Hashemite University
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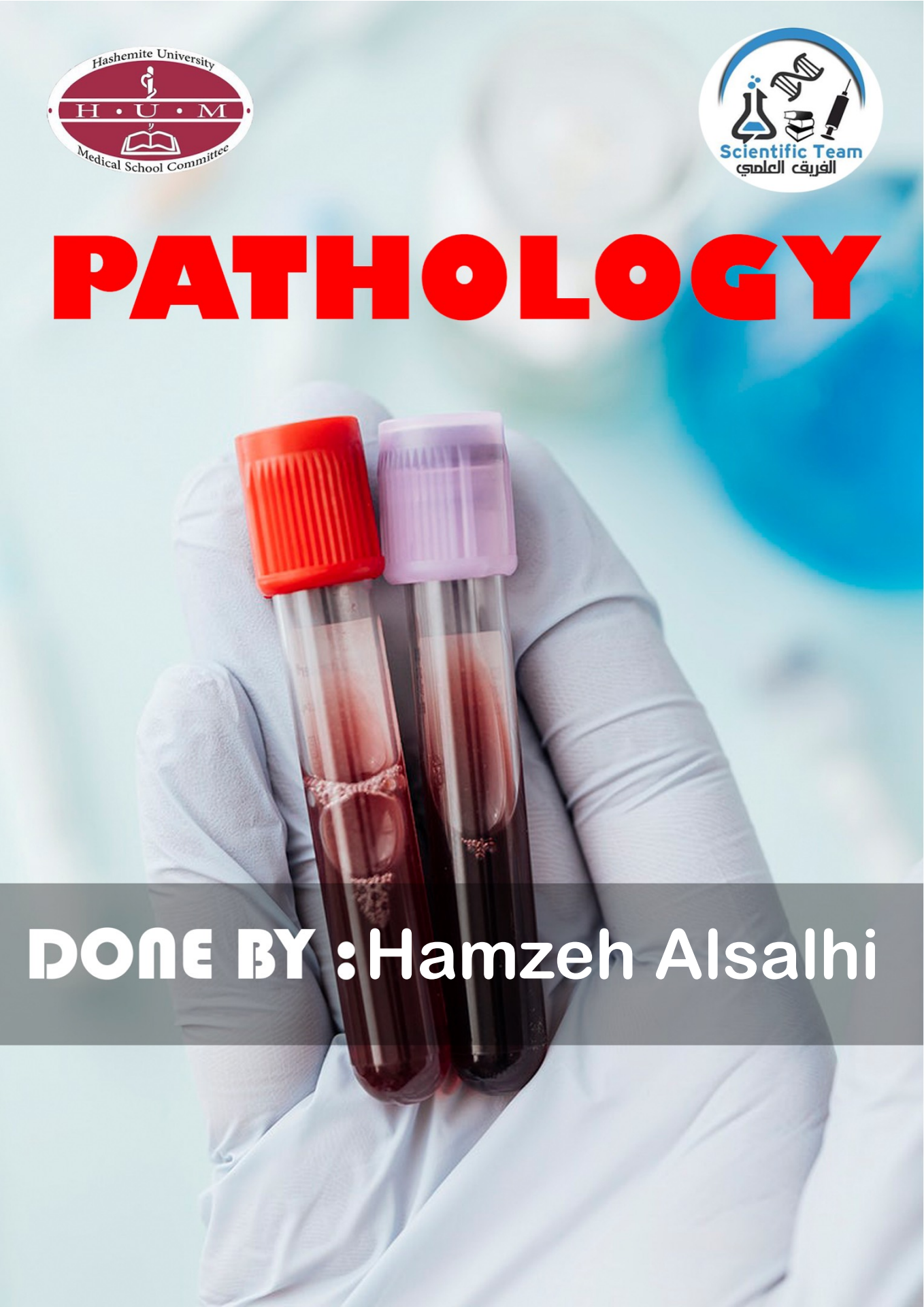
Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY



DONE BY : Hamzeh Alsalhi

Leukodystrophies

★ Are **inherited dysmyelinating diseases** in which the clinical symptoms derive from either **abnormal myelin synthesis or turnover.** Some disorders involve lysosomal enzymes, while others involve peroxisomal enzymes; a few are associated with mutations in myelin proteins. **Most are autosomal recessive, although X-linked diseases** occur (Table 23-2).

