Casual Friday Series

Interrupting Neuropathy

A Biogenetix Clinical Presentation

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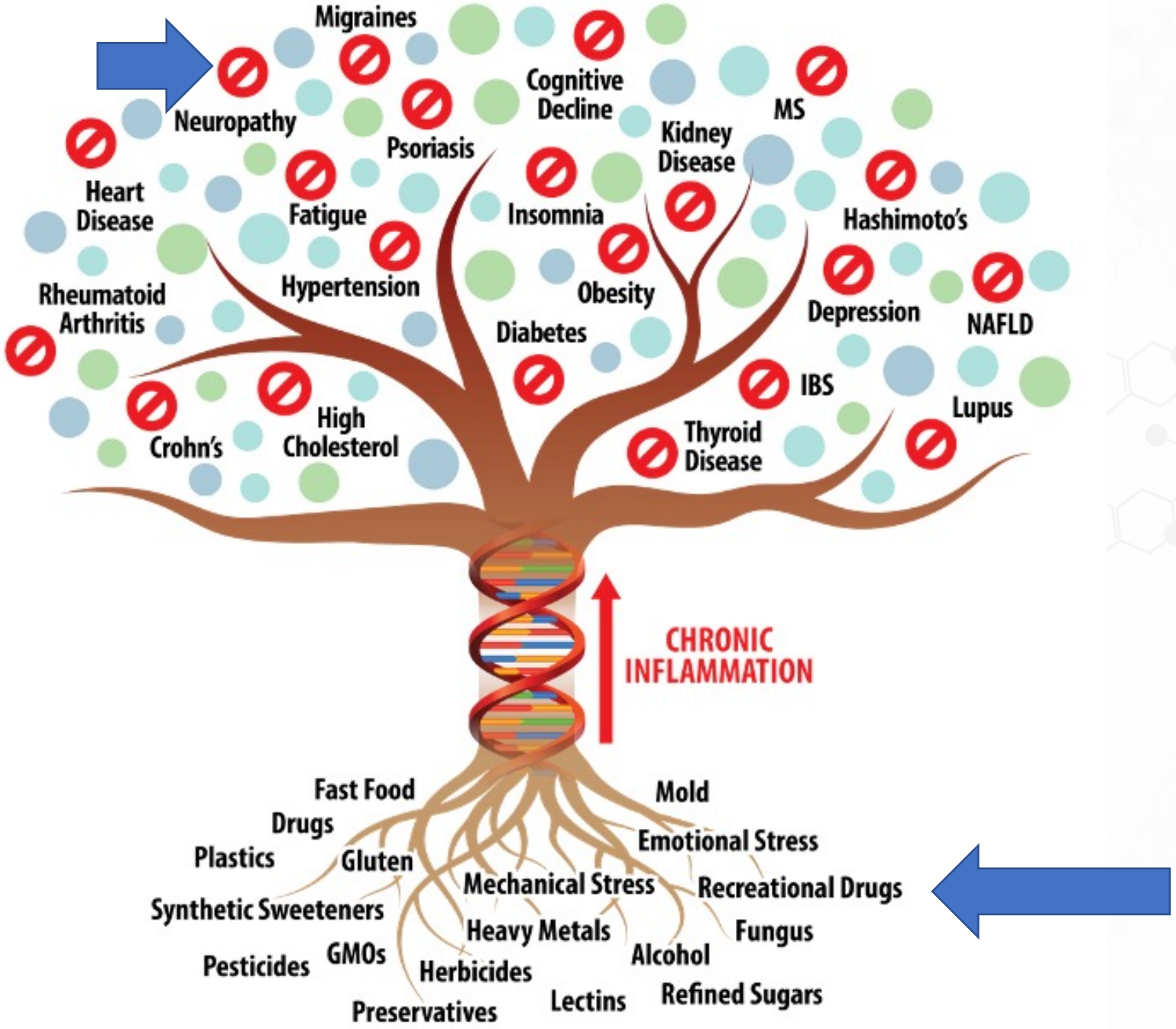
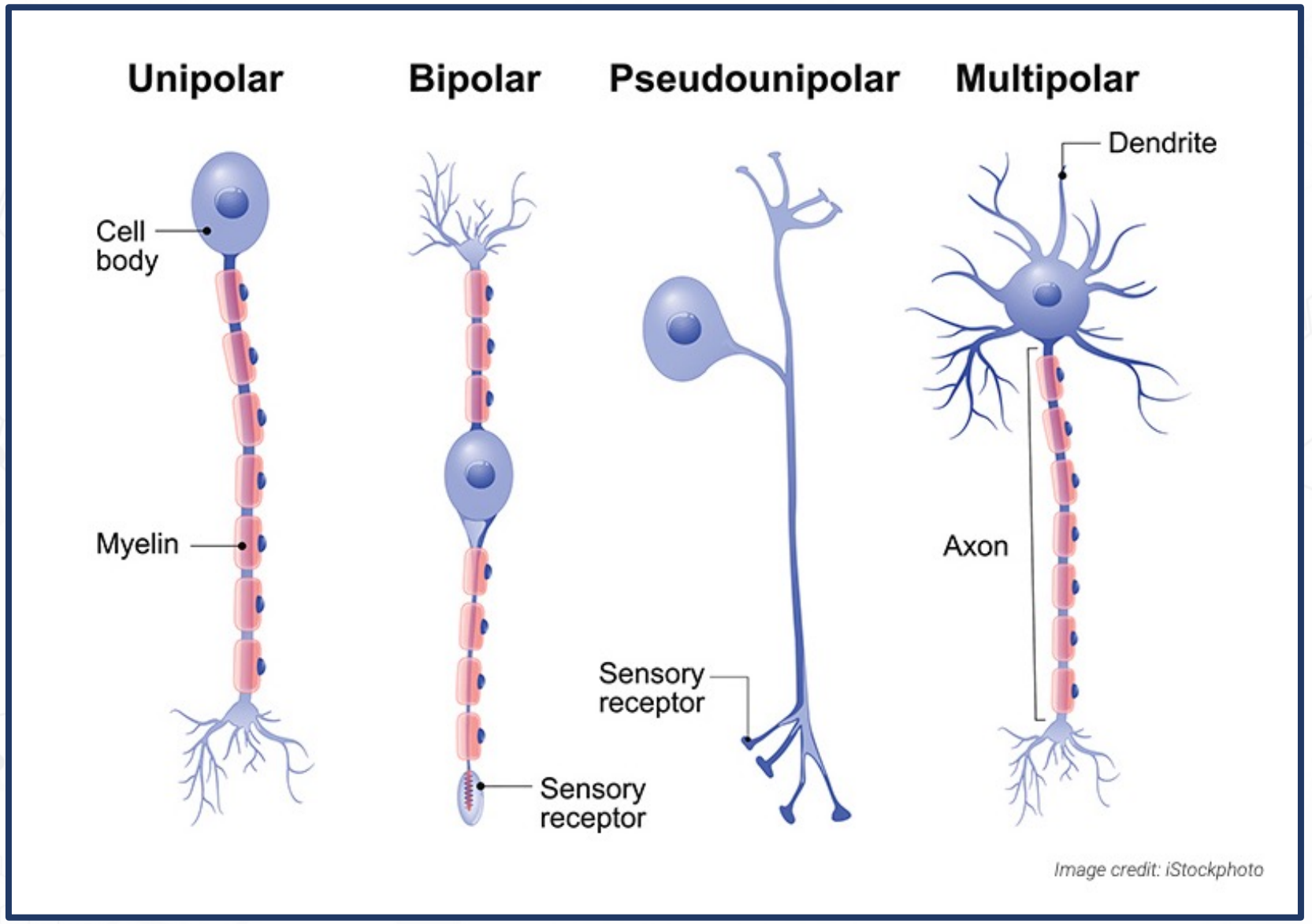
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Refined Sugars
Lectins
Preservatives


