CNS pathology 2024/ lecture 4
Myelin disease of the PNS

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ILOS

1. Compare diseases of myelin in the CNS and PNS.
2. List causes of demyelinating diseases in the PNS.
3. Describe the pathogenesis of Gillian Barrie syndrome.
4. Describe the pathogenesis and symptoms of diabetic neuropathy.

- This is an online lecture

Youtube link:

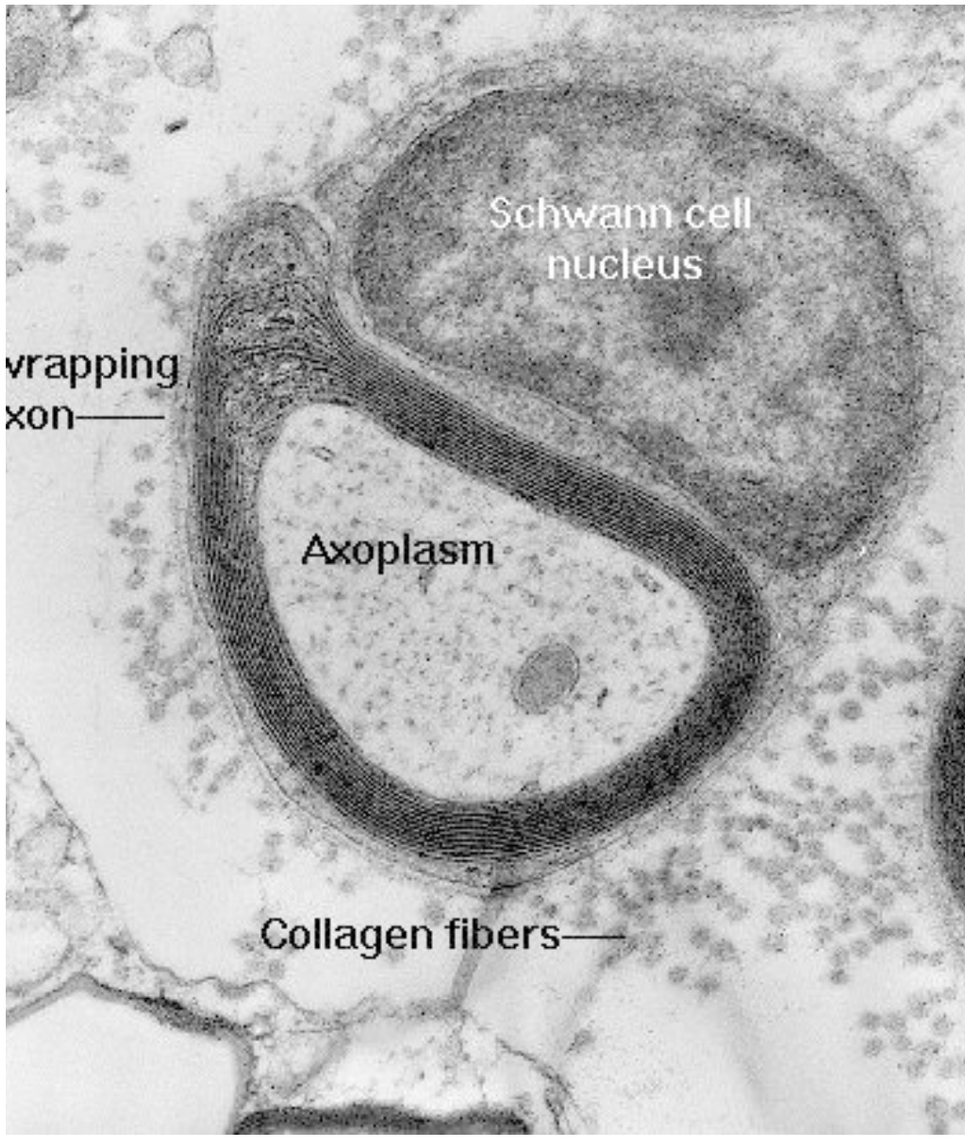
https://www.youtube.com/watch?v=aN5yEjJp940&t=672s

What is myelin?

- Myelin is a *protein-lipid complex* that is wrapped around the axons.
- Function: allows rapid propagation of signals.
- Composition: layers of plasma membranes assembled by ***oligodendrocytes (CNS) or Schwann cells (PNS)***
- Myelinated axons are the predominant component of white matter.

