CNS pathology
Third year medical students

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Lecture 3: Nerve trauma, regeneration and neural tumours

ILOS

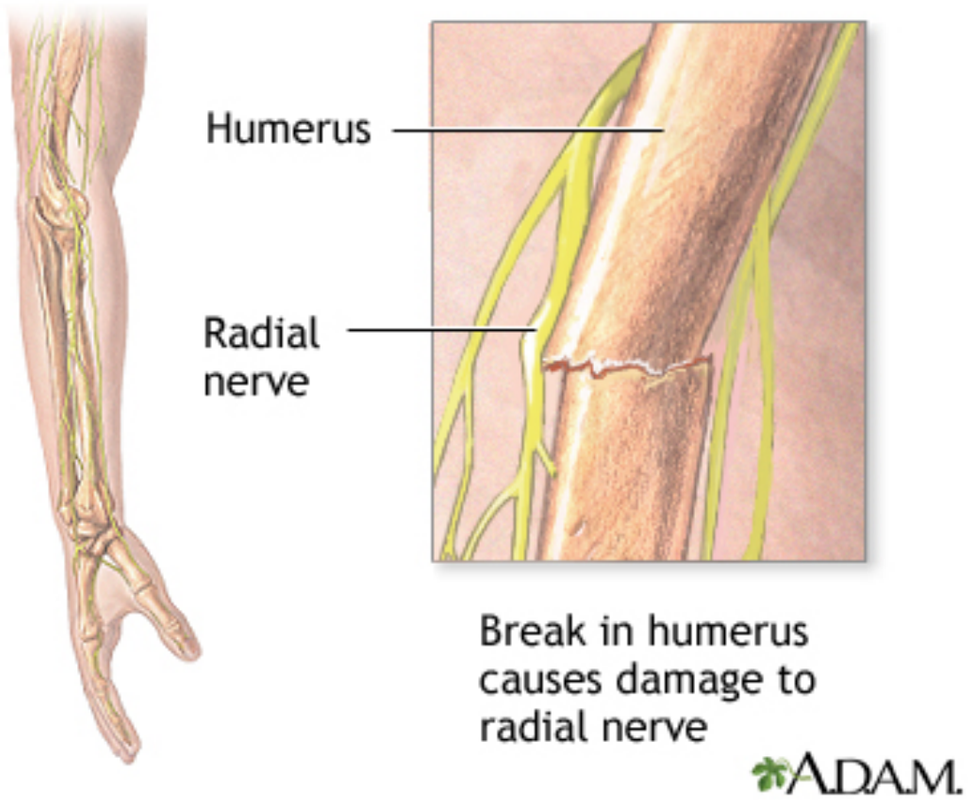
- 1. To understand Wallerian degeneration and its importance as a first step in regeneration
- 2. to know the effects of Schwann cells in axonal regeneration in the PNS
- 3. to understand the reasons behind the difference of regeneration in the CNS and PNS
- 4. to list the main tumours of PNS and know some of their features
- 5. to understand the difference between NF 1 and NF 2 and know their clinical presentation.

Nerve injury

- nerves can be injured during road traffic accidents, or compressed due to adjacent bone fracture, or in other accidents.

- nerves of the PNS can regenerate, but restoration of function is only possible if the injury is minimal.

- repair can be improved by surgical intervention.



nerve regeneration

- Peripheral nerves can regenerate after trauma.
- the axons of the CNS have a very limited capacity to regenerate, whereas the axons of the PNS can regenerate.
- *this difference between CNS and PNS regeneration is related mainly to the difference in response of oligodendrocytes and Schwann cells to injury.*