► **GROSSLY**, lesions of leukodystrophies are found in the **white matter,** in some diseases, there may be **early patchy** involvement; however, in the **end,** nearly all leukodystrophies **show diffusely affected abnormal white matter: (I)** in color (gray & translucent) & (II) in volume (decreased).

★With the loss of white matter, the brain becomes **atrophic**, the ventricles enlarge, & secondary changes can be found in the gray matter.

■ H, myelin loss is common, with macrophages stuffed with lipid. Some leukodystrophies also show specific inclusions, due to accumulation of particular lipids.

*Milestones → يعني متى بوقف، يمشي وهكذا

▼ ***Clinically,*** Each disorder of the various leukodystrophies has a characteristic **clinical presentation**, & most can be **diagnosed by genetic or biochemical methods.**

☺ Affected children are normal at birth, ☹ but begin to miss developmental milestones during infancy & childhood.

Diffuse involvement of white matter leads to deterioration in motor skills, spasticity, hypotonia, or ataxia.

DISEASES OF THE PERIPHERAL NERVOUS SYSTEM (NS)

★**The peripheral NS begins few mms from the pial surface of the brain & SC,** where **Schwann** cell processes replace oligodendroglial processes as source of **myelin.**

★ Peripheral NS myelin shares some structural similarities with CNS myelin, but also contains several proteins that are unique to the periphery. Abnormalities in some of these structural proteins have been implicated in the development of certain **hereditary peripheral neuropathies**.

☺ Normally, **myelinated axons** in the peripheral nerves are invested by concentric laminations of Schwann cell cytoplasm. The myelin sheath contributed by each Schwann cell is termed a ***myelin internode,*** & the space between adjacent internodes is termed the ***node of Ranvier***. Therefore, **each myelin internode is formed by a single, dedicated Schwann cell.**

★ The normal peripheral nerve also contains many smaller-diameter, **unmyelinated axons**, which lie in small groups **within** the cytoplasm of a single Schwann cell.

عكس الـ Oligodendrocytes اللي بتعطي myelin لمسافة كبيرة على طول الـ axon.

★ Groups of myelinated & unmyelinated axons, in turn, are compartmentalized into discrete fascicles by concentrically arranged ***perineurial cells.***

★ Similar to the blood-brain barrier, the axons are insulated from the interstitial fluids of the body by a "blood-nerve" barrier, formed by ⇨ tight junctions between EC of small peripheral nerve BV & tight junctions between adjacent **perineurial cells**.

★Peripheral NS disorders include peripheral **neuropathies & tumors** arising from Schwann & other nerve sheath cells.

Patterns of Nerve Injury

A variety of diseases can affect nerves (see Table 23-4).

★ In general, there are two main patterns of response of peripheral nerve to injury based on the target of the insult & whether it is the Schwann cell? or the axon?

★ **Diseases that affect primarily the Schwann cell** lead to a loss of myelin, referred to as *segmental demyelination.*

★ In contrast, **primary involvement of the neuron & its axon leads** to axonal degeneration. In some diseases, axonal degeneration may be followed by ***axonal regeneration.***

Segmental Demyelination.

★ Segmental demyelination occurs when there is either (1) dysfunction or death of the Schwann cell, or (2) damage to the myelin sheath;