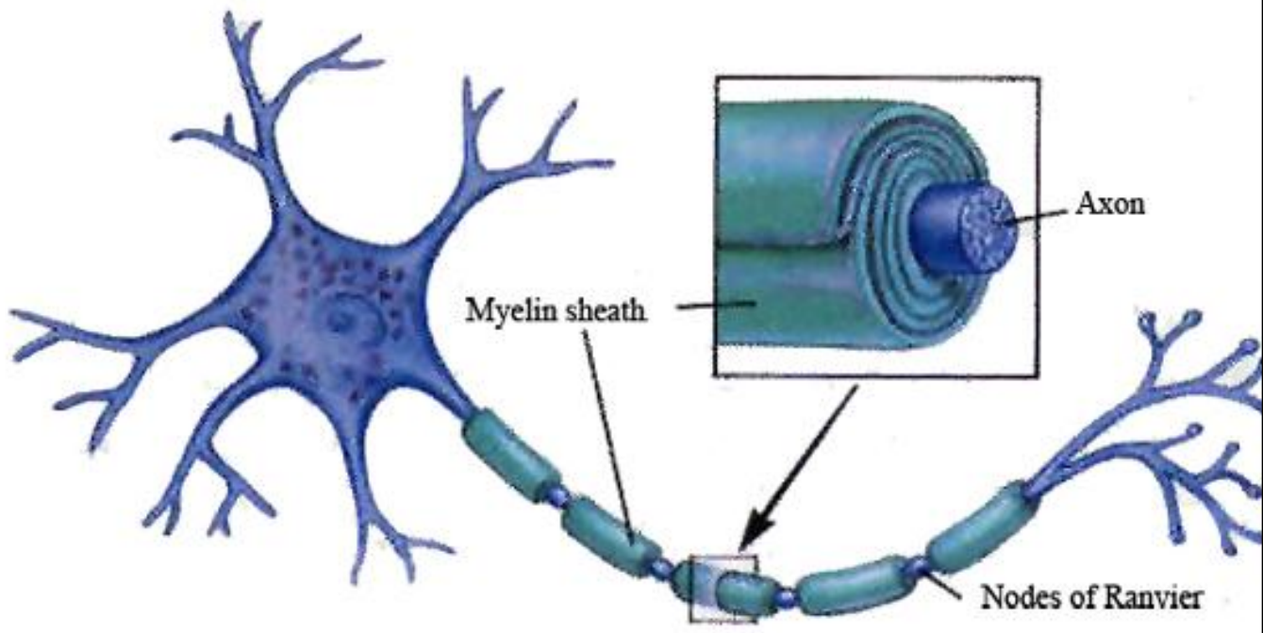
Myelin in the PNS

- As this EM picture shows, the part of neuron distal to the cell body has an axon (axoplasm and its surroundings in the pic) and a myelin sheath formed from Schwann cells.