Unipolar
Bipolar
Pseudounipolar
Multipolar
Cell body
Myelin
Sensory receptor
Sensory receptor
Dendrite
Axon
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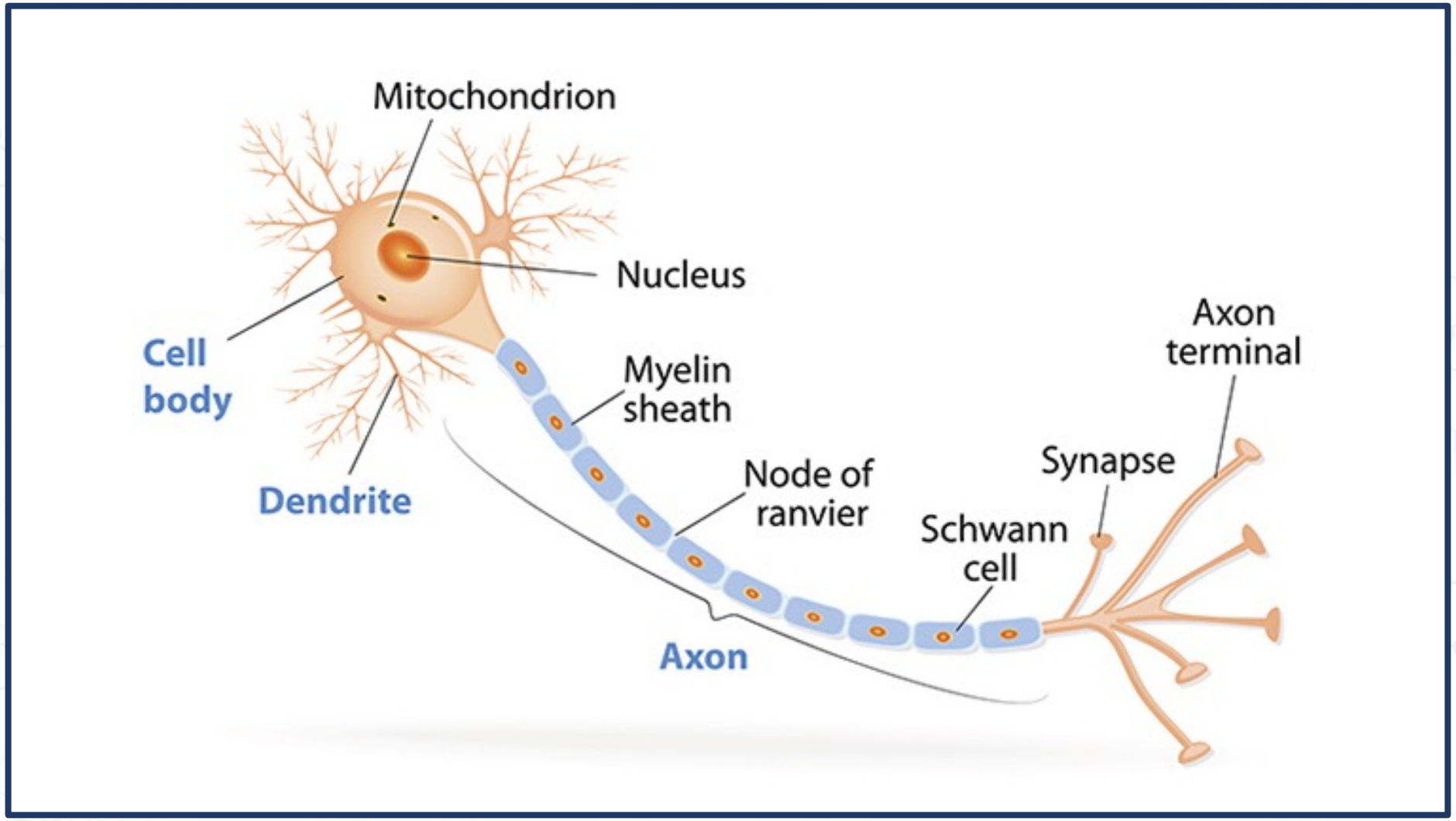

