Hashemite University
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Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY

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PRIMARY DISEASES OF MYELIN

☺ **Normally,** within the CNS, axons are tightly ensheathed by **myelin**, which serves as an **electrical insulator** to allow rapid propagation of impulses. عازل كهربائي.

★Myelin **consists** of multiple layers of the specialized plasma membrane of oligodendrocytes, with most of the cytoplasm excluded.

★These portions of the oligodenrocyte membrane contain **specialized proteins & lipids** that contribute to the orderly packing of the layers. التنظيم المنتظم حول ال axon.

★One oligodendrocyte cell extends processes toward many different axons & wraps a segment of roughly a few hundred microns of axon.

★ Each of these **segments** is called an ***internode,*** & the gaps between internodes are known as ***nodes of Ranvier.*** Although **myelinated axons** are present in all areas of the brain, they are the **dominant component in the *white matter***, therefore, *most diseases of myelin are primarily white matter disorders*.

☺ **Normally,** the myelin in peripheral nerves is similar to the myelin in the CNS but, has several important differences:

(1) Peripheral myelin is made by **Schwann cells,** not by oligodendrocytes;

(2) Each **Schwann cell** in the peripheral nerve contributes to only **one internode**, while in the CNS, many internodes comes from a single oligodendrocyte; &

(3) The **specialized proteins & lipids are also different**.

☺ Therefore, **Thank God**, most diseases of CNS myelin do not significantly involve the peripheral nerves, & vice versa

* إذا الـ myelin فُقد في مكان على طول الـ axon راح يخرب الـ impulse transmission لكل الـ axon.

★**If the myelin along a set of axons is disrupted**, there are **changes in the ability of these axons to transmit signals**, & the symptoms **depends on the site (or sites**, since most diseases of myelin are multiple, affecting **many** regions of the brain at the same time) where demyelination occurs.

★The **natural history** of demyelinating diseases is determined, in part, by (1) **the limited capacity of the CNS to regenerate normal myelin** & by (2) **the degree of secondary damage to axons** that occurs as the disease runs its course.

Generally, diseases involving myelin are of 2 broad **groups**:

(I) ***Demyelinating diseases*** of the CNS: are **acquired** conditions, characterized by **damage to previously normal myelin**. The commonest diseases in this group result from (1) **immune-mediated injury**, such as multiple sclerosis **(MS)** & related disorders.

Other processes that can cause *demyelination* include (2) **viral infection of oligodendrocytes** as in progressive multifocal leukoencephalopathy {**PML,** discuss before}, & (3) injury caused by **drugs & other toxic agents.**

▼In contrast to *demyelinating diseases,*

(II) ***Leukodystrophy or dysmyelinating diseases, occur when the myelin is not formed properly or it has abnormal turnover kinetics;*** *&* are associated with **mutations affecting the proteins** required for formation of normal myelin, or mutations that affect the synthesis or degradation of myelin lipids.

Multiple Sclerosis (MS)

- **MS** is an **autoimmune demyelinating disorder** characterized by (1) *distinct **episodes** of neurologic deficits, separated in **time**, attributable to (2) white matter **plaques** that are separated in **space***
- **MS** is the **commonest demyelinating disorders**, having a prevalence of **1/1000 persons** in US & Europe=like Malignancy
- **MS** may affect **any age**, although onset in childhood or after age 50 years is relatively rare. (20-40 years)
- **MS M/F ratio is 1:2.**
- **MS** shows **relapsing & remitting episodes** of neurologic deficits in most individuals. The frequency of relapses tends to ↓ during the course of the illness, but there is a steady neurologic deterioration in a subset of patients.
- A transmissible **agent** has been proposed as a cause of **MS,** but **never** been conclusively identified!
- **MS,** like other autoimmune diseases, is believed to be caused by a combination of **genetic** & **environmental** factors that result in a **loss of tolerance to self proteins** (the myelin antigens in the case of **MS**).

- **MS risk of development is X15-fold higher** when the disease is present in a first-degree relative.

- **MS** concordance rate for **monozygotic twins** is **25%,** with a much lower rate for **dizygotic twins** indicates a strong, but not causative, role for genes. Genetic linkage of MS susceptibility to the HLA-DR2 extended haplotype is well established.

* Is experimental allergic encephalomyelitis similar/the same as MS? Yes.

