Hashemite University
H · U · M
Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY

DONE BY : Volunteer

Neurofibroma

★ The most common form of neurofibroma occurs in the **skin** (***cutaneous neurofibroma***) or in peripheral nerve (***solitary neurofibroma***). These T arise sporadically or in association with type 1 neurofibromatosis (NF1).

Cutaneous neurofibroma

★ Present as skin **nodules**, sometimes with overlying hyperpigmentation; they may grow to be large & become pedunculated. The **risk of malignant transformation** from these T is extremely small, & **cosmetic** concerns are their major morbidity.

►**GROSSLY,** they present in the dermis & subcutaneous fat, as a **well-demarcated, unencapsulated, non invasive** T.

◘ T composed of spindle cells with highly collagenized stroma & containing little myxoid material.

Solitary neurofibroma within peripheral nerves is of identical histologic appearance.

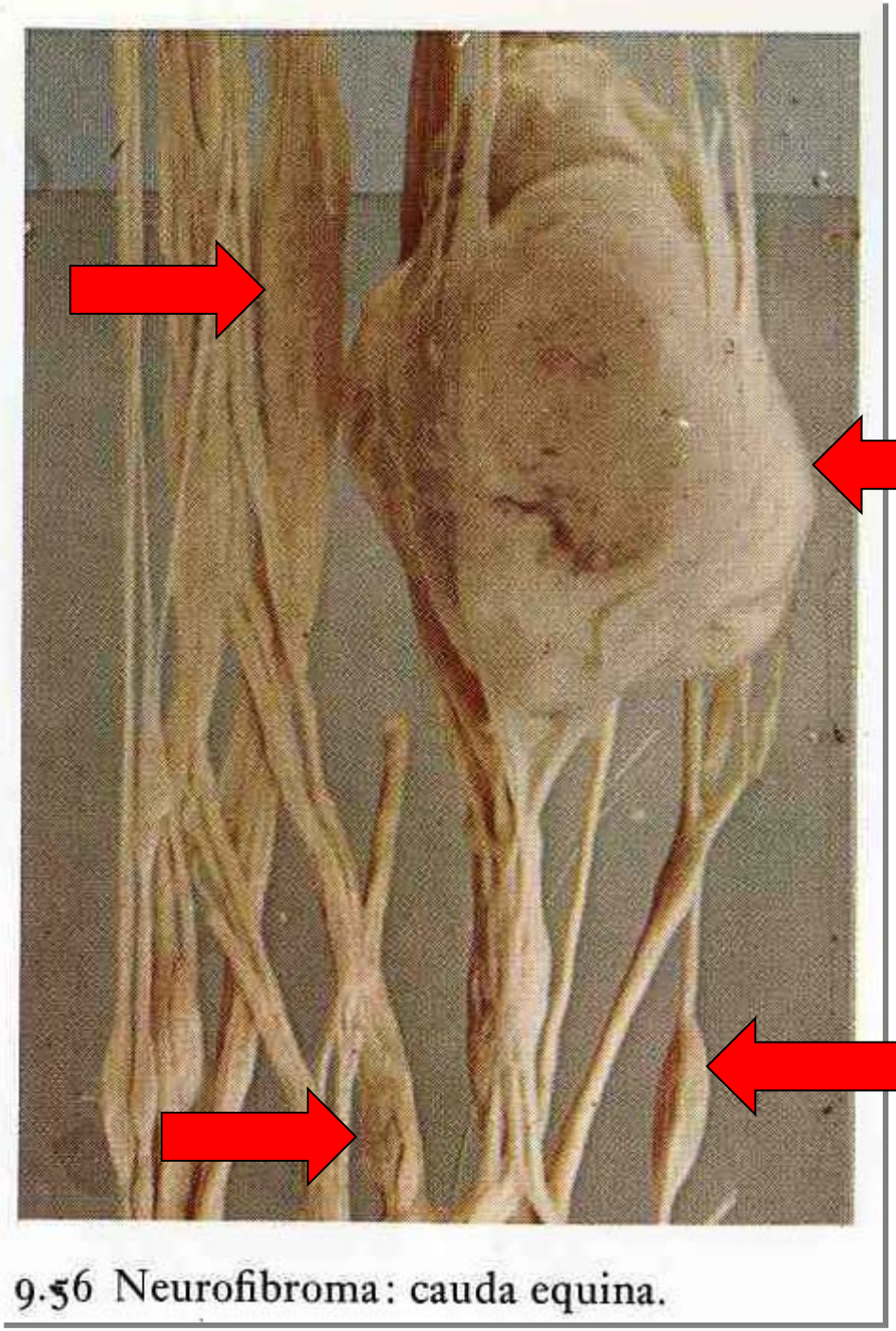
Plexiform neurofibroma

Mostly arising in individuals with NF1. Of major concern is the:
(1) Difficulty in surgical removal of these plexiform **T** when they *involve major nerve trunks* & their
(2) **Potential for *malignant transformation***.

▶ **GROSSLY,** these T may arise anywhere along a nerve, although the ***most common*** **site is the *large nerve trunks***. They are frequently ***multiple***.

☺ Unlike schwannomas, ☹ **it is not possible to separate the T from the nerve.** At the site of each lesion, the host nerve is irregularly expanded, as **each of its fascicles is infiltrated by the T** (F 9-56). The proximal & distal ends of the **T** have poorly defined margins, as fingers of **T** cells insert themselves between the nerve fibers.

◘ H, the lesion has a loose, myxoid background with a low cellularity. A number of cell types are present, including **Schwann** cells with typical elongated nuclei & extensions of pink cytoplasm, larger multipolar **fibroblastic** cells, & a sprinkling of inflammatory cells, often including mast cells.



9.56 Neurofibroma: cauda equina.

F 9-56: **Plexiform neurofibroma**: **cauda equina.** lower part of spinal cord.

A large, ovoid, lobulated neurofibroma has arisen from the nerve sheaths of the cauda equina.
Several thickened nerves blend with the capsule of the tumor.