☺ **there is no primary abnormality of the axon.**

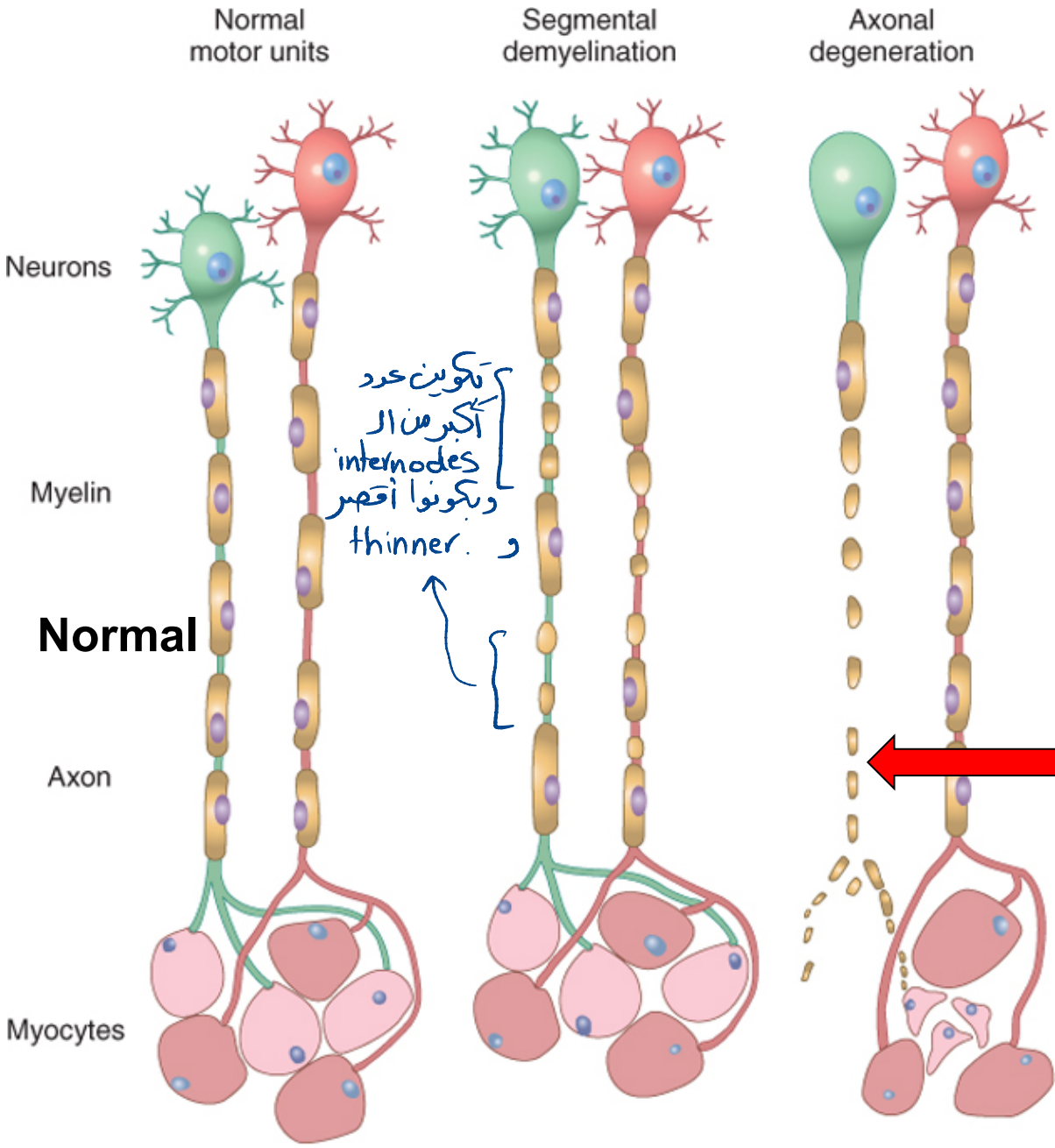
★ The process affects some Schwann cells & their corresponding internodes, while sparing others (F 23-32). It is patchy not diffuse

★The disintegrating myelin (■ 4.28) is engulfed initially by Schwann cells & later by macrophages.

★The **denuded axon provides a stimulus for remyelination**, with a population of cells within the **endoneurium differentiating to replace injured Schwann cells.**

☺ These cells proliferate & encircle the axon &, in time, remyelinate the denuded portion.

★**Remyelinated internodes** are (1) **shorter than normal** & several are required to bridge the demyelinated region(F23-32), & (2) have **thinner** myelin in proportion to the diameter of the axon than normal internodes.



