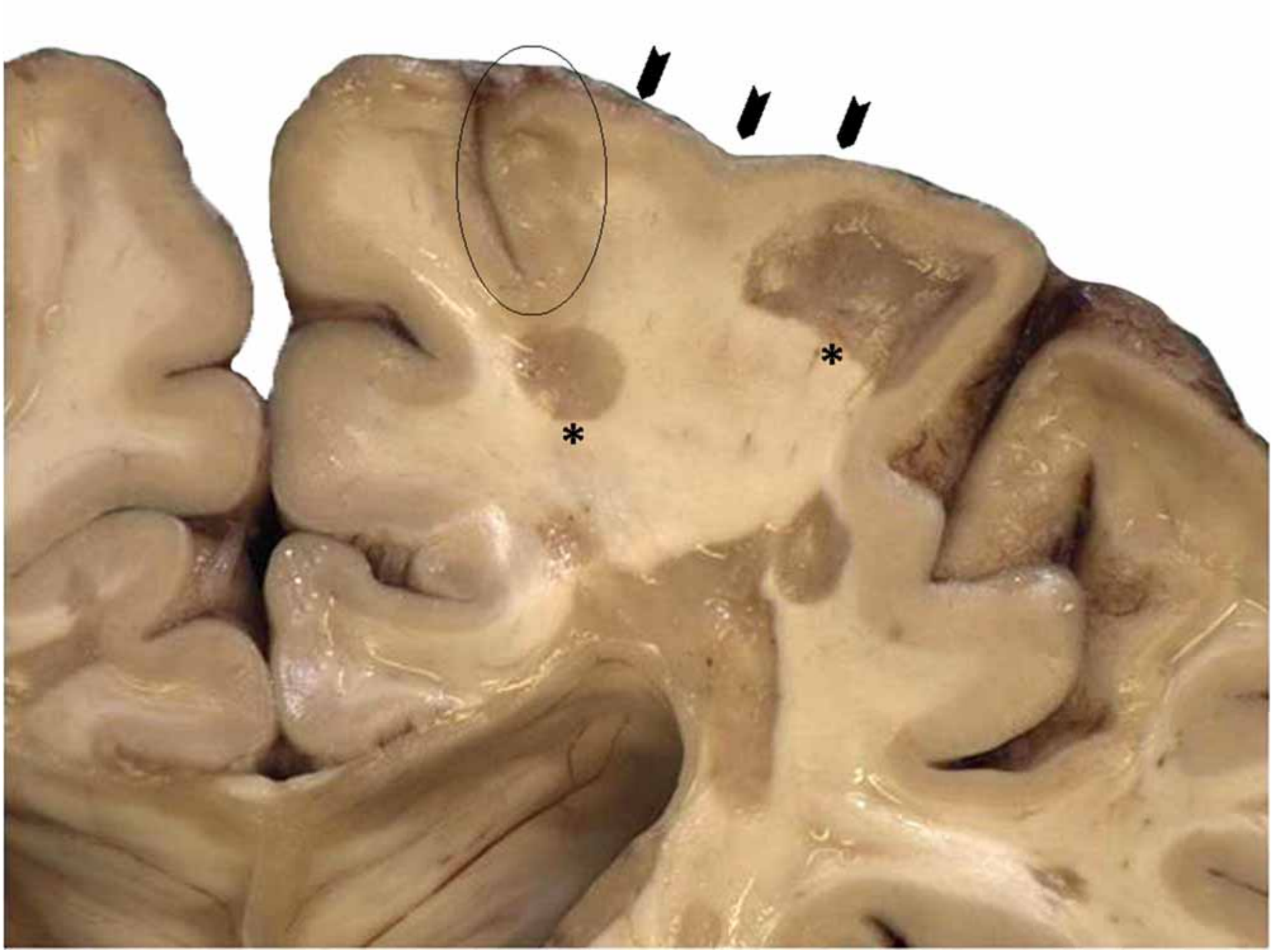
- immunomodulatory therapies reduce relapse rate but fail to prevent long term progression of disability

Good correlation between disease progression and grey matter atrophy

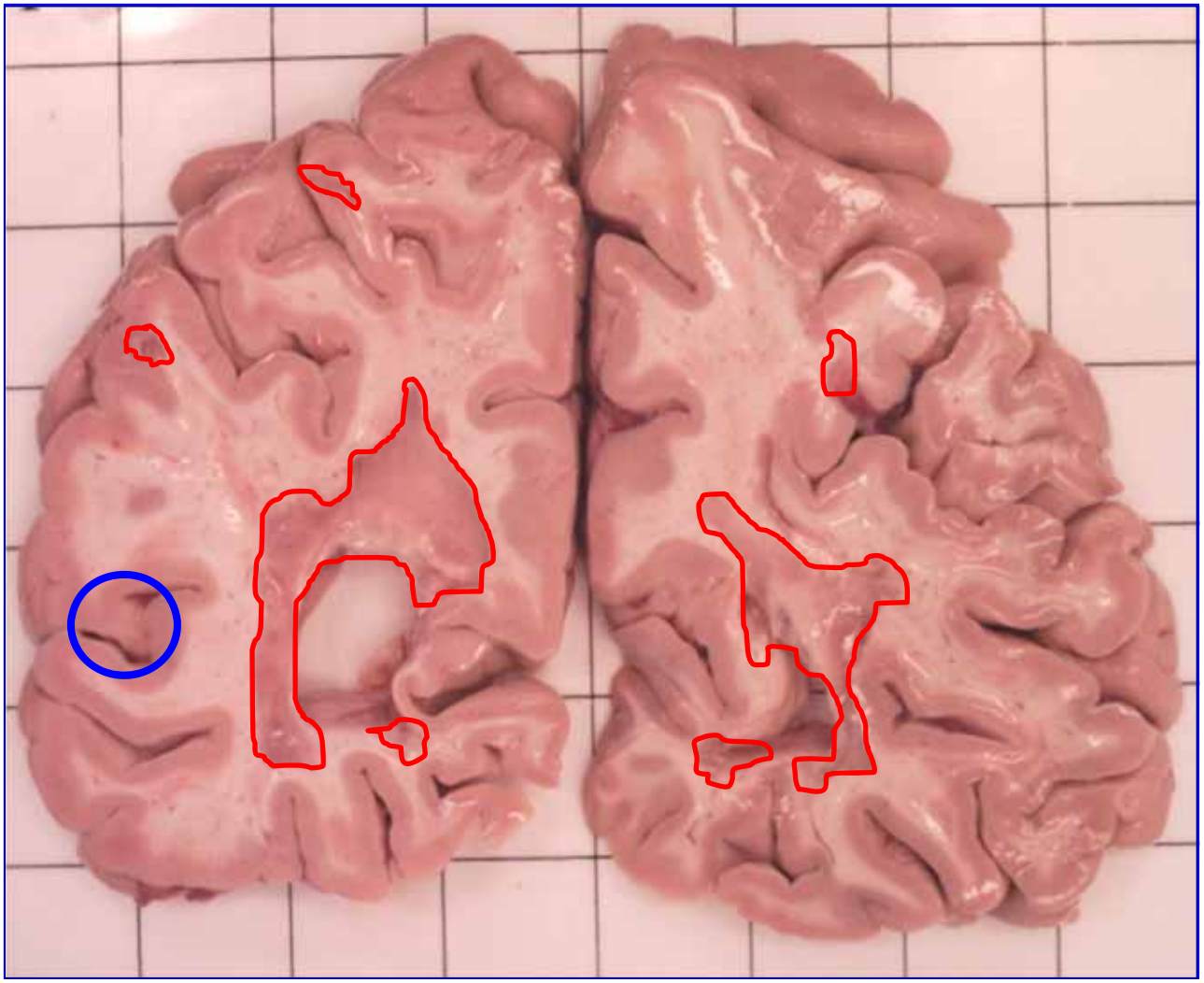
(Fisniku et al, 08)

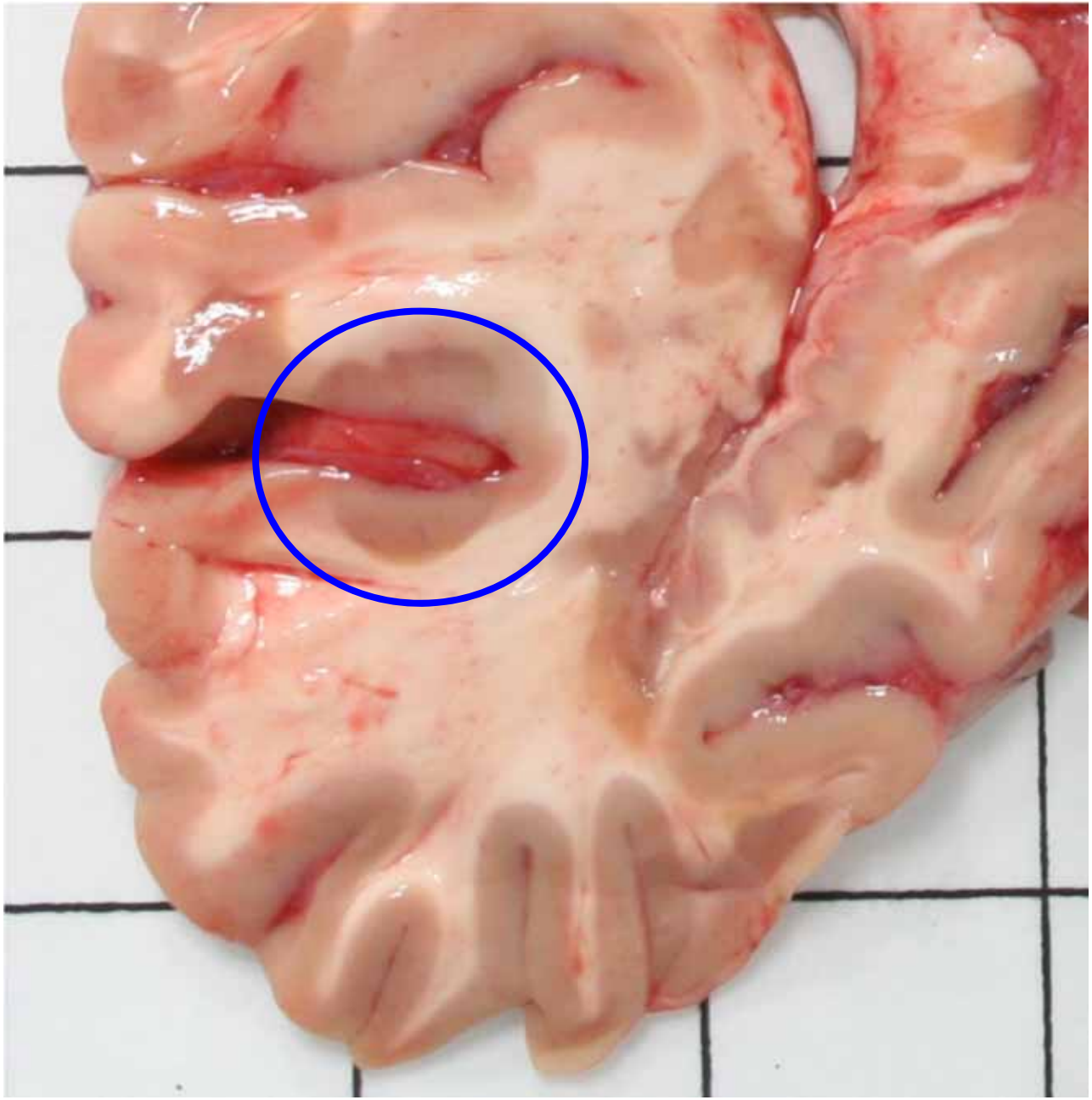
Cortical Pathology

- **Earlier either overlooked or underestimated but recently attracted increased attention**
- **Chronic MS: average 15-25% cortical demyelination, even up to 70%**
- **Extensive cortical demyel - in 90% pts in Ch MS.**
- **Not only cortex but deep grey matter and spinal GM**.

