Post Industrial Neuropathy Pt II

A Biogenetix Clinical Presentation

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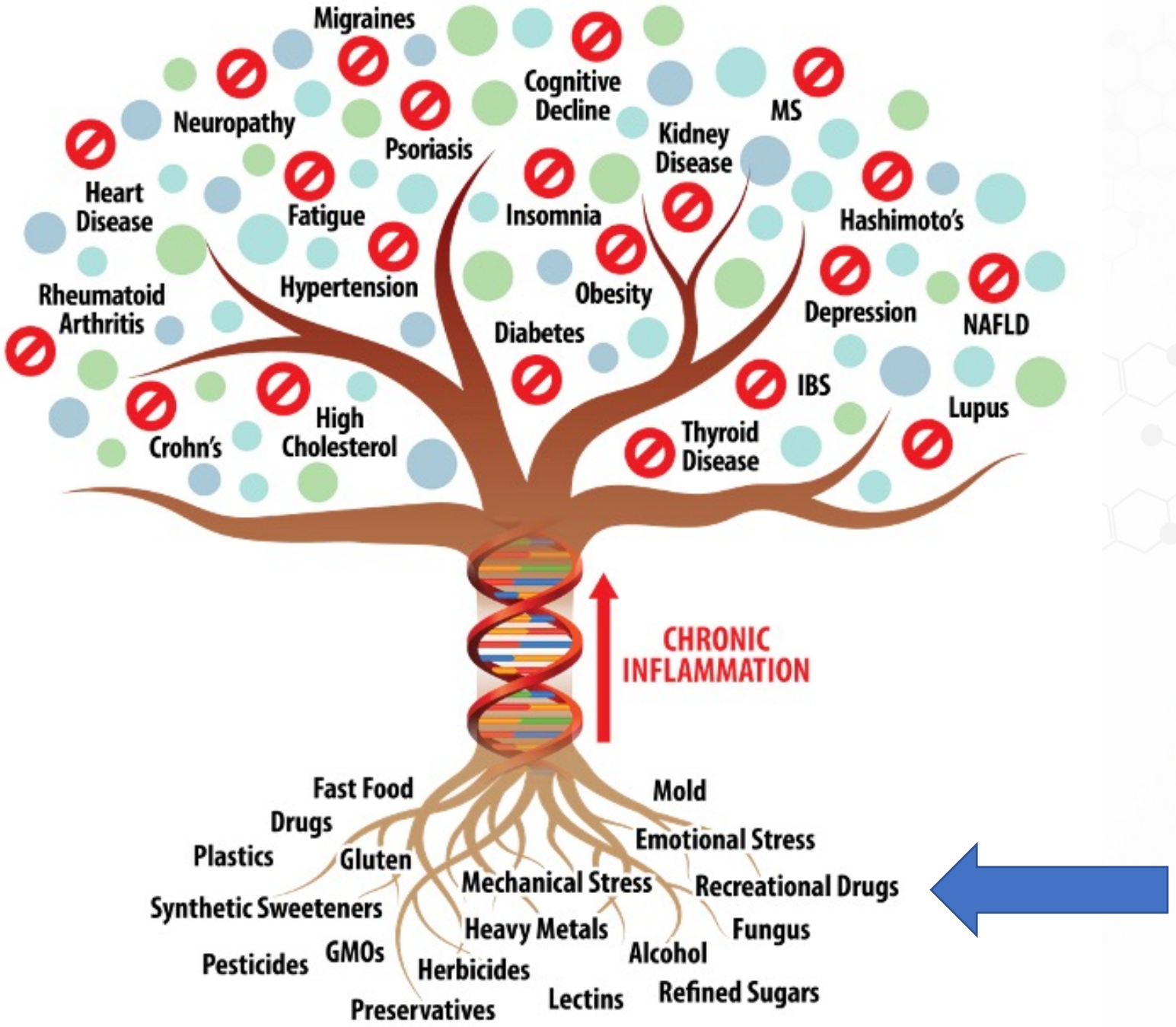
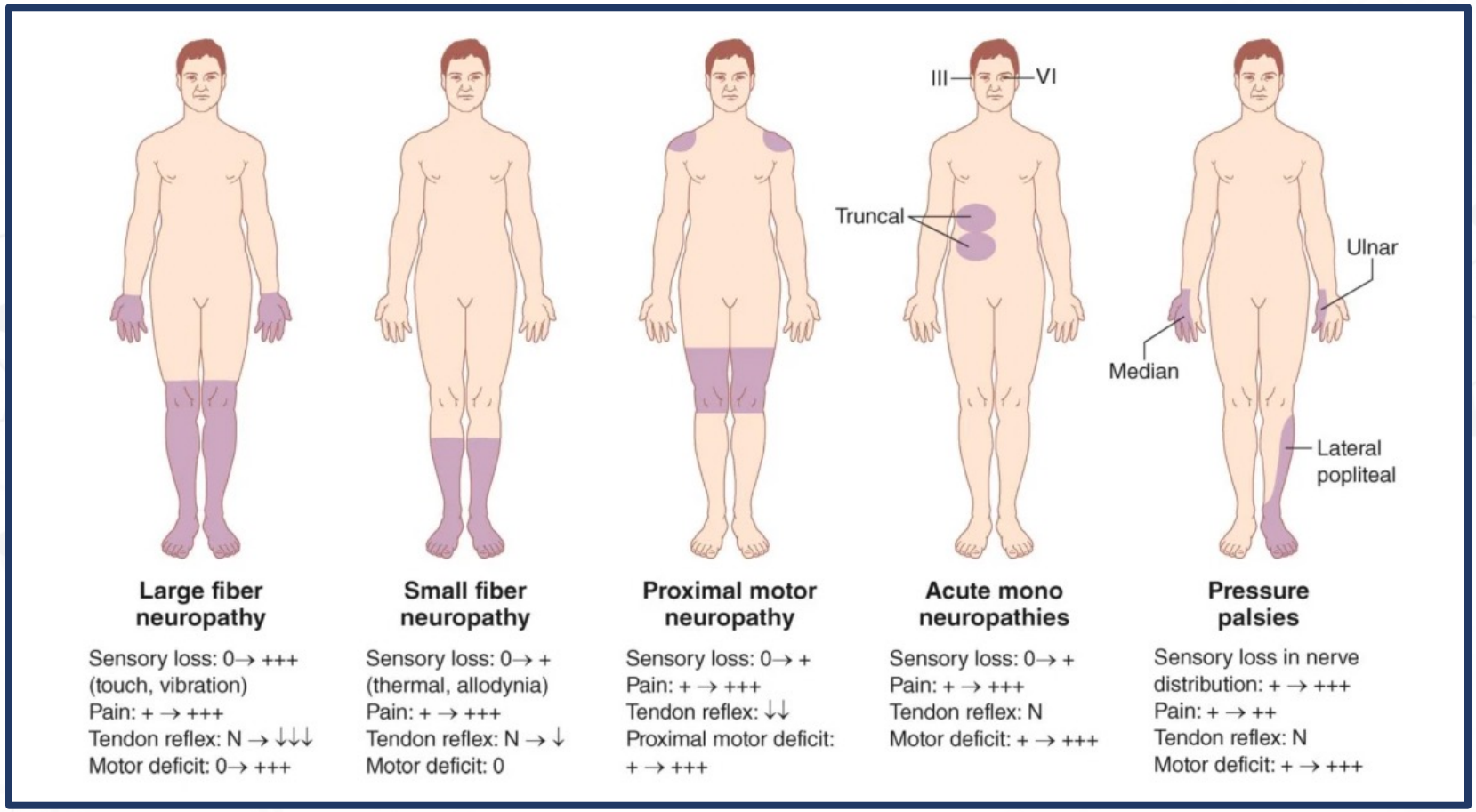

Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten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



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: + → +++

Review > Toxicol Pathol. 2020 Jan;48(1):152-173. doi: 10.1177/0192623319854326.
Epub 2019 Jun 10.

Toxic Peripheral Neuropathies: Agents and Mechanisms

William M Valentine [1]

Affiliations + expand

PMID: 31181992 PMCID: PMC6901819 DOI: 10.1177/0192623319854326

Toxic neuropathy mainly a peripheral neuropathy.

3 mechanisms:

- Covalent modifications (bonding).
- Oxidative stress.
- Disruption of ionic gradients across membranes.

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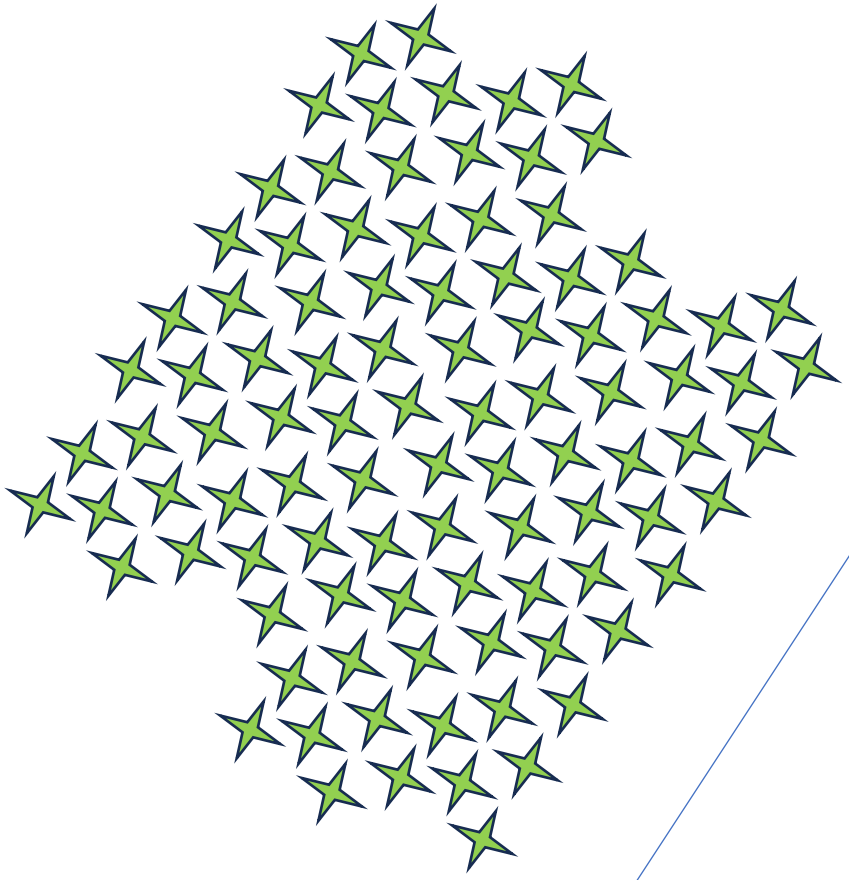
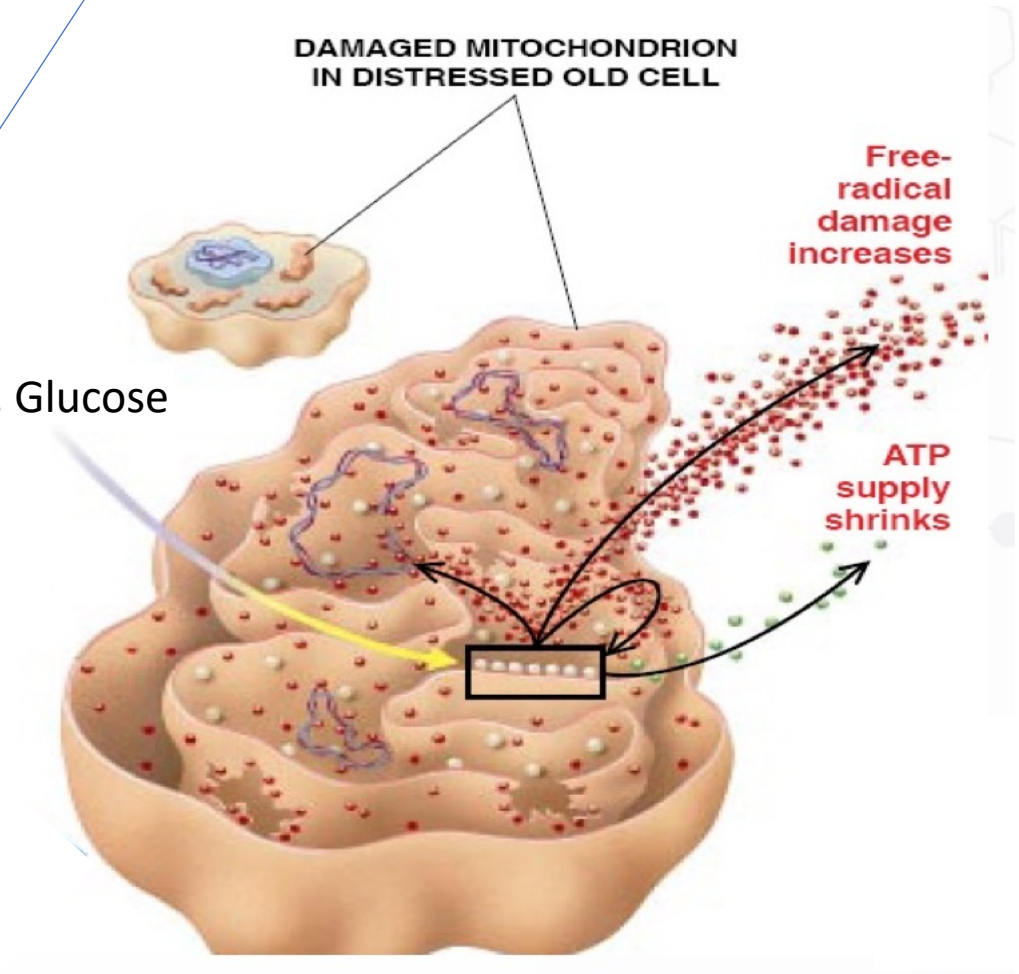
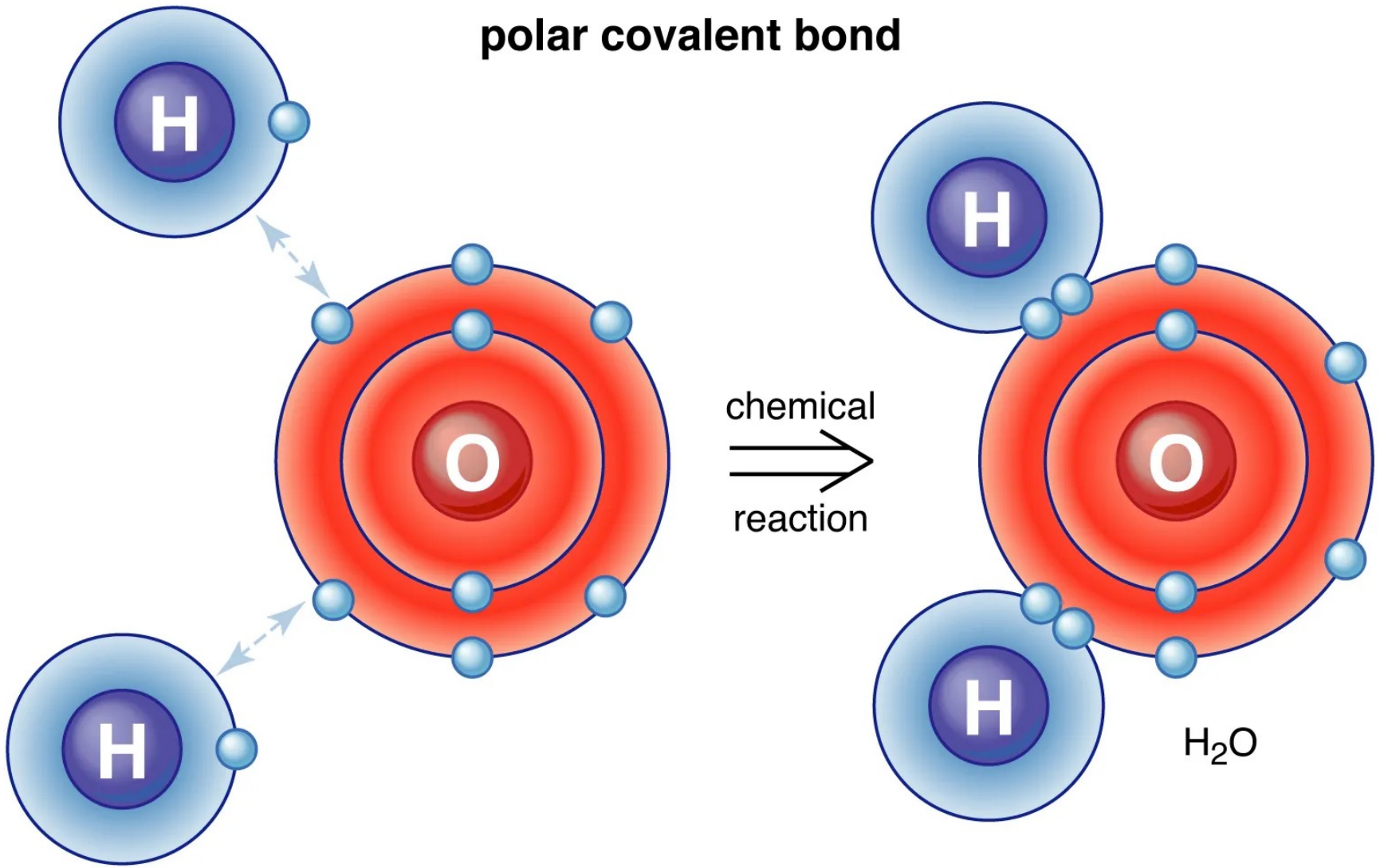
Oxidative Mechanism