Many of the other nerves show small fusiform swellings (lower right).

لذلك كل سهم هو عبارة عن neurofibroma.

Malignant Peripheral Nerve Sheath Tumor → very rare.

★ These are highly malignant sarcomas that are locally invasive, frequently leading to multiple recurrences & eventual metastatic spread. Despite their name, these T do not arise from malignant transformation of schwannomas. Instead, they (I) **arise de novo** or (II) **from transformation of a plexiform neurofibroma**. These T can also occur after radiation therapy.

►**GROSSLY,** the T are **poorly defined** masses with frequent infiltration along the axis of the parent nerve as well as **invasion** of adjacent soft tissues. **Necrosis** is common.

◘ H, the T cells resemble Schwann cells, with elongated nuclei & prominent bipolar processes. Fascicle formation may be present. Mitoses, necrosis, & extreme nuclear anaplasia are common. Some, but not all, malignant peripheral nerve sheath T, **are immunoreactive for S-100 protein**.

* hamartomas :- normal tissue collected in abnormal way.

FAMILIAL TUMOR SYNDROMES

★ Several inherited syndromes are associated with an ↑ risk of particular types of T. Those discussed here are inherited diseases characterized by the development of hamartomas & T throughout the body with particular involvement of the nervous system. Most of these syndromes are linked to loss of T suppressor genes. Symptoms are referable in part to the location of hamartomas or T; developmental delay & seizure disorders may contribute to disability in some affected individuals.

Type 1 Neurofibromatosis (NF1)

➔ An autosomal **dominant** disorder characterized by: multiple **neurofibromas** (solitary & plexiform) + **gliomas** of the optic nerve + pigmented nodules of the iris (***Lisch nodules***) + cutaneous hyperpigmented macules (***café au lait spots***).

- With a frequency of **1/3000** it is a common genetic disorders,

☹ **Risk** of individuals with NF1 neurofibromas to **undergo malignant transformation** is at a **higher rate** than that observed for neurofibromas without NF1 mutation.

Dark brown in color.

★ This is especially true for plexiform neurofibromas. The *NF1* gene is a tumor suppressor gene, but how *NF1* mutations lead to **T** development? is unknown.