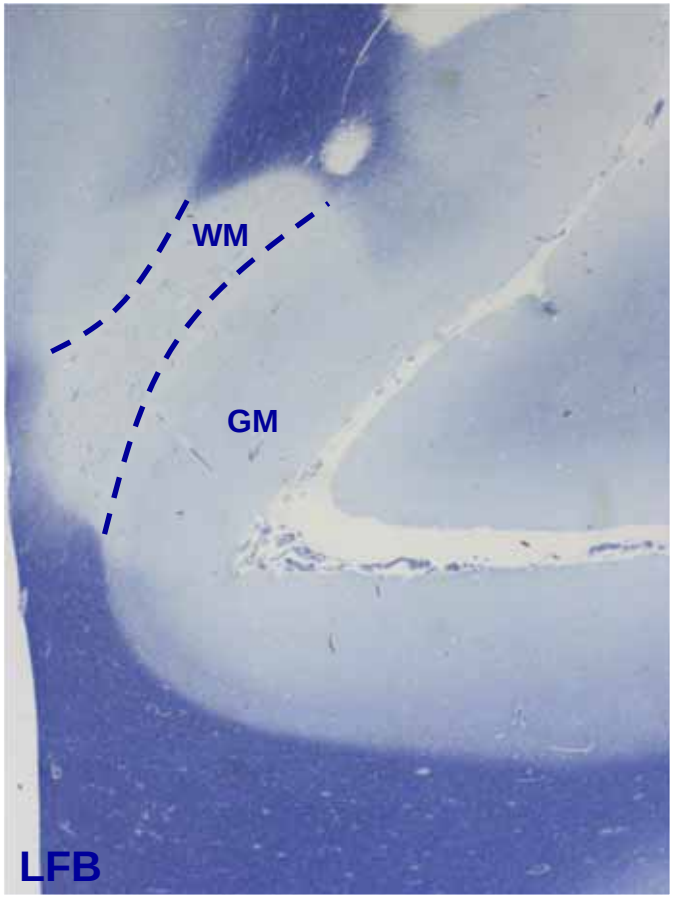


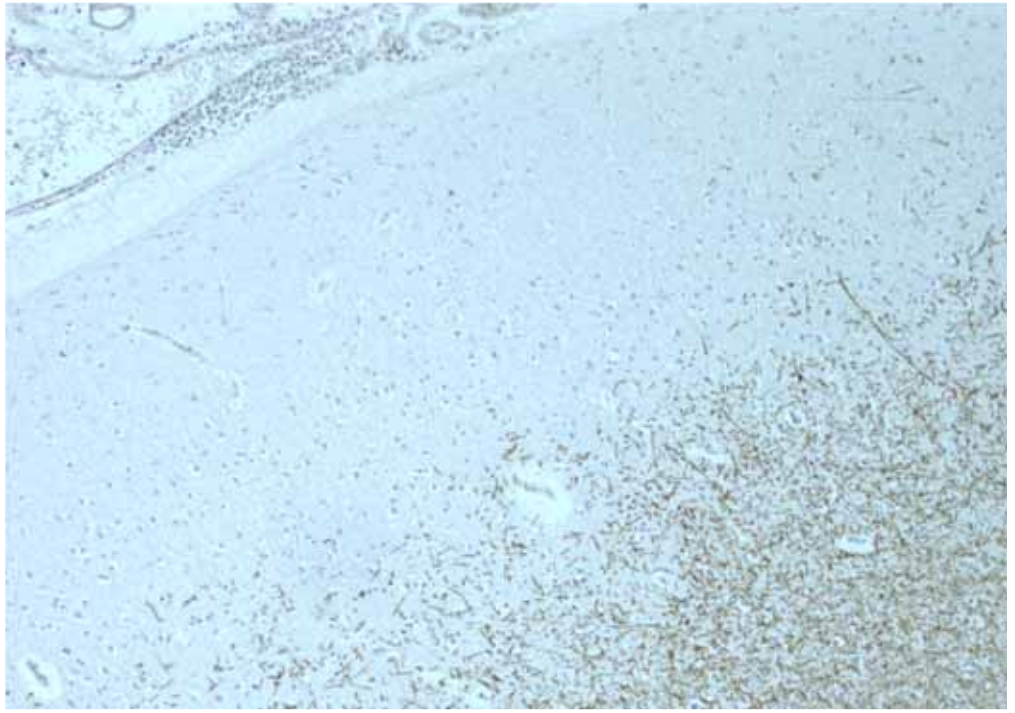
Multiple areas of damage to the grey matter



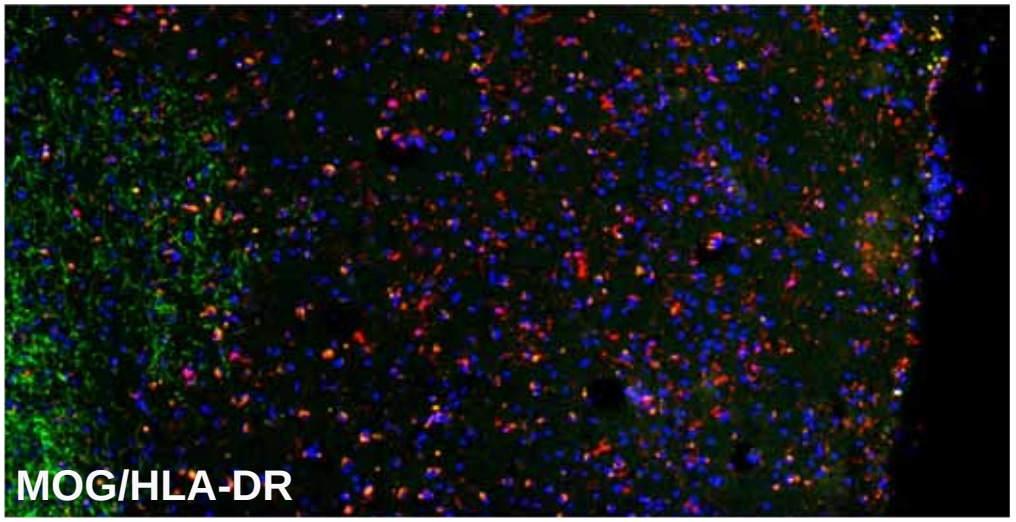


Pathogenesis of grey matter lesions

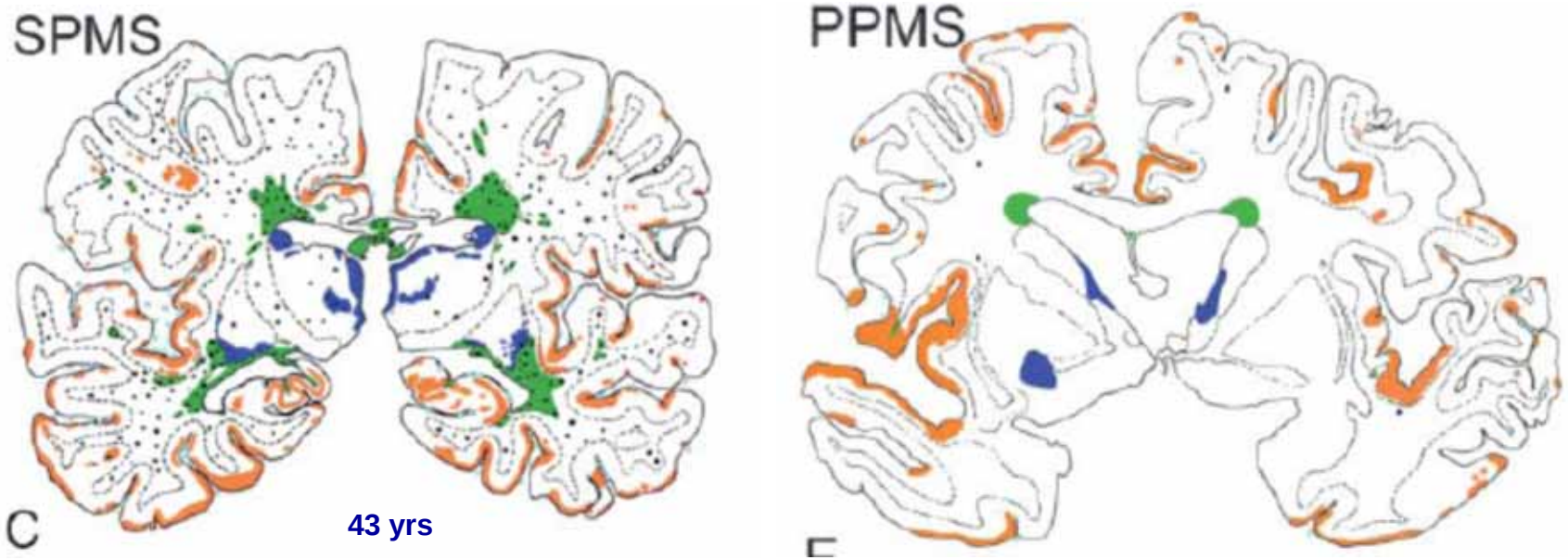




Grey matter lesions are best identified using myelin protein immunostaining



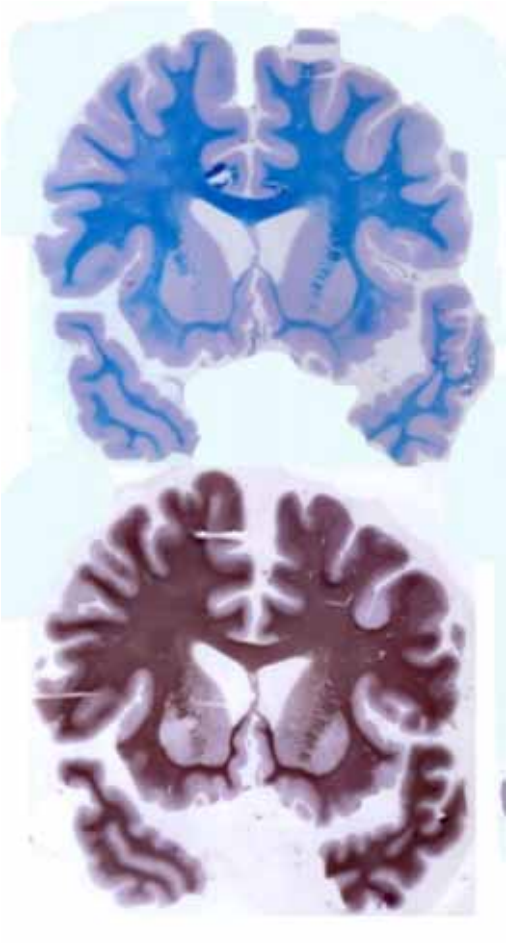
In many MS cases cortical grey matter demyelination covers as extensive an area as WM demyelination



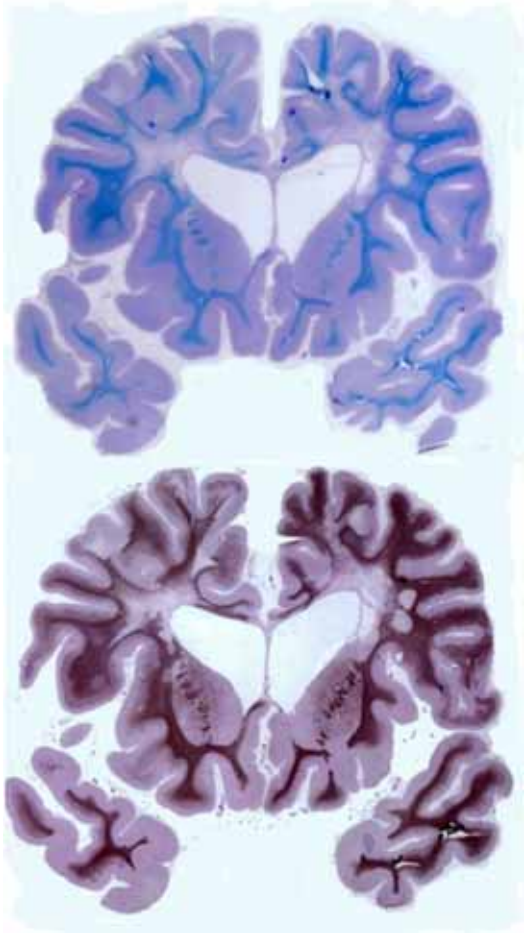
Kutzelnigg et al, 2005

- **type I leucocortical lesions**
- **type II intracortical lesions**
- **type III subpial lesions – cover greatest area of neocortex**