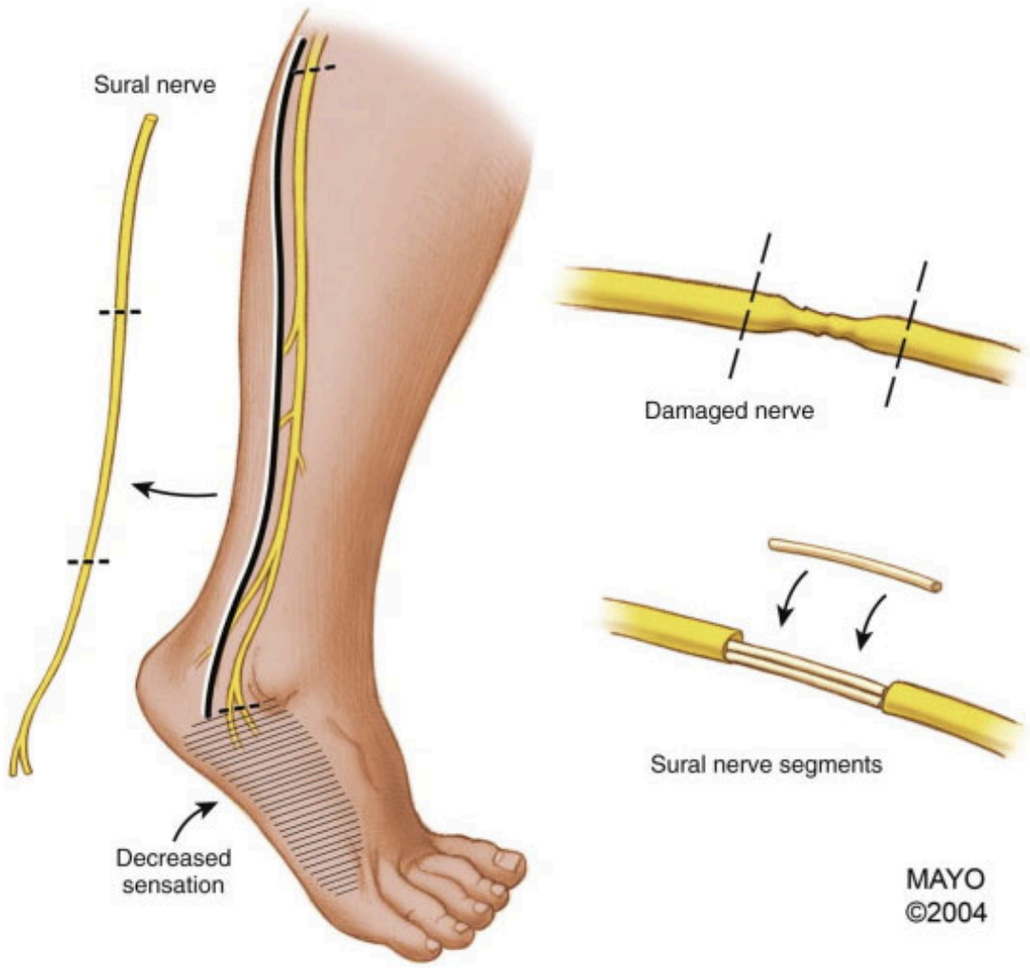
Important note

- Although PNS axons have a capacity to regrow, the functional recovery of nerve function depends on the extent of injury and can be improved by surgical approximation of injured nerve or by nerve grafts.

- nerve graft is a surgical technique where a segment of an unaffected nerve is used to replace or bridge an injured nerve. The donor nerve is usually a sensory nerve where if a section is taken from it, some numbness will occur but there will be no serious effects. Example of a donor nerve is the Sural nerve.

nerve graft

- When the nerve cut is long a graft might be needed.
- Part of a nerve, usually a sensory nerve, like the Sural nerve is taken and grafted
- note that the removed segment will cause some effects, like numbness or decreased sensations.



Regeneration

- for nerves to regenerate, **first the debris happening due to the damage must be cleared**.

- Schwann cells and macrophages are the most important cells that clear this debris, mainly by phagocytosis.

Steps during neural regeneration

- Injury to a nerve elicits an inflammatory response of non- neuronal cells, mainly Schwann cells and macrophages.

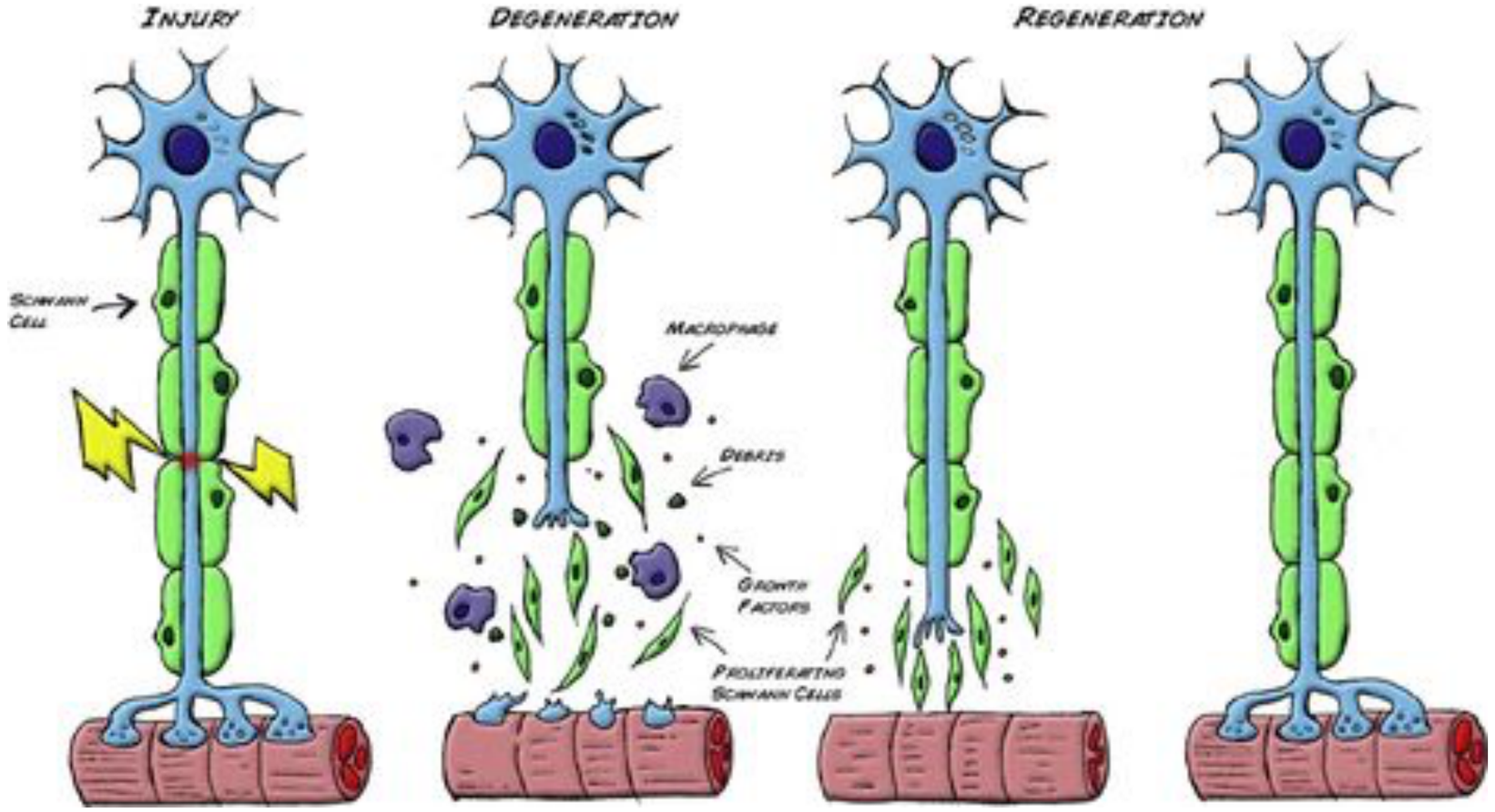
- these cells cause degeneration of the the part of the nerve distal to the injury