https://qbi.uq.edu.au/brain/brain-anatomy/axons-cable-transmission-neurons

CLINICAL FEATURES

Symptoms

Since the peripheral nervous system consists of motor, sensory and autonomic nerves, symptoms can fall into all three of these categories.

•Sensory symptoms include distal dysesthesias, pain and numbness. A characteristic pattern of numbness is one in which the distal portions of the nerves are first affected, the so-called "stocking-glove" pattern. This pattern occurs because nerve fibers are affected according to length of axon, without regard to root or nerve trunk distribution.

•Motor symptoms include weakness, which once again is distal, and typically involves extensor groups rather than flexor groups of muscles.

•Autonomic dysfunction is common and includes orthostasis, impotence in males and gastroparesis.

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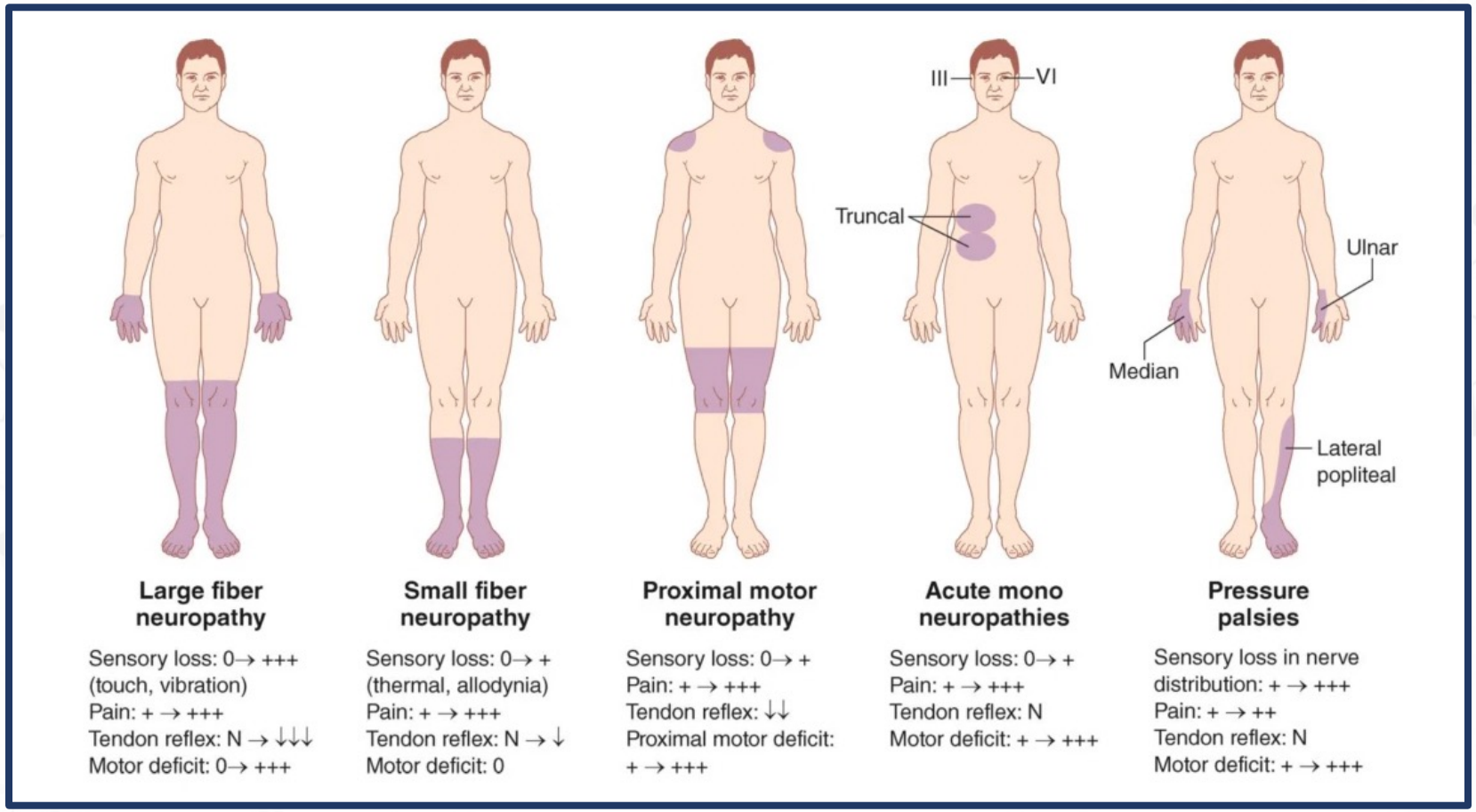