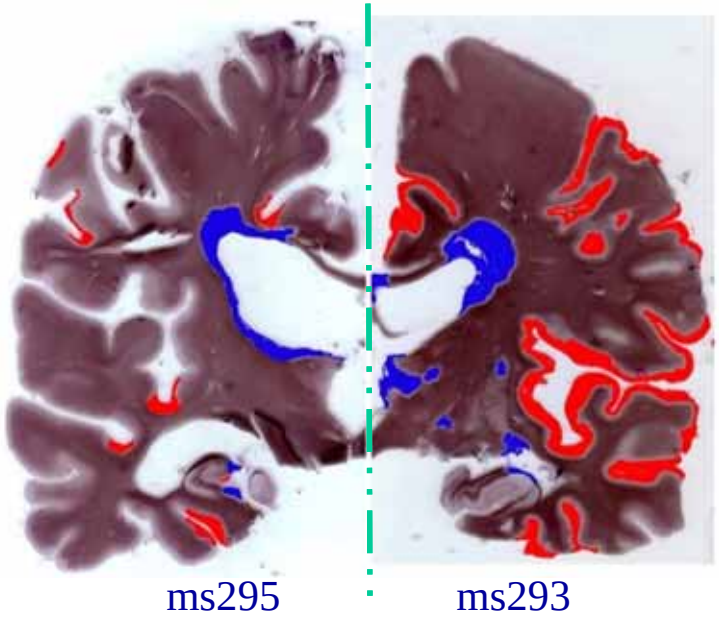
Grey matter demyelination is extensive in some cases



ms226



ms366

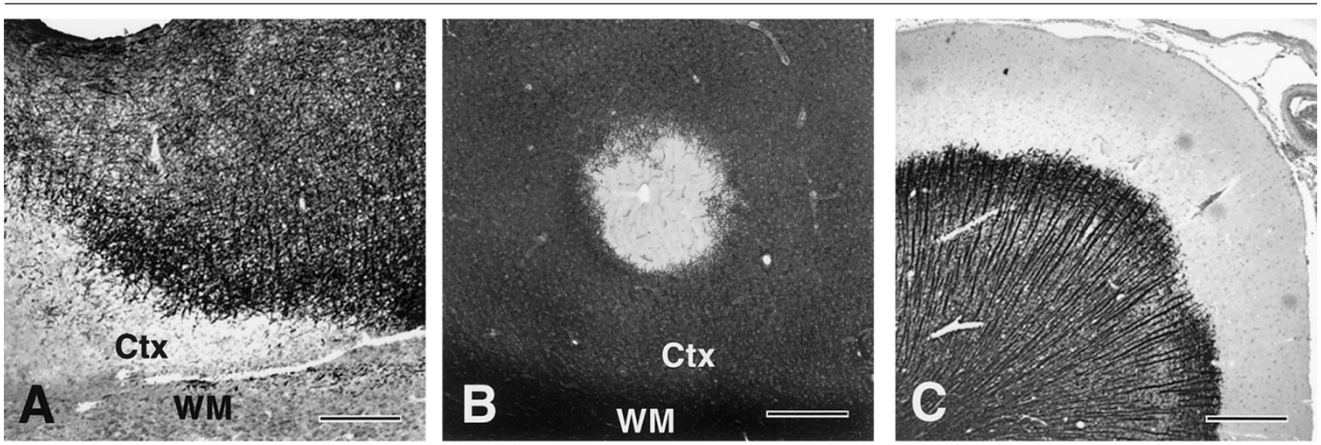


ms295 ms293

White matter lesions

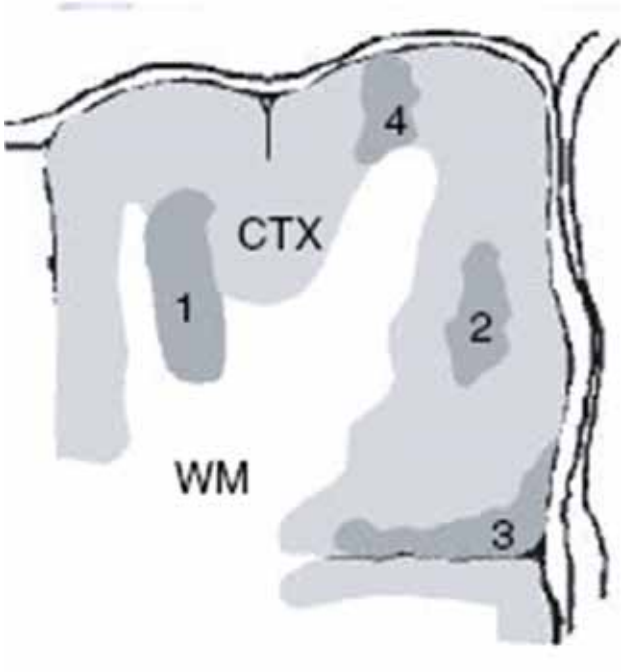
Grey matter lesions

Grey matter lesion location rather than inflammatory activity defines type



Peterson, AnnNeurol 2001

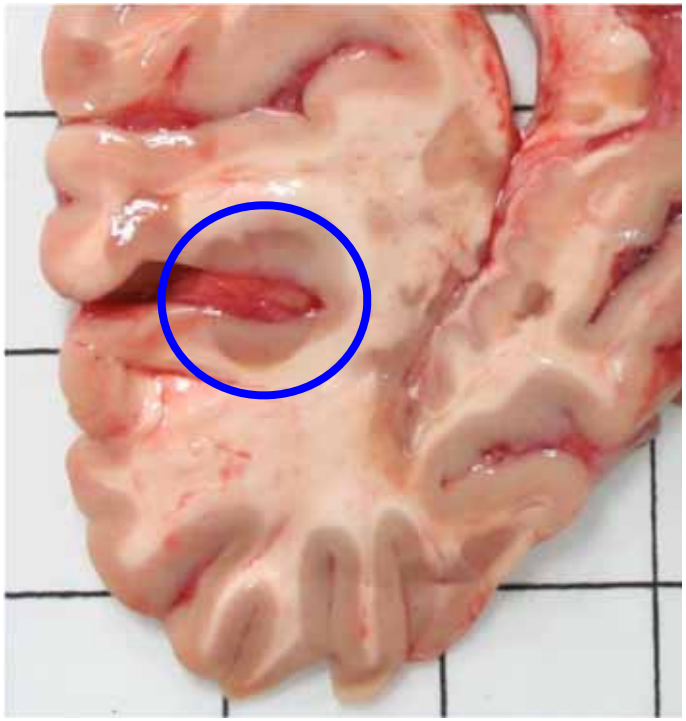
type I leucocortical lesions; type 2 intracortical lesions; type 3 subpial lesions



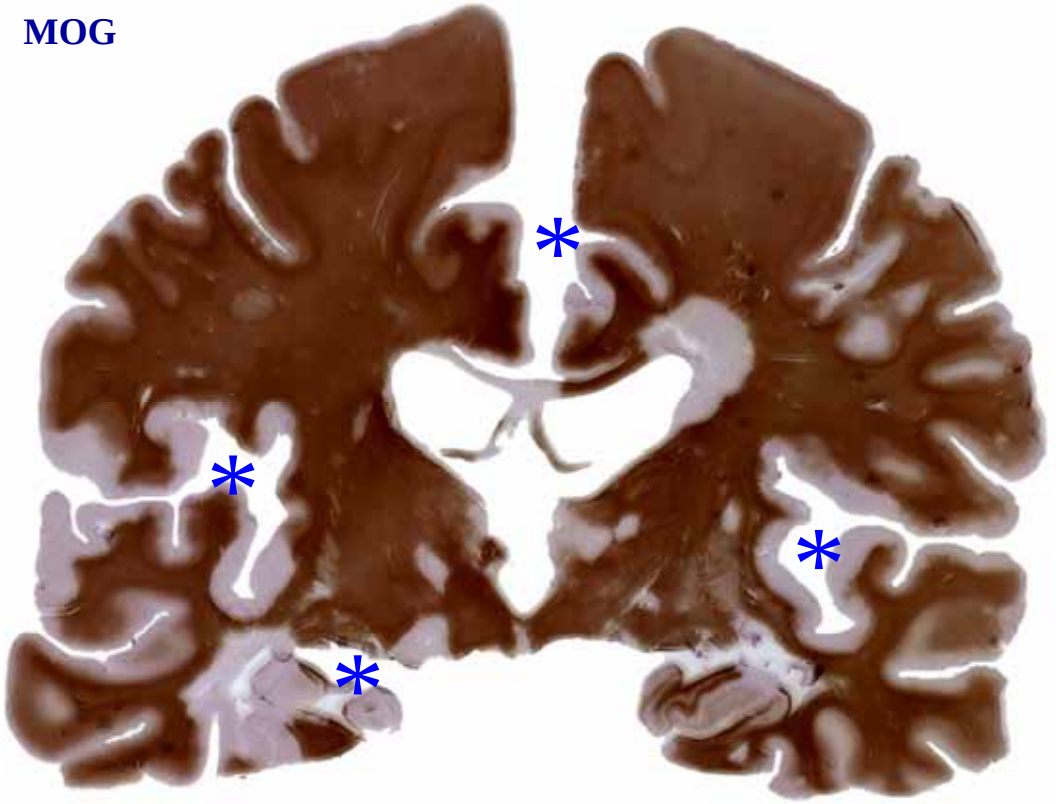
Type 4= extend the entire width of the GM to the WM

• Type 3 lesions account for the largest area of cortical demyelination. Seen as a 'ribbon' of demyelination that can often extend over multiple gyri

Grey matter demyelination is extensive and often covers a greater area than WM demyelination



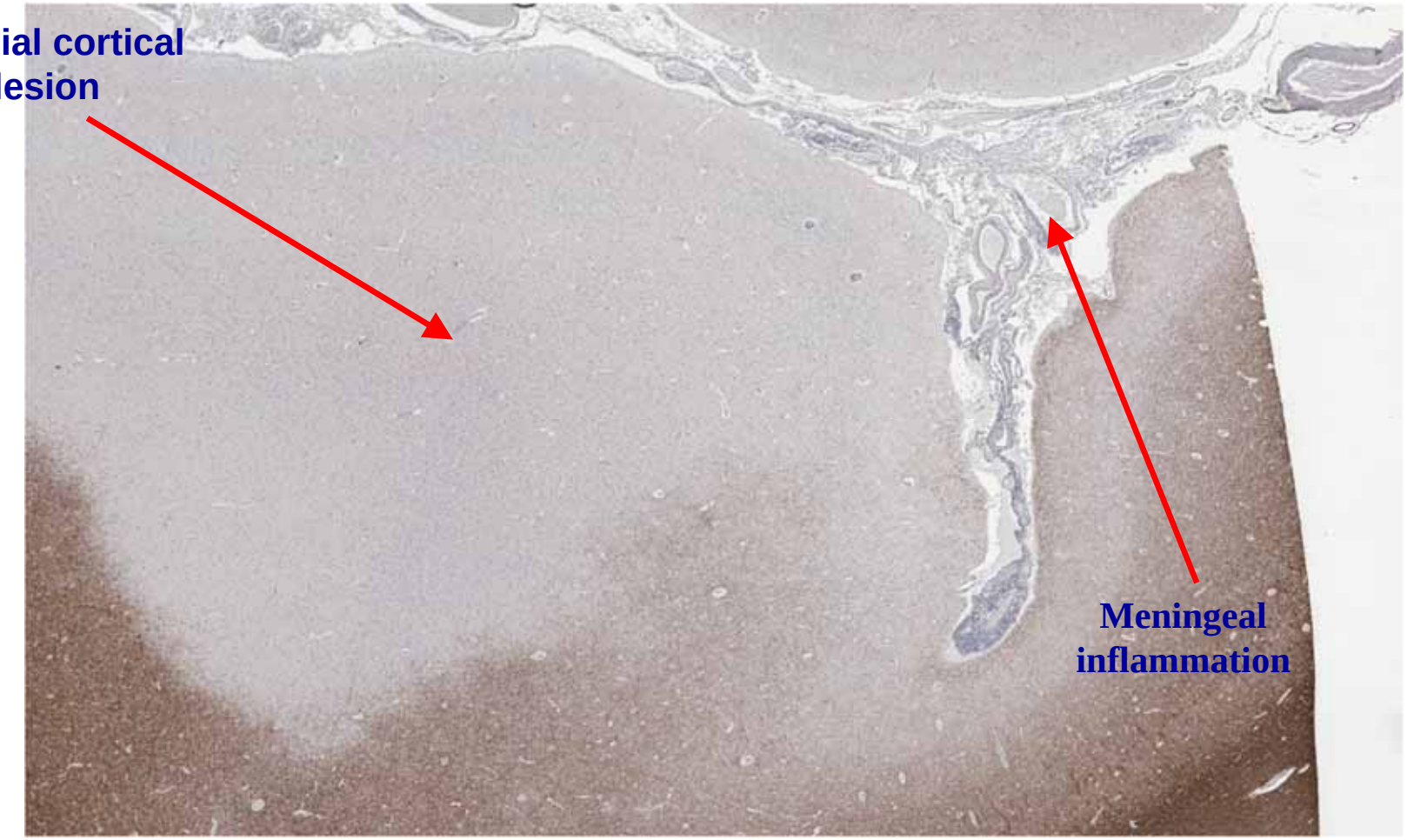
MOG



- Sub-pial lesions are commonest and extend over multiple gyri
- GM demyelination also extensive in other CNS areas that are exposed to the CSF

Is the degree of cortical pathology is controlled by the level of the inflammatory milieu in the CSF of the subarachnoid space?