F23-32: ★**Two adjacent Normal motor units.**

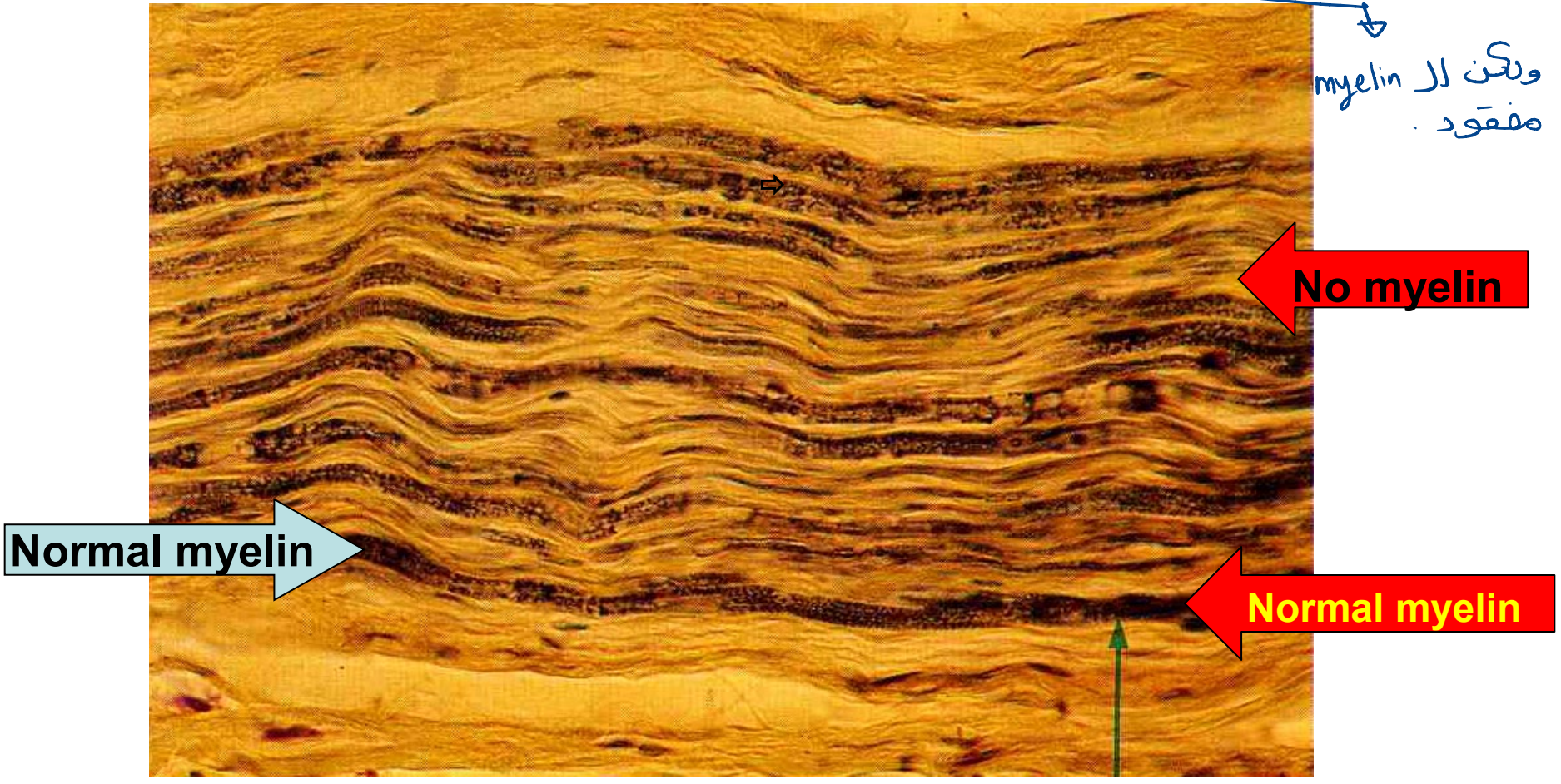
★ **Segmental demyelination:** Random internodes of myelin are injured & are remyelinated by multiple Schwann cells, while the axon & myocytes remain intact.

more severe.

★**Axonal degeneration:** The axon & its myelin sheath undergo anterograde degeneration (shown for the green neuron), with resulting denervation atrophy of the myocytes within its motor units. (skeletal muscle fibers).