Large fiber neuropathy

Sensory loss: 0→ +++ (touch, vibration)
Pain: + → +++
Tendon reflex: N → ↓↓↓
Motor deficit: 0→ +++

Small fiber neuropathy

Sensory loss: 0→ + (thermal, allodynia)
Pain: + → +++
Tendon reflex: N → ↓
Motor deficit: 0

Proximal motor neuropathy

Sensory loss: 0→ +
Pain: + → +++
Tendon reflex: ↓↓
Proximal motor deficit: + → +++

Acute mono neuropathies

Sensory loss: 0→ +
Pain: + → +++
Tendon reflex: N
Motor deficit: + → +++

Pressure palsies

Sensory loss in nerve distribution: + → +++
Pain: + → ++
Tendon reflex: N
Motor deficit: + → +++

Signs

Signs of peripheral neuropathy also include sensory, motor and autonomic components.

- Sensory disturbance is manifest as distal loss of pin, temperature and vibratory perception as well as proprioception. Initial signs are frequently confined to the toes and feet. A positive Romberg sign is frequently present due to proprioceptive loss in the lower extremities.
- Motor signs include distal weakness, primarily in extensor groups, and most prominent in the lower extremities initially. Distal muscles are often atrophic, and one should carefully assess the bulk of the extensor digitorum brevis muscles in the feet and of the intrinsic muscles of the hands. Muscle tone is reduced and often is flaccid.
- Muscle stretch reflexes are frequently lost, and most patients with peripheral neuropathy have absent ankle jerks as one of the first signs of the disorder.
- The most prominent autonomic sign of neuropathy is orthostatic hypotension

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CLASSIFICATION

There are many ways to classify peripheral neuropathy. One helpful method is to consider four categories, namely **etiology, distribution, pathology and modality**.

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Etiology

Most peripheral neuropathies fall into three etiologic categories, namely hereditary, toxic/metabolic, and those associated with systemic disease.

Hereditary:

This is a large group of disorders in which the onset of symptoms is insidious and progression is indolent over years or decades. Three of these hereditary neuropathies will be discussed:

•**Charcot-Marie-Tooth Disease** (Hereditary Sensory-Motor Neuropathy [HSMN] I). This is the most common hereditary neuropathy that has an autosomal dominant pattern of inheritance. Phenotypic expression is often variable, such that affected family members of a propositus may have no symptoms and minimal neurologic findings. Characteristic clinical findings include striking atrophy of the calves, resulting in an inverted "champagne-bottle" appearance to the lower extremities. Peripheral nerves are often palpably enlarged. Large fiber sensory loss is present, with a marked reduction in vibratory perception and proprioception. Ankle jerk reflexes are lost. Since this is a demyelinating polyneuropathy, nerve conduction velocity measurements are characteristically slow, at approximately 50% of normal values.

•**Dejerine-Sottas Disease** (HSMN III). This is a rare pediatric disorder with autosomal recessive inheritance that causes severe weakness and numbness, markedly enlarged peripheral nerves with "onion-bulb" formation and markedly slowed conduction velocities.

•**Refsum's Disease** (HSMN IV). This autosomal recessive disorder is caused by an enzymatic defect that results in accumulation of phytanic acid. The clinical triad includes peripheral neuropathy, retinitis pigmentosa and dry, scaly skin. Treatment includes dietary restriction of phytanic acid and plasmapheresis.

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Etiology

Toxic/Metabolic:

Numerous drugs and toxins can cause peripheral neuropathy. A partial list follows:

1. **Drugs:** amiodarone, cis-platinum, dapsone, INH, phenytoin, pyridoxine, vincristine, nitrofurantoin, ddI, ddC.

2. **Toxins:** heavy metals including mercury, arsenic, lead, zinc and thallium; alcohol; and the organophosphates.

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Etiology

Neuropathy Associated with Systemic Diseases:

•Many pathologies including infections and cancers can produce neuropathy.

•Diabetes mellitus is perhaps the most common cause of neuropathy in the United States. Both symmetric and asymmetric diabetic neuropathies can occur, as follows:

- Symmetric polyneuropathies: These are the most common and include a sensory/motor polyneuropathy and an autonomic neuropathy.
- Asymmetric neuropathies are less common. Mononeuropathy multiplex results in simultaneous dysfunction of several peripheral nerves, and is due to ischemic infarction of the vasa nervorum. Cranial neuropathies, truncal radiculopathies and diabetic amyotrophy (ischemic infarction of the lumbosacral plexus) are other forms of asymmetric neuropathies. Entrapment neuropathies, including carpal tunnel syndrome, are also commonly seen in diabetics.

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NERVE DAMAGE FROM OXIDATIVE STRESS

OXIDATIVE FREE RADICAL
Unstable molecule containing an unpaired electron

ANTIOXIDANT MOLECULE
Molecule stable enough to donate an electron to a free radical

OXIDATIVE AGENTS: A chemical species that steals electrons from another substance, leading to the oxidation. These are reactive oxygen species (ROS), referring to a group of highly reactive molecules and free radicals containing oxygen.

