



- **Histology:** there are three covering of the nerve made up of connective tissue. These are:

• **Epineurium:**

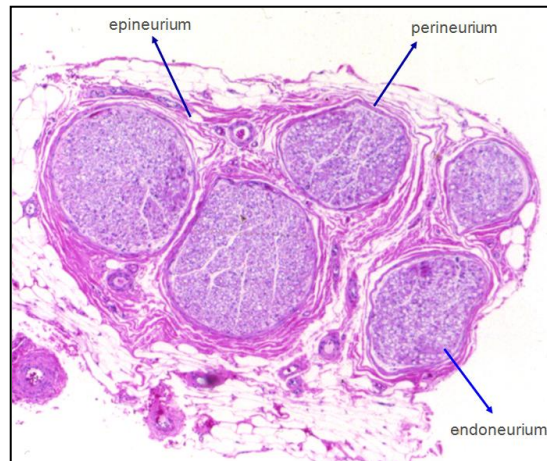
- ✓ It is the outermost layer covering the entire nerve.
- ✓ It is made up of dense, irregular connective tissue.
- ✓ It contains blood vessels and fat cells.

• **Perineurium:**

- ✓ Surrounding each fascicle.
- ✓ A fascicle is composed of myelinated & unmyelinated nerve fibers. Unmyelinated axons are more numerous and they range in size from 0.2-3 μm.

• **Endoneurium:**

- ✓ It is made up of loose connective tissue.
- ✓ Surrounding the myelin sheath of each myelinated nerve fiber.
- ✓ It contains capillary blood vessels.



- **A typical neural cell is composed of:**

• Dendrites.

• A cell body (soma) with centrally located nucleus and prominent nucleolus. Note that in pathological conditions, this central nucleus will be pushed to the periphery of the cell body.

• **An axon which is surrounded by myelin sheath:**

✓ Cells which produce myelin:

- ❖ *CNS* → oligodendrocytes → each oligodendrocyte can form myelin sheath for several/many axons.
- ❖ *PNS* → Schwann cells → each Schwann cell will form myelin sheath for a single axon.

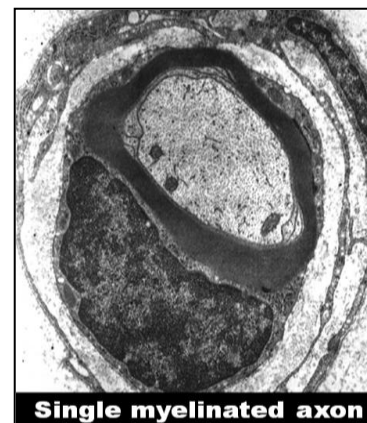
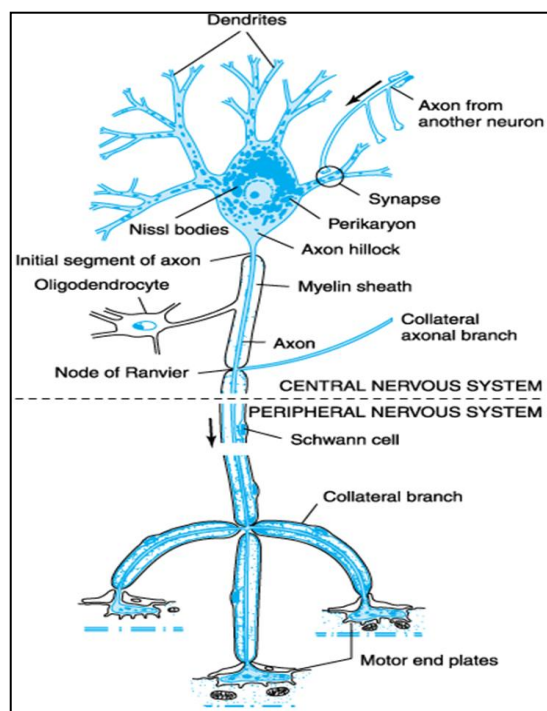
✓ Myelin sheath is composed of:

- ❖ *Proteins (30%)*: proteins are different between CNS and PNS.
- ❖ *Lipids (70%)*: lipids are similar between CNS and PNS.

✓ Nodes of Ranvier: points of discontinuity between adjacent myelin sheaths in which the axon is not covered by myelin.

✓ Functions of myelin:

- ❖ Electrical insulator.
- ❖ Increasing conduction velocity by salutatory conduction.



- **Patterns of neuropathy:**

- Axonopathy
- Myelinopathy
- Or combination of both (axonopathy + myelinopathy).