◘ Immune mechanisms that may be the cause of myelin destruction have been investigated because of **prominence of chronic inflammatory cells** within & around **MS** plaques,

➔ *Experimental allergic encephalomyelitis* is an **animal model** of **MS** in which **demyelination & inflammation occur after immunization with myelin, myelin proteins, or certain peptides from myelin proteins**.

➔In this model, the lesions are **caused by a T cell-mediated DHR (Type IV) to myelin** proteins, & the same immune mechanism is thought to be central to the pathogenesis of **MS**.

😐 While **MS** characterized by demyelination out of proportion to axonal loss, however some injury to axons does occur.

▶**GROSSLY**, **MS** is a white matter disease, The affected areas show **multiple well-circumscribed plaques, glassy, gray-tan, slightly depressed irregular** lesions.

★**Plaques** commonly occur **beside the ventricles, & are** frequent in the optic nerves & chiasm, brain stem, ascending & descending fiber tracts, cerebellum, & spinal cord (F23-27A & 9-26 & 27),

◘ H, the lesions have **sharply** defined borders {F23-27B & ◘ 4.21&23},

★In an **active plaque** there is evidence of ongoing:

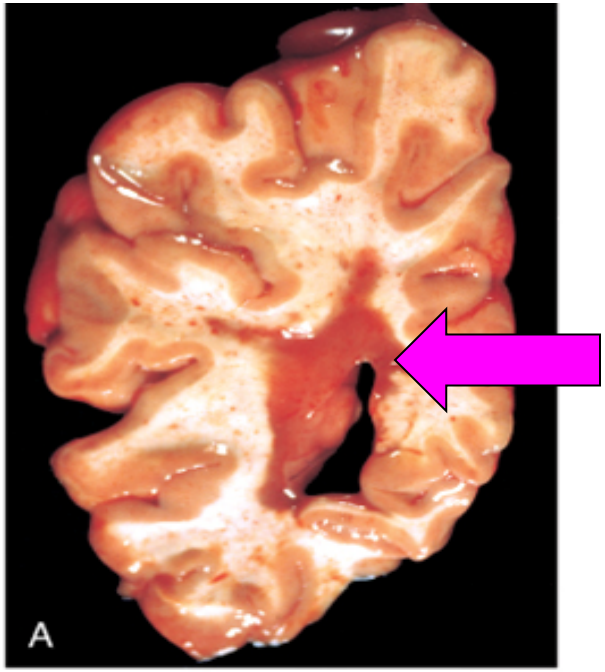
(1) **Perivascular cuff of lymphocytes & monocytes**

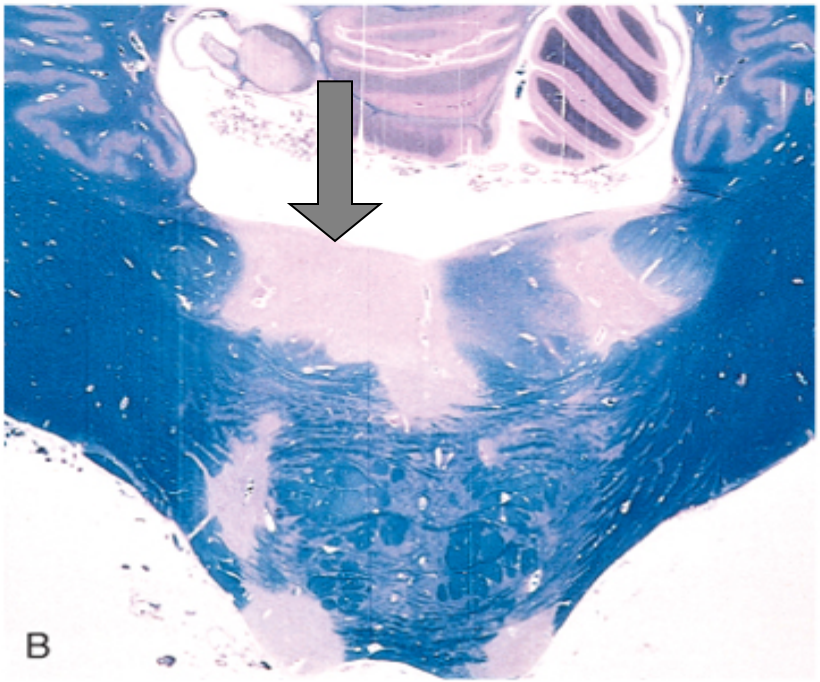
(2) **Abundant macrophages containing myelin debris**.