ANTIOXIDANTS: Molecules that help protect the body from the damage caused by ROS and free radicals. Antioxidants neutralize free radicals by donating an electron without becoming destabilized themselves.

Distribution

Nerve damage in peripheral neuropathy may be symmetrical generalized, multifocal or focal.

Symmetrical generalized polyneuropathies produce signs and symptoms in a distal-to-proximal gradient, the so-called "stocking-glove" pattern. The reason for this is that the "offending agent" causing the neuropathy affects protein synthesis in the cell body of the peripheral nerve. Hence, neuronal dysfunction will first occur in the distal portions of the longest axons, and thus produce symptoms of weakness and numbness in the most distal portions of the extremities, i.e. the feet and hands.

Multifocal Neuropathies (Mononeuropathy Multiplex): Patients with these forms of neuropathy develop more-or-less simultaneous dysfunction of several peripheral nerves. The underlying pathologic mechanism is felt to be ischemic infarction of the vasa nervorum due to vasculitis, as can occur with SLE, rheumatoid arthritis, polyarteritis nodosa and diabetes mellitus. These neuropathies are frequently painful and cause profound weakness. Prognosis for recovery is good, assuming that the underlying disease process leading to nerve infarction can be suppressed.

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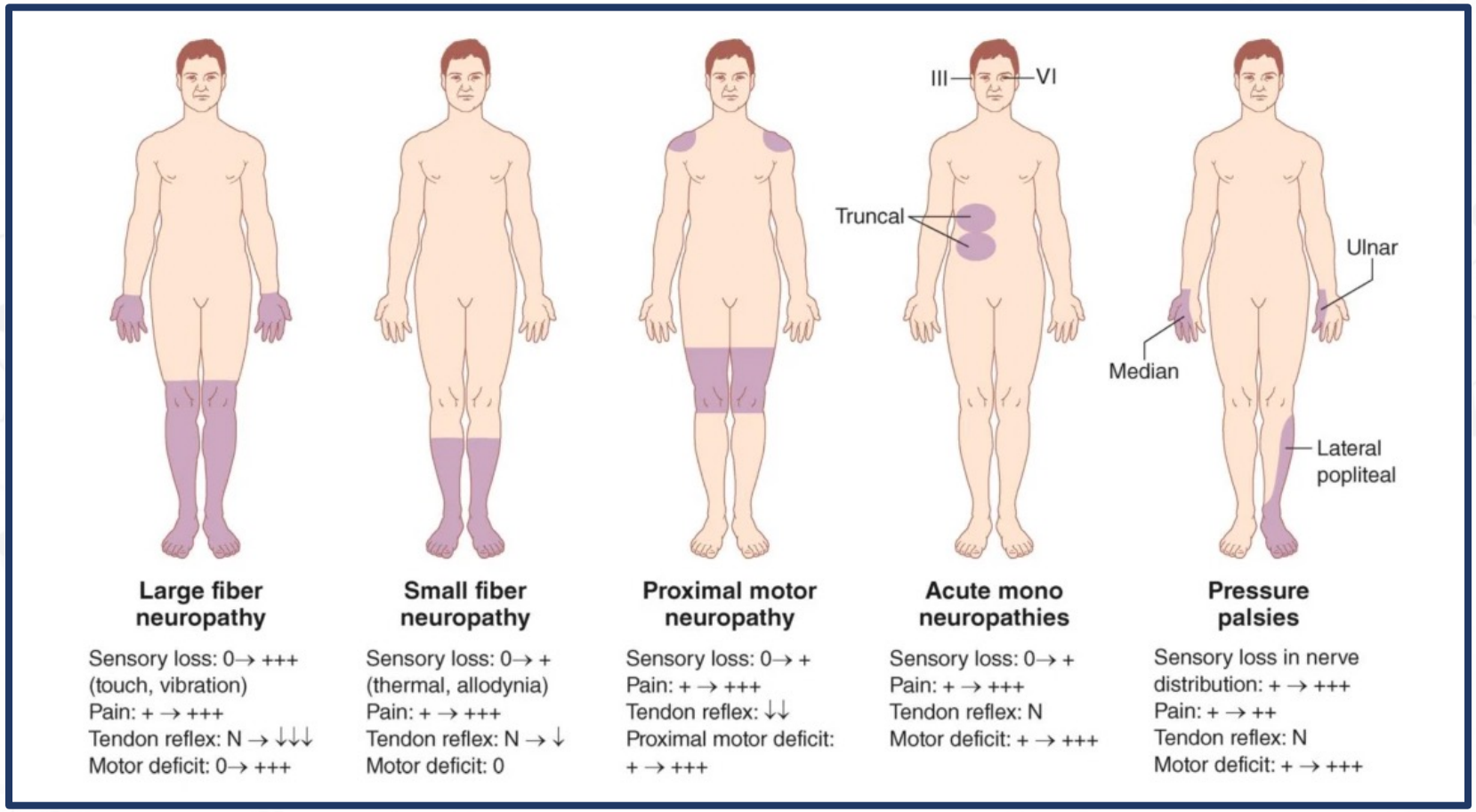

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Distribution

Nerve damage in peripheral neuropathy may be symmetrical generalized, multifocal or focal.