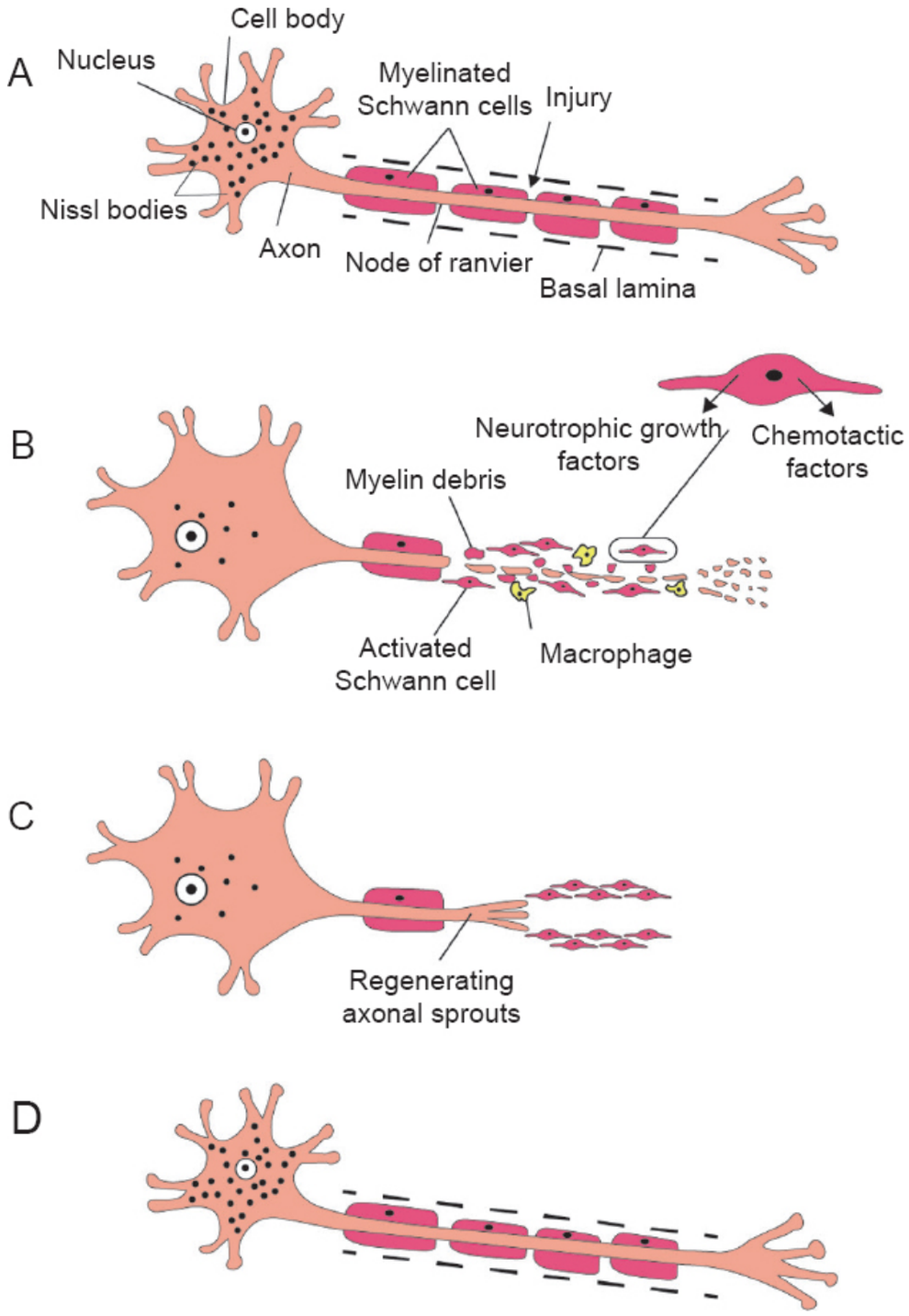
- This degeneration is called: ***Wallerian degeneration***

- this degeneration **clears** the inhibitory debris in the peripheral nerve and to the production of an environment that **supports axon regrowth**.

Wallerian degeneration was studies first on nerves from frogs!

Nerve regeneration: Wallerian degeneration is the first step in the regeneration process as it clears the debris that inhibits regeneration.




A
Cell body
Nucleus
Myelinated
Schwann cells
Injury
Nissl bodies
Axon
Node of ranvier
Basal lamina
B
Neurotrophic growth
factors
Chemotactic
factors
Myelin debris
Activated
Schwann cell
Macrophage
C
Regenerating
axonal sprouts
D

functions of Schwann cells during regeneration

- soon after injury, Schwann cells start to dedifferentiate, they alter gene expression, so they stop producing myelin, and they up regulate regeneration associated genes

- they divide: hyperplasia of Schwann cells.

- they remove myelin debris which is a barrier to growth of the axon. So they have some **phagocytic activity.**

- they also secrete trophic factors that help growth, mainly cytokines.