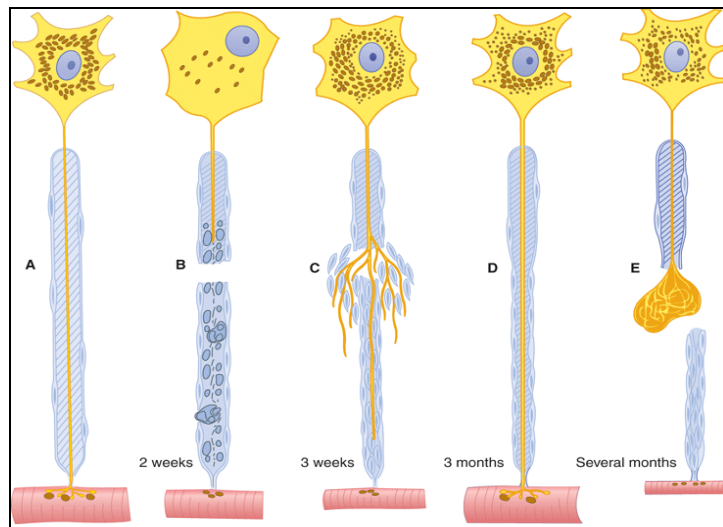
Note that in most neuropathies, the sural nerve biopsy can only establish the diagnosis of neuropathy and distinguish axonopathy from myelinopathy and acute from chronic neuropathy, but cannot determine the cause of neuropathy.



- **Axonopathy:**

• **Axonal degeneration:**

- ✓ **Definition:** primary injury to the axon followed by secondary disintegration of the myelin sheath.
- ✓ **Types:**
 - ❖ **Focal:** represented by Wallerian degeneration in which axonal degeneration starts distal to the site of injury. This can be caused by: trauma, infarction of peripheral nerves and neoplastic infiltration.
 - **Wallerian degeneration (occurring in neurotemesis & axonotemesis):** when the axon is cut, the proximal part of it will still get nourishment from the cell body and thus sprouts will start to form, in addition, a lot of proteins will be produced in the cell body of neurons resulting in central chromatolysis in which the nucleus is going to be pushed to the periphery. Regeneration can occur effectively only if the endoneurial lining of the axon is intact (1-3 mm/day). In the figure below: (A) shows normal neural cell – (B) there is a cut in the axon – (C) shows Wallerian degeneration which will end to (D) if the endoneurial tube is formed or to (E) if endoneurial tube is not formed.



- ❖ **Generalized:** represented by diabetic neuropathy in which axonal degeneration starts in the most distal part and extends proximally in a progressive continuous fashion (eventually the axons become atrophic and break down). This can be caused by industrial poisons and drugs such as: pesticides, acrylamide, and organic phosphatase.

- **Myelinopathy:**

• **Segmental demyelination:**

- ✓ In this condition, the axon remains intact and there is no change in the neuronal body but there will be decrease in conduction velocity and conduction block.
- ✓ Dead myelin will be removed by macrophages and Schwann cells will form new myelin.
- ✓ Recurrent demyelination and remyelination by concentric lamellae of Schwann cell processes and collagen around the axon will lead to hypertrophic neuropathy (onion-bulbs). Onion bulbs are also seen in other conditions such as diabetic neuropathy and CIDN.



- **Causes of peripheral neuropathy:**

• **Malnutrition/ Metabolic:**

✓ Diabetic neuropathy (developed in 30-60% of diabetic patients):

❖ *Diabetes causes several types of neuropathy which include:*

- ✚ Peripheral symmetrical polyneuropathy.
- ✚ Proximal neuropathy (diabetic amyotrophy).
- ✚ Mononeuropathy.
- ✚ Cranial radiculopathy.

❖ *Pathogenesis:* diabetic neuropathy is caused by 4 factors:

- ✚ Microvascular disease.
- ✚ Polyol pathway.
- ✚ Protein kinase C.
- ✚ Advanced glycated end products.

❖ *Characterized by:* numbness, parasthesia and pain.

❖ *Diabetic autonomic neuropathy is characterized by:* male impotence-neurogenic bladder – postural hypotension and diarrhea/constipation.

• **Inflammatory:**

✓ Non-infectious/ immune-mediated: Guillain-Barre syndrome in which antibodies and activated T-lymphocytes will react with antigens present on peripheral nerves causing an inflammatory and macrophage reaction which will destroy myelin and axons. It is a life threatening disease in which there will be increased levels of proteins in CSF (due to inflammation) and mortality is usually caused by respiratory paralysis.

✓ Infectious: leprosy.

• **Hereditary:** which is divided into several groups:

✓ Hereditary motor and sensory neuropathy (HMSN): affecting both (motor + sensation).

HMSN-I (Charcot-Marie-Tooth: X-linked)	In childhood/early adulthood – atrophy of distal muscles
HMSN-II (autosomal dominant)	Present at later age – similar to HMSN-I – no nerve enlargement
HMSN-III (Dejerine-Sottas disease: autosomal recessive)	In childhood, trunk & limb muscles involved – there is nerve enlargement and onion-bulb formation

✓ Hereditary sensory and autonomic neuropathy (HSAN): affecting sensation and causing autonomic dysfunction.

HSAN-I (autosomal dominant)	Sensory neuropathy – in young adults – with axonal degeneration of myelinated fibers
HSAN-II (autosomal recessive)	Sensory neuropathy – in infants – with axonal degeneration of myelinated fibers
HSAN-III (autosomal recessive in Jewish children)	Autonomic neuropathy – in infants – with axonal degeneration of unmyelinated fibers

✓ Familial amyloid polyneuropathy: associated with amyloid deposition with the nerve.

✓ Adrenoleukodystrophy: associated with biochemical abnormalities.

• **Certain cancers:** which will infiltrate nerves through lymphatics.

• **Amyloidosis.**