Focal Neuropathies (Mononeuropathies): Traumatic injuries and entrapment of peripheral nerves at the usual sites of compression are the most common causes of focal mononeuropathy. The most frequently seen entrapment neuropathies include:
Compression of the median nerve across the wrist (carpal tunnel syndrome)
Compression of the ulnar nerve across the elbow (tardy ulnar palsy)
Compression of the radial nerve at the spiral groove (Saturday night palsy)
Compression of the peroneal nerve at the fibular head (peroneal nerve palsy)
Compression of the distal branches of the tibial nerve at the ankle (tarsal tunnel syndrome)

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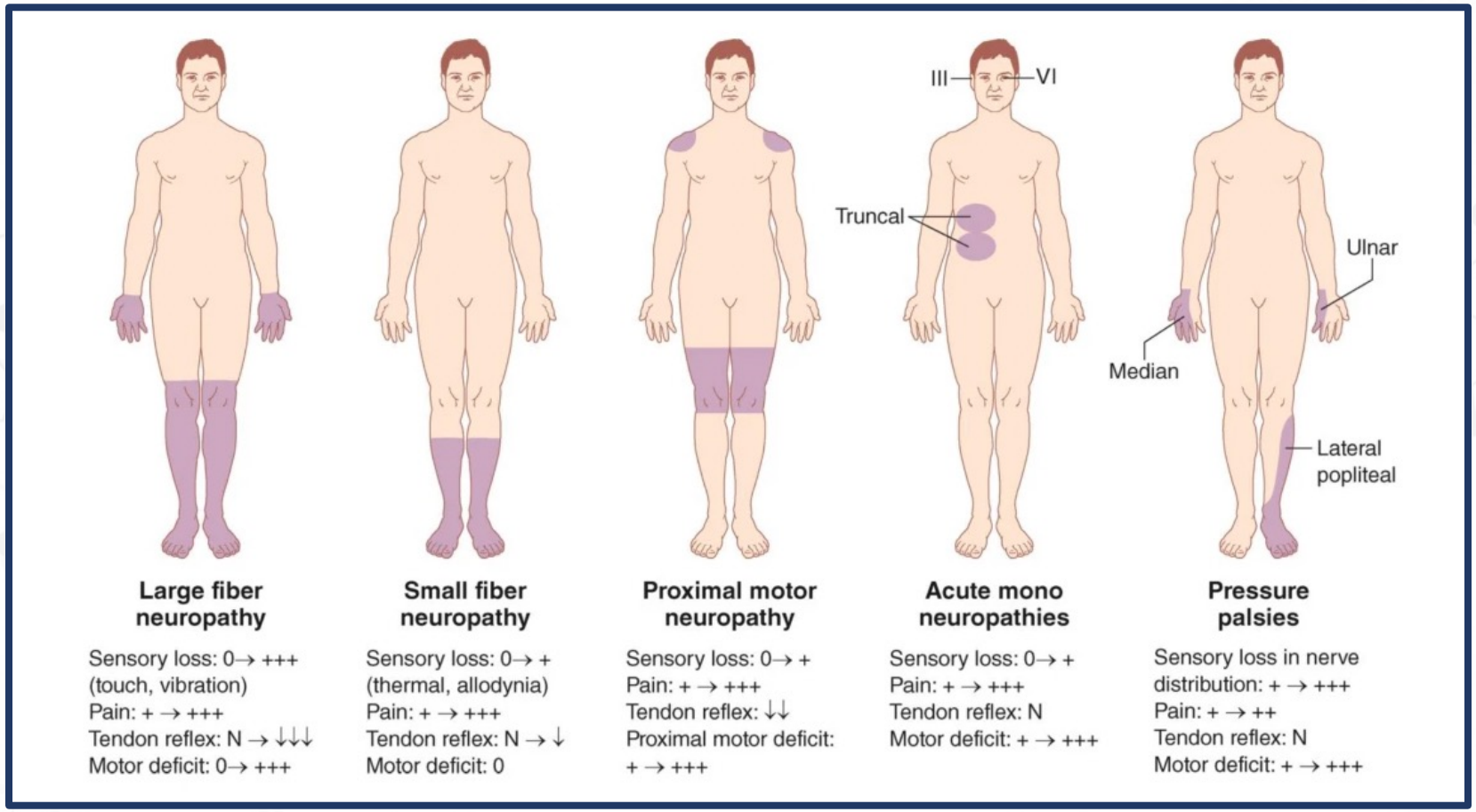

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Pathology

There are three major pathologic mechanisms causing peripheral neuropathy: distal axonopathy, myelinopathy, and neuronopathy.

Distal Axonopathy:

In this form of neuropathy, a metabolic abnormality causes failure of protein synthesis and axonal transport, resulting in degeneration of distal regions of axons. For this reason, axonal neuropathies characteristically produce a "stocking-glove" distribution of numbness and weakness. Small-diameter axons are most susceptible to metabolic injury because of their small neuronal size and lack of "reserve". Hence, initial symptoms of an axonal neuropathy typically include autonomic dysfunction and small-fiber sensory modalities, including loss of pain and temperature perception, since these modalities are subserved by small, unmyelinated or thinly myelinated axons.

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Pathology

Myelinopathy:

An immune-mediated attack on peripheral nervous system myelin is the characteristic pathologic change in this group of neuropathies. Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) are the two most common forms of demyelinating polyneuropathy.