O2, Glucose




polar covalent bond
H
O
H
chemical
reaction
H
O
H
H_2O
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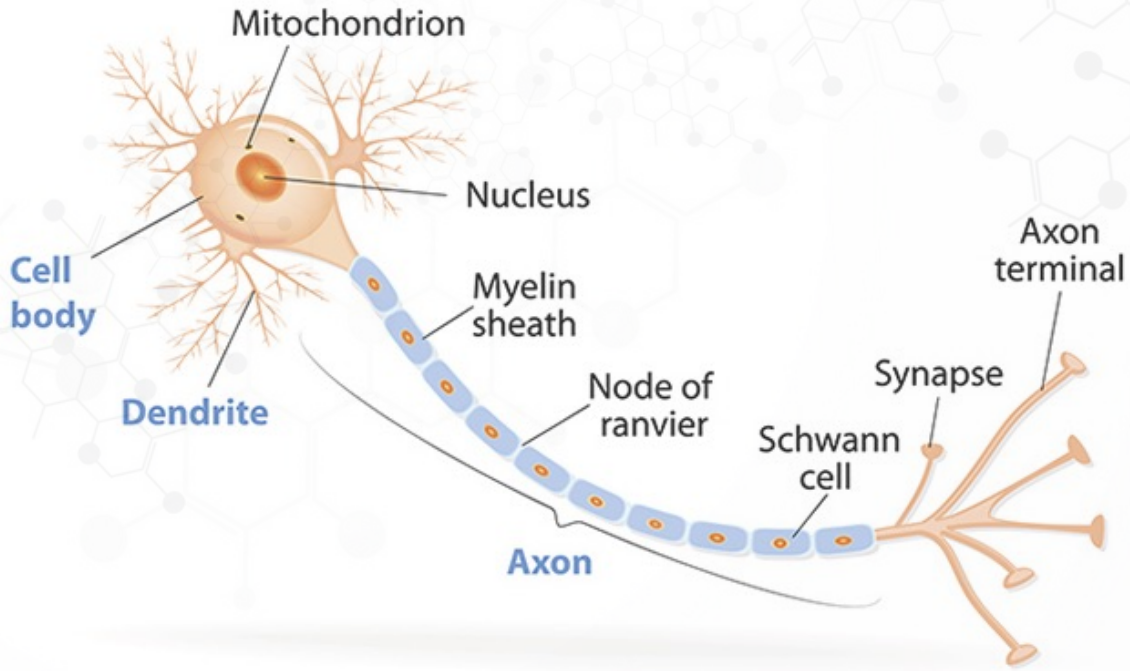
*A + B = C

3 types of pathology in neuropathy:

- Neuron cell body
- Axonopathy
- Myelopathy



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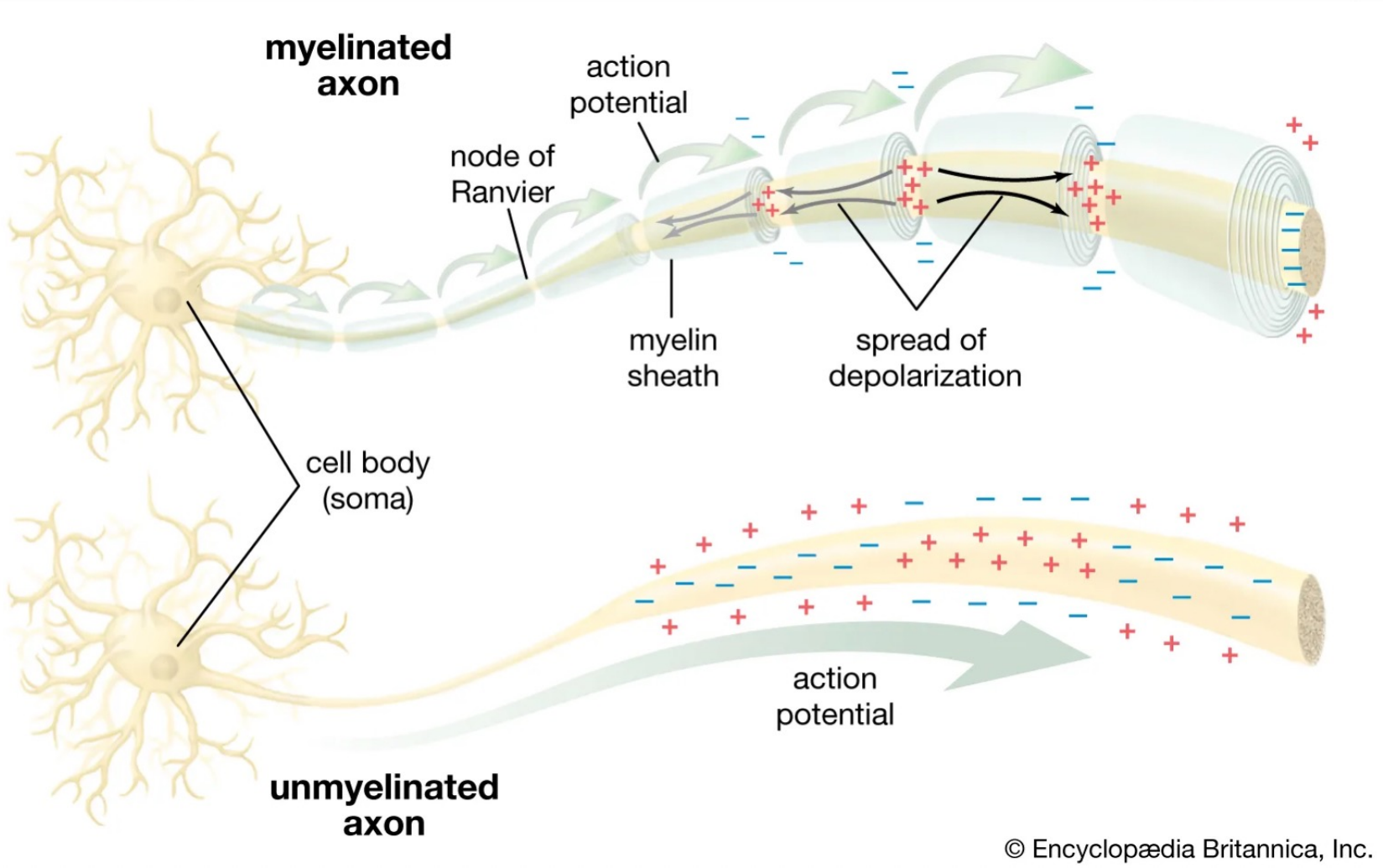