Meningeal inflammation and lymphoid-like structures in MS

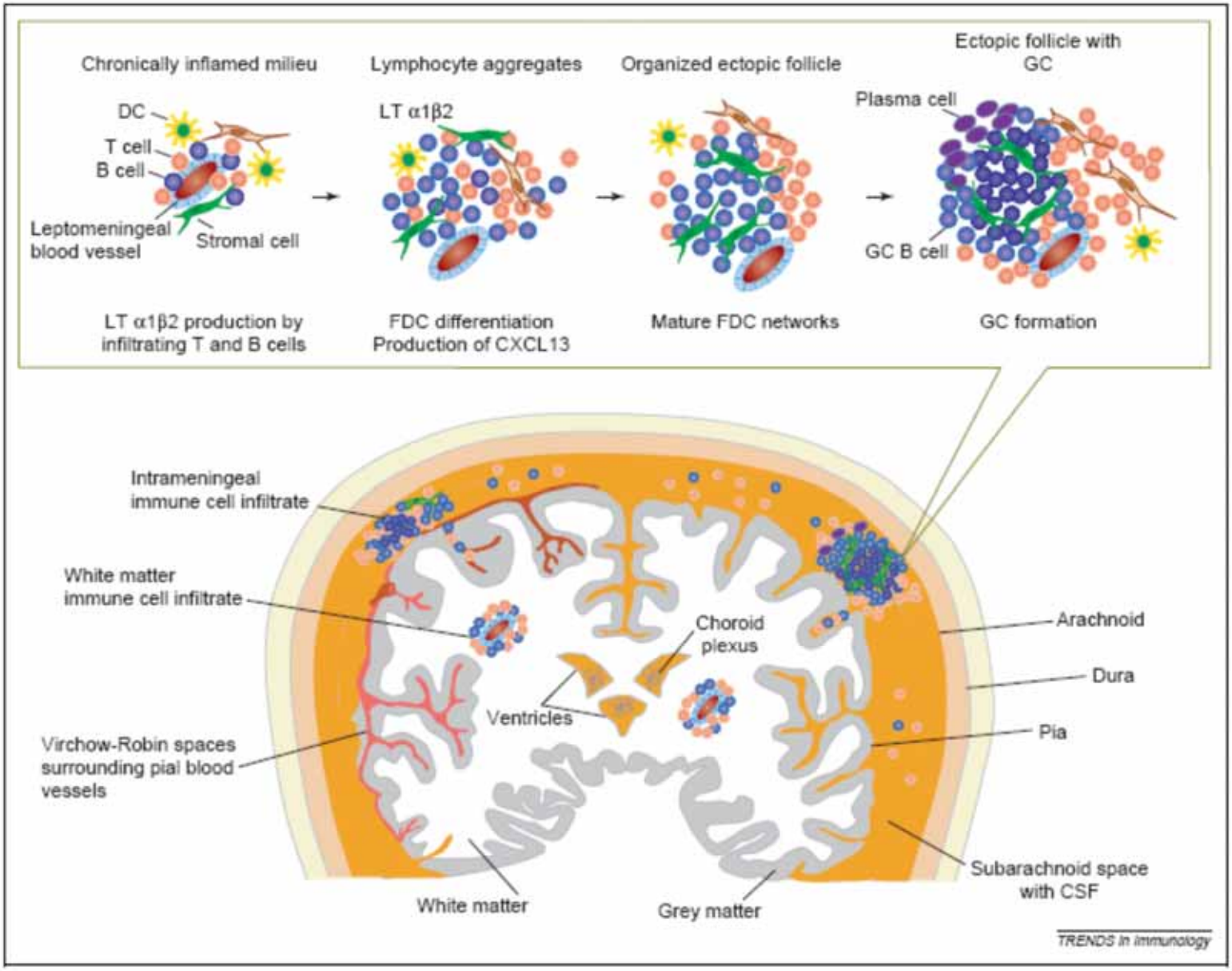


The presence of the tertiary lymphoid structures in the depths of the cerebral sulci:

- reduced CSF flow
- protected microenvironment
- favours the homing and retention of inflammatory cells

Serafini et al 2004 Brain Pathol

A role for B-cells in cortical pathology

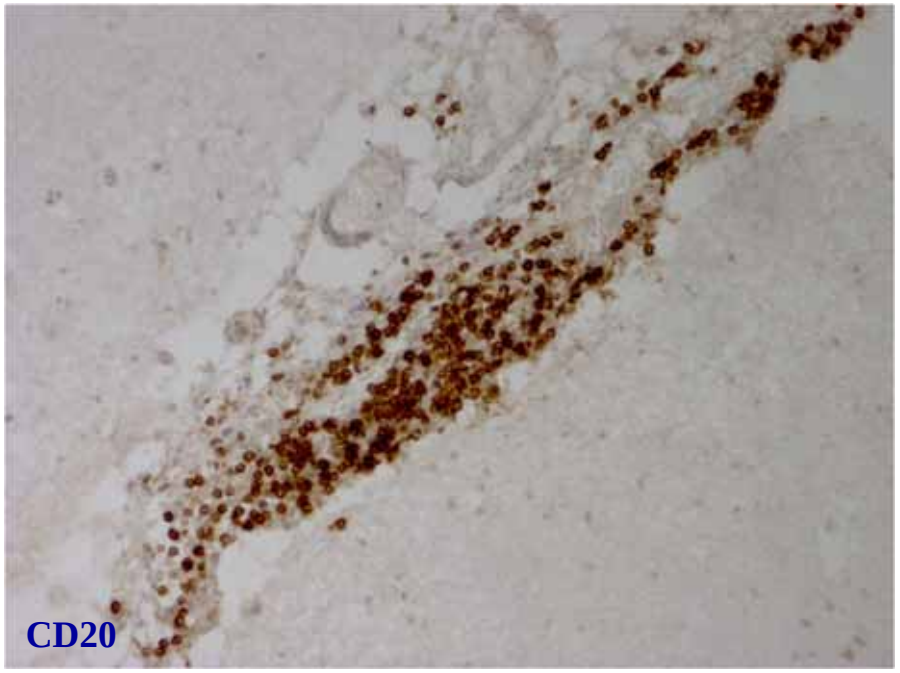


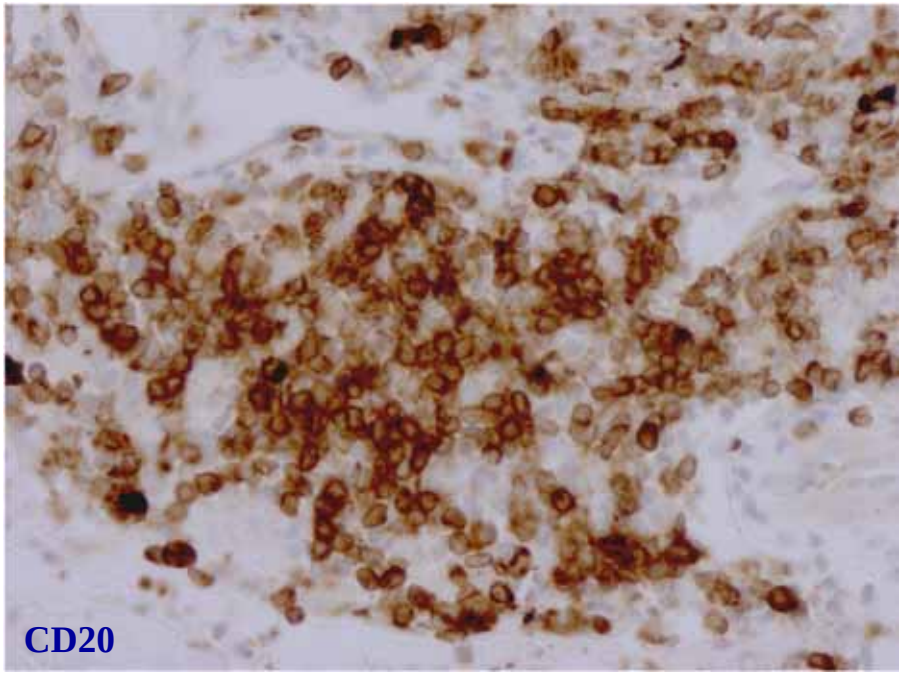
Tertiary lymphoid structures are a feature of MS grey matter pathology:

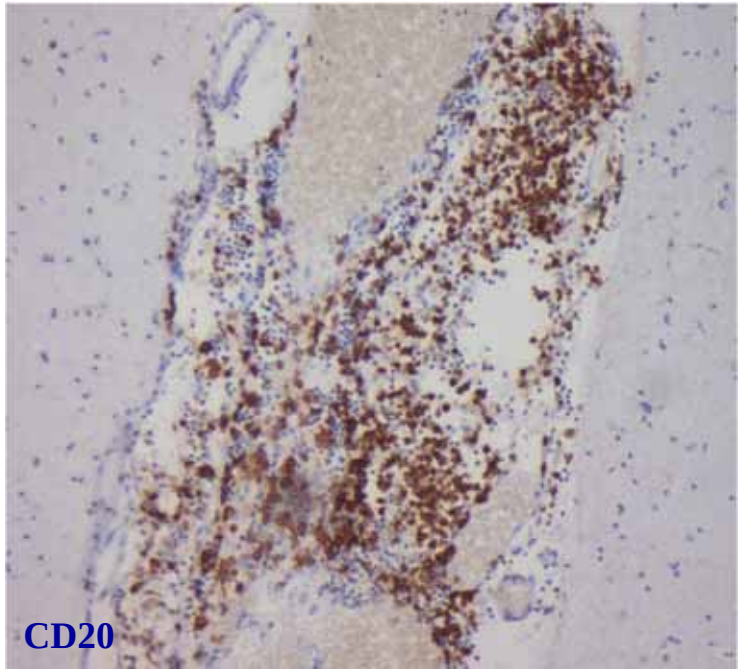
- ectopic meningeal lymphoid structures characterised as B-cell follicles due to: CD20+ B-cells; Ki67+ B-cells; Ig+ plasma cells; CD35+ FDCs; CXCL13+ FDCs; CD3+ & CD8+ T-cells

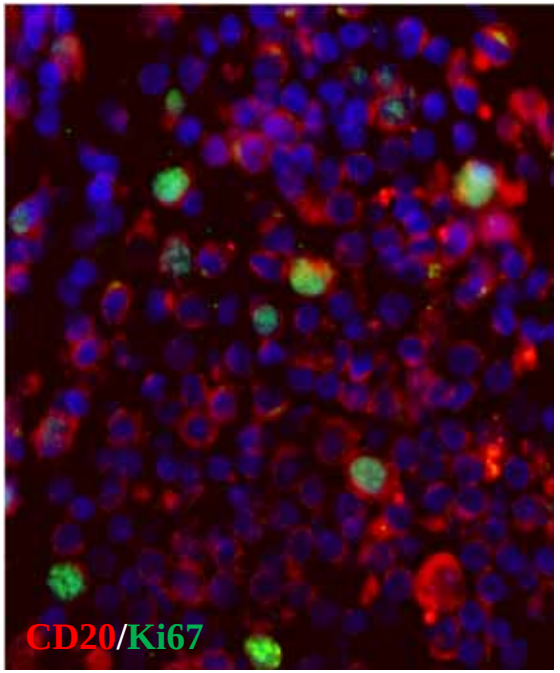
- cellular composition reminiscent of tertiary lymphoid structures: sites of B cell activation, clonal expansion and maturation

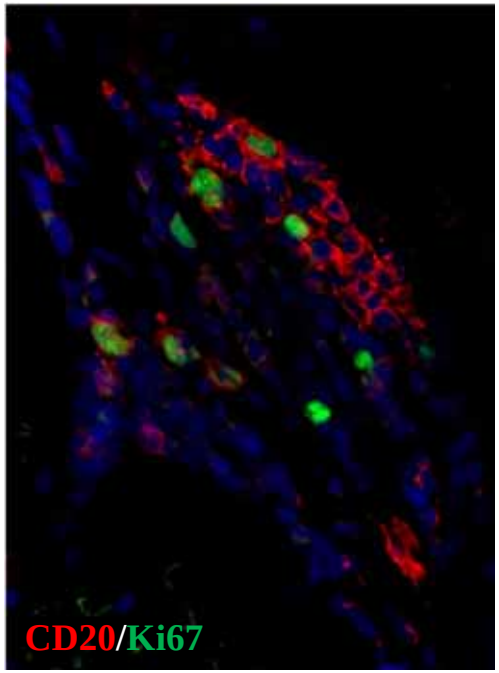
- hallmark of a range of autoimmune conditions such as Hashimoto's thyroiditis, Graves disease, rheumatoid arthritis where they associate with a more damaging disease.