- they recruit macrophages which continue removing the debris

- Secrete factors that support neural survival and growth

- Schwann cells can survive and support the nerve for 8 weeks. after the 8th week their function deteriorates and they die by apoptosis.

- This time scale limits successful long distance regeneration

- in general nerves regenerate at a rate of 1mm per day.

Why axonal regeneration is limited in the CNS

- Oligodendrocytes respond to neural injury by **apoptosis or entering a quiescent state** and they have **very little phagocytic activity**. So clearance of degenerate debris is ineffective in the CNS.

- Astrocytes are activated during injury causing gliosis and **producing inhibitory cytokines**. this decreases the ability of axons to regenerate.

WALLERIAN DEGENERATION

- The degenerative changes the distal segment of a peripheral nerve fiber (axon and myelin) undergoes,

REGERNERATION

- Regrowth of the axon will take place down the endoneurial tube.
- Regeneration of the axon will grow at the rate of 1-2 mm/day.

Traumatic neuroma

- if the ends of a cut nerve are not approximated, the regenerating axons might grow in a haphazard fashion, forming a mass called traumatic neuroma.

- So: traumatic neuromas are non-neoplastic masses related to a previous trauma and composed of a haphazard mixture of axons, Schwann cells and connective tissue.

- traumatic neuromas contain abnormal nerve bundles, so the mass is usually **painful.**

Tumours of PNS

- Tumours arising from peripheral nerves can be benign or malignant

- Benign tumours include schwannoma and neurofibroma

- Malignant tumours include: malignant peripheral nerve sheath tumour. (MPNST)

Schwannoma

- Benign , encapsulated tumours that are composed of proliferation of Schwann cells.

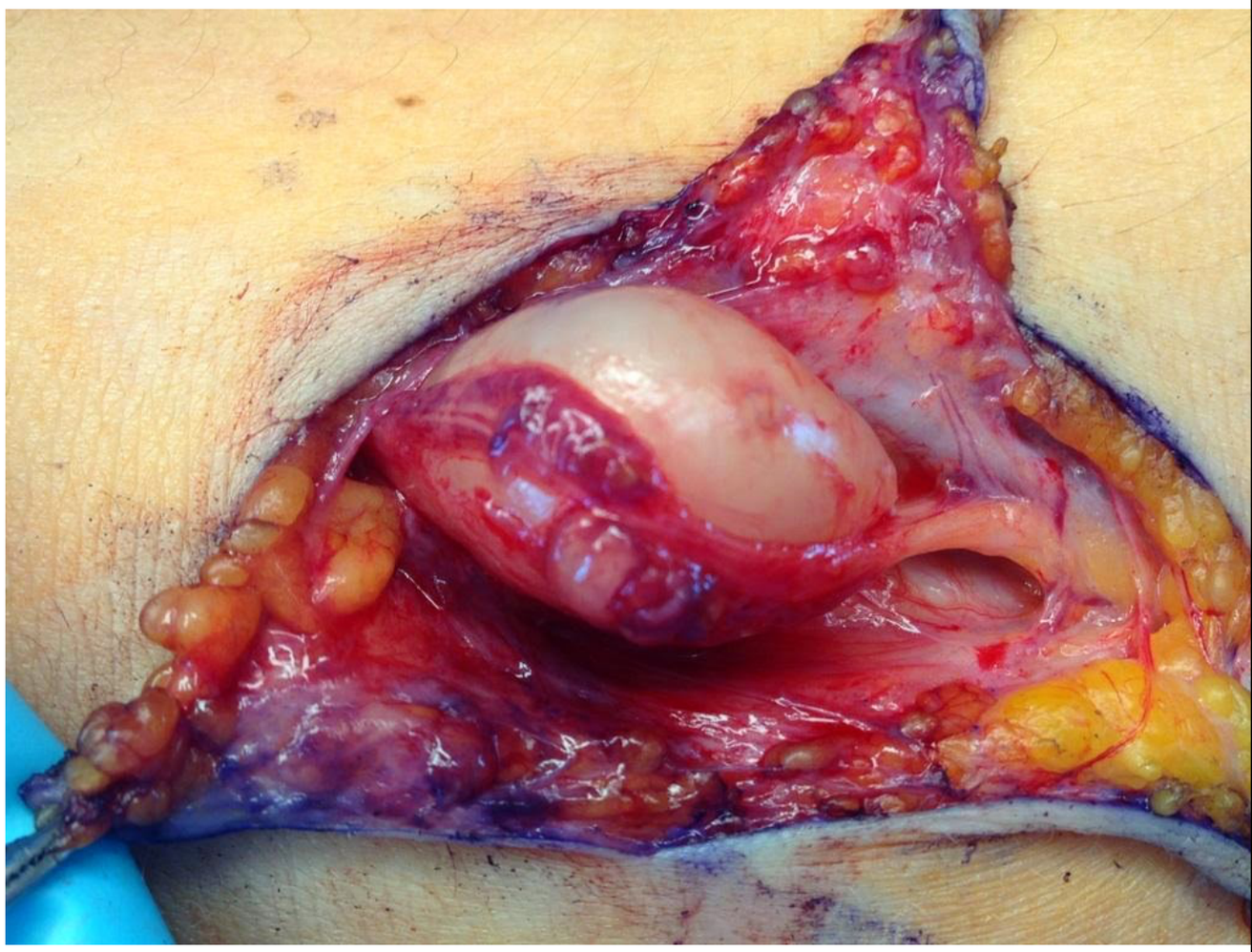
- Can arise in soft tissue, internal organs, spinal roots or cranial nerves

- *the most cranial nerve affected is the vestibular portion of the eighth cranial nerve which can result in hearing loss*.