Saltatory conduction describes the way an electrical impulse skips from node to node down the full length of an axon, speeding the arrival of the impulse at the nerve terminal in comparison with the slower continuous progression of depolarization spreading down an unmyelinated axon.

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Toxic Peripheral Neuropathies: Agents and Mechanisms

William M Valentine [1]

Affiliations + expand

Schwann cells associated with larger-diameter axons produce myelin that increases conduction velocity and decreases energy requirements for membrane repolarization.[146] They form a lipid-rich wrapping of compact myelin that acts as insulation along axons. This insulation is interrupted at nodes of Ranvier where ion channels are expressed enabling localized depolarization and repolarization that is not perpetuated through the myelin but can depolarize adjacent nodes. The result is saltatory conduction having an increased speed and lower energy requirement than a continuous membrane depolarization along the length of the axon. To perform its insulating function peripheral nerve myelin is ~80% lipid as compared to most plasma membranes that are ~50% lipid.[147] The polyunsaturated fatty acids in the myelin plasma membrane are susceptible targets for lipid peroxidation resulting from agents producing free radicals directly or that increase oxidative stress through other mechanisms. The formation and maintenance of compact myelin is dependent upon a number of membrane-associated proteins and the metabolism of specific lipids present within the lipid bilayers (Fig. 8). MBP is a myelin protein thought to stabilize the closely opposed inner

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As described for axonopathies, myelinopathies can be classified as either primary or secondary. Once demyelination is initiated, the morphological changes including paranodal retraction, collapse of Schmidt-Lanterman incisures, lysosome induction and certain molecular changes are shared suggesting the existence of a common demyelinating phenotype.[73] For the case of secondary myelinopathies resulting from axonopathies, similar stages of response are expected for all of the Schwann cells along the entire length of the affected axon section. In contrast individual Schwann cells, typically those maintaining the longest internodes and thickest myelin sheaths of the largest axons, are affected initially in primary demyelination. This can result in segmental demyelination and is thought to result from the greater metabolic demands placed upon this population of Schwann cells (Figs. 9a,b). Significantly, the loss of a single internode can be sufficient to interrupt saltatory conduction.

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Hexachlorophene

The use of hexachlorophene in soaps and detergents as an antimicrobial has resulted in neurotoxicity in newborn humans and animals. This compound is hydrophobic, is absorbed through skin, and enters the nervous system where it accumulates in myelin. The greater susceptibility of newborns is thought to result from the incompletely developed blood-brain barrier during this period. A myelinopathy is produced in both the central and peripheral nervous systems that is characterized by splitting of myelin at the intraperiod lines.[151–154] The largest axons appear to be the most susceptible and the optic nerve is particularly vulnerable. Mechanistic studies have supported the ability of hexachlorophene to uncouple oxidative phosphorylation and inhibit carbonic anhydrase.[155–157] Both of these effects are thought to interfere with the ability of myelin to exclude water resulting in intramyelinic edema that separates the compact myelin at the intraperiod line.

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Triethyltin

Neurotoxicity of triethyltin has been recognized through contamination of medications and as an industrial pollutant. It is most recognized for its central nervous system effects although at high concentrations it also affects the peripheral nervous system.[158] Splitting at the intraperiod line with myelin swelling is the characteristic lesion.[159] Triethyltin can concentrate in myelin due to its hydrophobicity and the presence of high-affinity binding sites for this compound on myelin.[160] Investigations have identified several potential mechanisms to contribute to the myelin lesions. Inhibition of oxidative phosphorylation resulting from inhibition of Mg^{2+}-ATPase has been proposed as one mechanism.[161–163] Triethyltin appears to alter ion transport across membranes including the mitochondrial inner membrane anion channel and may directly allow Cl^- entry into the intraperiod line.[164,165] All of these mechanisms could disrupt the active processes required to exclude water or enhance osmotic pressure to draw an increased volume of water into the intraperiod line.

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Tellurium

Toxicity in humans is rare but tellurium provides an experimental model to study primary demyelination. When tellurium is administered to weanling rats, it produces segmental demyelination with the longest axons affected earliest leading to hind limb weakness.[166–169] Typically only peripheral nerve is affected and older animals are resistant. The myelin injury results from inhibition of squalene epoxidase, an enzyme involved in cholesterol synthesis.[170,171] The susceptible period coincides with a period of rapid myelination in the young animals and a correspondingly high requirement for cholesterol.[172] Inhibition of cholesterol synthesis in the rapidly growing peripheral nerve results in decreased expression of myelin-related genes including P_0 and MBP.[173] The down-regulation occurs in all Schwann cells and can lead to apoptotic cell death.[174] Because the exposure to tellurium is systemic, it is interesting that the effects are selective for peripheral nerve myelin. The liver is the major source of peripheral cholesterol and the activity of the hepatic rate-limiting enzyme for cholesterol synthesis, hydroxymethylglutaryl-CoA (HMGCoA) reductase, is upregulated in response to tellurium. As a result the circulating levels of cholesterol are maintained for most organs but access of the circulating cholesterol to the nervous system is prevented by the blood-nerve barrier.[175] Because Schwann cells do not upregulate HMGCoA reductase, there is a localized deficiency of cholesterol in the most rapidly developing regions of the nervous system.