CD20

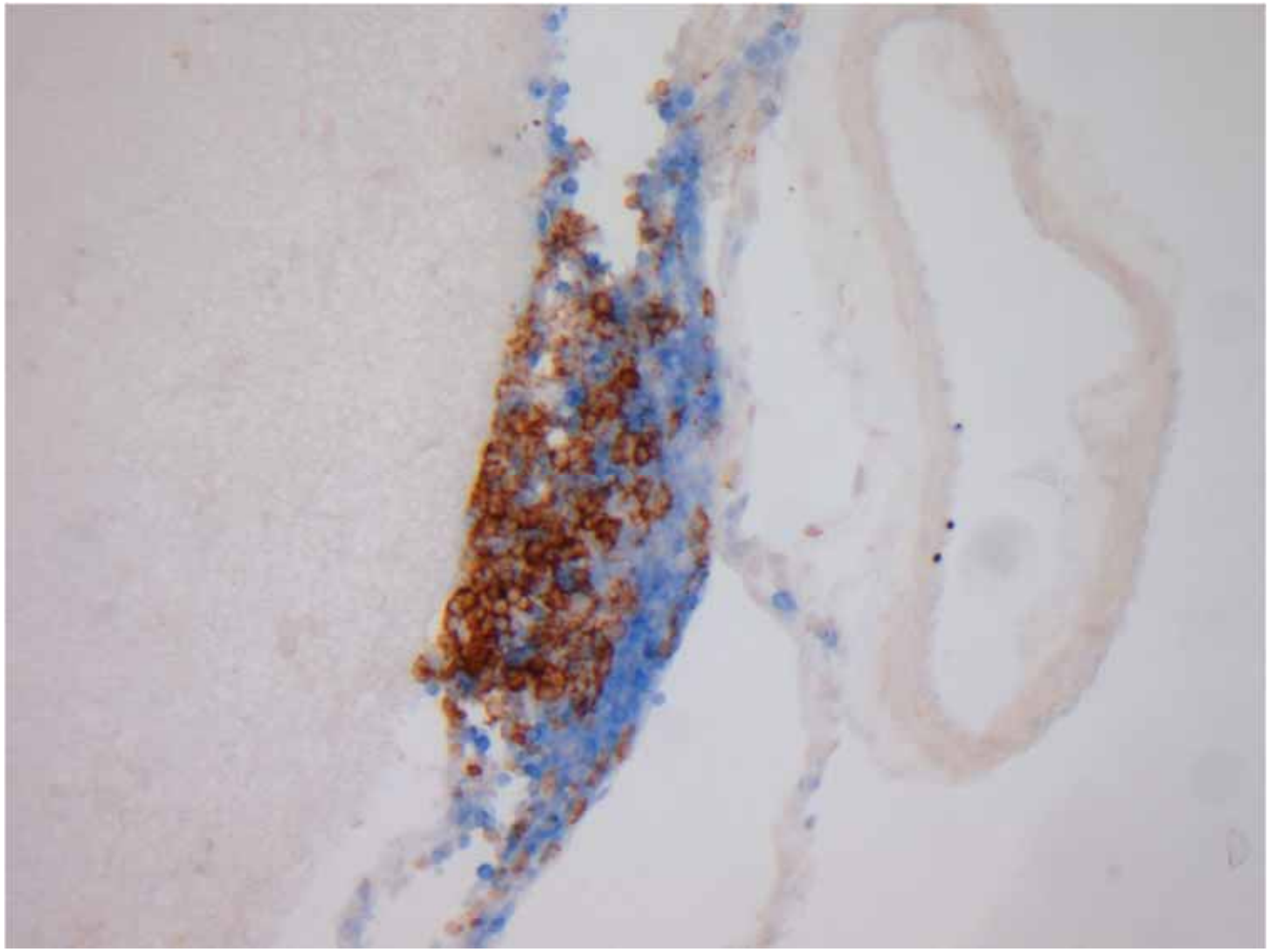

CD20

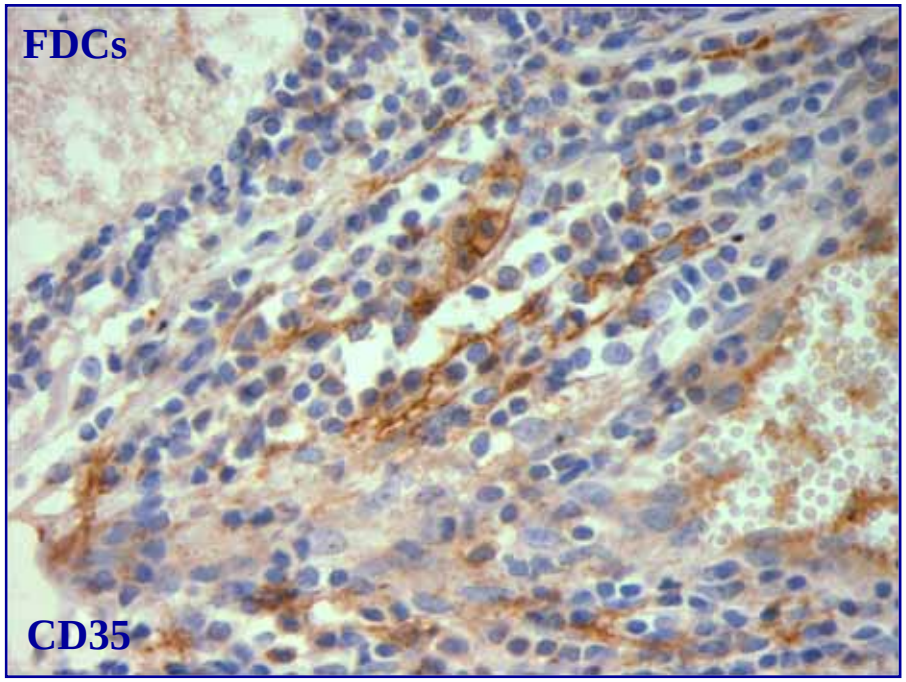

CD20

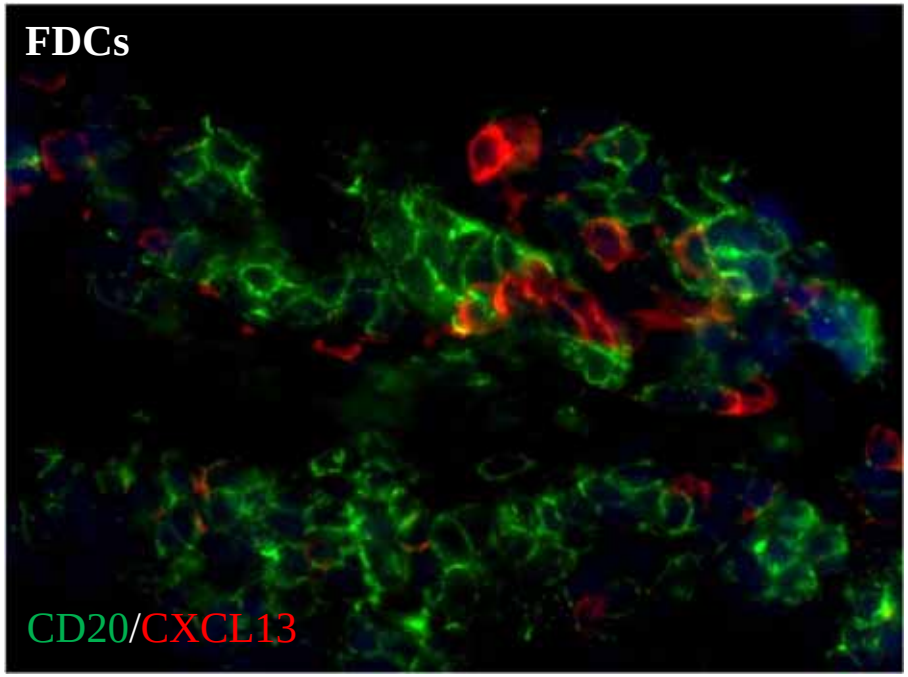

CD20/Ki67

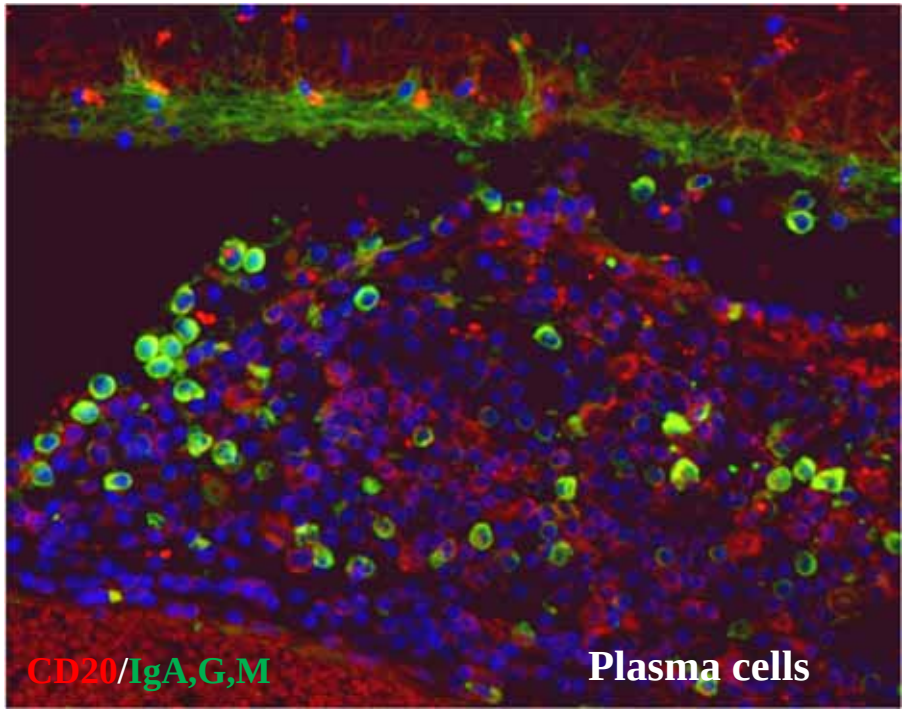

CD20/Ki67

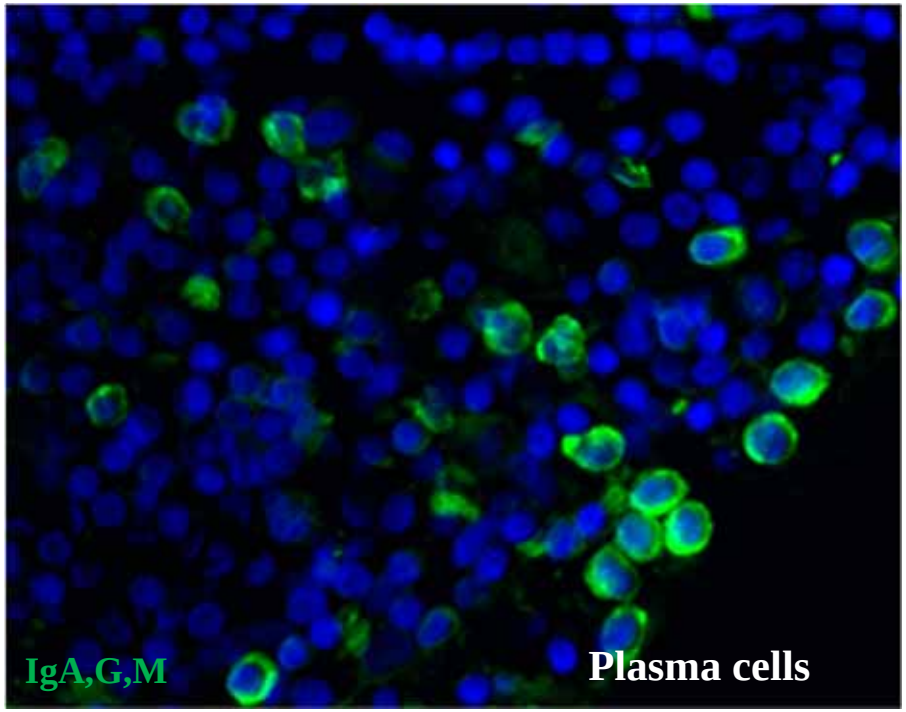
T-cell and B-cell zones?