GBS is a monophasic, immune-mediated demyelinating neuropathy that frequently follows a viral infection and causes an acute and frequently severe progression of weakness and numbness over several weeks. CIDP is a chronic demyelinating polyneuropathy that can have a slowly progressive or a relapsing course. In both of these neuropathies antibodies have been found that cross-react with peripheral nerve myelin. Elevated CSF protein and slowed nerve conduction velocities are characteristic of the demyelinating neuropathies.

In general, demyelinating neuropathies affect large-diameter, myelinated axons at the start of the illness, and hence produce significant motor weakness and large-fiber sensory loss, including loss of vibratory perception and proprioception.
In diphtheritic neuropathy, the bacterium produces a toxin that inhibits Schwann cell synthesis of myelin constituents, producing severe weakness and large-fiber sensory loss.

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Pathology

Neuronopathy:

Selective involvement of the cell bodies of motor, sensory and autonomic nerves is the hallmark of this group of neuropathies.

•**Somatic motor neuronopathies** result from isolated involvement of the anterior horn cells. Amyotrophic lateral sclerosis and the spinal muscular atrophies are two examples of somatic motor neuronopathies.

•**Somatic sensory neuronopathies** result from disruption of the metabolism of sensory nerve cell bodies, followed by degeneration of their processes. Special permeability of the blood vessels in the dorsal root and Gasserian ganglia make these neurons particularly vulnerable to certain toxins. Two common examples of somatic sensory neuronopathies include the paraneoplastic subacute sensory neuropathy seen with oat-cell carcinoma of the lung, and the sensory neuronopathy associated with Sjogren's syndrome.

•**Autonomic Neuronopathy:** This unusual group of neuropathies results from isolated involvement of post-ganglionic autonomic neurons and causes idiopathic orthostatic hypotension.

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Modality

Peripheral neuropathies can be sub-classified based on their involvement of motor, sensory or autonomic neurons.

Modality-Specific Neuropathies: The somatic motor, somatic sensory and autonomic neuronopathies described above are examples of modality-specific neuropathies. The pathologic lesion in this group of neuropathies is confined to the cell bodies.

Mixed-Modality Neuropathies: The majority of peripheral neuropathies is not modality-specific, and includes various combinations of motor, sensory and autonomic dysfunction. The reason for this finding is that most peripheral nerves include a mixture of motor, sensory and autonomic axons. Hence, axonal neuropathies typically present with mixed symptomatology. Likewise, since most axons are myelinated to a greater or lesser extent, demyelinating neuropathies also produce a mixture of motor, sensory and autonomic symptoms.

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The mnemonic ***DANG THERAPIST*** is helpful in recalling the more common causes of peripheral neuropathy:

Diabetes Mellitus
Alcohol
Nutritional (B_{12} deficiency)
Guillain-Barre Syndrome
Toxins (Pb, As, Zn, Hg)
Hematologic (cancers, etc.)
Endocrine (hypothyroid)
Rheumatologic (SLE, rheumatoid arthritis, vasculitis)
Amyloid
Porphyria
Infectious (syphilis, HIV)
Sarcoid
Tumor (paraneoplastic neuropathy)

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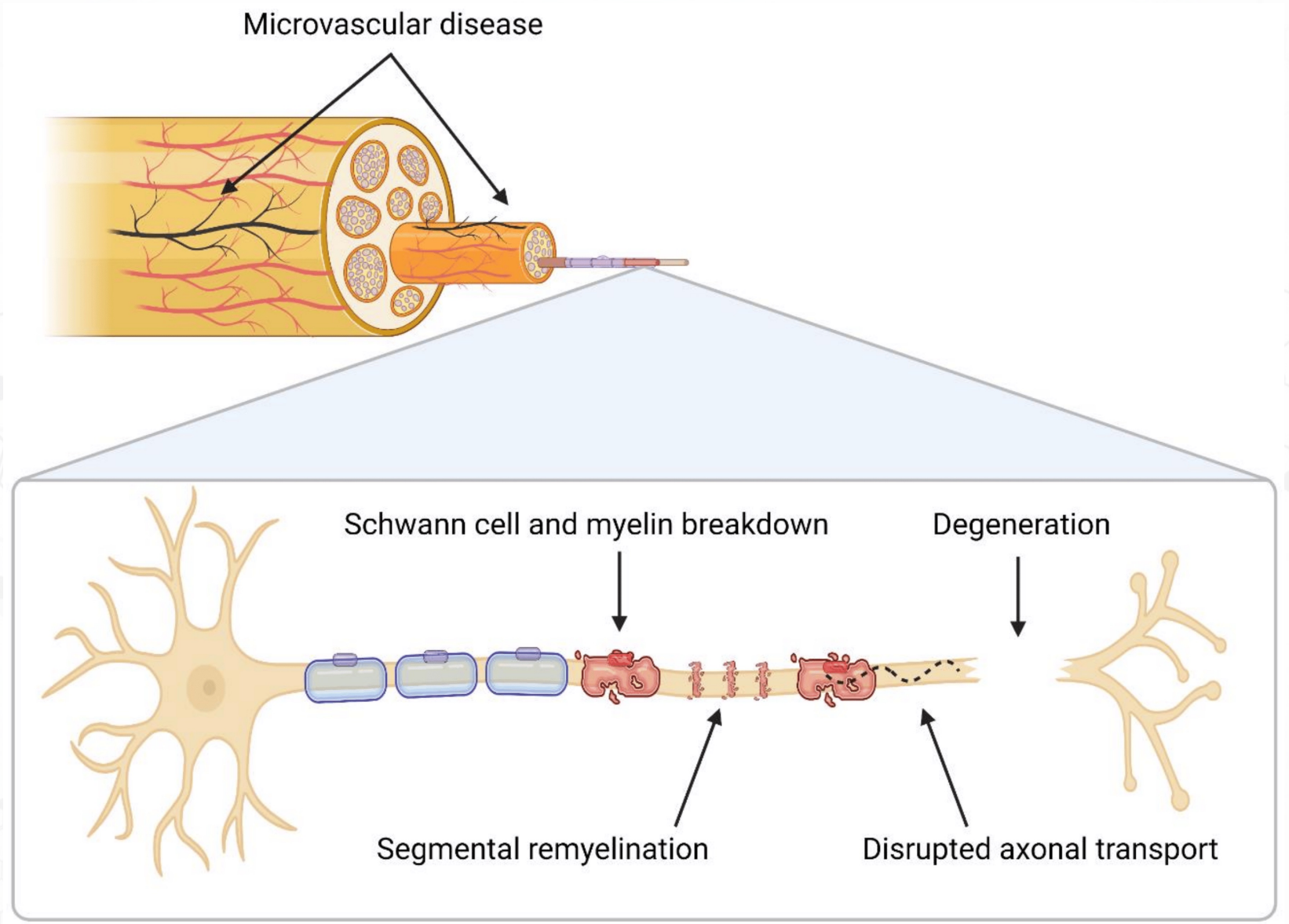