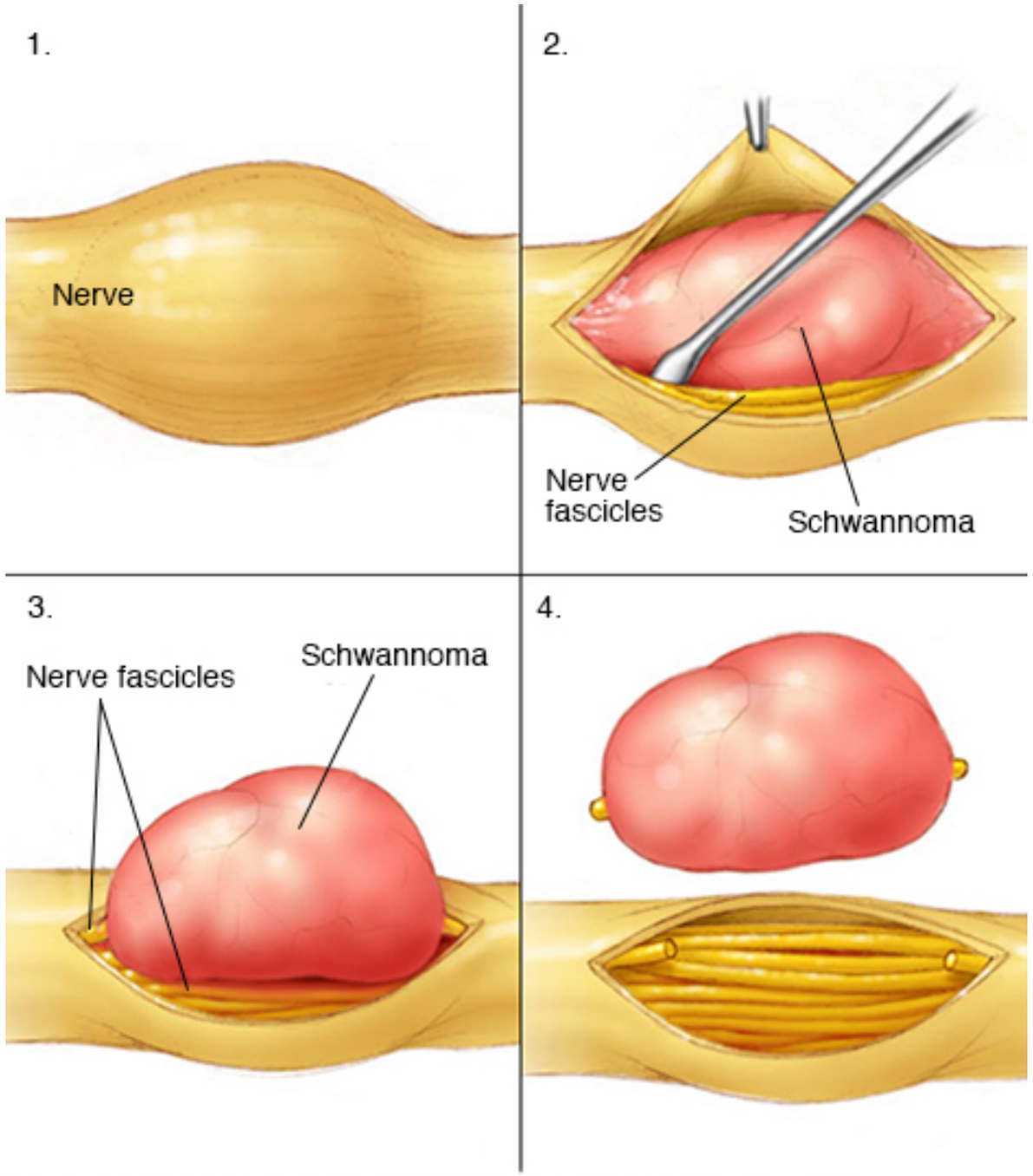
- Can be sporadic or familial

Shwannoma

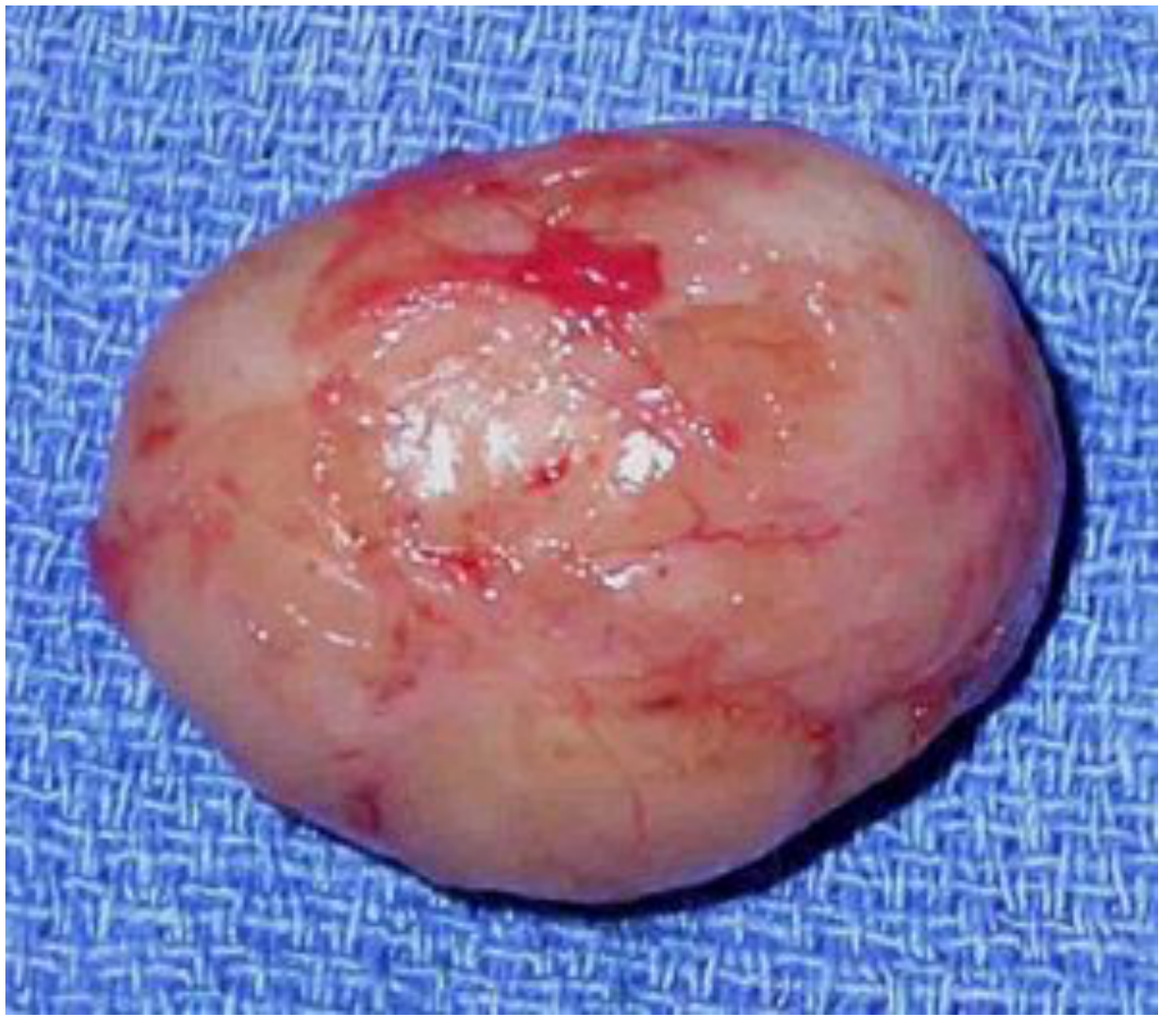
Note that the tumour is well circumscribed, encapsulated and abuts a nerve (as if it hugs the nerve but not actually arsing from it.. this is because it is a proliferation of Schwann cells that are adjacent to the nerve.)



Schwannoma



Schwannoma: note the encapsulation which makes it easy for full surgical removal the tumour