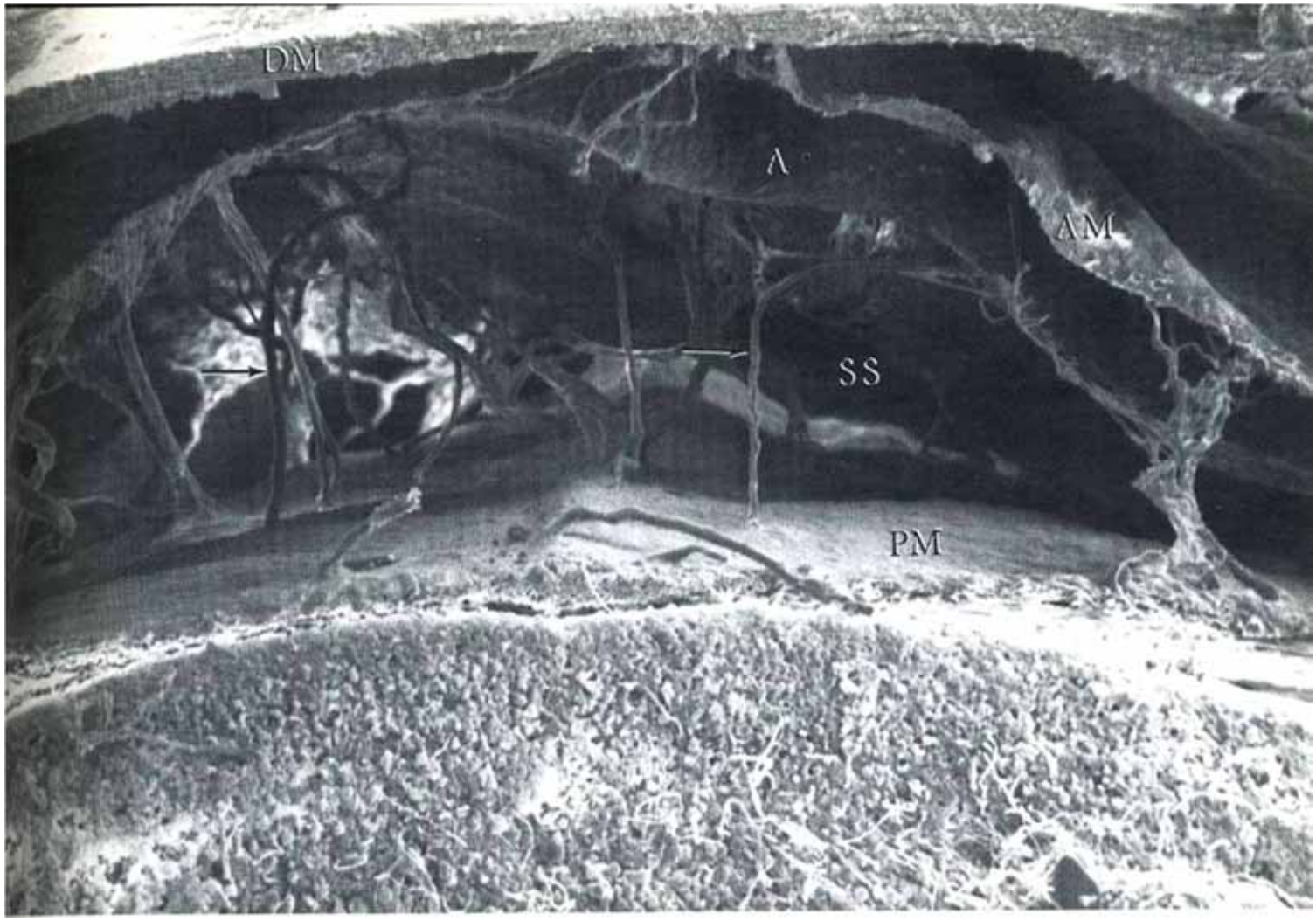



FDCs
CD35


FDCs
CD20/CXCL13

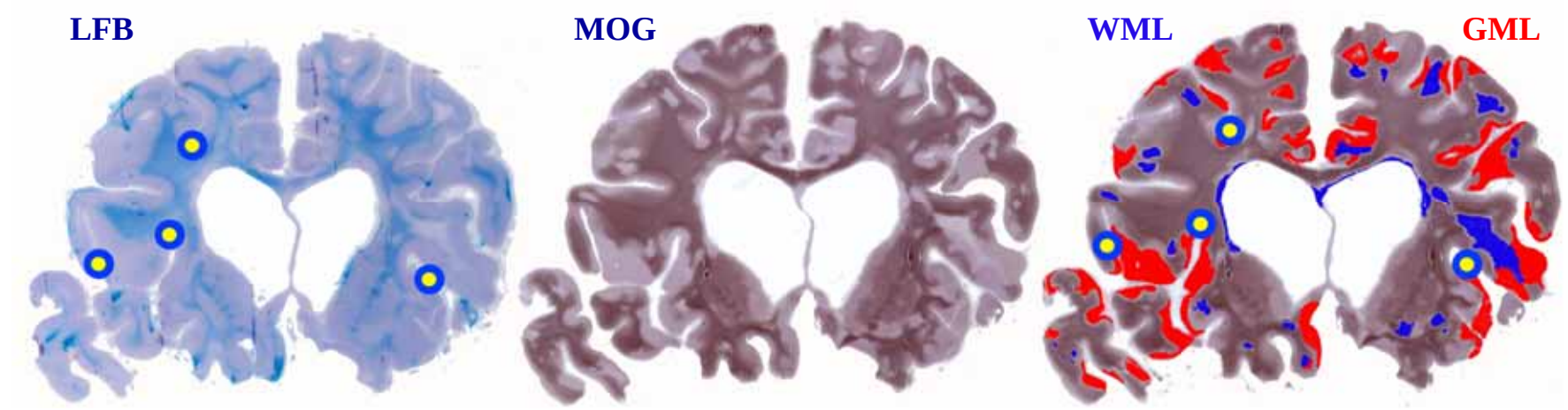

CD20/IgA,G,M
Plasma cells


IgA,G,M
Plasma cells

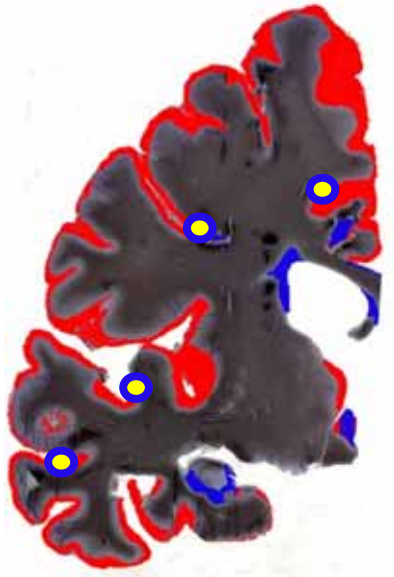


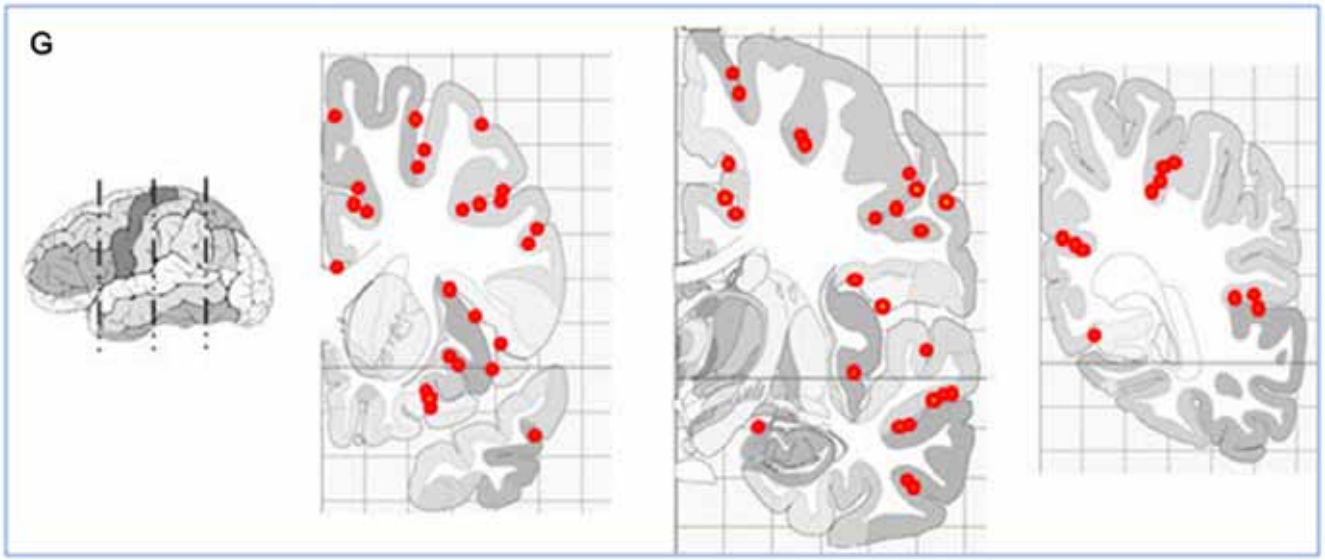
- the formation of true tertiary lymphoid structures with a germinal centre is constrained by the architecture of the subarachnoid space, a fluid filled space with variable rate of flow.
- architecture of the subarachnoid space may determine the structure, size and organisation of the tertiary lymphoid follicles