ممكن الـ mutation يكون موجود وما يعمل أشي وممكن يعمل تأثيرات متعددة.

★ The **course** of the disease is **highly variable** & independent of the particular mutation, with some individuals carrying a mutated gene & having no symptoms, while others develop progressive disease with spinal deformities, disfiguring lesions, & compression of vital structures, including the SC.

Type 2 Neurofibromatosis

➔ This is a **rare** autosomal **dominant** disorder {frequency of **1 in 40,000 to 50,000}** in which patients develop a range of tumors, most commonly: معلم جداً

① Bilateral vestibular (acoustic) **schwannomas** + ② Multiple **meningiomas** + ③ **Gliomas**, typically ④ ependymomas of the SC + ⑤ non-neoplastic **hamartomas** within the nervous system, where Schwann cells or glial cells are present in small collections in inappropriate places.

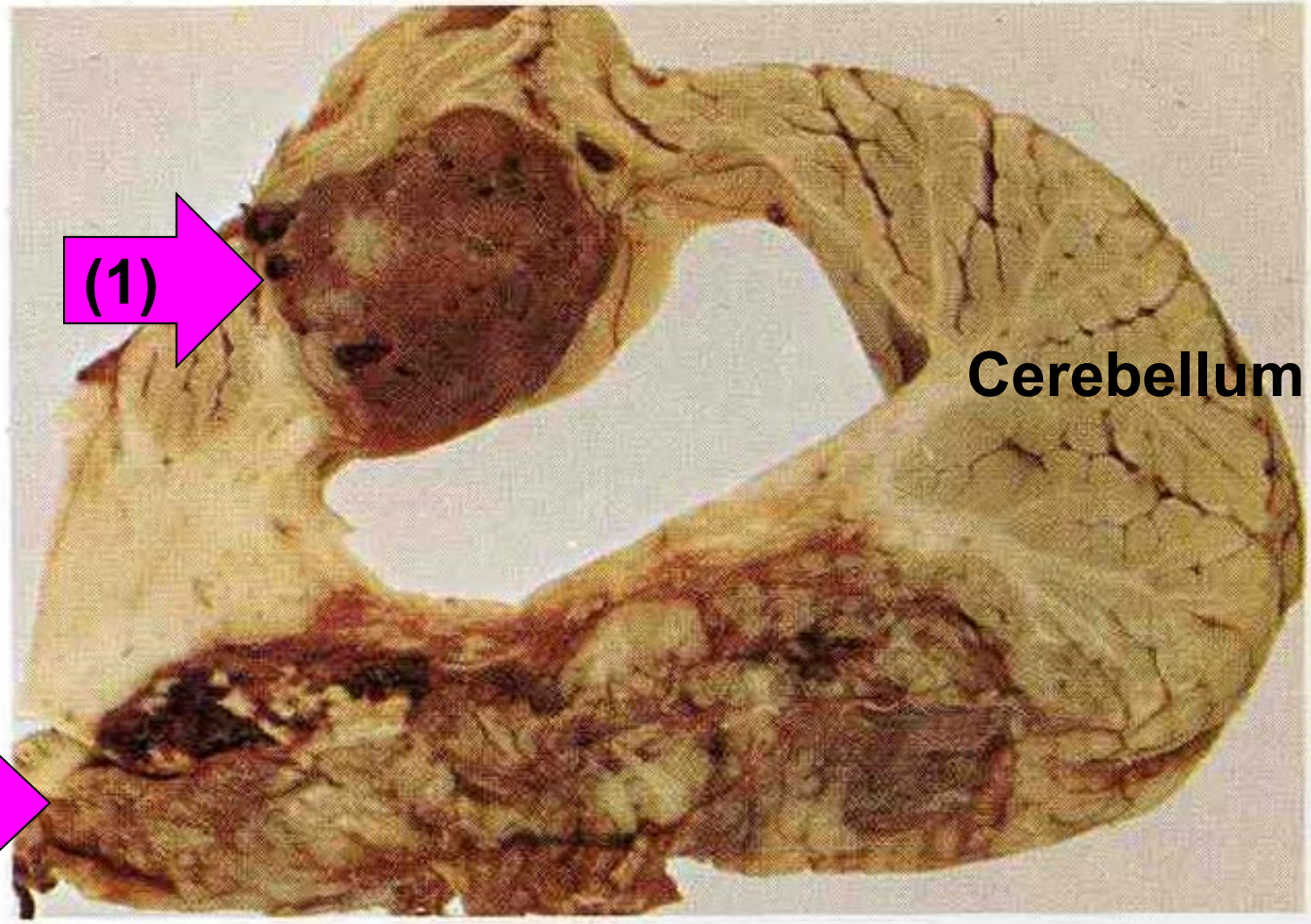
Von Hippel-Lindau Disease

★Rare **autosomal dominant inherited disease** {frequency is 1 in 30,000 to 40,000} **duo to** Missense mutations in the tumor-suppressor gene *VHL*. Affected individuals develop:
(1) Hemangioblastomas within the cerebellar hemispheres, retina, & less commonly the brain stem & SC;
(2) Cysts of the pancreas, liver, & kidneys, &
(3) High risk to develop adrenal pheochromocytoma & Renal cell carcinoma.

▶**GROSSLY,** the main neurologic lesion is the **cerebellar capillary hemangioblastoma** (F 9-73), a highly vascular T that occurs as a mural nodule associated with a large, fluid-filled cyst.

◘ 4.43, H, It consists of variable proportions of (1) thin-walled **capillaries** with (2) intervening **stromal** cells showing vacuolated, lightly PAS-positive, lipid-rich cytoplasm & dens basophilic nuclei.

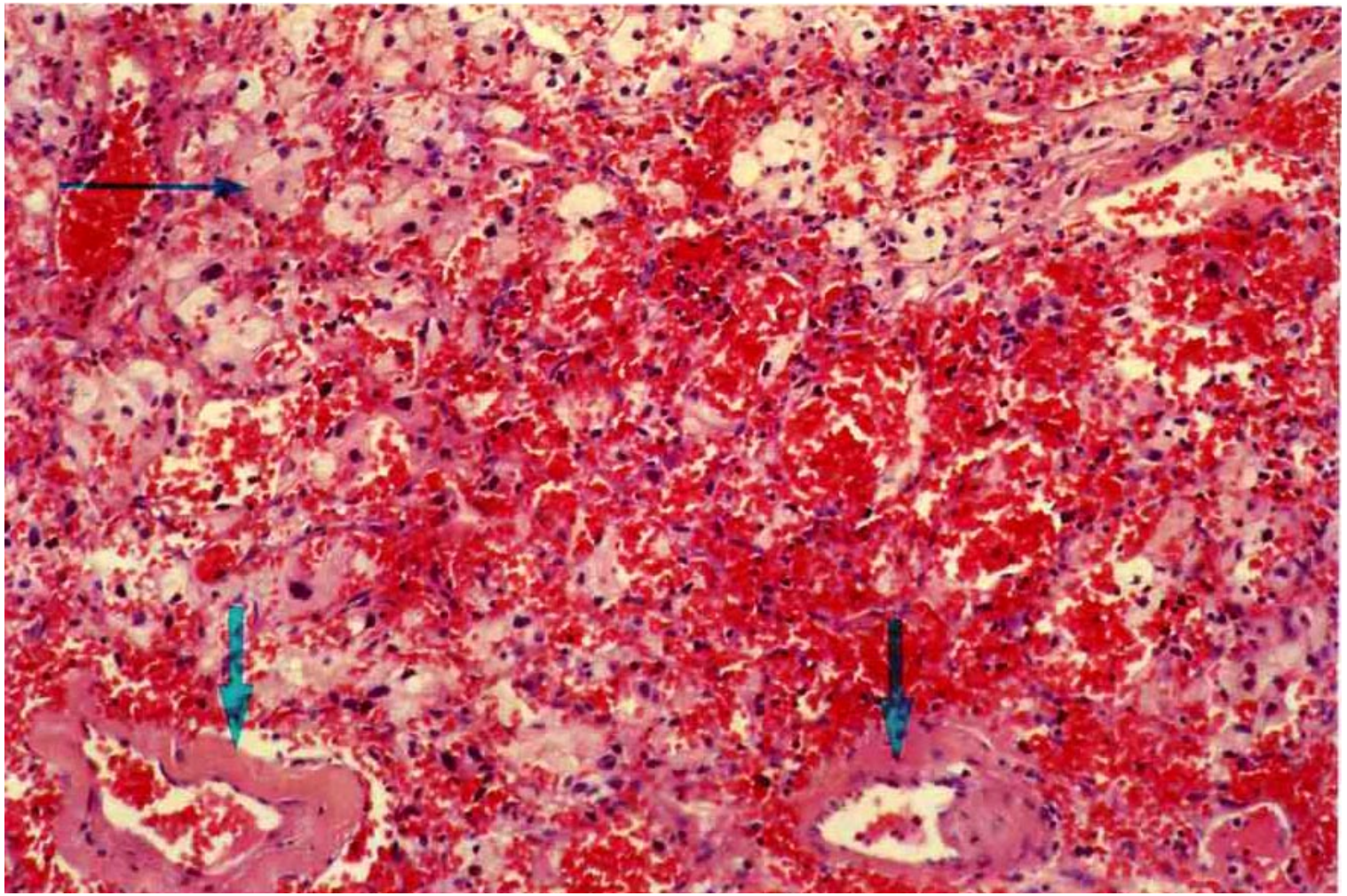
F 9-73: **Hemangioblastoma: cerebellum.** The lateral lobe of the cerebellum contains large cyst cavity with two tumor nodules in its wall: **(1)** round, red-brown at top, & **(2)** larger brownish necrotic tumor mass in the bottom. 2 tumor nodules in the same cerebellum.