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Chemotherapeutic Platinum Derivatives

Cisplatin, oxaliplatin and carboplatin are platinum based compounds used to treat lung, breast, ovarian and gastrointestinal cancers. In addition to other side effects these chemotherapeutics are associated with a high prevalence of peripheral neuropathy. Large-diameter sensory fibers appear to be the most sensitive resulting in symmetrical glove-stocking distribution of sensory loss including numbness and paresthesias. Neurotoxicity is related to cumulative dose, can persist for months to years and can even worsen for a period following cessation of treatment. In addition, oxaliplatin is recognized to produce an acute non-dose-dependent neuropathy very shortly after infusion exhibited by cold induced paresthesia and dysesthesia of distal extremities These agents target DRG through their ability to accumulate and interact with DNA in this location.[219–221] The high density of capillaries[27] that are relatively permeable[28,29] contribute to an incomplete blood-nerve barrier allowing platinum drugs preferential access to this region of the peripheral nervous system. Uptake by the sensory neurons may also be facilitated by two types of specific transporters, the copper transporter 1 (CTR1) and the organic cation transporter-2 (OCT2).[222–224]

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Methylmercury

Environmental mercury is an important pollutant that exists in both inorganic and organic forms, both of which can produce neurological and developmental effects in humans and wildlife. Methylmercury (organic form) has been responsible for a number of human poisonings and has been the focus of considerable investigation.[238] The clinical signs associated with methylmercury intoxication include sensory impairment of the extremities, cerebellar ataxia and visual field constriction.[239] In addition to neuron loss in the visual area of the calcarine cortex and granule cells of the cerebellum, methylmercury also produces degeneration of neurons in the DRG along with their associated axons while sparing the peripheral nerve motor axons.[239–243]

Methylmercury exerts its neurotoxic affects in DRG partly through the ability to accumulate there due to the high density of fenestrated capillaries.[26–29] Although the molecular targets and mechanisms of methylmercury are still being delineated, the experimental evidence supports contributions from several processes including disrupted calcium homeostasis, increased oxidative stress and altered glutamate homeostasis leading to excitotoxicity.[238,244] Methylmercury alters intracellular calcium levels through disrupting sequestration of intracellular calcium pools and through increasing permeability of the plasma membrane for calcium.[245] Elevated oxidative stress may be mediated through the ability of methylmercury to interact with sulfhydryl and selenocysteine functions of antioxidants and antioxidant proteins. Oxidative stress could also be elevated through the accumulation of methylmercury in mitochondria that decreases ATP production and depolarizes the mitochondrial membrane potential.[245] Consistent with the affects on

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63 yo male, DM2, bilateral neuropathy and PAD.

Moderate (75th-95th percentile)

Mycotoxins Heavy Metals

TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT / PREVIOUS RESULT	REFERENCE
Aflatoxin B1 (AFB1)	5.93		0 – 3.9 – 6.93	≤6.93 ng/g
Aflatoxin M1	6.04		0 – 3.6 – 6.4	≤6.4 ng/g
Citrinin (CTN)	11.55		0 – 7.05 – 12.5	≤12.53 ng/g
Patulin	8.54		0 – 6.53 – 11.6	≤11.6 ng/g
Arsenic*	17.45		0 – 11.9 – 52	≤52 ug/g
Cadmium*	0.47		0 – 0.29 – 0.8	≤0.8 ug/g
Cesium*	6.42		0 – 6.37 – 10.3	≤10.3 ug/g

* Indicates NHANES population data reference ranges.

63 yo male, DM2, bilateral neuropathy and PAD.

Moderate (75th-95th percentile) — Heavy Metals — Environmental Toxins

TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT / PREVIOUS RESULT	REFERENCE
Tellurium	0.74		0 — 0.42 — 0.89	≤0.89 ug/g
Tin*	2.89		0 — 1 — 3.72	≤3.72 ug/g
Tungsten*	0.17		0 — 0.12 — 0.33	≤0.33 ug/g
Butylparaben*	3.59		0 — 0.25 — 4.39	≤4.39 ug/g
Dimethyldithiophosphate (DMDTP)*	2.08		0 — 0.67 — 6.12	≤6.12 ug/g
Dimethylthiophosphate (DMTP)*	11.13		0 — 5.91 — 33.7	≤33.7 ug/g
Propylparaben*	63.33		0 — 36.7 — 222	≤222 ug/g
Tiglylglycine (TG)	0.14		0 — 0.09 — 3.24	≤3.24 ug/g
Triclosan (TCS)*	38.41		0 — 29.9 — 358	≤358 ug/g