Familial schwannomas

- 10% of schwannomas are familial, these occur in association with **neurofibromatosis type 2.**

- Familial schwannomas are usually **multiple**.

- **the presence of bilateral vestibular schwannoma is a hallmark for NF 2**

- Patients with NF 2 can have **other CNS tumours** like meningiomas and ependymomas

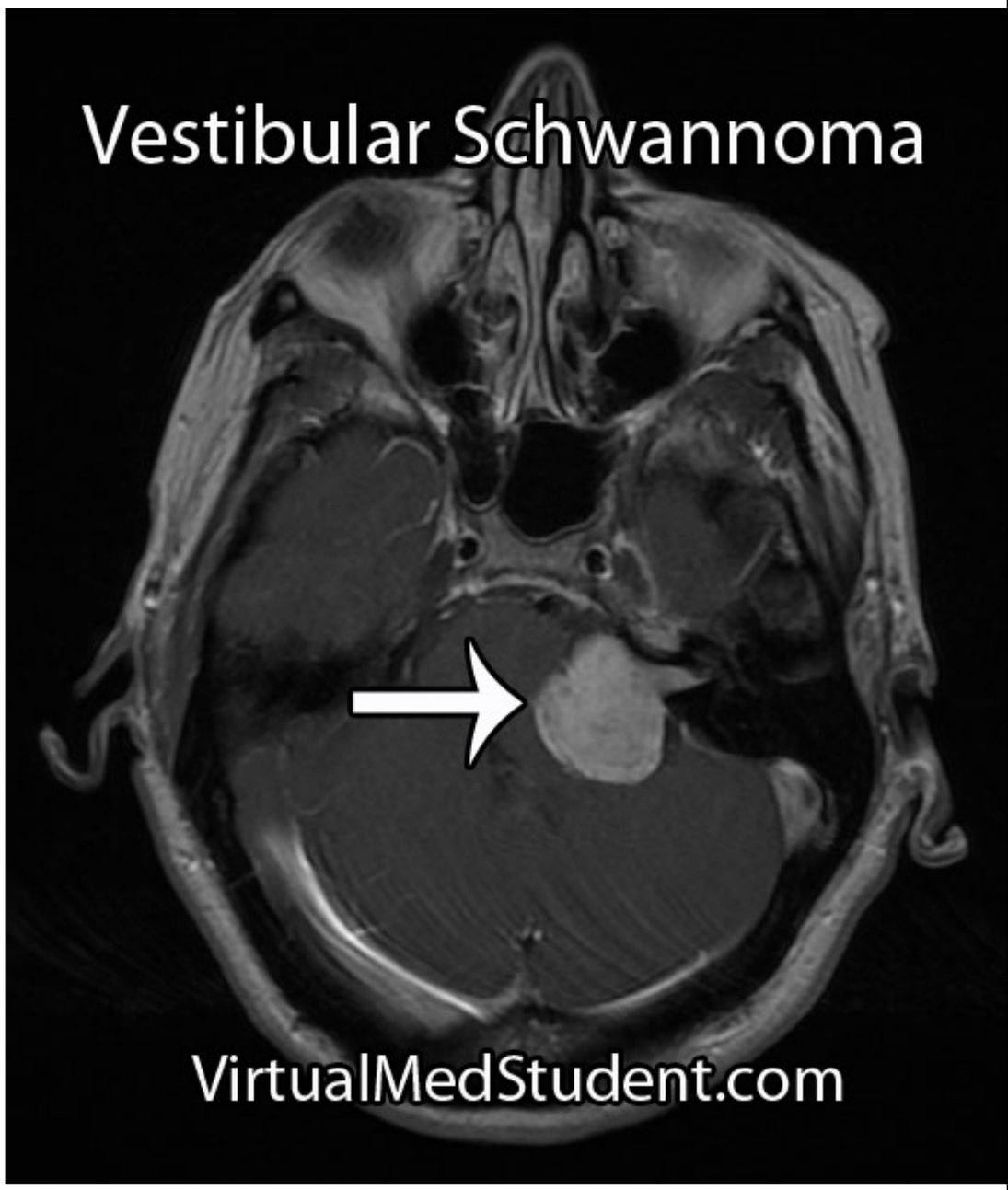
- ***Although the syndrome is called neurofibromatosis, patients do not have neurofibromas!!!!***

