

Non-Diabetes Peripheral Neuropathy

Peripheral Neuropathy

- Perplexing to the pedorthist (...and to the physician...and to the patient)
- Occurs as a component of many common and rare diseases
- Heterogenous in etiology
- Diverse in pathology
- Varied in severity
- More common than you think

Diabetes

- Diabetic peripheral neuropathy is the most common form of neuropathy worldwide.
- Diabetes is far and away the leading cause of nontraumatic polyneuropathy in the US (>50% of cases).
 - CDC says approximately 50% of people with diabetes will develop peripheral neuropathy in their lifetime. (WebMD claims 60%-70%)
- However, there are over 100 other documented causes. This is important for two reasons:
 1. You are not *only* seeing patients with diabetes.
 2. What if your patient has diabetes *and* one or more of these other conditions?

Let's explore:

- How peripheral neuropathy works
- What are the complications of peripheral neuropathy
- How peripheral neuropathy is diagnosed
- With what diseases/conditions is peripheral neuropathy associated
- How peripheral neuropathy is treated
- How this all relates to the certified pedorthist

Incidence

- Worldwide prevalence and incidence unknown
- Hicks CW, Wang D, Windham BG, Matsushita K, Selvin E. Prevalence of peripheral neuropathy defined by monofilament insensitivity in middle-aged and older adults in two US cohorts. Sci Rep. 2021 Sep 27;11(1):19159. doi: 10.1038/s41598-021-98565-w. PMID: 34580377; PMCID: PMC8476511.
 - Prevalence in middle-aged US adults is 10.4%
 - Prevalence in older US adults is 26.8%-39.2%



What Is Peripheral Neuropathy Exactly?

- Neuro-: From the Greek word “neuron,” meaning “nerve.”
- -pathy: From the Greek word “pathos,” meaning “affliction” or “condition.”
- Peripheral nerves send many types of sensory information to the central nervous system. They also carry signals from the CNS to the rest of the body. Best known are the signals to the muscles that tell them to contract so we can move. There are different types of signals that help control everything from our heart and blood vessels, digestion, urination and sexual function to our bones and immune system.

What Is Peripheral Neuropathy Exactly?

- The nerve signals can be affected in a number of ways:
 - Weakening of signals being sent
 - Loss of signals normally sent
 - Disruption of signals being sent
 - Errors that distort the messages being sent
 - Inappropriate signaling when there shouldn't be any
- Some forms of neuropathy involve damage to only one nerve (mononeuropathy). Neuropathy affecting two or more nerves in different areas is called multiple mononeuropathy or mononeuropathy multiplex. More often, many or most of the nerves are affected (polyneuropathy).
- About 75% of polyneuropathies are “length-dependent,” meaning the farthest nerve endings in the feet are where the symptoms develop first or are worse.