(Alcoholic neuropathy).

■ 4.28: **Peripheral neuropathy: Sural nerve, X335.** A man of 43 who had drunk 25 pints of beer/day for years, P/ W S&S of peripheral neuropathy. Sural nerve biopsy, **stain for myelin {Solochrome cyanin, deep blue, arrow**) shows marked segmental ***demyelination of all the nerve fibers.*** Another special stain however showed that the ☺ axons are intact.



وبكون ال myelin مفقود.

★ **With repetitive cycles of demyelination & remyelination,** there is an accumulation of tiers of Schwann cell processes that, on transverse section, appear as concentric layers of Schwann cell cytoplasm & redundant basement membrane that surround a thinly myelinated axon (***onion bulbs***) (**F23-33**).

★In time, many chronic demyelinating neuropathies give way to axonal injury.

Table 23-4. Causes & Types of Peripheral Neuropathies

Nutritional & Metabolic Neuropathies

most common causes:-

Diabetes, *alcoholism* (■ 4.28), thiamine or phyridoxine deficiency, renal failure

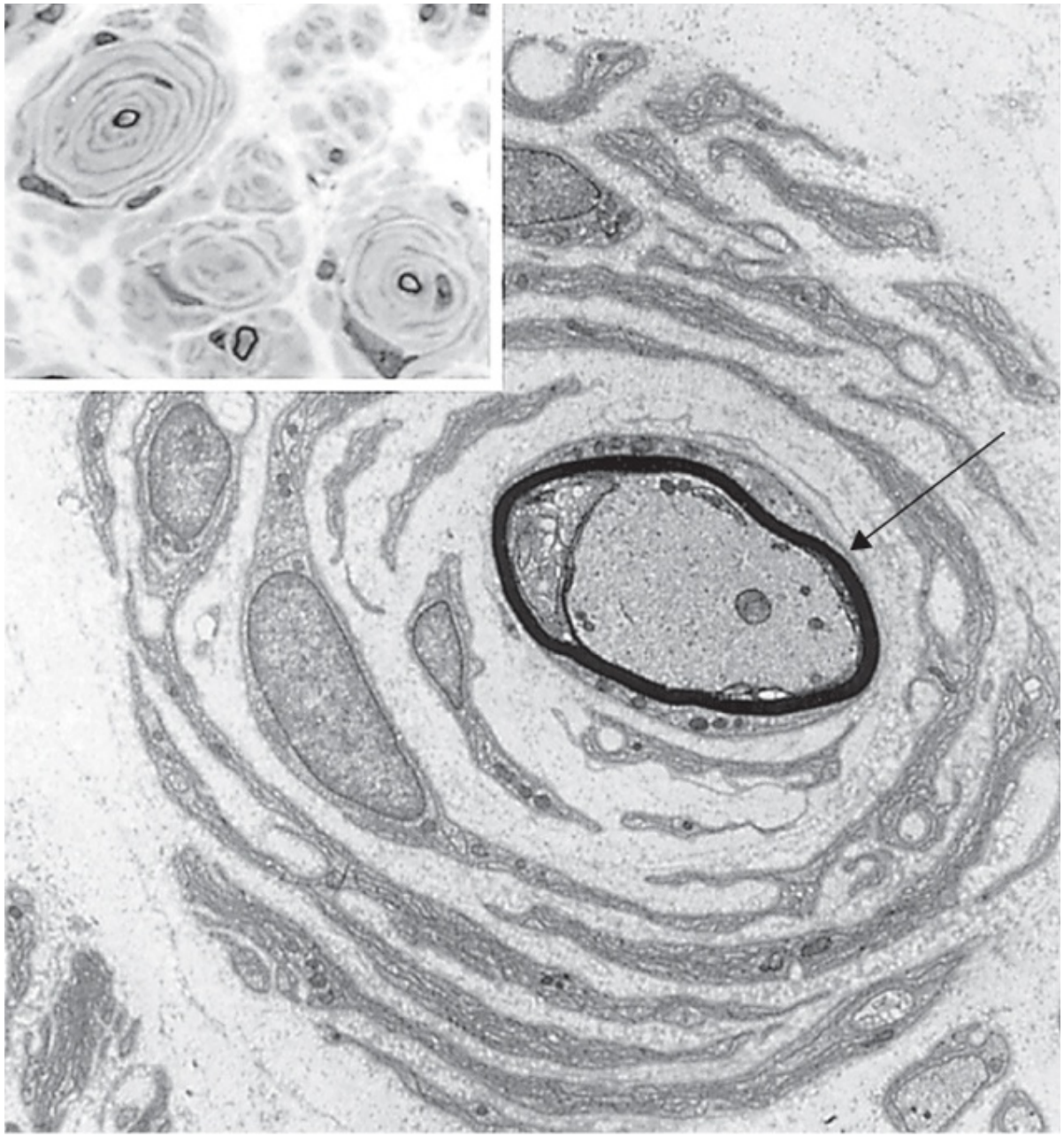
Toxic Neuropathies

cisplatin vincristine, organic solvents, Lead, arsenic,

Inflammatory Neuropathies

most important.

Guillain-Barré syndrome, chronic inflammatory demyelinating neuropathy, vasculitic neuropathy, leprosy, sarcoidosis



F23-33: **EM micrograph of a single, thinly myelinated axon** (arrow) surrounded by concentrically arranged Schwann cells, forming an onion bulb.

indicates chronic damage to the nerve.

Inset, Light microscopic LP appearance of an onion bulb neuropathy, characterized by "onion bulb" surrounding axons.

Hereditary Neuropathies

Hereditary motor & sensory neuropathies (Charcot-Marie-Tooth disease, Refsum disease, Dejerine-Sottas disease), hereditary sensory neuropathies, leukodystrophies

Miscellaneous

Amyloid neuropathy, paraneoplastic neuropathies, neuropathies associated with immunoglobulin abnormalities

Axonal {*Wallerian*} Degeneration

★ **Axonal degeneration is the result of primary destruction of the axon,** due either to a:
(1) focal event occurring at some point along the length of the nerve e.g., **trauma or ischemia,** or to