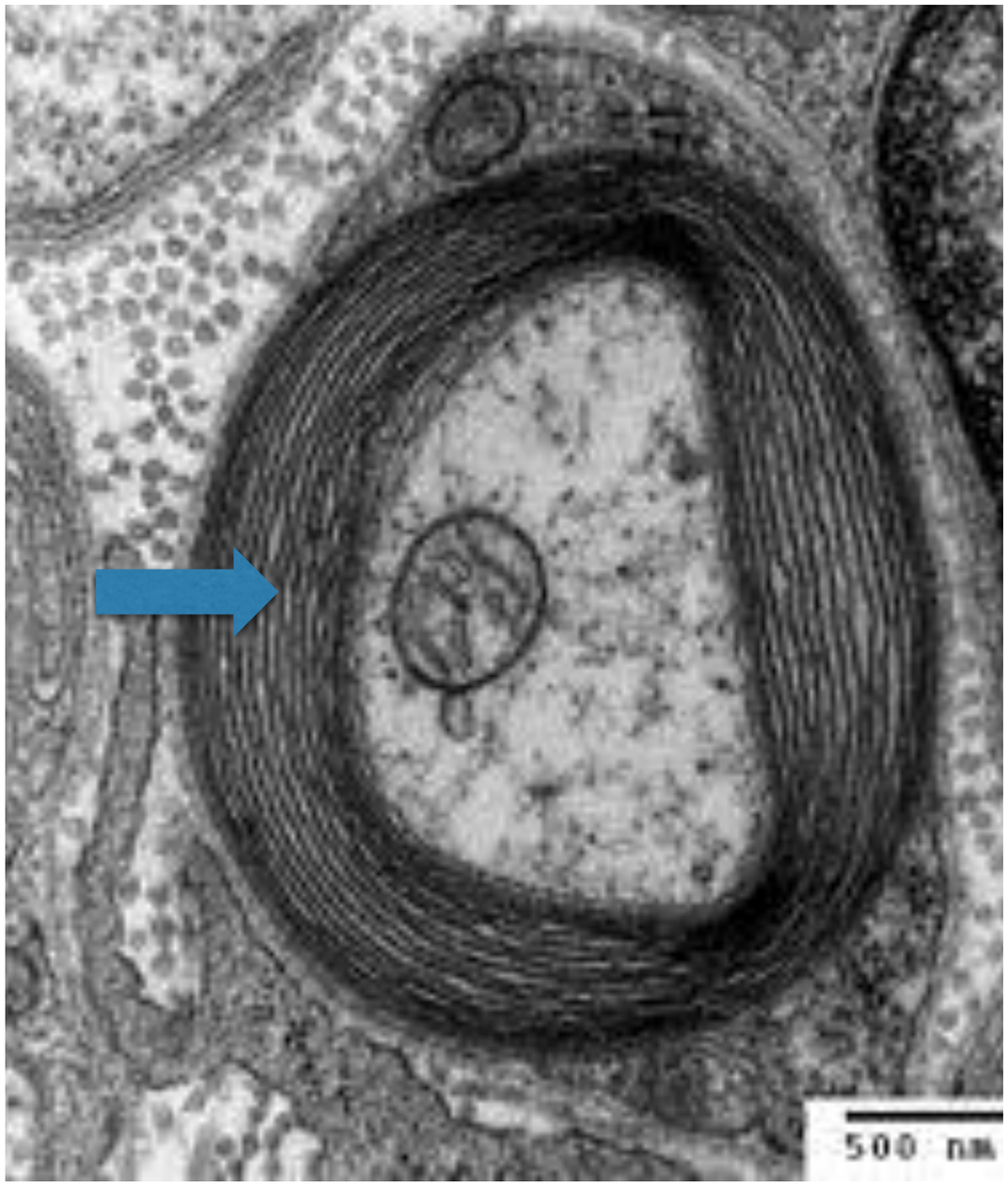


Myelin in the CNS

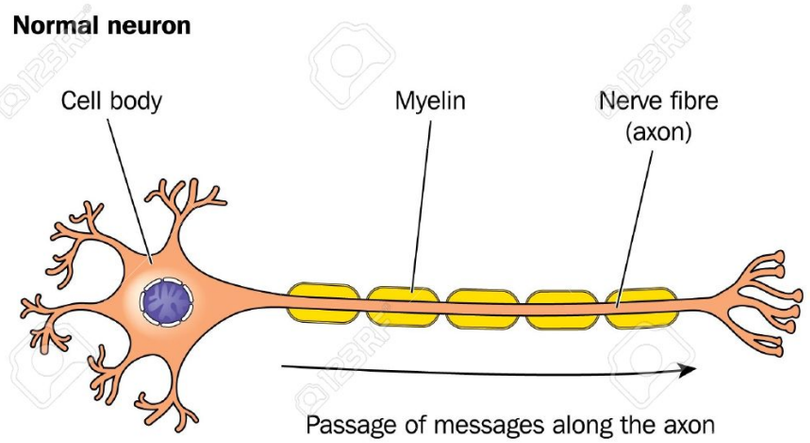
- Note that myelin is composed of layers of plasma membrane wrapped around the axons.

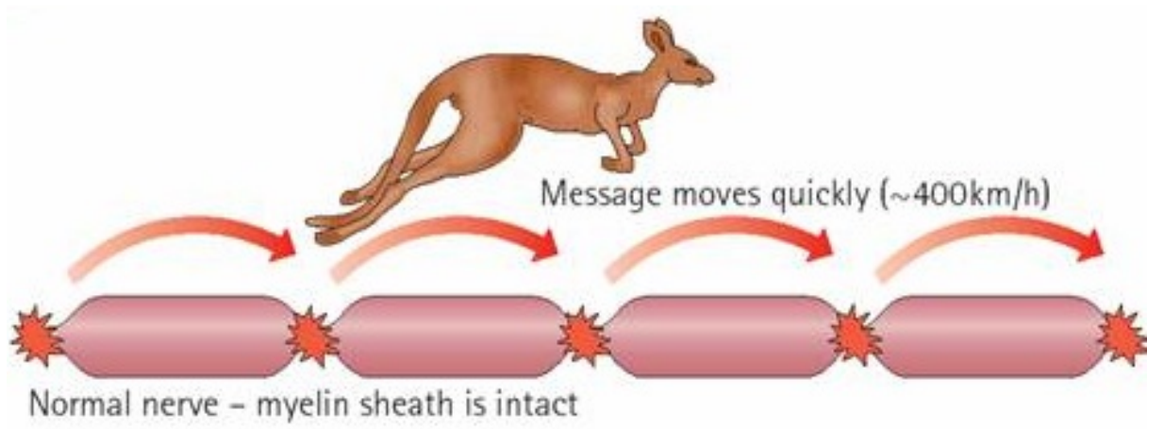


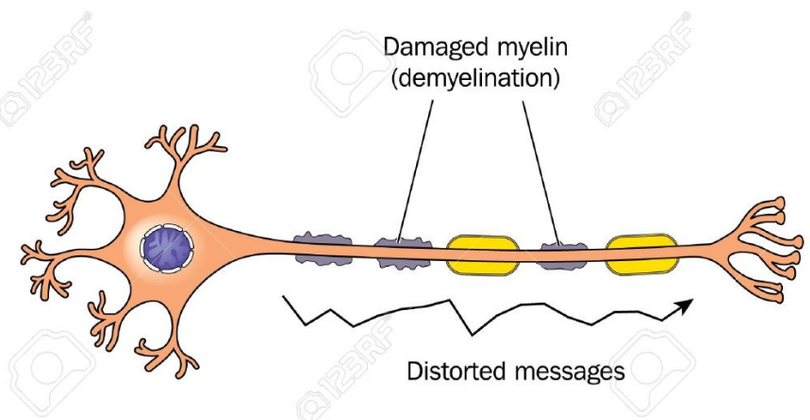
- Myelin in this electron microscopic picture appears as layers of plasma membrane wrapped around the axon.