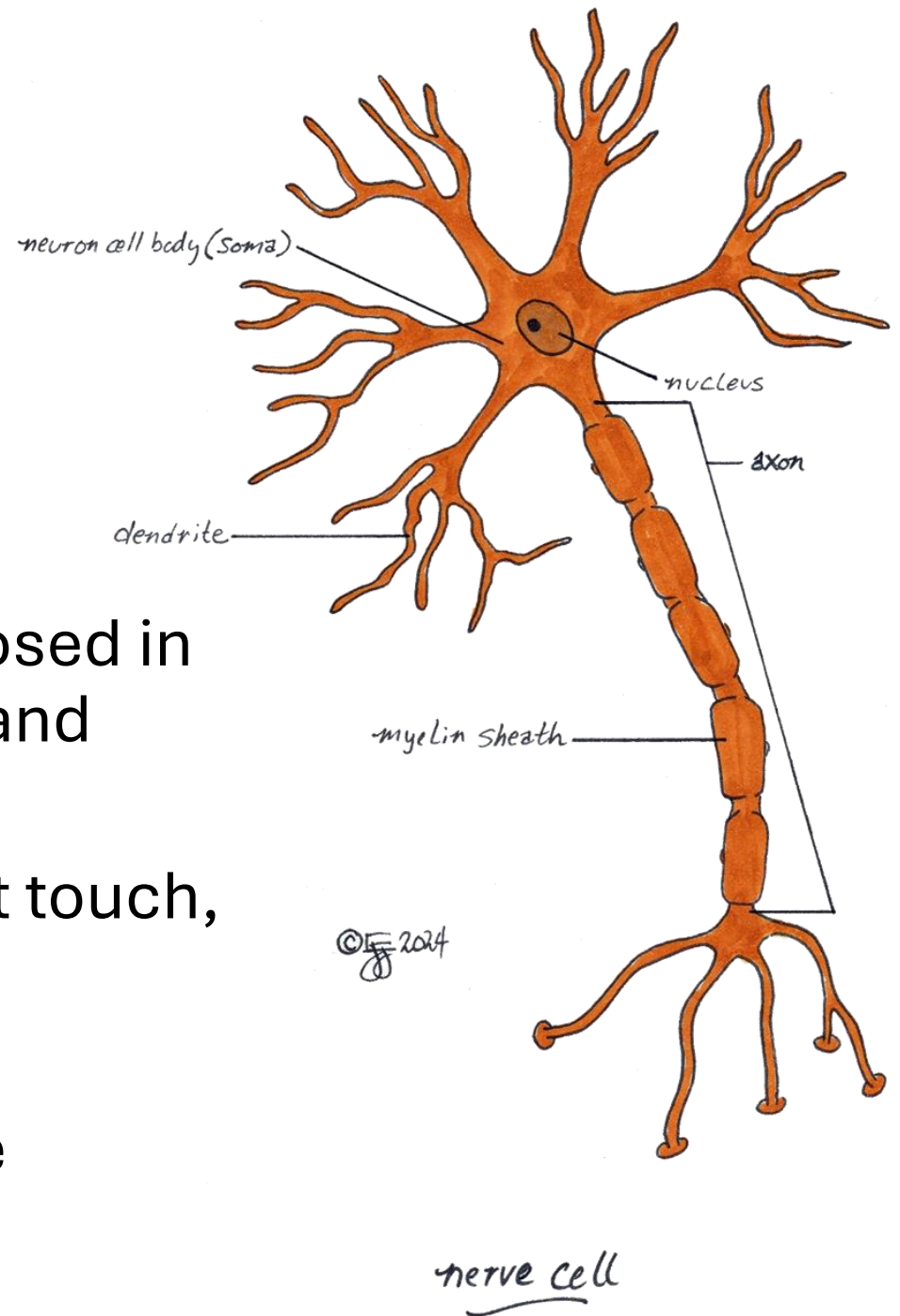
Symptoms of Peripheral Neuropathy

- Symptoms of peripheral neuropathy might include:
 - Gradual onset of numbness, prickling, or tingling in the feet or hands; may spread upward into the legs and arms.
 - Sharp, jabbing, throbbing or burning pain.
 - Extreme sensitivity to touch.
 - Pain during activities that shouldn't cause pain, such as non-weightbearing pain in your feet.
 - Lack of dexterity and coordination; stumbling or falling.
 - Muscle weakness.
 - The feeling as if one is wearing gloves or socks when they are not.
 - Inability to move if motor nerves are affected.

How Does Neuropathy Work?

Anatomy

- Neuron
 - Axon
 - Myelin
- Large sensory and motor axons enclosed in myelin register vibration, light touch and proprioception
- Small myelinated axons register light touch, pain and temperature
- Small unmyelinated axons are also responsible for pain and temperature



Components of Peripheral Neuropathy

- 1) Sensory neuropathy
 - 2) Motor neuropathy
 - 3) Autonomic neuropathy
- Most common presentation is distal symmetric sensorimotor dysfunction.
 - Also categorized as *focal*, *multifocal* or *generalized*.

Autonomic Neuropathy

- Autonomic nerves control things you either can't control (digesting food), or don't necessarily have to consciously control (blinking, breathing, swallowing).
- Autonomic nerve damage affects the axons in small-fiber neuropathies.
- Common symptoms include:
 - Excess sweating
 - Heat intolerance
 - Inability to regulate body temperature
 - Inability to expand and contract the small blood vessels that regulate blood pressure
 - Gastrointestinal symptoms
 - Problems eating or swallowing if the nerves that control the esophagus are affected (rare)
 - Lack of awareness of hypoglycemia
 - Autonomic nervous system also regulates blood pressure, vascular tone and heart rate.