B cell follicles and cortical pathology



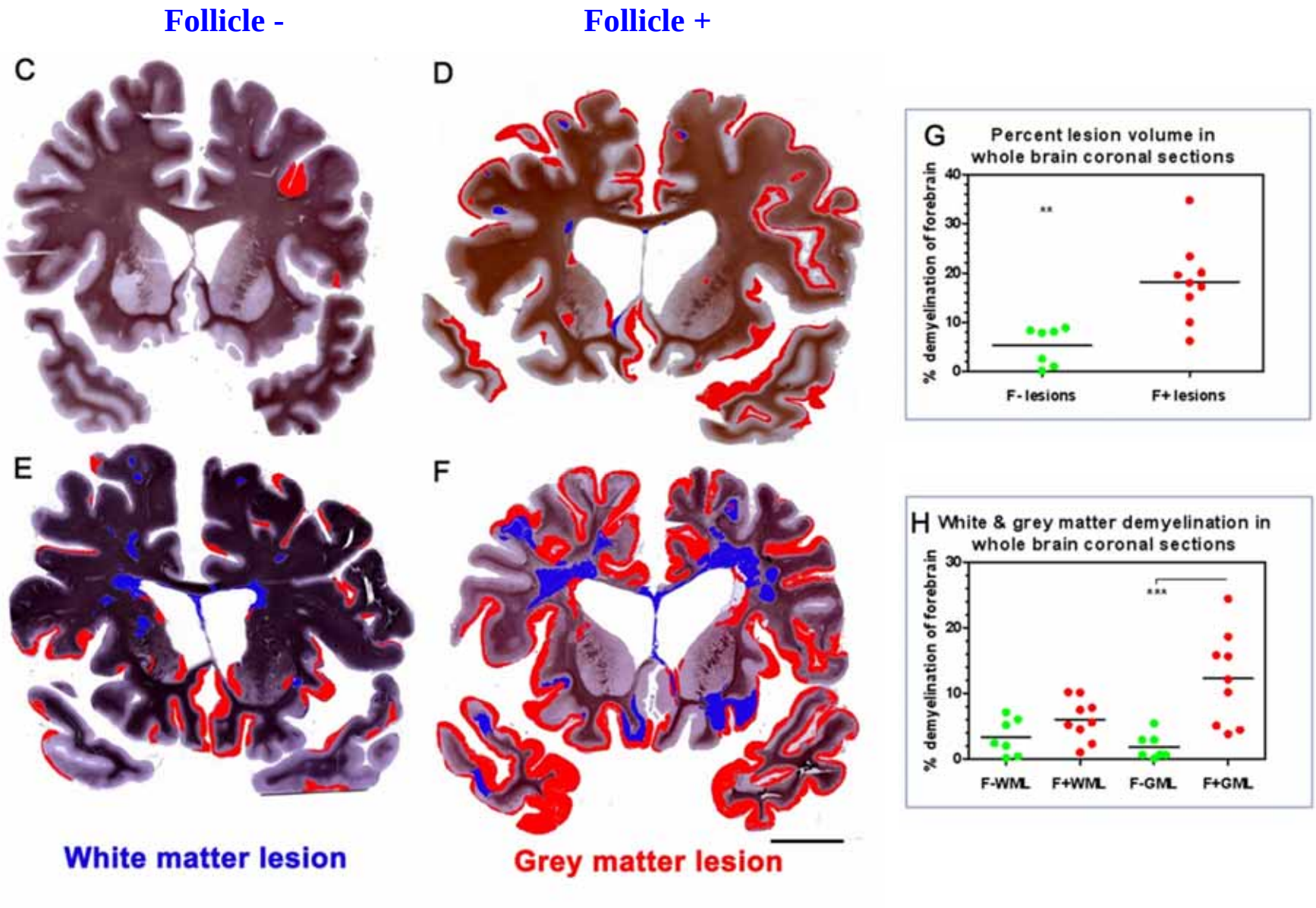
Location of meningeal follicle





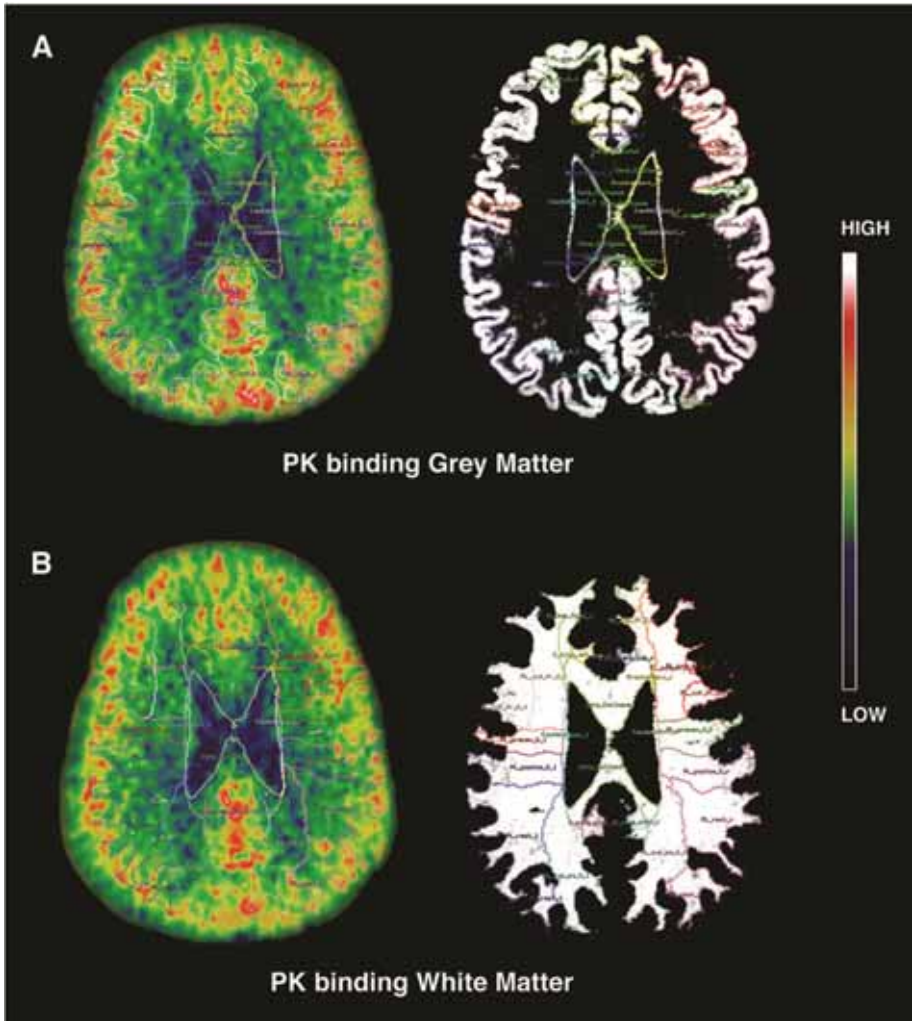
Analysed whole hemispheric sections to study frequency and distribution in forebrain

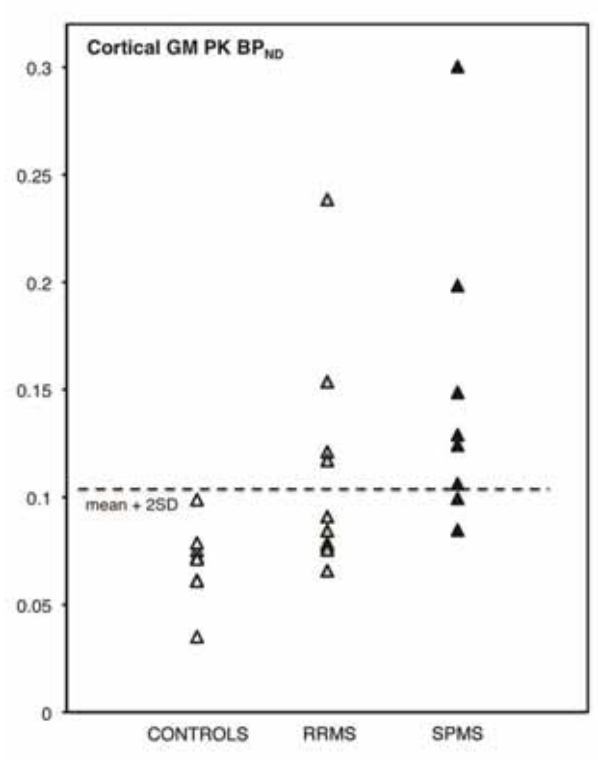
- **Variable in size and location**
- **Found in 18.1% of blocks analysed (6-67%)**

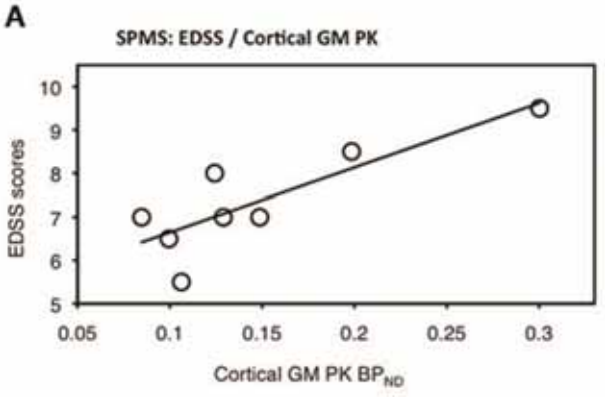


F+ cases have proportionally greater GM demyelination

In vivo PET imaging of cortical pathology





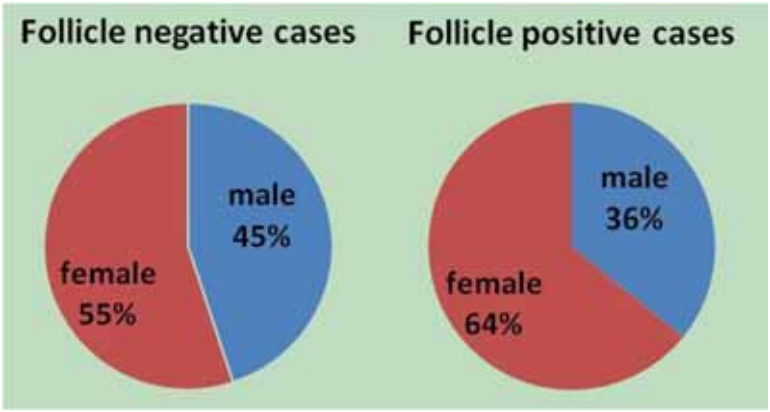


Incidence and clinical outcome measures of F+ and F- cohorts

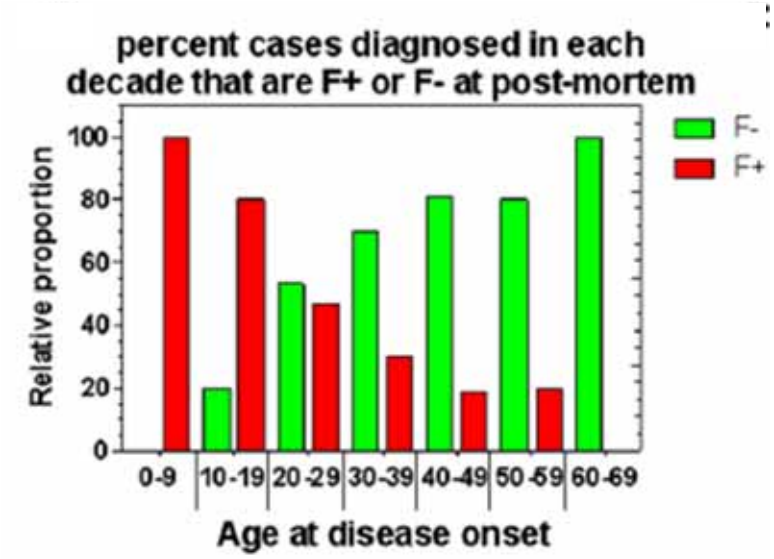
- Substantial proportion of MS are F+

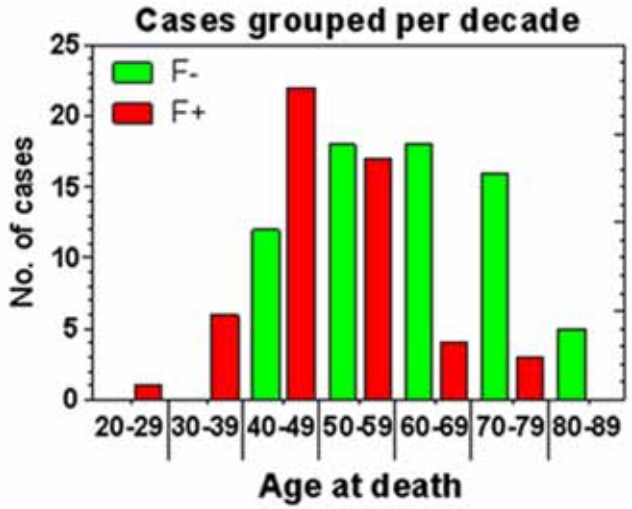
126 cases screened → 49 cases meningeal follicles = **40%**