(3) **Myelin breakdown,** with

(4) Small active plaques are often **centered** on small veins, &

(5) **Axons are relatively preserved**, although they may be reduced in number.





F23-27: **Multiple sclerosis**

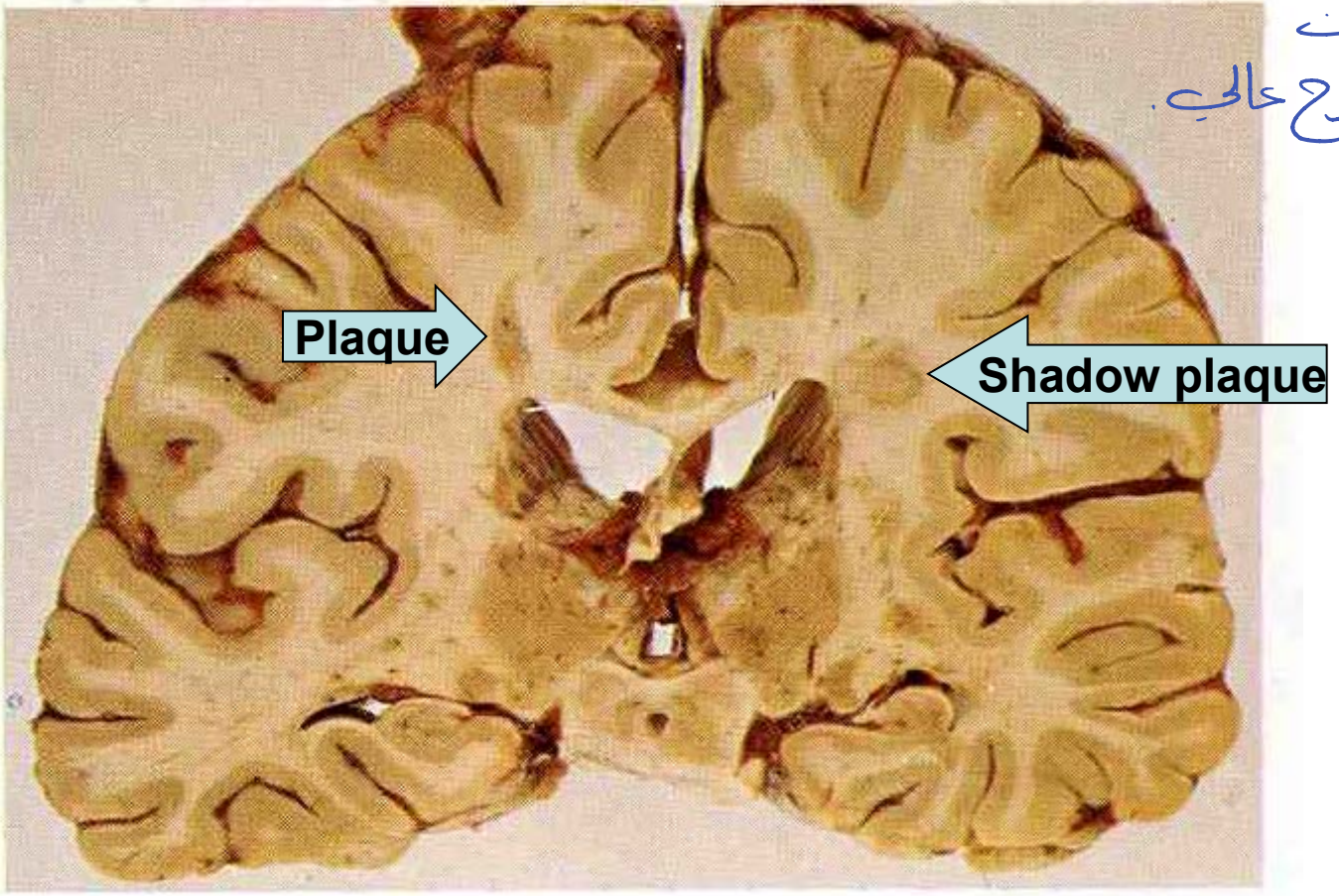
A, Fresh brain section showing a well-circumscribed, slightly depressed, gray-tan, irregularly shaped plaque around occipital horn of the lateral ventricle.