Motor Neuropathy

- Motor nerves innervate our muscles and allow us to move.
- Motor nerve damage is most commonly associated with muscle weakness.
- Other symptoms include:
 - Painful cramps
 - Fasciculations (uncontrolled muscle twitching visible under the skin)
 - Muscle atrophy
 - Lack of muscle control
 - Lack of dexterity
 - Loss of reflex
 - Paralysis

Sensory Neuropathy

- Abnormal sensation
 - Glove and stocking distribution – Begins in the feet and hands.
 - Paresthesia – “Extra” feelings; buzzing, tingling, itching, etc.
 - Dysesthesia – Nerve pain; shooting, stabbing, burning, electric shock, cramping, pins and needles, etc.
 - Hypesthesia – Decreased sensation
 - Anesthesia – Loss of sensation
 - Allodynia – Painful response to a non-painful stimulus
- Damage to large sensory fibers harms the ability to feel vibrations and touch, especially in the hands and feet. This may also contribute to the loss of reflexes (as can motor nerve damage). Loss of proprioception often makes people unable to coordinate complex movements like walking, fastening buttons, or maintaining their balance when their eyes are shut.
- Small-fiber polyneuropathy can interfere with the ability to feel pain or changes in temperature. It is often difficult for medical caregivers to control, which can seriously affect the patient’s emotional well-being and overall quality of life.
- Neuropathic pain is frequently worse at night, disrupting sleep. It can be caused by pain receptors firing spontaneously without any known trigger, or by difficulties with signal processing in the spinal cord that may cause severe pain (allodynia) from a light touch that is normally painless. For example, one might experience pain from the touch of the bedsheets, even when draped lightly over the body.

Proprioception

- Sensory Neuropathy Negatively Affects Proprioception
 - The unconscious perception of movement and spatial orientation arising from stimuli within the body itself - an awareness of movement derived from muscular, tendinous and articular sources.
 - From the latin *proprius*, meaning “one’s own”.
 - We have six extroceptive senses - sight, smell, taste, hearing, touch & equilibrioception (balance); as well as introspective senses - by which we sense the pain and/or movement of internal organs.
 - Proprioception is a third, *distinct* sensory modality.



Pathophysiology

- Axonal loss
 - Degeneration and eventual death of nerve fiber
 - Disruption of axons results in degeneration of axon and myelin sheath distal to injury site.
 - In toxic/metabolic cases, the most distal portion of axons degenerate w/ concomitant breakdown of myelin sheath (“dying-back”).
 - The longer a neuron is, the worse the effect. Hence axonal degeneration conditions tend to involve the legs and feet, which are farthest from the spinal cord and rely on connections using longer axons.
 - Axonal degeneration is the most common pattern seen with peripheral neuropathy.
- Demyelination
 - This happens when the myelin coating on the axon deteriorates or can’t form correctly. That affects the way signals travel through the neuron.
 - Loss of myelin = slowing of conduction
 - If and when axon is spared, recovery can be rapid and complete
- Radiculopathy
 - Neuropathy that affects nerve roots

Diagnosing Neuropathy

Diagnosing Neuropathy

A study of 3563 patients with type II diabetes showed that 62.4% of patients with neuropathy were not diagnosed as such by their treating physicians. This includes 39% who could not feel the 5.07 monofilament.

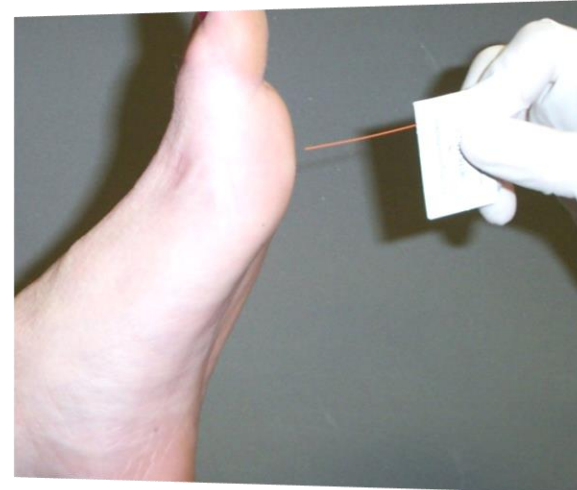
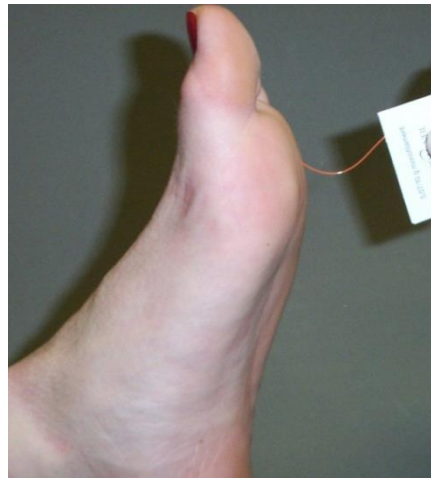
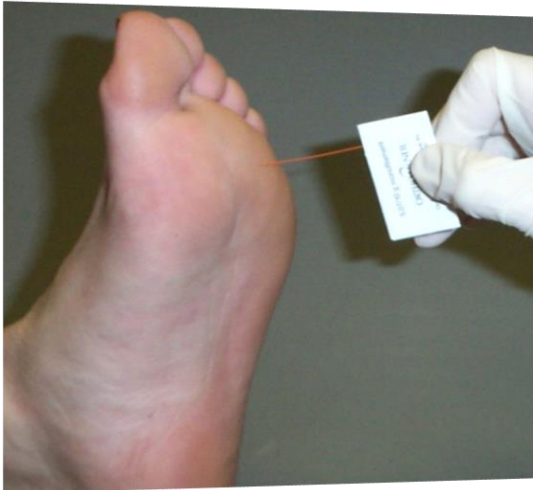
(W. Herman, L. Kennedy - 2003)