Vestibular schwannoma

- Note that vestibular schwannomas can be sporadic or familial.

- if a patient has bilateral vestibular schwannomas , this almost always means that the patient has NF 2

- Note: not all patients with NF2 will have bilateral schwannomas.



Genetic mutation in NF 2

- NF2 is caused by loss of function mutation in **merlin** gene on chromosome 22.

- Merlin is a cytoskeletal protein that is a tumour suppressor gene by facilitating E cadherin mediated contact inhibition.

- **With mutated merlin contact inhibition is lost so tumours can proliferate.**

merlin protein and contact inhibition

- Please remember that contact inhibition is an important process to limit and regulate cell growth

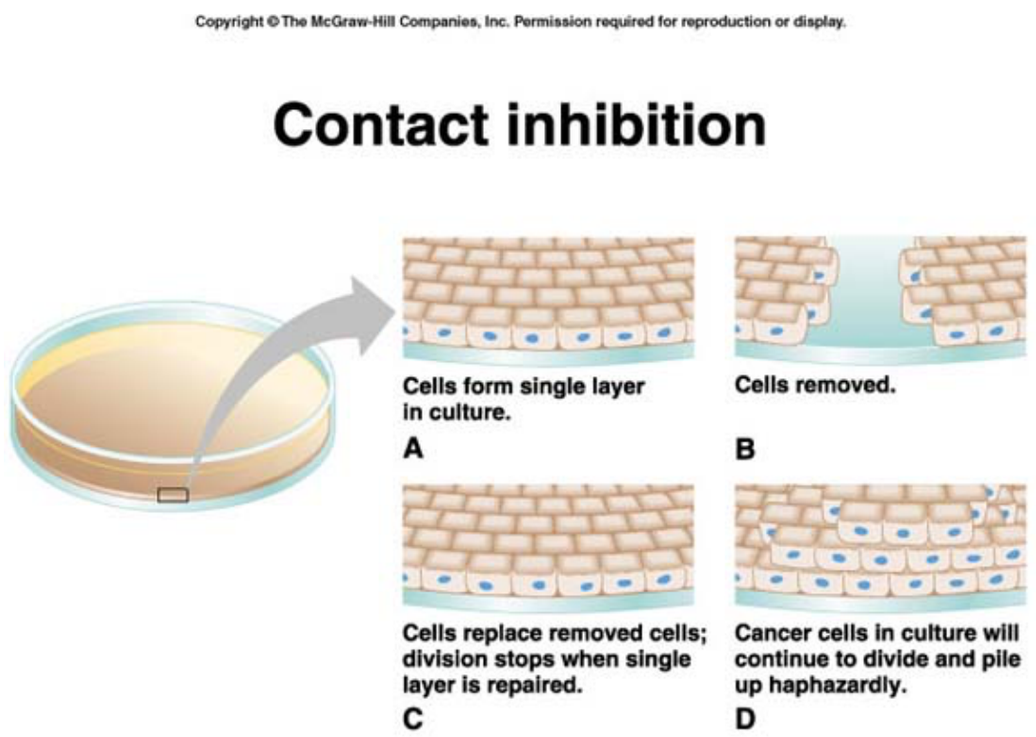
- If contact inhibition is lost growth can go unchecked

- E cadherin is the most important factor causing contact inhibition

- Merlin protein facilitated contact inhibition

- if merlin is lost then contact inhibition is lost and tumours occur

- Loss of function mutation in merlin protein is the underlying genetic defect in NF2



Neurofibroma

- Benign peripheral nerve sheath tumours.
- they are benign but not encapsulated
- Composed of proliferating Schwann cells admixed with other cells including mast cells and fibroblasts.
- Can be sporadic or familial (neurofibromatosis type 1= NF 1)