B, Unstained region of demyelination (**MS plaque**) around the fourth ventricle. (Luxol fast blue-PAS stain for myelin.)

منطقة غير مصبوغة لأنها demyelinated.

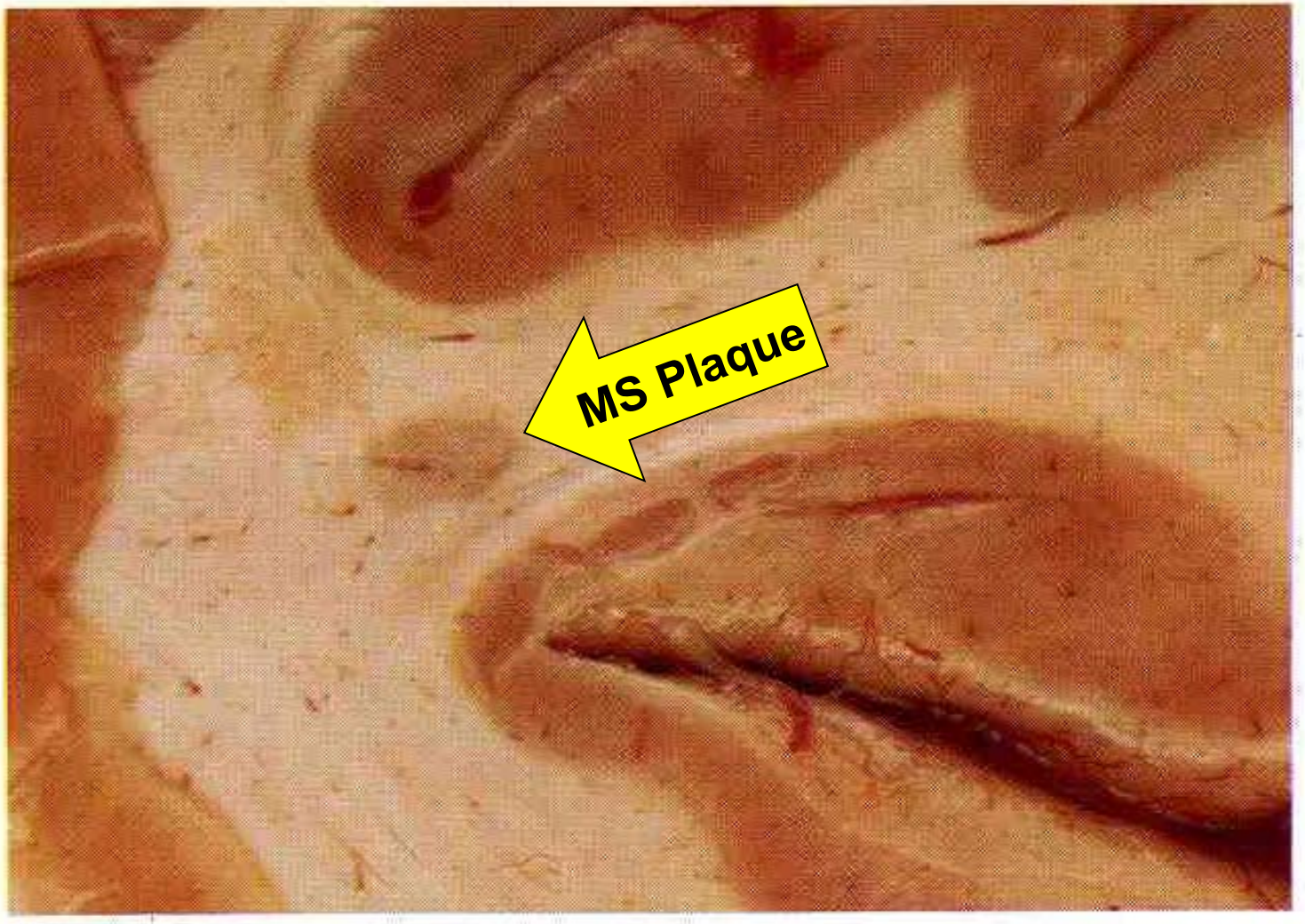
F 9-26: **Multiple sclerosis: brain.** Coronal section of the brain showing well-defined greyish-brown chronic plaques of demyelination at the upper angles of both lateral ventricles within the white matter of the centrum semiovale. The right plaque shows features of **'shadow plaque'.**