- Greater female bias

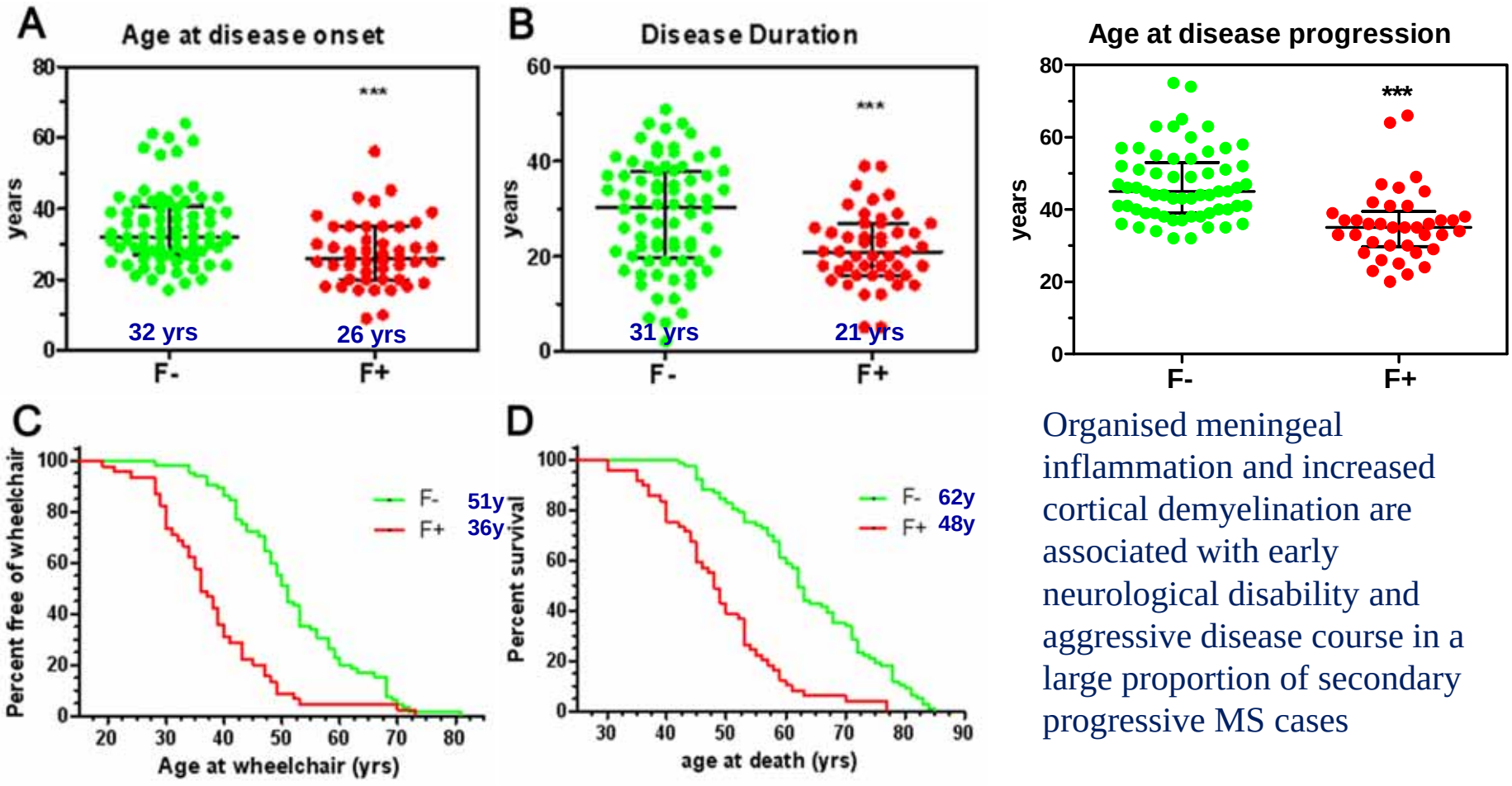


1.2F: 1M **1.8F: 1M**

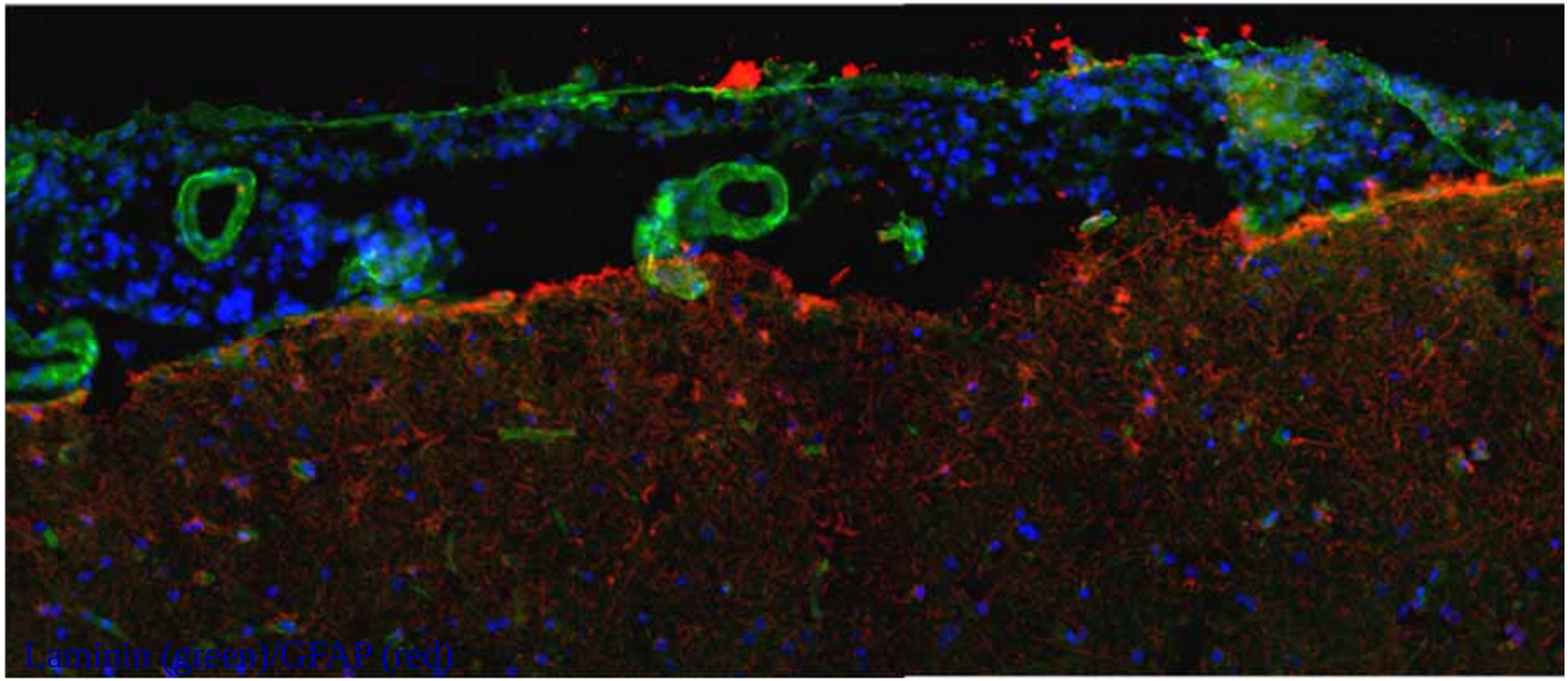


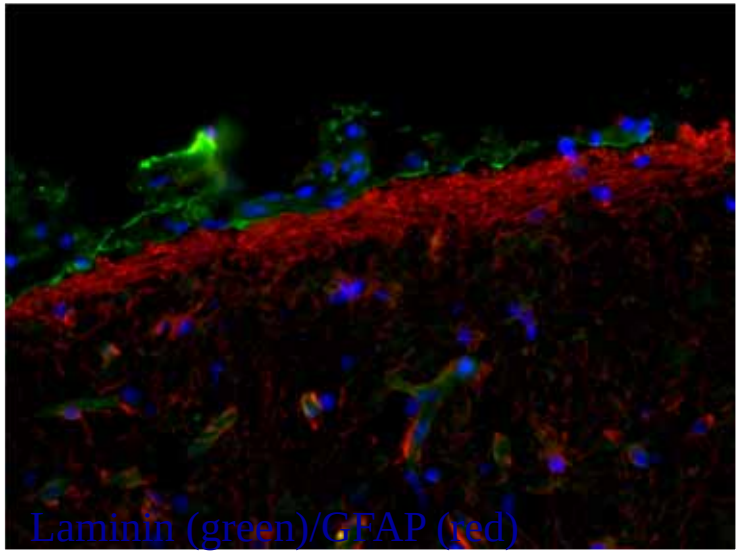


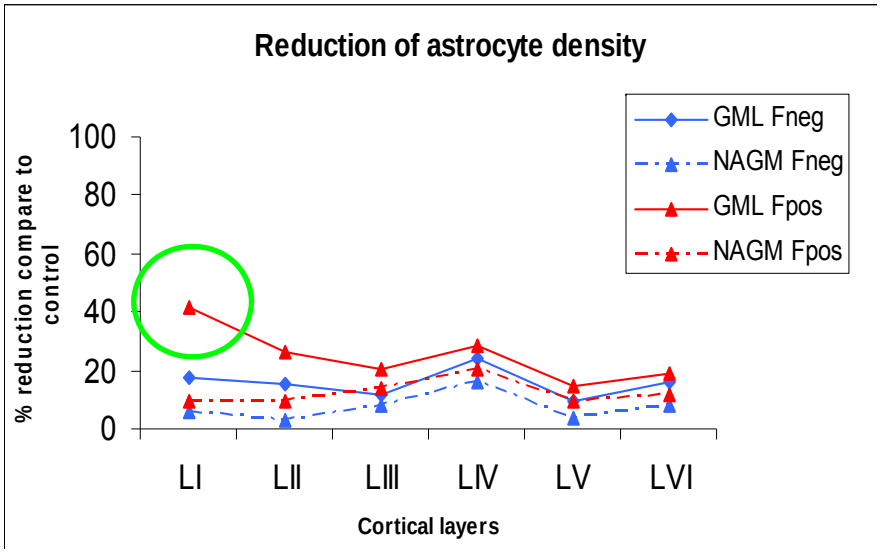
Incidence and clinical outcome measures of F+ and F- cohorts



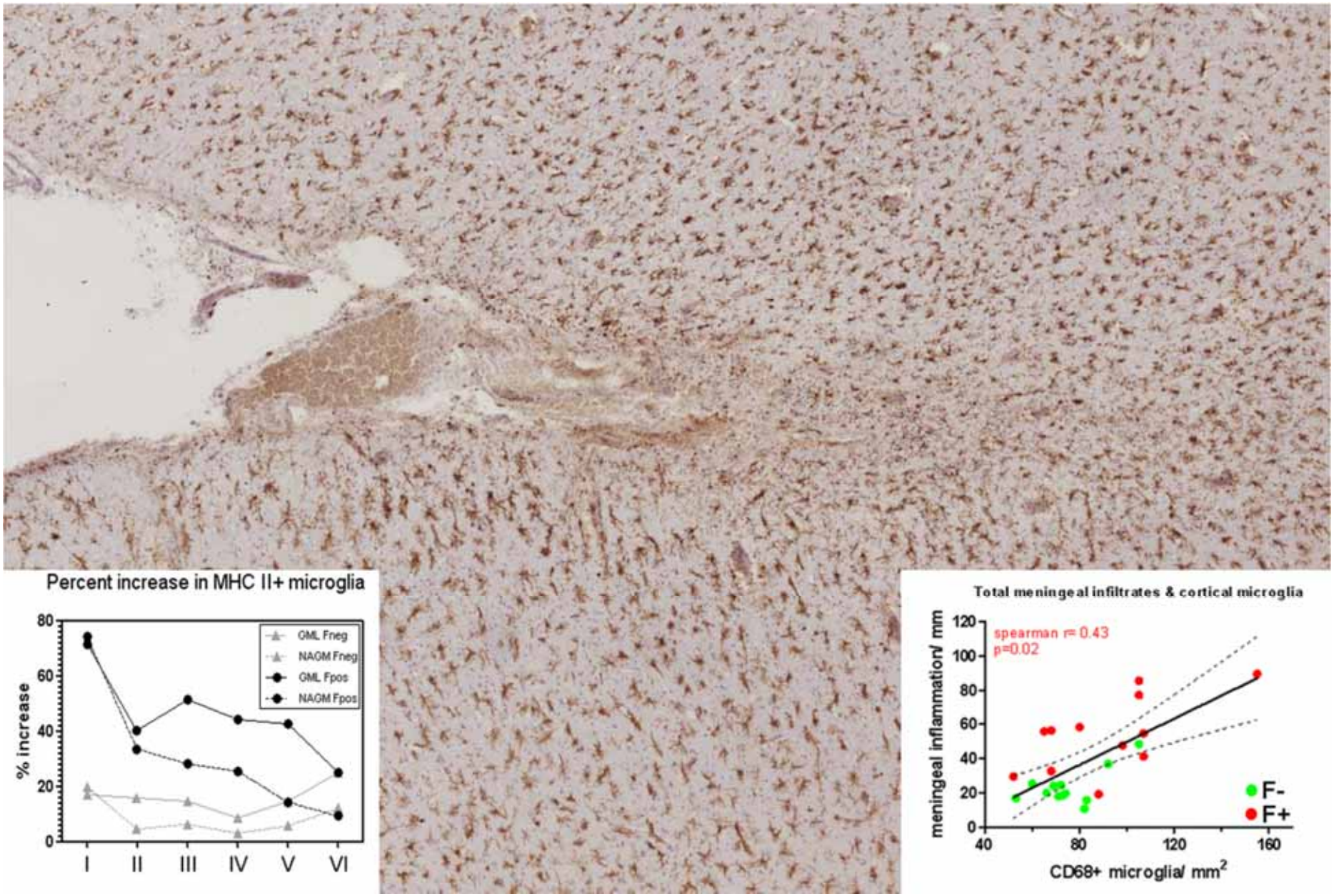
Organised meningeal inflammation and increased cortical demyelination are associated with early neurological disability and aggressive disease course in a large proportion of secondary progressive MS cases


Laminin (green)/GFAP (red)


Laminin (green)/GFAP (red)


Reduction of astrocyte density
% reduction compare to control
100
80
60
40
20
0
LI
LII
LIII
LIV
LV
LVI
Cortical layers
GML Fneg
NAGM Fneg
GML Fpos
NAGM Fpos

A gradient of microglial numbers and activation state



Clinico-pathological correlations in MS

- inflammatory foci without demyelination	- acute relapses
- primary demyelination	- acute & chronic
- axonal loss in lesions	- progressive symptoms
- grey matter demyelination	- progressive
- grey matter neuronal and axonal loss	- progressive motor, sensory and cognitive
- diffuse white matter changes	- fatigue?
- diffuse grey matter changes	- motor, sensory and cognitive symptoms

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