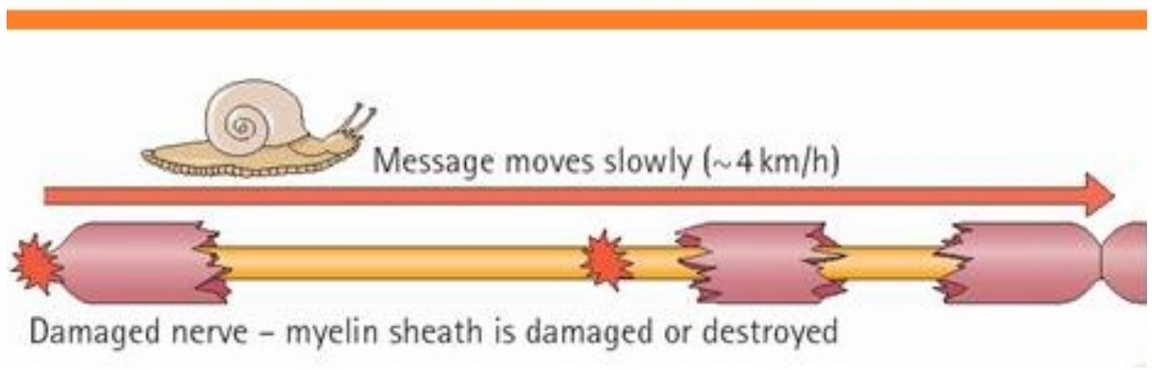


Function of myelin: to insulate axons and allows quick transmission of neural signals









Diseases of myelin in the PNS

- The main pattern of myelin injury in the PNS is known as segmental demyelination.

- In these diseases myelin sheath breaks but the underlying axons remains viable.

- The demyelinating neuropathies are caused mainly by **hereditary causes or immune destruction** of myelin.

Segmental demyelination

- Occurs due to Schwann cell dysfunction which could be **primary** if the injury is related to Schwann cells or the myelin sheath or **secondary** if demyelination is due to underlying axonal abnormality.

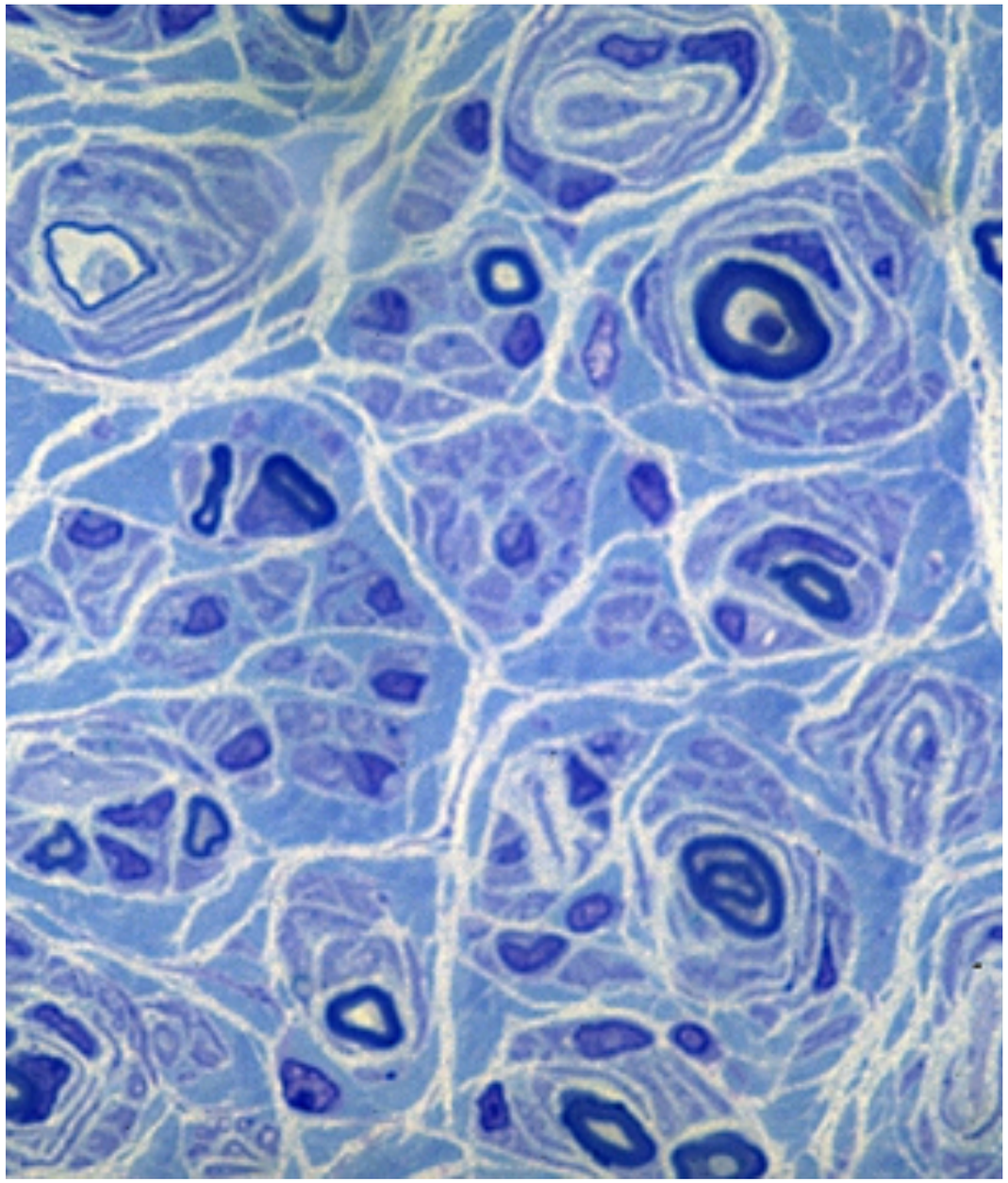
Segmental demyelination

- In these diseases **re-myelination occurs via proliferation of Schwann cells and function can be restored (depending on the extent of damage)**

- If there are repeated demyelination- re-myelination cycles, this will cause increased number of Schwann cells that encircle the axon causing enlarged nerves (**hypertrophic neuropathy**) and these are seen as **onion bulb** appearance under the microscope.