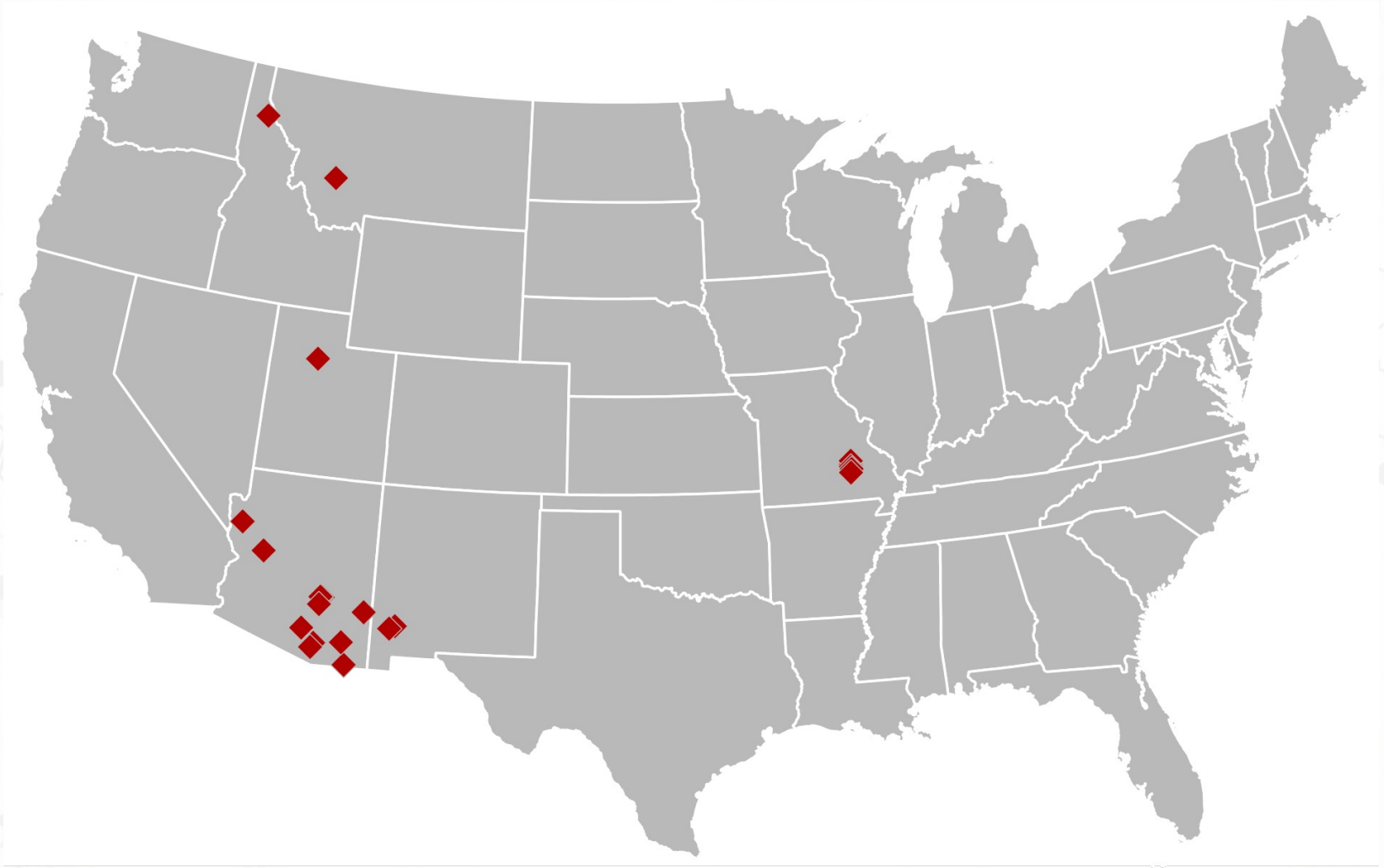
* Indicates NHANES population data reference ranges.

51 yo male, DM2, bilateral neuropathy.

Moderate (75th-95th percentile) — Mycotoxins — Heavy Metals

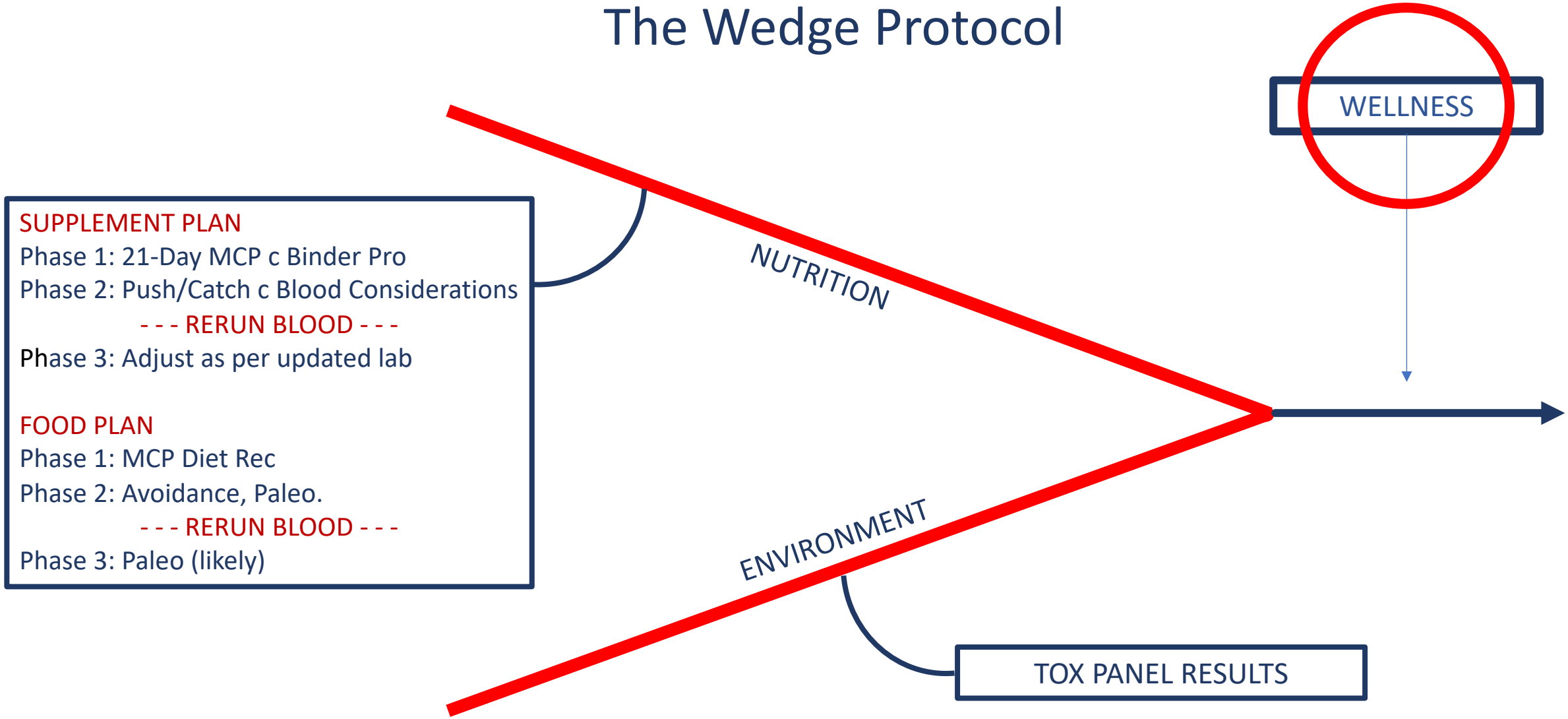
TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT / PREVIOUS RESULT	REFERENCE
Aflatoxin G2	10.35		0 — 6.08 — 10.8	≤10.8 ng/g
Aflatoxin M1	3.67		0 — 3.6 — 6.4	≤6.4 ng/g
Dihydrocitrinone	12.96		0 — 9.3 — 16.5	≤16.53 ng/g
Fumonisins B1	6.02		0 — 3.45 — 6.13	≤6.13 ng/g
Fumonisins B2	5.11		0 — 4.05 — 7.2	≤7.2 ng/g
Patulin	9.33		0 — 6.53 — 11.6	≤11.6 ng/g
Bismuth	1.35		0 — 0.58 — 2.53	≤2.53 ug/g
Mercury*	0.58		0 — 0.57 — 1.61	≤1.61 ug/g
Tellurium	0.43		0 — 0.42 — 0.89	≤0.89 ug/g