Diagnosing Neuropathy

- Diagnosing neuropathy is complicated and expensive
- History and physical exam
- Complete family history
- EMG
- Nerve conduction study
- Nerve biopsy
- Blood test to screen for conditions associated with neuropathy

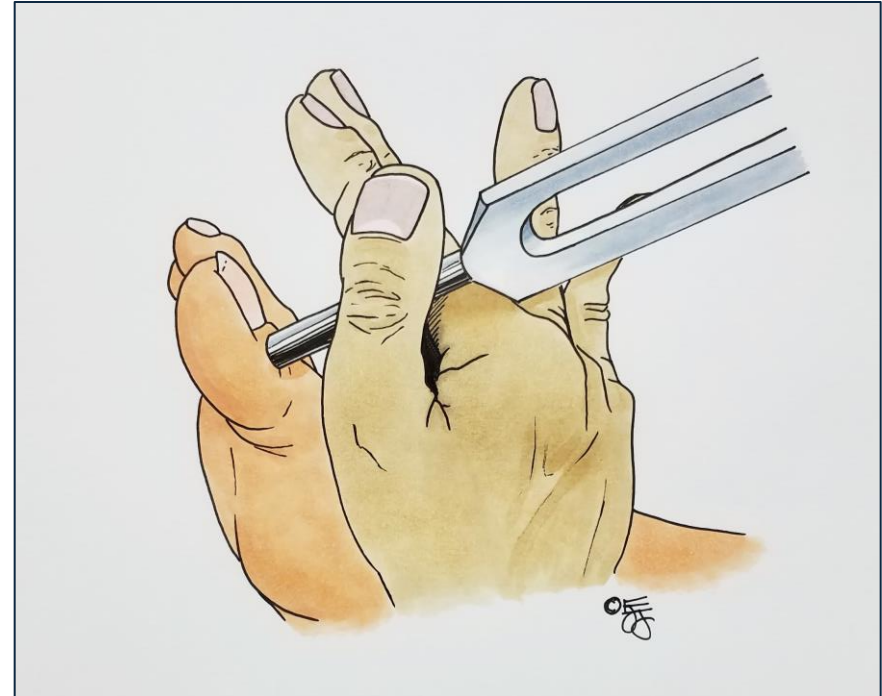
5.07/10g Semmes-Weinstein Monofilament

- The general consensus regarding the definition of *loss of protective sensation* involves inability to sense the 5.07/10 g Semmes Weinstein monofilament. The gauge of this monofilament is 5.07, a number derived from the logarithm of the applied force in milligrams. The buckling force for the 5.07 monofilament is 10 grams, which is also the force felt by the patient when the monofilament bends.
- Have patient close eyes
- Place filament perpendicular to skin
- With a smooth motion and a three-step sequence:
 1. Place on site
 2. Apply pressure to bend filament
 3. Release pressure and remove from skin



128 Hz Tuning Fork

- Using the 128-Hz tuning fork, gripping by the stem (not the prongs), strike the fixed weights against a firm surface and test at the dorsum of the great toe proximal to the nail bed.
- Presence or absence of patient's ability to sense vibration should be noted.



Electrodiagnostic Testing

- Two components
 - Nerve Conduction Study (NCS)
 - Motor study
 - Sensory study
 - Electromyography (EMG)