(2) a more generalized abnormality affecting the neuron cell body (*neuronopathy*) or its axon (*axonopathy*)},
with secondary disintegration of its myelin sheath.

★When axonal injury occurs as the result of a **focal lesion**, such as traumatic transection (cut) of a nerve, the distal portion of the fiber undergoes ***Wallerian degeneration*** (F23-32).

★ **Within a day**, the axon breaks down, & Schwann cells begin to degrade the myelin & then engulf axon fragments, forming small oval compartments (***myelin ovoids***). Macrophages phagocytose axonal & myelin-derived debris. The stump of the proximal portion of the cut or severed nerve shows degenerative changes involving only the most distal two or three internodes & then undergoes regenerative activity.

ما يتبقى من طرف العقب (السجائر)

★ **The proximal stumps of degenerated axons can develop new growth cones (►) as the axon regrows,** cones use the Schwann cells vacated by the degenerated axons to guide them, if properly aligned, with the distal nerve segment.

★ The presence of (***regenerating cluster***) of axons, a multiple, closely aggregated, thinly myelinated small-caliber axons is evidence of regeneration

★ ***Regrowth*** *of axons is a* ***slow,*** *1-2 mm per day,* limited by the rate of the slow component of axonal transport, the movement of tubulin, actin, & intermediate filaments. However, axonal regeneration accounts for some of the potential for functional recovery following peripheral axonal injury.

Guillain-Barré Syndrome

★ **This is one of the most common life-threatening diseases of the peripheral nervous system.**

★ It may develop **spontaneously** or **after a systemic infection** (usually viral) or other stress. Patients present with **rapidly progressive, ascending motor weakness** that may lead to **death** from failure of respiratory muscles.

★ Sensory involvement is usually much less striking than is motor dysfunction.

not axonal degeneration.

◘ H, there is **segmental demyelination** with **scant infiltration** of peripheral nerves by macrophages & reactive lymphocytes.

★**CSF:** contains increased levels of protein, but only a minimal cellular reaction.