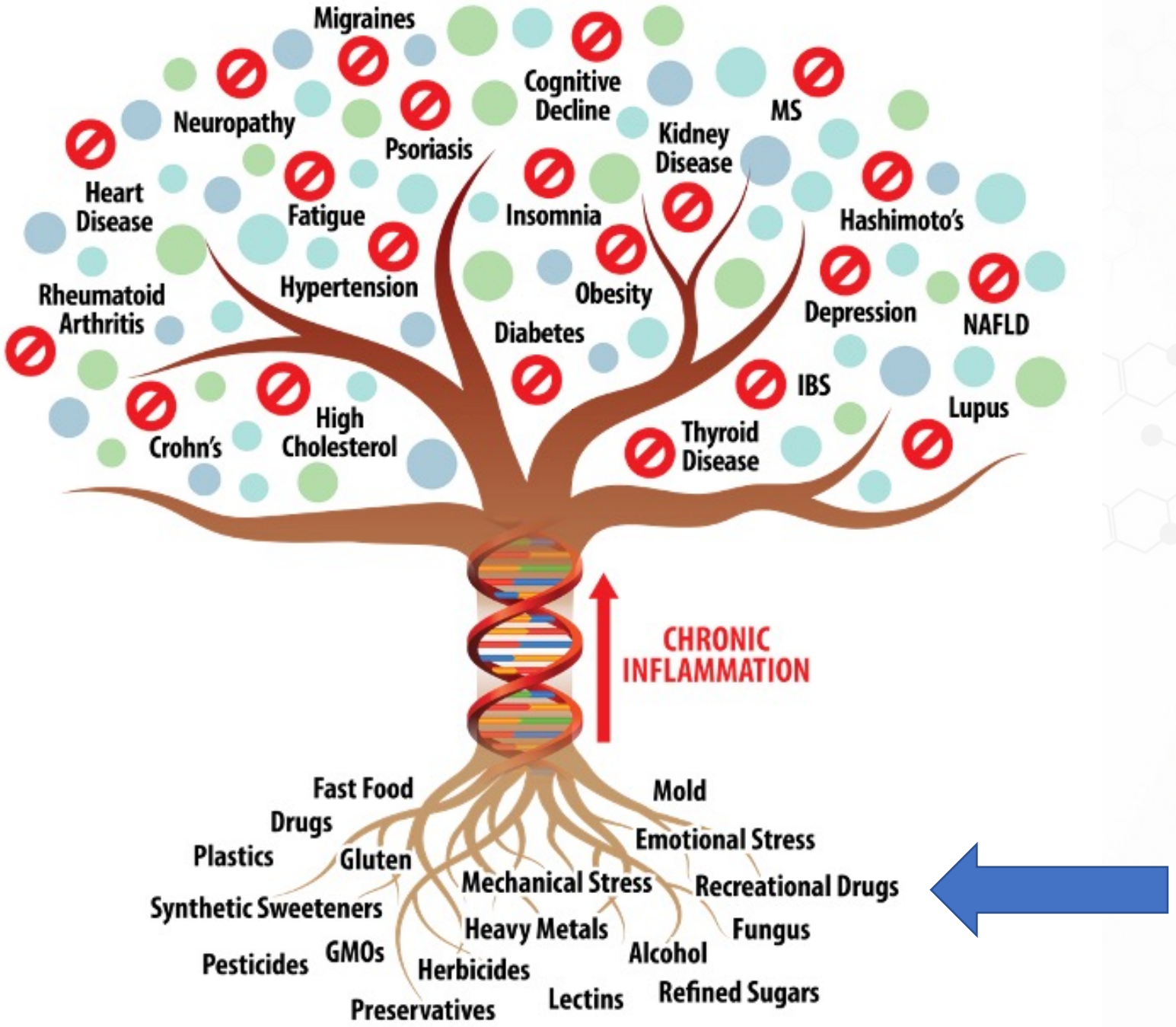
* Indicates NHANES population data reference ranges.



Tellurium exposure also occurs during electrolytic copper refining where tellurium is formed in the anode slime.

The Wedge Protocol

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