Onion bulb appearance

- This pic shows the thickened nerve fibres due to increased number of schwan cells after several cycles of de and re-myelination
- The appearance is termed: onion bulb
- It manifests clinically as hypertrophic neuropathy.



Clinical features

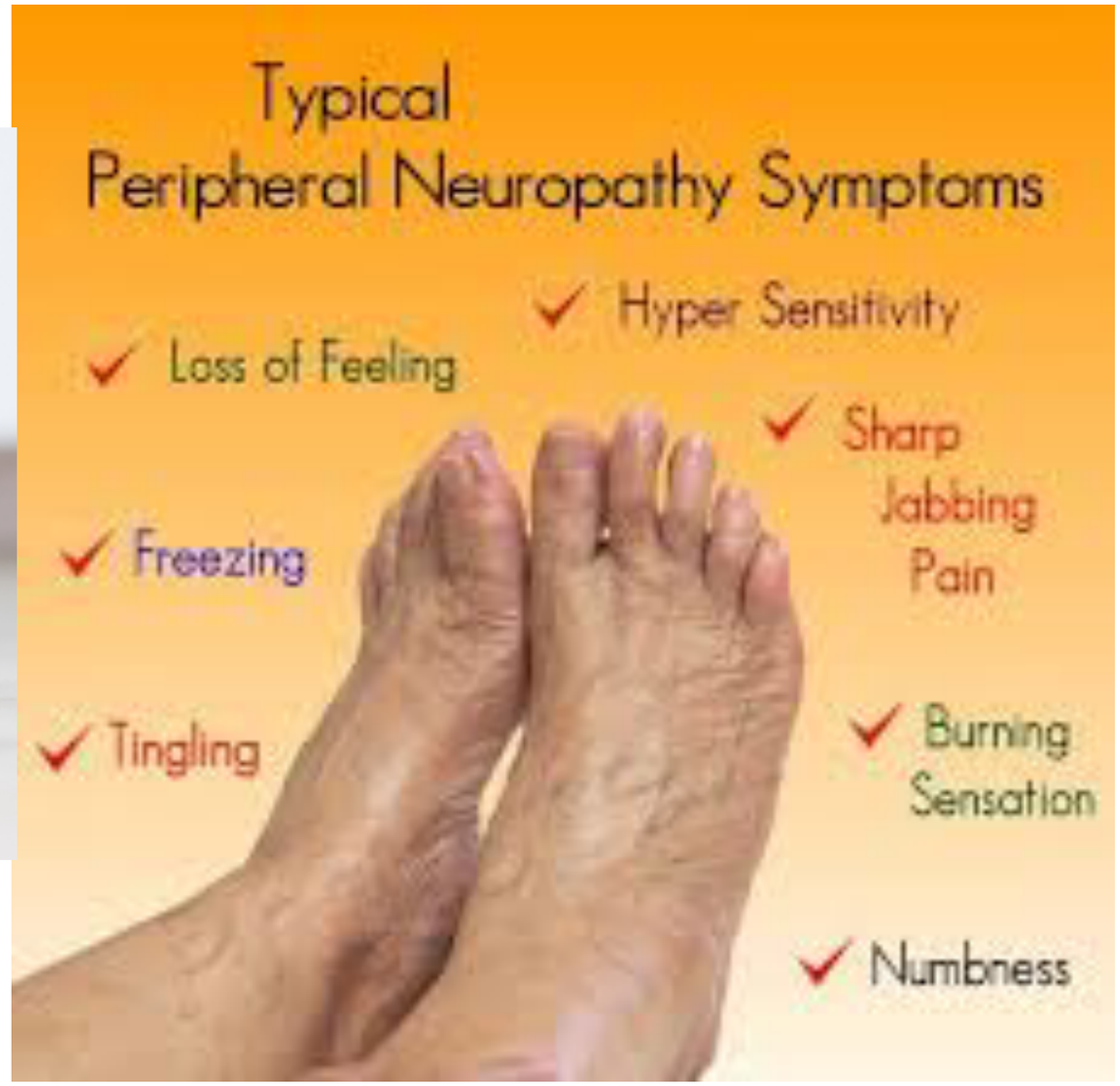
The symptoms are related to impaired function of the damaged nerve, these include:

- Muscle weakness and atrophy
- Sensory loss
- Pain
- Parasthesia = any abnormal sensation including numbness, tingling, pricking, or burning sensation with NO physical explanation of the sensation
- autonomic dysfunction which might include loss of bowel and bladder control.