9.73 Haemangioblastoma: cerebellum

in lower part of the spinal cord. ← مع ... في cerebellum هل ممكن أن يوجد خارج ال

■ 4.43: **Hemangioblastoma, Cerebellum X150.** Consisting of (1) large number of very thin-walled dilated capillaries, with foci of hemorrhages, (2) intervening stromal cells with vacuolated lipid-rich cytoplasm & dens basophilic nuclei (thin arrow).



Tuberous Sclerosis (TS)

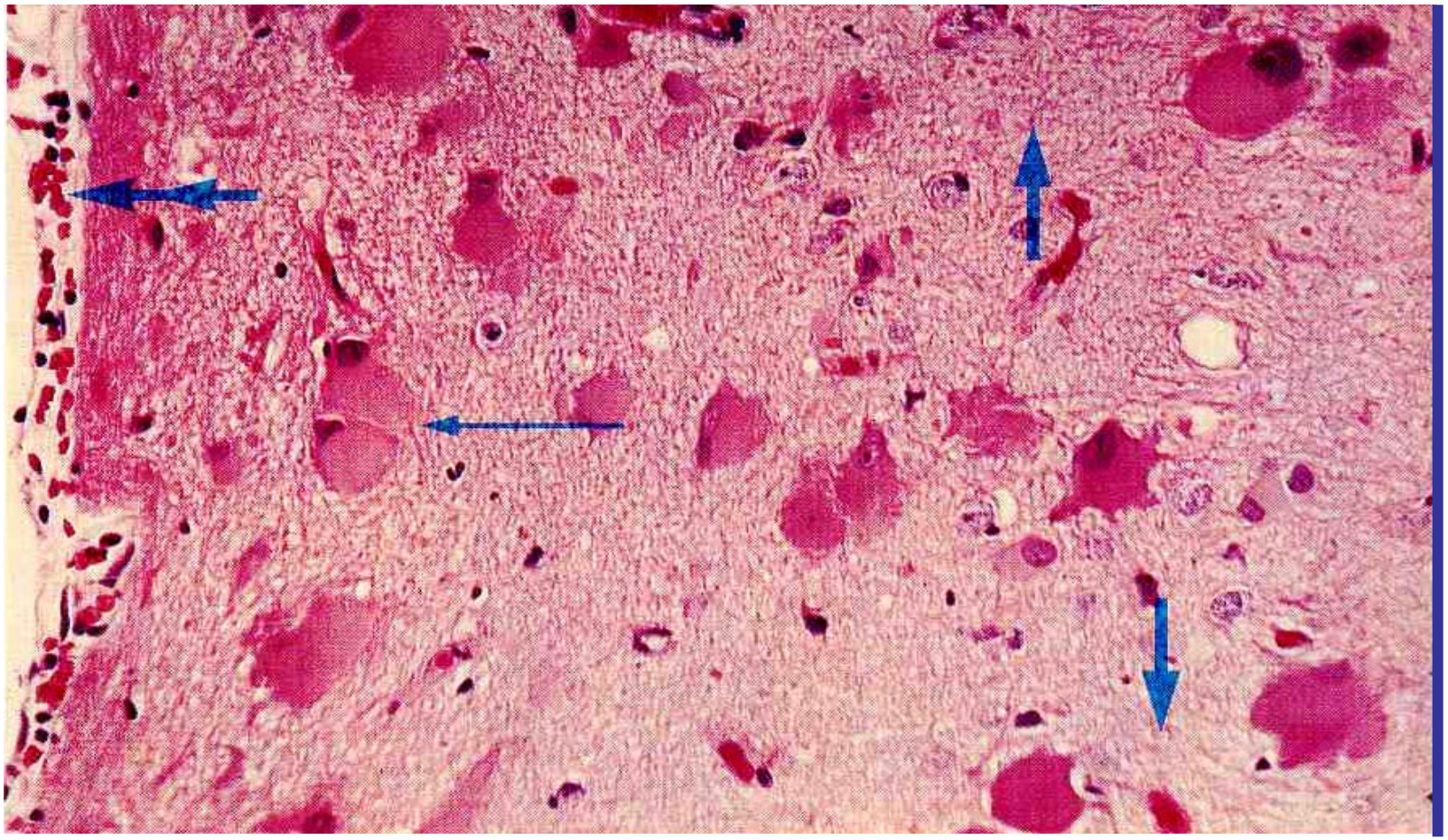
★ An **autosomal dominant syndrome,** characterized by the development of hamartomas & benign T involving the brain & other tissues; including:

- **CNS hamartomas** are (1) **cortical tubers** (▣ 4.13), associated with seizures, which can be difficult to control with antiepileptic drugs, & **(2) subependymal hamartomas**

- **Extracerebral lesions** include ➔ **renal angiomyolipomas** + retinal glial hamartomas + pulmonary lesions + cardiac rhabdomyomas + **Cysts** of the liver/kidneys/& pancreas +
- **Cutaneous lesions** include angiofibromas, leathery thickenings in localized patches, hypopigmented areas , & subungual (under the nail) fibromas.

► **Tuberous Sclerosis** results from disruption of ***TSC1*** tumor suppressor genes, which encodes hamartin, or ***TSC2,*** which encodes tuberin. These two proteins regulate protein synthesis & cell proliferation. Abnormalities of the proteins may alter neuronal proliferation, differentiation, & migration.

◘ 4.13: **Tuberous sclerosis; Brain.** Part of Cortical hamartomas nodule (likened to **potatoes**), bounded by a dilated thin-walled BV (double arrow). The normal cortex has been replaced by tissue consisting of: (I) Abundant **glial fibers** (thick arrow) & (II) Characteristic TS **bizarre giant cells** (thin arrow) some have features of neurons & others of astrocytes.



►**GROSSLY, cortical hamartomas** of TS are firm areas of the cortex that, in contrast to the softer adjacent cortex, have been **likened to potatoes, hence the name "tubers."**

◘ H, these hamartomas composed of **haphazardly arranged neurons** that lack the normal laminar organization of the cortex. These large cells may express a **mixture of glial & neuronal features**, having large vesicular nuclei with nucleoli, resembling neurons, & abundant eosinophilic cytoplasm like gemistocytic astrocytes. Similar hamartomatous features are present in the **subependymal nodules,** where the large astrocyte-like cells cluster beneath the ventricular surface.

☺ **END of CNS I+II Lectures in 133 W + 95F = 230 PPP;**

@ 7-4-2019, Lectures prepared by Associated Professor Dr. Mohammad Kamel Alwiswasi, MBChB, PhD, FRC Path