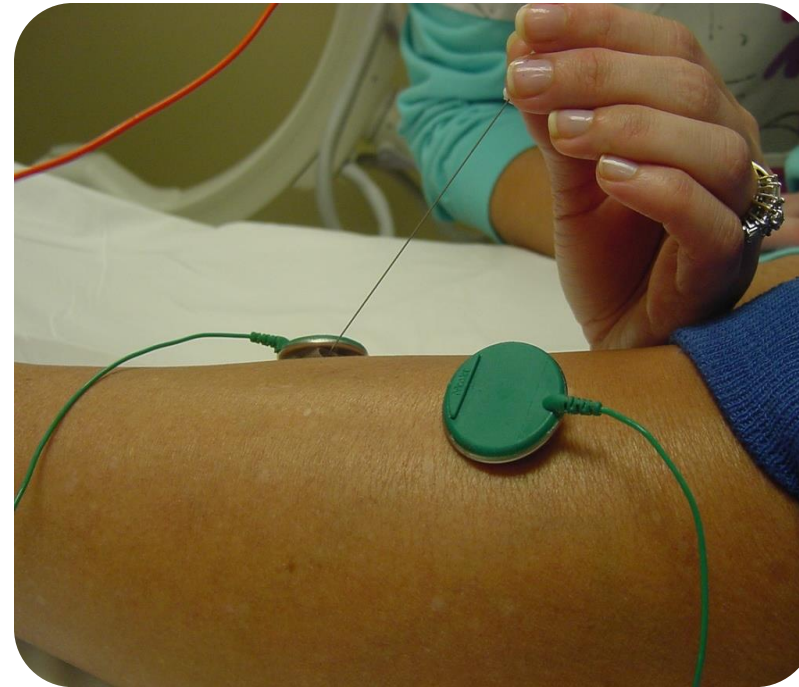
Electrodiagnostic Testing

- Nerve Conduction Study
 - Electrical stimulator
 - Placed over nerve
 - Recording electrode
 - Over muscle – motor
 - Over nerve – sensory
 - Reference electrode
 - Ground electrode



Electromyography

- Needle inserted into skeletal muscle to record electric potentials
- No electrical stimulus given
- Normal muscle at rest is electrically silent
- Muscles examined in selective fashion to look for a pattern of distribution



Making a Diagnosis

- Must correlate with history and exam
- Analyze overall pattern
 - Diffuse vs. localized findings
 - Number of limbs involved
 - Number of nerves involved
 - Proximal vs. distal findings
 - Motor vs. sensory findings

Laboratory Testing

- Sedimentation rate – general marker of inflammation
- Complete blood cell count (CBC)- anemia, infection
- Metabolic panels – electrolytes, kidney function, liver enzymes, glucose
- Thyroid stimulating hormone (TSH)
- RPR, VDRL – syphilis
- B-12 level

MRI

- Good for imaging soft tissues (disc, tendon, ligament)
- Images brain, spinal cord and spinal nerves well
- Abnormal musculature
- Minimal information on peripheral nerves



Epidemiology of Neuropathy

Epidemiology of Neuropathy

- Over 100 different documented causes of neuropathy
- Causes include:
 - Metabolic and endocrine disorders
 - Infections and immune disorders
 - Inherited genetic disorders
 - Exposure to toxins
 - Kidney disorders
 - Hormonal imbalances
 - Vitamin deficiencies
 - Vascular damage and blood diseases
 - Connective tissue disorders
 - Cancer and benign tumors



Key: A=axonal, D=demyelinating, M=mixed

Metabolic neuropathy

- Diabetes (M)
 - Leading cause of neuropathy in US
 - Diabetes affects nerves in *two* ways:
 - Blood glucose of level of 140 mm/dL is toxic to nerves; hyperglycemia alters metabolism of nerves, causing generalized, distal neuropathy
 - Inflammation of small blood vessels impairs blood flow to nerves, causing a focal neuropathy or multifocal neuropathy.
 - Both mechanisms are active to some degree in most cases of DPN
 - Can also cause diabetic amyotrophy (lumbosacral plexopathy)
 - 2.5 x more likely to have DPN 7 years after diagnosis. (Cheng YJ, et al, 2006)
 - Prevalence rises from 7.5% at diagnosis to 50% after 25 years. (Pirat J, 1977)
 - 27% of direct medical costs of DM may be attributed to DPN: \$13.7 billion (Gordois A, et al, 2003)
 - Improved glycemic control can prevent or delay progression of diabetic neuropathy (DCCT 1993)
- “Borderline” Diabetes
 - Up to 56% of patients diagnosed with idiopathic sensory neuropathy have impaired glucose tolerance (Sumner, et al, 2003)

Metabolic neuropathy

- Amyloidosis (A)
 - Amyloid is a starchlike protein-carbohydrate complex, deposited abnormally in tissue and organs in amyloidosis
- Uremia (from kidney failure) (M)
 - Results in axonal degeneration with secondary segmental demyelination
- Hypothyroidism (A)
 - Reductions in large myelinated fibers and Renaut bodies, as well as axonal degeneration
- Celiac disease (gluten allergy) (A)
 - Peripheral neuropathy is one of the most frequently reported neurologic manifestations associated with celiac disease