Peripheral neuropathies

- This is a process that affects the function of one or more of the peripheral nerves.
- Neuropathies can be due to **axonal degeneration or segmental demyelination.**
- As such they are divided to : axonal neuropathy or demyelinating neuropathy
- 80-90% of neuropathies are axonal

Clinical features of neuropathy



Causes of peripheral neuropathies

- The demyelinating neuropathies are caused mainly by hereditary causes or immune destruction of myelin.
- Axonal neuropathies have a very diverse list of causes. Any disease process that affects the nerves or their blood supply can cause axonal neuropathy.

- **The most common cause of generalised peripheral neuropathy is diabetic neuropathy**
- Other causes include: hereditary, alcoholism, chronic renal failure, neurotoxic drugs, autoimmune diseases, nutritional deficiencies, vasculitis, infections, tumours , trauma and amyloidosis. So : any toxins , infections, or infiltrative disease process or vascular disease can affect the nerve and cause neuropathy.

Diabetic neuropathy

- Neuropathy is the **most common complication of diabetes**.
- The prevalence of diabetic neuropathy ranges from 7% within 1 year of diagnosis to 50% for those with diabetes for >25 years.
- Risk of developing neuropathy depends on: duration of diabetes, and level of control of blood sugar; the worse the control the higher the possibility of developing neuropathy.
- The presence of cardiovascular autonomic neuropathy dramatically shortens the patients' life expectancy.
- Loss of feeling in the lower limbs is a high risk for limb amputation, which occurs in 1–2% of diabetic patients.

Diabetic neuropathy: clinical manifestations

- Can manifest as polyneuropathy or mononeuropathy
- Several forms of neuropathy can occur:
- . 1**distal symmetric sensorimotor polyneuropathy which is the most common form.** Symptoms include numbness, tingling, and weakness. It can also cause pain. These symptoms usually start in the longest nerves in the body and so first affect the feet and later the hands. This is sometimes called the "**stocking-glove**" pattern.
- . 2**autonomic** neuropathy causing changes in bowel, bladder, or cardiac function
- . 3**Lumbosacral** neuropathy causing pain in lower legs.

Symptoms of peripheral diabetic neuropathy

- Numbness or reduced ability to feel pain or temperature changes
- Tingling or burning sensation
- Sharp pains or cramps
- Increased sensitivity to touch — for some people, even the weight of a bedsheet can be painful
- Muscle weakness
- Loss of reflexes, especially in the ankle
- Loss of balance and coordination
- Serious foot problems, such as ulcers, infections, and bone and joint pain

Pathogenesis of diabetic peripheral neuropathy

- Increased glucose in diabetics damages the nerves by two ways:
- 1. formation of advanced glycated end products that damage small blood vessels supplying the nerves. This results in ischemic damage to the nerves.
- 2. changes in polyol pathway resulting in increased sorbitol and decreased NADPH and reduced glutathione, this results in direct nerve damage.

1. Advanced glycation end products (AGE)

- AGE: formed by nonenzymatic interaction between glucose derived precursors and the amino groups on the proteins.

- So: glycated proteins are formed.

- These glycated proteins have receptors (RAGE) which are present on macrophages, T lymphocytes, endothelial cells and vascular smooth muscle cells.

- Interaction between AGE and RAGE causes several effects..