لأنه العمر تتجه أكثر
لذلك ما يكون
مبين بوضوح عالي



9.26 Multiple sclerosis: brain

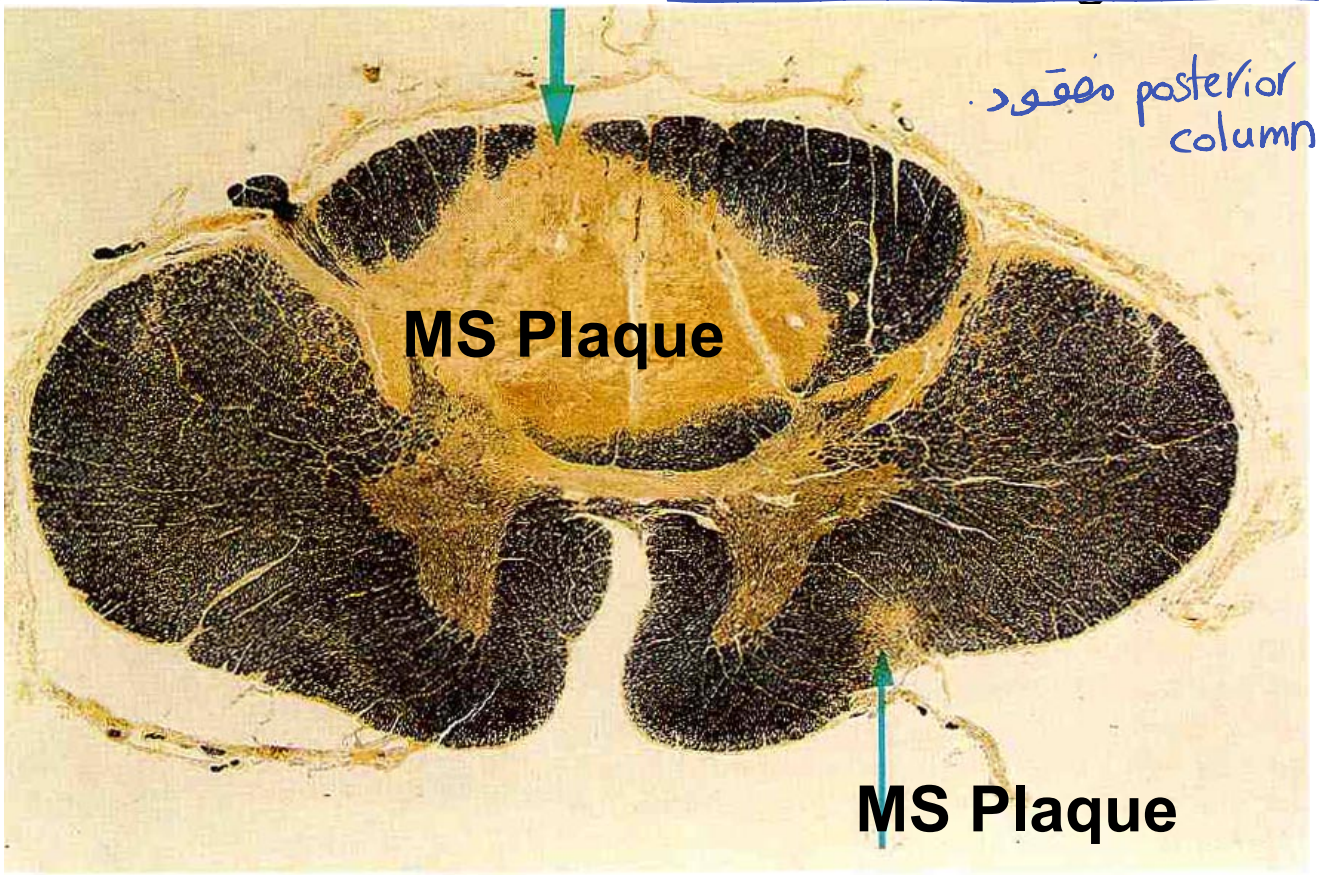
F 9-27: **Multiple sclerosis (MS) : brain.** Close-up view. A recently-formed oval, pinkish-grey plaque is present in the white matter beneath the cortical ribbon. This is a characteristic site.