Inflammatory, Infectious and Immune Disorders

- Leprosy (A)
 - Leading cause of neuropathy worldwide
- Diphtheria (D)
- Chagas disease (A)
 - Most common infectious disease in Central & South America
- Lyme disease (A)
 - Adams, Blasko & DiDomenico described an unusual case of bilaterally symmetrical neuropathic osteoarthropathy in the midfoot (Foot and Ankle International, Feb 2003)
- Herpes varicella-zoster (shingles) and other members of herpes family (D)
- HIV/AIDS (M)
 - 1/3 of people w/ HIV will develop symptoms of peripheral neuropathy (Society for Neuroscience, 2007)
- West Nile Virus (D)
- Rheumatoid arthritis (A)
 - 3.39% prevalence of foot ulcerations (Firth, et al, 2008)
- Guillain-Barre syndrome (D)
 - body's immune system mistakenly attacks the nerves in the body
- Chronic Inflammatory Demyelinating Polyradiculoneuropathy (D)
- Lewis Sumner syndrome (Multifocal Motor Neuropathy and Multifocal Demyelinating Sensorimotor Neuropathy) (D)
- Hepatitis C (A)
- Crohn's (A)
- Sjögren Syndrome(A)
 - 15% prevalence of PN
- Sarcoid neuropathy (M)
- Syphilis (A)

Genetic Disorders

- Charcot-Marie-Tooth disease (Type I – D, Type II – A)
 - Also called Hereditary Sensory Motor Neuropathy (HMSN)
 - Leading genetic cause of neuropathy in US – 125,000 (Society for Neuroscience, 2007)
- Familial amyloid polyneuropathy (M)
- Friedreich's ataxia (A)
- Metachromatic leukodystrophy (D)
- Refsum disease (D)
 - Also called HMSN-IV

Exposure to Toxins

- Alcoholism (A)
 - 2nd leading cause of PN in US
- Metals / Chemicals (A)
 - Gold, Lead, Mercury, Nickel, Cadmium, Chromium, Arsenic, Thallium, Styrene, PCBs, Carbon Disulfide
- Solvents (A)
- Agrichemicals, including organophosphate pesticides (A)
- Glues, thinners, acetone, toluene, etc. (A)
- Tetanus (A)

Drug-Induced Neuropathies

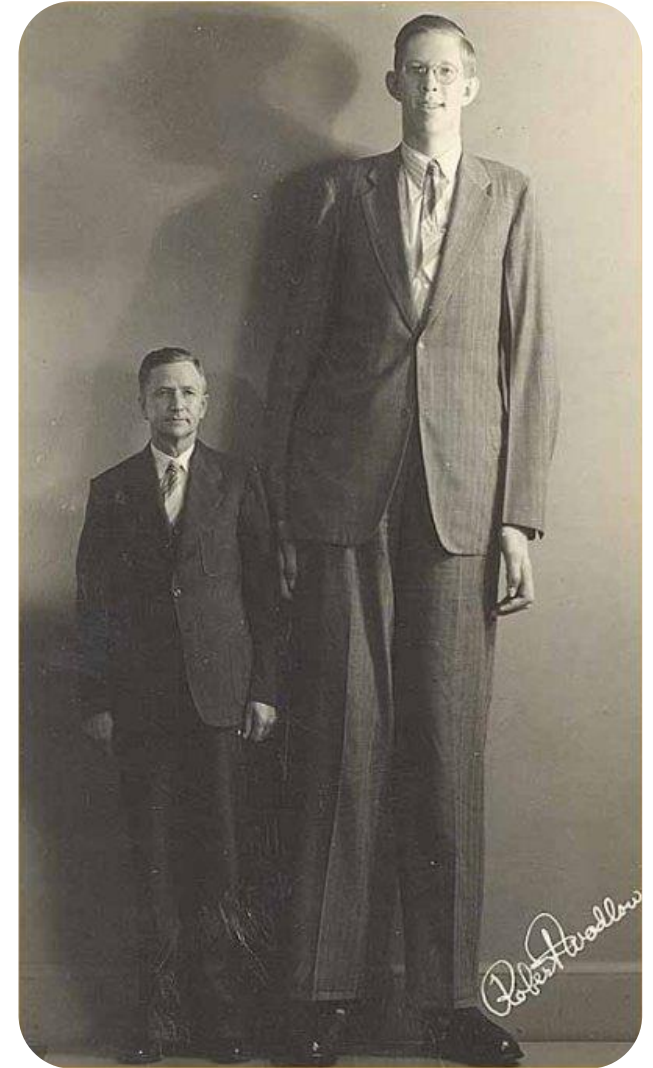
- Neuropathy and Charcot due to Amiodarone (Dhatariya, et al, 2009) (M)
 - Amiodarone is used to treat cardiac arrhythmias
- Chemotherapy drugs
- Lithium (used to treat manic depressive or bi-polar disorders) (A)
- Amitriptyline (anti-depressant, also used to *treat* neuropathy)
- Tagamet (used to treat gastric ulcers, GIRD)
- Antibiotics:
 - Flagyl
 - Nydrazid
 - Laniazid
 - Chloramphenicol
 - Cipro, Levaquin
 - Linezolid
 - Nitrofurantoin
- Topamax (used to treat migraines and seizures)
- Chloroquine (used to treat malaria and rheumatologic diseases) (D)
- Colchicine (antiinflammatory)
- Metronidazole (used to treat trichomoniasis and other anaerobic bacterial infections)
- Dapsone (used to treat leprosy and other dermatologic disorders)
- Disulfiram (used in the treatment of chronic alcoholism)
- Steroids
- Nucleoside Analogs (used to treat HIV-1)
- Indomethacin (used to treat inflammation in RA)
- Phenytoin (used to treat epilepsy)
- Ethambutol (used to treat tuberculosis)
- Procainamide (used to treat cardiac arrhythmias)
- Statins (used to lower cholesterol) (A)
- Tacrolimus (used to prevent transplant organ rejection)