★ Because of those cases with infectious antecedents, an immunologic basis is considered most likely; treatments include **plasmapheresis** or intravenous immunoglobulin, which can shorten the course of the disease. ☺ With **supportive care**, most affected individuals recover over time.

Tumors (T) of the Peripheral Nervous System

★ These T arise from cells of the peripheral nerve, including Schwann cells, perineurial cells, & fibroblasts.

★ Many express **Schwann cell characteristics, including mainly the presence of S-100 antigen** as well as the potential for melanocytic differentiation.

schwann cell. ← إذا صبغناها وطلعت (+) فإذن

★ **Recall:** as nerves exit the brain & spinal cord, there is a transition between myelination by oligodendrocytes & myelination by Schwann cells.

★ This occurs within **few millimeters** of the substance of the brain; therefore; in addition to arising along the peripheral course of nerve… ☹ remember that

➔ **these peripheral nerves tumors can arise within the confines of the dura** causing changes in adjacent brain or spinal cord!

Schwannoma

★ Benign T arising from Schwann cells.

★ **Symptoms** are referable to **local compression of the**
(I) involved nerve, or
(II) of adjacent structures (such as brain stem or SC).

★ They are often encountered **within the cranial** vault in the cerebellopontine angle, where they are ***attached to the vestibular branch of the 8th nerve*** (F23-34A). These patients often present with tinnitus & hearing loss, & the T is often referred to as an **acoustic neuroma**, although it is more accurately called a **vestibular schwannoma.**

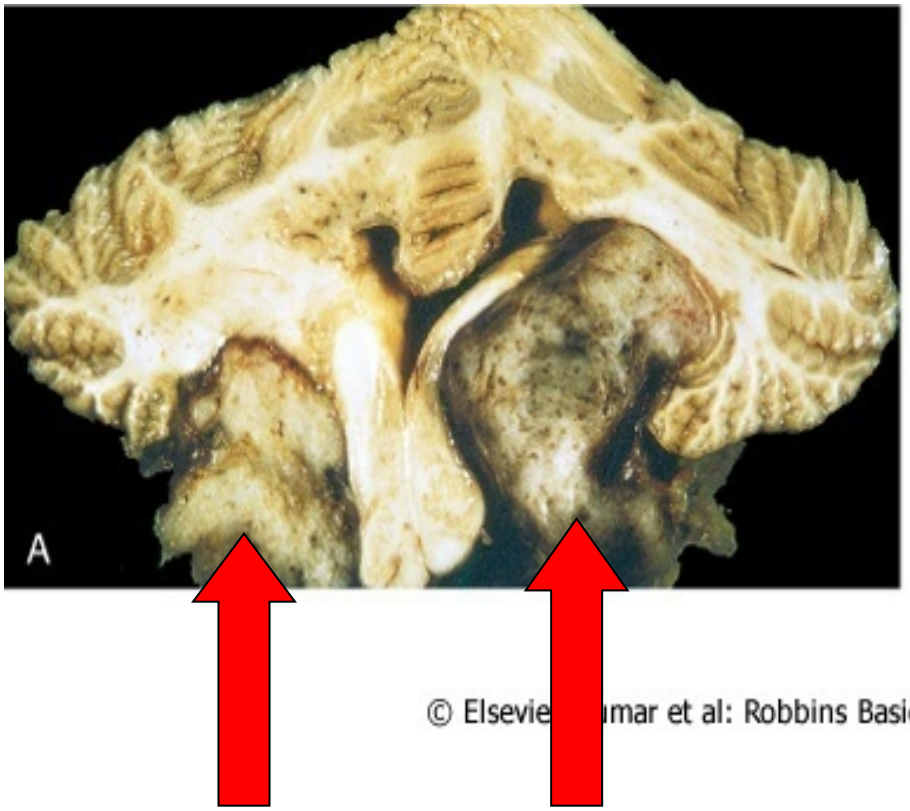
★ Elsewhere **within the dura**, sensory nerves are preferentially involved, eg branches of the **trigeminal nerve & dorsal roots**.