9.27 Multiple sclerosis: brain

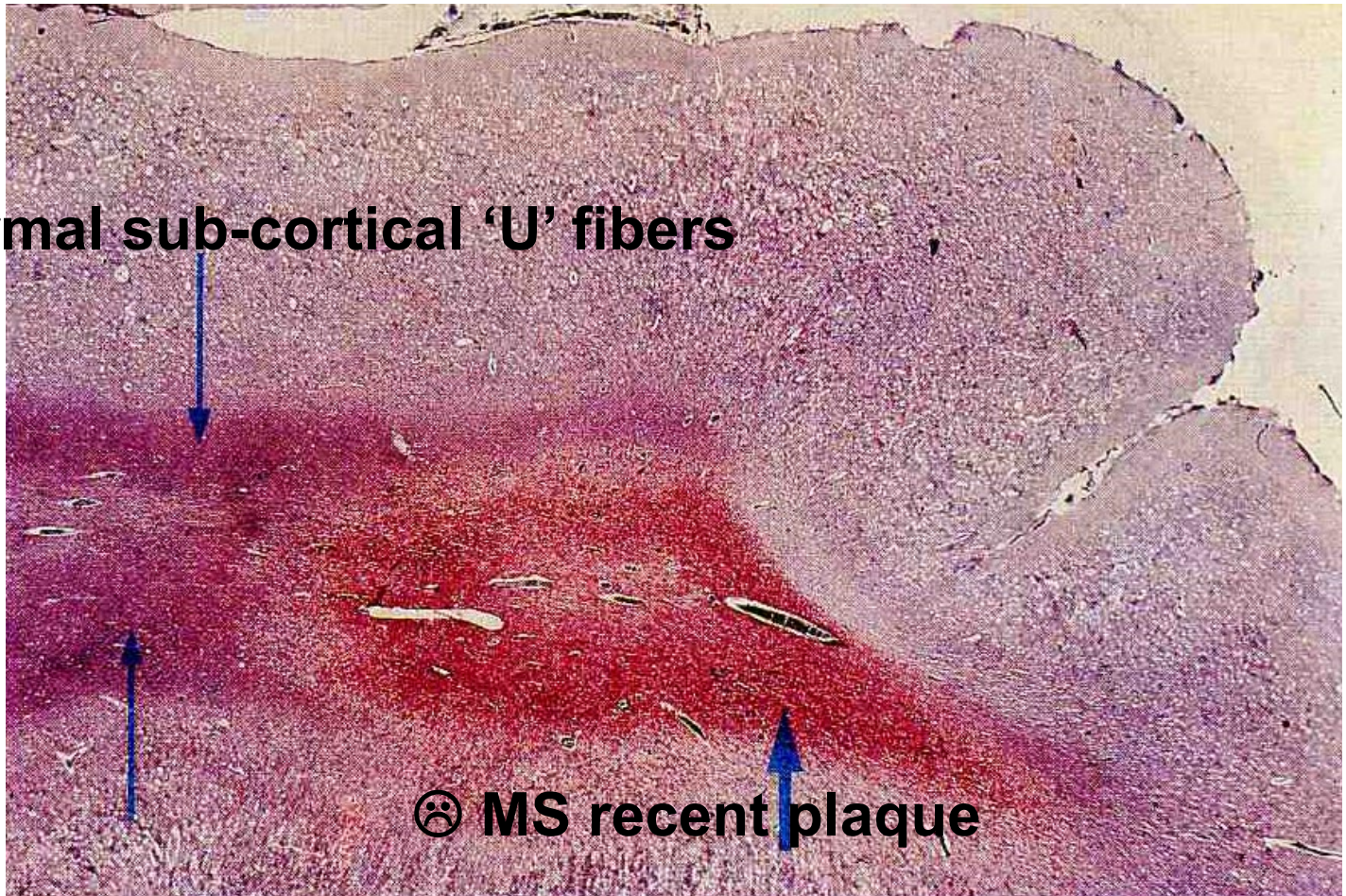
■ 4.21: **Multiple sclerosis (MS) X9.** Cervical spinal cord section, stained by the Weigert-Pal method, which colors the myelin black, **showing 2** plaques of demyelination: (1) a small round one in the ventrolateral part of the cord (thin A), (2) much larger, **irregular** shaped one (thick A) which affects most of the posterior columns, with **complete loss of the myelin & sharp line of demarcation** between it & the surrounding tissues.