NF 1

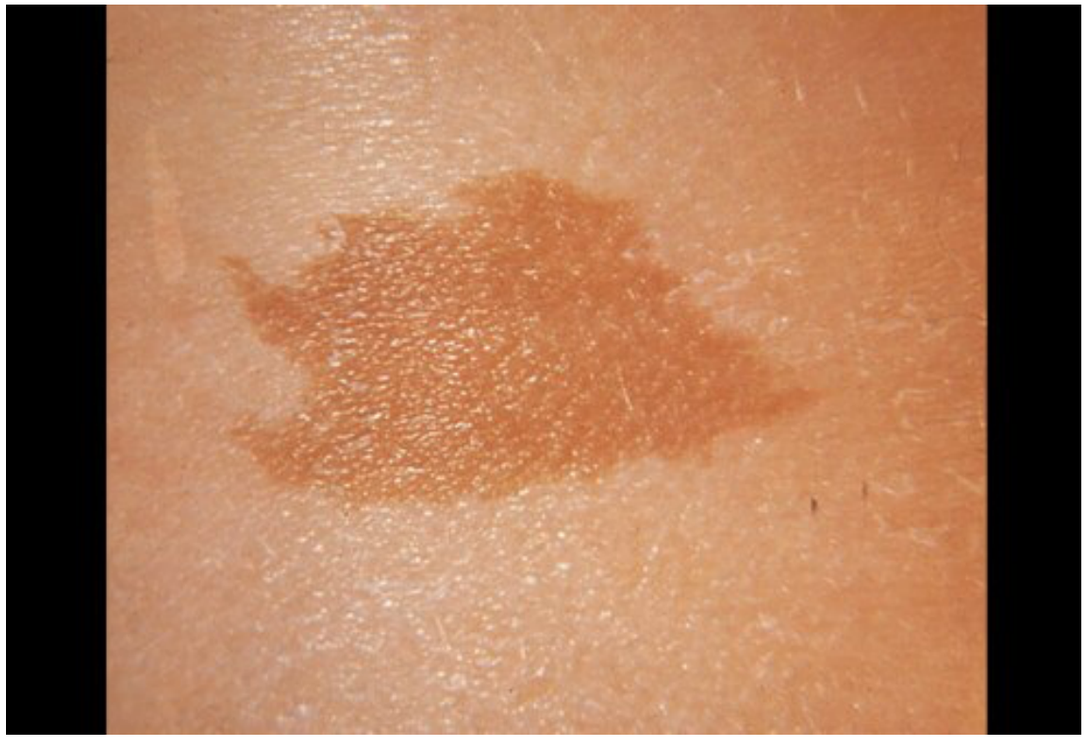
- Autosomal dominant disorder caused by mutation in neurofibromin

- neurofibromin is a tumour supressor gene encoded on chromosome 17. It is a negative regulator of the Ras oncoprotein.

- Patients have multiple neurofibromas, malignant peripheral nerve sheath tumour, optic gliomas, and other glial tumours.

- Patients also have learning disability, seizures, pigmented nodules in the iris and pigmented skin lesions= cafe- au-lait spots.

Cafe-au-lait spots
the word means: coffee with milk, referring to the colour of the spots!



Neurofibromatosis 1: multiple neurofibromas

Malignant peripheral nerve sheath tumour MPNST

- Malignant tumours arising from Schwann cells

- 50% occur in the setting of NF 1

- Histologically: highly cellular, anaplastic, pleomorphic, and show necrosis and a high mitotic rate.

Question

- Which of the following patients least likely has neurofibromatosis type 2?
- A. A 30 year old patient suffering from decreased hearing acuity. he was found to have bilateral tumors of the 8th cranial nerves.
- B. A 43 year old woman having an ependymoma. 3 years ago she underwent surgical excision for a meningioma. her mother removed several tumours, all were reported as schwannomas.
- C. A 12 year old boy, who had a genetic test that revealed mutation in the merlin gene.
- D. A 24 year old woman suffering from multiple skin masses which were non-capsulated and composed of proliferation of Schwann cells admixed with fibroblasts and mast cells.

Explanation of the question

- the answer is D. the description of the lesions is that of a neurofibromas, and neurofibromas are not seen in NF 2

Summary 1/3

- Axons of the PNS can regenerate at a rate of 1mm per day.
- This regeneration can restore function if the injury is mild. More severe injuries need surgical approximation or grafting to improve regeneration.
- the first step in regeneration is Wallerian degeneration which involves proliferation of Schwann cells that dedifferentiate: they decrease myelin production, phagocytose myelin debris resulting from injury, produce cytokines that stimulate nerve growth and recruit macrophages that also phagocytose debris resulting from the injury.
- Clearance of the necrotic debris is essential for nerve regeneration.
- this clearance doesn't occur in the CNS and that’s why axonal regeneration of CNS is very limited.
- The regeneration is limited by the fact that Schwann cells’ efficiency decreases after 8 weeks of injury.

summary 2/3

- oligodendrocytes in CNS die by apoptosis or become quiescent in response to injury, they cannot clear the necrotic debris that inhibits regeneration.
- Astrocytes also inhibit regeneration by forming gloiosis and secreting inhibitory cytokines.
- Traumatic neuromas are painful, non neoplastic proliferations of haphazardly arranged axons, Schwann cells and connective tissue, resulting after trauma.
- Neurofibroma is a benign non encapsulated tumour of Schwann cells mixed with fibroblasts and mast cells
- Schwannomas are benign encapsulated tumours of Schwann cells.
- Peripheral nerve sheath tumour is a malignant tumour of Schwann cells. Half of cases are familial (NF1)

summary 3/3

- NF 1 is an autosomal dominant syndrome characterised by multiple neurofibromas, PNST, gliomas and cafe au last skin lesions.

- NF 1 is caused by a mutation in neurofibromin, an inhibitor of Ras oncogene.

- NF 2 is characterised by multiple schwannomas (including acoustic schwannomas that can be bilateral), meningiomas and ependymomas BUT NOT NEUROFIBROMAS.

- NF 2 is caused by a mutation in merlin protein resulting in loss of contact inhibition.


THANK YOU