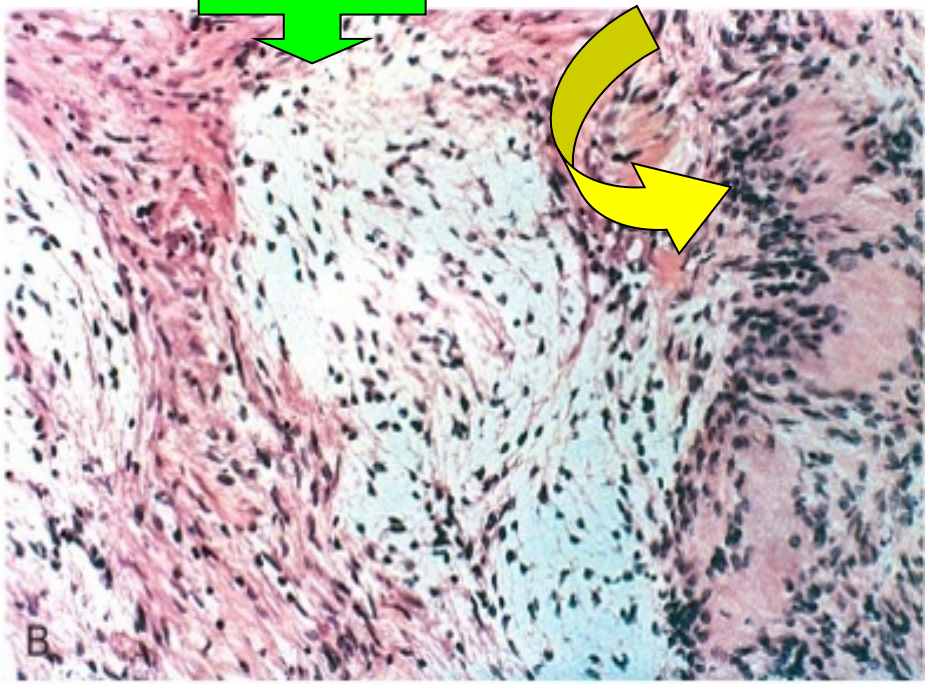
★ When **extradural**, schwannomas are most commonly found in association with **large nerve trunks**, where motor & sensory modalities are intermixed. Sporadic schwannomas are associated with mutations in the *NF2* gene on chromosome 22.

F23-34: **Schwannoma.**

مهم للاب.

A, Bilateral eighth (8th) cranial nerve **Schwannomas.**
B, Tumor showing cellular areas (**Antoni A**), including **Verocay** bodies (far right), as well as looser, myxoid regions (**Antoni B**) areas.





►**GROSSLY,** Schwannomas are encapsulated, well-circumscribed T that are **attached to the nerve but can be separated from it,** forming firm, gray masses but may also have areas of cystic & xanthomatous change.

■ H, Two growth patterns are seen (F23-34B & ■ 4.46).

(I) **In the Antoni A pattern of growth**, elongated cells with cytoplasmic processes are arranged in fascicles in areas of moderate to **high cellularity** with little stromal matrix; the "nuclear-free zones" of processes that lie between the regions of nuclear **palisading** are termed **Verocay bodies**.

(II) **In the Antoni B pattern of growth,** the T is **less densely** cellular with a loose meshwork of cells along with microcysts & myxoid changes.

★ The individual T cells (in both growth patterns) is similar, with elongated cell cytoplasm & regular oval nuclei.

★ Because schwannoma **displaces the nerve of origin** as it grows, axons are largely excluded from the T.

لذلك عملية إزالته سهلة.

★T are usually **uniformly immunoreactive for S-100 protein.**

◘ 4.46: **Schwannoma: Spinal nerve X235. (I)** The **Antoni type A** tissue is highly cellular (thick A), consisting of elongated tumor cells arranged as long eosinophilic cords & compact ovoid bodies (Verocay bodies, double arrows). The nuclei are elongated, round & most of them are palisaded & located at the periphery of the ovoid bodies, whereas the centers of the bodies are occupied by a mass of fibrillary eosinophilic cytoplasm. (II) The **Antoni type B, less densely** cellular tumor cells with very loose, vacuolated, myxomatous stromal tissue (thin arrow).