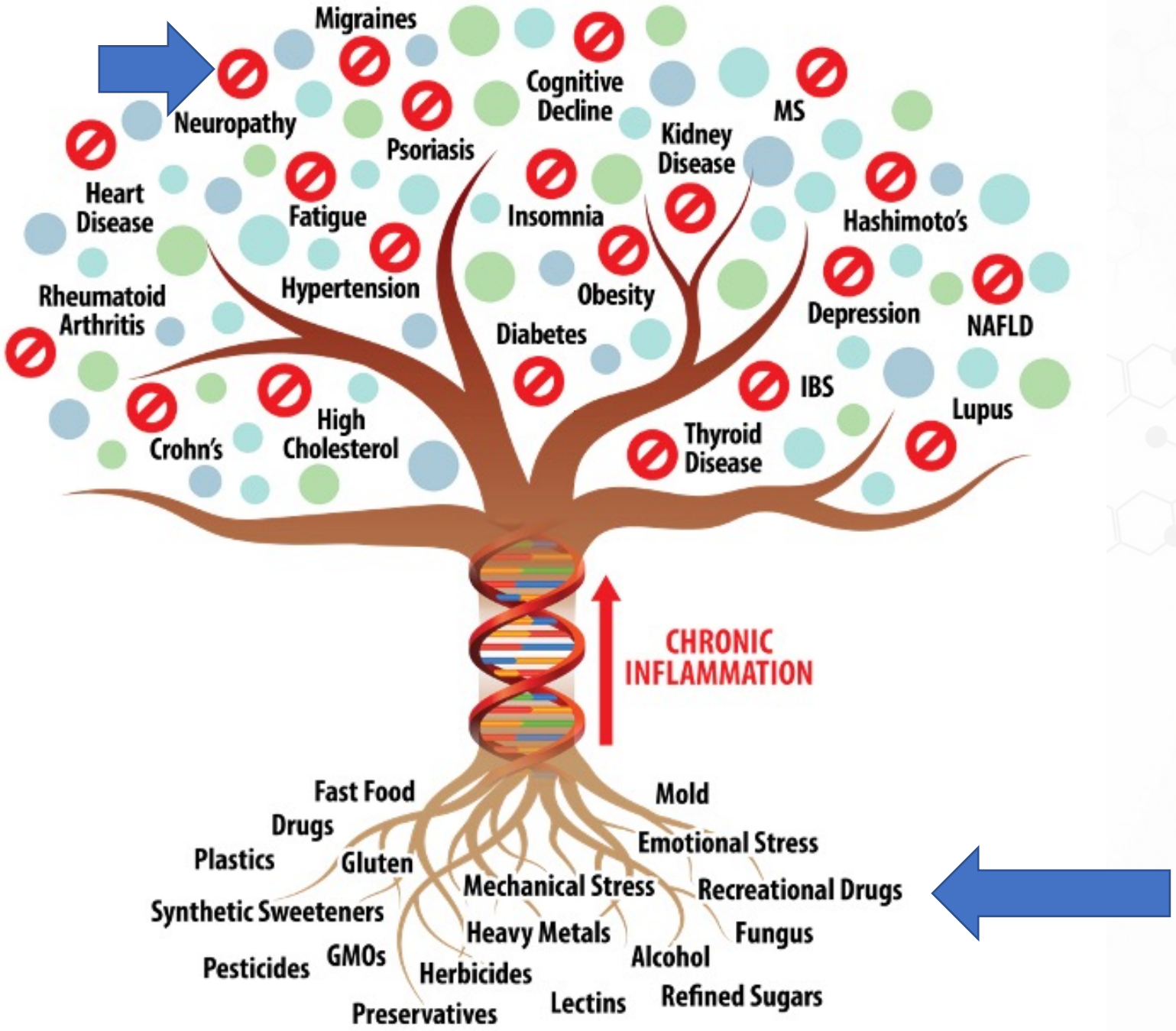
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