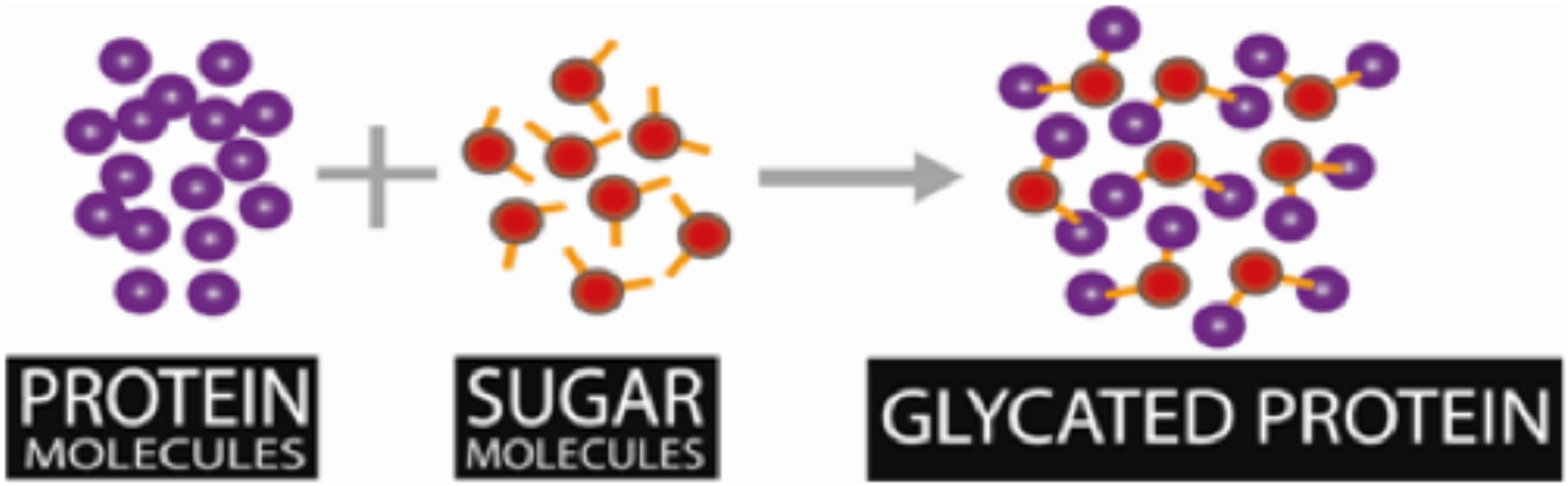
AGE- RAGE interaction effects

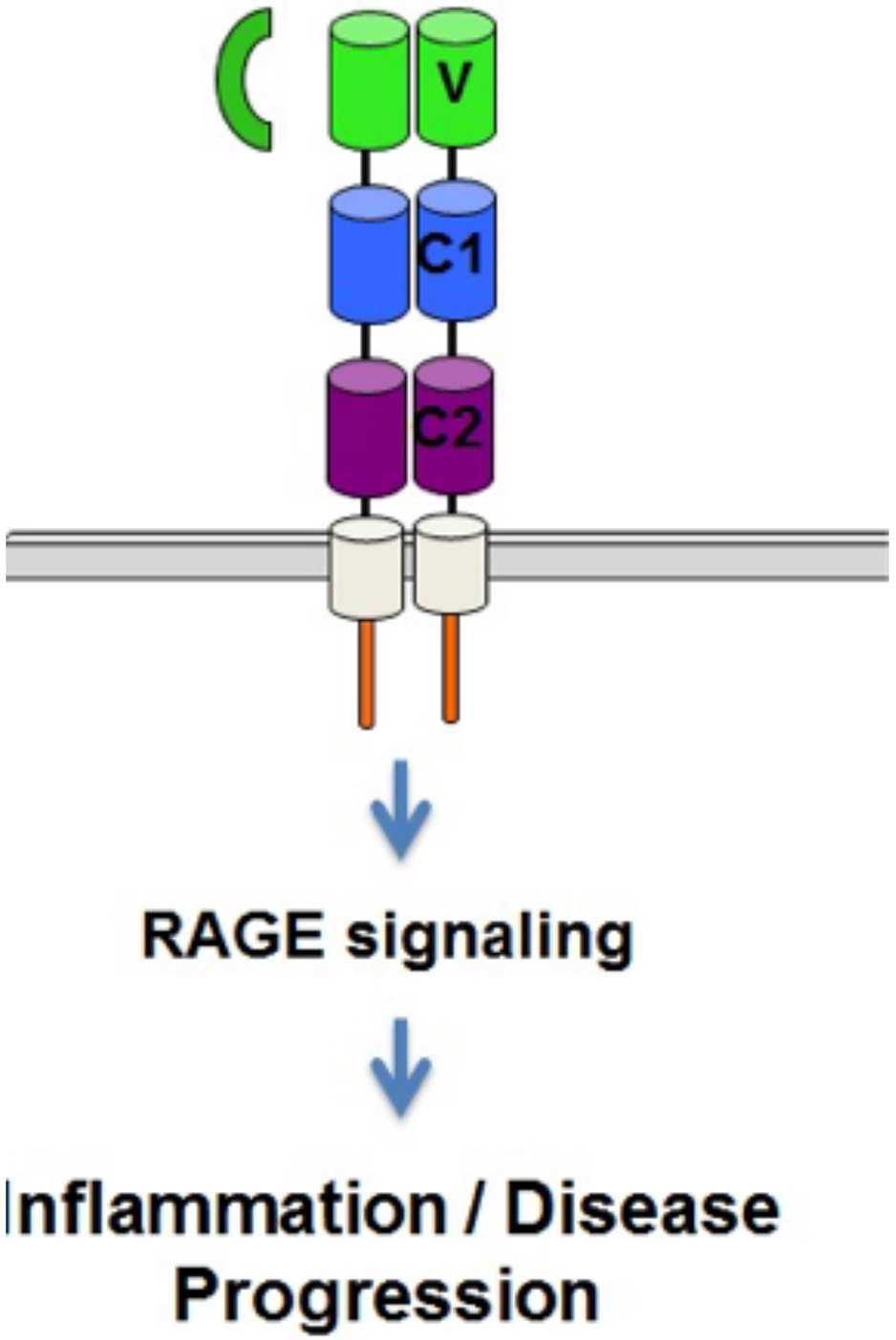
1. Formation of reactive oxygen species (ROS).. Causing tissue damage
2. Cytokines and growth factors formation
3. Procoagulant activity
4. Proliferation of smooth muscle cells and Increased extracellular matrix.

2-4 above cause thickening of the vessel wall. This is called microangiopathy because it affects small vessels like those innervating nerve endings.