Disorders Affecting the Central Nervous System

- Spinal cord injury (M)
- Spinal cord tumor (M)
- Spina bifida
- Cerebrovascular accident (stroke) (A)
- Syringomyelia
- Myelodysplasia (D)
- Cerebral palsy (D)
- Tabes dorsalis (A)
- Poliomyelitis (A)

Other Causes

- Systemic lupus erythematosus (A)
- Vitamin deficiencies (A)
 - E, B₁ (Thiamin), B₆ , B₁₂
- Exposure to nitrous oxide (A)
 - Causes B₁₂ deficiency
- Height > 175.5cm (5'9")
 - Prevalence in highest quartile is 2.3 x that in third quartile (5'6") and twice that of second quartile (5'3") (Cheng, et al, 2006)
 - Exact pathogenesis of height and PN is not known
- Ischemia (A)
- Parkinson's disease (A)
- Lymphoma (M)
- Cancer / Tumors (M)
- Physical injury
- Nerve entrapment
- Prolonged exposure to cold
- Fibromyalgia (?)
 - This is a tricky one as the peripheral nerves are not actually damaged in any way...

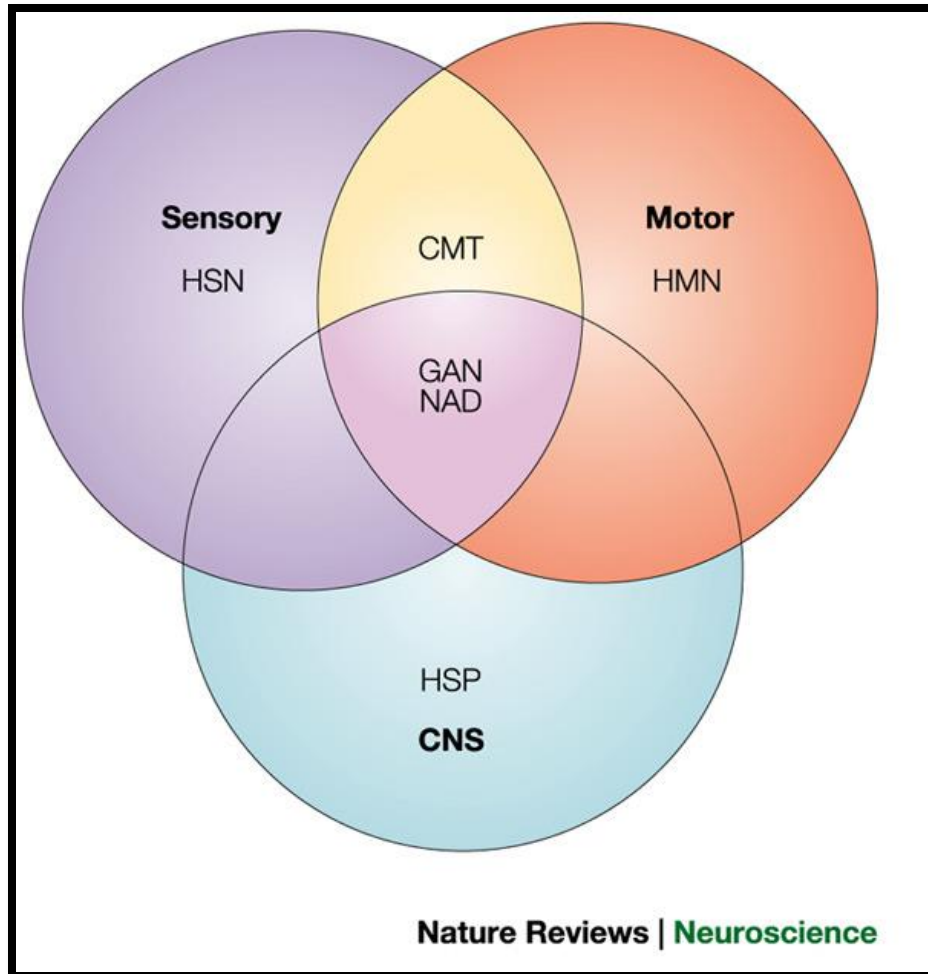


Epidemiology of Neuropathy

- In 25% of cases, cause is deemed idiopathic.



Relationships between inherited neuropathies and other diseases



- HSN: Hereditary Sensory Neuropathy
- CMT: Charcot-Marie-Tooth
- GAN: Giant Axonal Neuropathy
- NAD: Neuroaxonal Dystrophy
- HSP: Hereditary Spastic Paraparesis
- HMN: Hereditary Motor Neuropathy

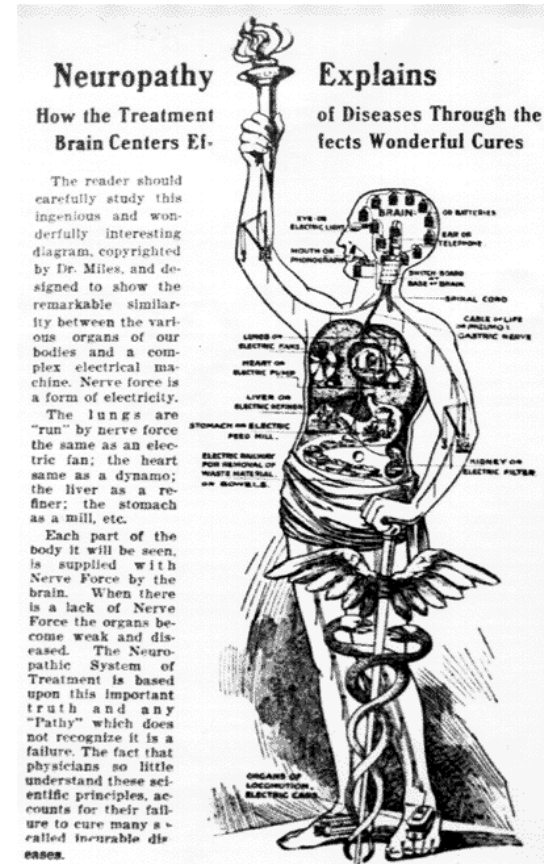
Taken from:

Nature Reviews Neuroscience **4**, 714-726 (Sept 2003)

Treatment and Research

Treatment – Underlying Disease

- Many causes of peripheral neuropathy are not treatable