المناطق الصفراء هي غير طبيعية



أغلب ال

◘ 4.23: **Multiple sclerosis (MS): Brain, Sudan IV X11.** Frozen section of cerebellar recent plaque, stained with **Sudan IV** to show **fat** (**orange-red color**, thick A) from the presence of much stainable fat which comes from the breakdown of myelin lipids. Above & to the left of the plaque there is purplish-blue sheet of normal, unaffected sub-cortical 'U' fibers (thin A).



هادئ

◘ **Inactive plaques MS** (when plaques become quiescent),
(1) **Disappearance of inflammation,** leaving behind little or
(2) **No myelin**. Instead, there is

shadow plaque. إلى active plaque تحوّلت من

(3) **Gliosis** & prominent astrocytic proliferation &
(4) **Shadow plaques may be seen (F 9-26),** where the border between normal & affected white matter is not sharply circumscribed. Here, thinned-out myelin sheaths can be demonstrated, especially at the outer edges, suggesting that this border region represents either (1) incomplete myelin loss or (2) partial remyelination.

قاعدة عامة لهذا المرض هي relapse and remission و بتعاد هذه الدورة .

►***Clinically,*** **commonly,** there are multiple episodes of injury (***relapses)*** followed by episodes of recovery (***remissions)***; typically, the recovery is not complete, with **gradual**, **often stepwise, accumulation** of ↑ neurologic deficits.

كل نكسة بتترك آثار.

★ **Unilateral visual impairment,** occurring over the course of a few days is a frequent initial symptom of MS due to optic nerve involvement (***optic neuritis***, ***retrobulbar neuritis***).

★Involvement of the **brain stem** produces cranial **nerve signs & ataxia**, & can disrupt conjugate eye movements.

★ **Spinal cord** lesions give rise to **motor & sensory impairment of trunk & limbs,** spasticity, & difficulties with the voluntary control of bladder function.

☹ **In any individual patient, it is hard to predict when the next relapse will occur!**

▼**CSF** shows (1) in 1/3 of cases there is moderate pleiocytosis.

(2) A mildly elevated protein level with an ↑ **proportion of γ-globulin**, which when examined further, show ***oligoclonal bands,*** representing **antibodies directed against a variety of antigenic targets.**

➔ Although these antibodies constitute a **marker for disease activity**, it is not clear if they are a critical part of the disease mechanism.

يعني الـ MS موجودة بكثرة وأكثر مما يمكن توقعه عن طريق الـ examination.

▼ **MRI can show the distribution of lesions across the CNS during active disease.** From this, it has become clear that there are often **more lesions** in the brains of MS patients **than might be expected by clinical examination** & that lesions can come & go much more often than was previously suspected!

Other Acquired Demyelinating Diseases

☹ Immune-mediated demyelination can occur after a number of systemic infectious, including relatively **mild viral diseases**, which are not thought to be related to direct spread of the infectious agents to the nervous system, rather…

➔ it is believed that the **immune response to pathogen-associated antigens cross-reacts with myelin antigens,** & resulting in myelin damage (Cytotoxic reaction, Type II)

★ Two patterns of post-infectious, immune-mediated demyelination recognized, both, unlike MS, are
• **monophasic illnesses with relatively • abrupt onset:**

(I) ➔ ***Acute disseminated encephalomyelitis***, symptoms typically develop • a week or two after the antecedent infection & suggest • diffuse brain involvement (rather than the focal findings typical of MS) with headache, lethargy, & coma, which progress rapidly, to a **fatal outcome in about 20% of cases**; in the remaining patients there is complete recovery.

(II) ➔ ***Acute necrotizing hemorrhagic encephalomyelitis*** is a more devastating, typically affects young adults & children.

Central pontine myelinolysis

Myelin. ذوبان مادة ال

★ Is **nonimmune process** characterized by **loss of myelin involving the center of the pons**, **most often after rapid correction of hyponatremia.**

► It occurs in a variety of clinical settings including **severe electrolyte or osmolar imbalance & alcoholism .**

☹ Most characteristic lesion occurs in the pons fibers, which carry signals to motor neurons in the spinal cord, resulting in rapid **quadriplegia**.

شلل رباعي

viral infection.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease that occurs following reactivation of JC virus in immunosuppressed patients (See CNS infection).