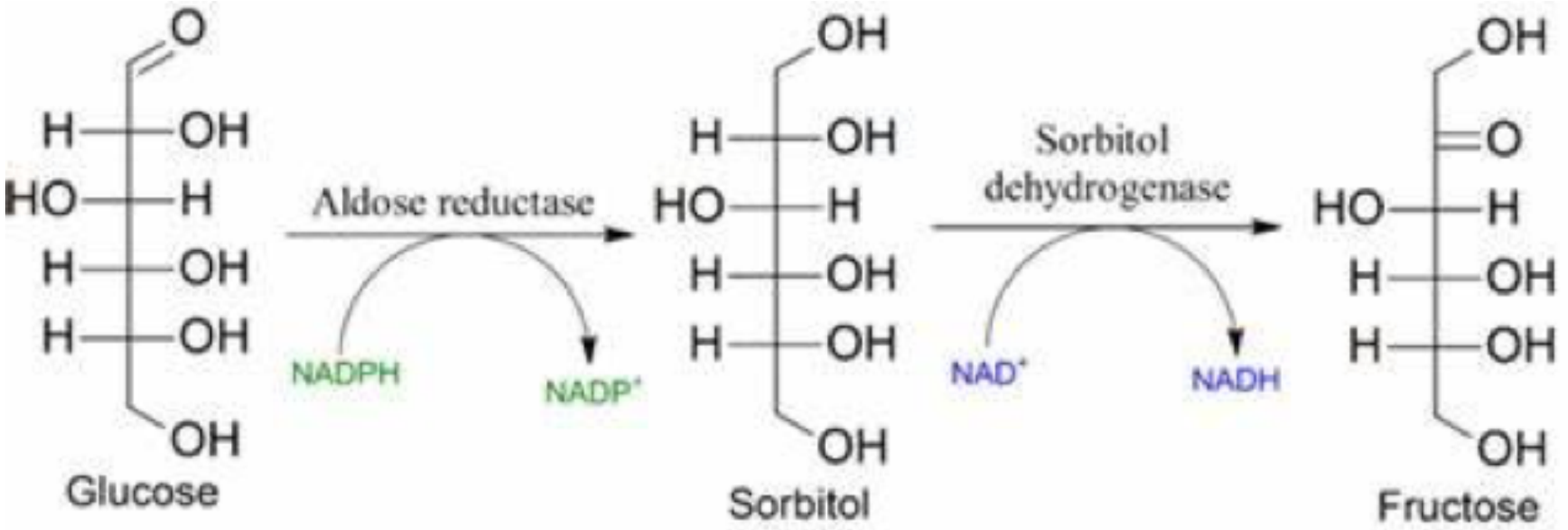
Microangiopathy causes ischemia to the nerves and ischemic damage.

AGE




V
C1
C2
RAGE signaling
Inflammation / Disease
Progression

2. Polyol pathway



- The polyol pathway is a two-step reaction that metabolises glucose to sorbitol then to fructose.

- In DM, glucose is increased and this pathway is activated.

- Sorbitol cannot cross the plasma membrane so it accumulates in cells causing increased osmotic pressure, so water enters cells resulting in edema and damage.

- Also the polyol pathway uses NADPH,, so less NADPH is available to reduce glutathione. Reduced glutathione is an important antioxidant, when it decreases oxidative stress in cells increases resulting in damage in the neurones.

Guillian Barre syndrome

- Is an ***<u>autoimmune neuropathy.</u>***

- Often follows bacterial, viral or mycoplasma infection
- Can follow immunization or surgery
- Most commonly after Campylobacter jejuni, CMV, EBV
- CSF: increased proteins and few WBC

Clinical features of Gullian Barre

- Acute symmetric neuromuscular paralysis often begins distally and ascends proximally
- Sensory and autonomic disturbances may also occur
- 5% of patients present with ophthalmoplegia, ataxia and areflexia = if these symptoms exist , it is called Fisher syndrome
- Muscle paralysis may cause respiratory difficulty, which might cause death.
- Autonomic involvement may cause cardiac arrhythmia, hypo or hypertension
- **Neuropathy resolves 2-4 weeks after onset and most patients recover**

Note

- Several studies reported association between COVID 19 infection and **Guillian Barre syndrome** (GBS).

- So: patients with COVID 19 can develop GBS

Chronic inflammatory demyelinating polyneuropathy CIDP

- Chronic acquired inflammatory polyneuropathy characterised by mixed sensorimotor polyneuropathy that persists for 2 months or more.
- It is immune mediated but usually there is no previous history of infection.
- Occurs in patients with other autoimmune diseases and in AIDS patients.

Summary 1/3

- In the PNS: Segmental demyelination can be primary or secondary to axonal damage.
- Chronic, repeated de and re-myelination cause hypertrophic neuropathy due to increased Schwann cells. this is seen as onion bulb under EM.
- Axonal neuropathies occur due to any disease affecting the nerve: vessel diseases causing ischemic damage, infiltrative diseases, tumours…
- Demyelinating neuropathies can be acute (Gullian Barre syndrome) or chronic (CIDP)

Summary 2/3

- Guillian Barre is an acute autoimmune disease occurring after infections or immunisation. it causes symmetric paralysis that starts in lower limbs and ascends. it can cause sensory and autonomous symptoms as well
- Guillian Barre (G-B) is life threatening if respiratory muscles are affected
- CIDP is similar to G-B regarding symptoms but is chronic and associated with other autoimmune diseases and HIV. Usually it is not preceded by infection.

Summary 3/3

- Diabetic neuropathy is the most common cause of peripheral neuropathies. it can present as mono or poly neuropathy, can be sensory, motor or autonomic and risk increases with increased detain of diabetes and poor control of blood sugar.
- formation of advanced glycated end products and changes in the polyol pathway are the most important pathogenic factors in diabetic neuropathy.

thank you!