- Work up is typically focused on finding treatable conditions



Treatment – Underlying Disease

- Avoidance of offending agent
 - Alcohol
 - Heavy metals
 - Toxins
- Medications
 - Thyroid replacement
 - Antibiotics
- Replacement of nutritional deficiencies
- Neuropathies associated w/ autoimmune diseases can improve w/ treatment of the disease
- Neuropathy caused by nerve entrapments can be treated w/ PT, surgery or injections

Treatment –Symptoms

- Medications
 - Antiepileptics (Neurontin, Tegretol)
 - Antidepressants (Elavil)
 - Topical agents (Capsaicin)
- Modalities
 - TENS unit
- Injections –
 - If well localized



Research

- Identify genetic defects
- Better understand biological mechanisms of diabetic peripheral neuropathy
- Better understand effects of how immune system of contributes to peripheral neuropathy
- Gene replacement therapies
- Presymptomatic diagnosis
- Reversing effects of diabetic peripheral neuropathy
 - i.e. Pulsed infrared light therapy



Conclusion

- These feet have same needs as diabetic feet.
 - Unfortunately, many managed health care organizations fail to recognize this.
- Remember that much neuropathy goes undiagnosed.
 - If suspected, refer to a physician who can help.
- Neuropathies can take variable courses depending on underlying causes.
 - May progress slowly or rapidly.
 - May improve with treatment.
- Patients with neuropathy are most likely dealing with much more than loss of sensation in their feet.

The End