The decision to biopsy peripheral nerve should begin with a discussion between the requesting clinician and neuropathologist regarding the differential diagnosis since specialized procedures or an unusual sampling scheme may be required. Nerve biopsy has been shown to contribute to the diagnosis of primary and secondary neoplastic, ischemic (especially vasculitides, particularly those confined to nerve), hereditary (Charcot-Marie-Tooth, HNPP, giant axonal neuropathy), dysimmune (GBS, CIDP, paraprotein), infectious (leprosy, Herpes zoster, HIV, Lyme borreliosis), metabolic (amyloidosis), toxic (glue-sniffer’s neuropathy, amiodarone) and other (sarcoid) processes. However, chronic idiopathic axonal polyneuropathy is a common entity in older patients and a significant public health problem in which a definitive diagnostic entity may not be identified. Analysis of nerve conduction studies on 3,969 patients determined by neurologists to have a normal neurologic examination showed some 24% of individuals aged 70–79 years had absent sural sensory responses (and less than 1% younger than 50, Rivner et al, 2001), the former typically showing axonal degeneration. Nerve biopsy is typically more helpful in patients with distal, acute, demyelinating, asymmetric, and multifocal types of neuropathy than in those with chronic, symmetric axonal types which often have metabolic, toxic or inherited etiologies. Based on the identification of likely or defined hereditary neuropathy in a family, genetic tests may replace nerve biopsy in the evaluation of family members.

I. Normal Peripheral Nerve and Methods of Analysis
The most frequently sampled peripheral nerve is the sural, a predominantly sensory nerve distributed to the lateral aspect of the foot. Skin biopsies are being used more frequently than in the past and may contribute in particular to the analysis of small fiber neuropathology.

A) Basic Histology
A cross section of the sural nerve contains approximately 6-12 individual fascicles of axons, each fascicle surrounded by flattened perineurial cells. Outside of the perineurium is the epineurium, which contains connective tissue and an anastomotic vascular network distributed to the endoneurium. The endoneurium (technically the space inside of the perineurial cell layer and outside of the axon/Schwann cell unit) contains fluid, collagen, capillaries, venules, fibroblasts (10 fold fewer in number than Schwann cells), macrophages/monocytes, and scattered mast cells.

Basic histologic features of the biopsy are studied using classic hematoxylin and eosin (H&E), trichrome (connective tissues) and silver (axons) stained material as well as specialized stains as needed, e.g. Hirsch/Peiffer acidified cresyl violet stain for metachromatic materials and Congo Red or Thioflavin S for amyloid.

B) Immunohistochemistry
Immunohistologic localization permits the identification and detailed characterization of selected materials (neurofilaments, amyloid composition, and immunoglobulins), subtypes of inflammatory cells, and alterations of growth factors and receptors after nerve injury.

C) Teased Fibers
Lengths of individual lightly fixed, osmicated myelinated axons can be dissected or "teased" out of a fascicle. Each myelin internode, maintained by a single Schwann cell, ranges from 0.2 to 1.8 mm on axons of different sizes. Internode length increases linearly with axon diameter. Active demyelination or axonal degeneration is readily identified as well as evidence of previous degenerative or demyelinating-
D) Semithin Plastic Sections

One micron thick plastic embedded sections of peripheral nerve provide a wealth of information. Myelinated axons range in diameter from 2-18 microns (coarsely separated into small and large myelinated axon populations) with myelin thickness related directly to axonal diameter. The levels of neuregulin-1 (NRG1) type III expressed on axons triggers Schwann cell myelination via an ERK1,2 pathway, matching myelin sheath thickness precisely to axon caliber. NRG1 regulates myelination via the control of Schwann cell cholesterol biosynthesis which is a rate-limiting factor for myelin protein production and transport of the major myelin protein P0 from the endoplasmic reticulum into the growing myelin sheath. Sensory axons from NRG1 type III deficient mice are poorly ensheathed and fail to myelinate, a phenotype rescued by lentiviral-mediated expression of NRG1 type III. In a PTEN related process, Schwann cells may act to inhibit axonal stimulation of myelination, preventing overmyelination, myelin outfoldings and demyelination. The patterns of nerve damage visible in plastic sections may be characteristic of certain disease entities or pathogenetic processes, although histopathology by itself rarely is pathognomonic for a single disease entity. Qualitative information is provided on the degree of myelinated axon loss, the distribution of axon loss (patchy vs. diffuse), presence or absence of active axonal degeneration or demyelination, identification of regenerative clusters of axons, swollen axons with a variety of inclusions, onion-bulb formation, endoneurial cellular infiltrates or amyloid deposition, and a rough approach to numbers of or pathologic alteration in unmyelinated axons.

E) Ultrastructure

Ultrastructure provides a detailed look at the subcellular composition of individual axons and pathologic processes. Unmyelinated axons, which are 3-4 fold more numerous than myelinated axons in the sural nerve, range in diameter from 0.2-2.0 microns.

F) Morphometry

Morphometry provides quantitative data concerning axon number, relative axon and myelin dimensions, and axon size-frequency distribution. Certain pathologic processes selectively target discrete subpopulations of axons, as in the illustrated case of amyloid neuropathy which demonstrates selective loss of small myelinated axons. Large axons are preferentially targeted by uremia, abetalipoproteinemia, thallium, arsenic, acute intermittent porphyria, cisplatin, vincristine and Friedreich ataxia. Small axons are selectively damaged in amyloidosis, some forms of diabetic neuropathy (including that in impaired glucose metabolism), hypothyroidism, hyperlipidemia, complex regional pain syndrome I, HIV and antiretroviral drugs, acute pandysautonomia, alcohol, sarcoidosis, Sjogren syndrome, SLE, Parkinson disease, Vitamin B12 deficiency, leprosy, hepatitis C, celiac disease, Fabry disease, metronidazole, some chemotherapy agents, forms of hereditary sensory and autonomic neuropathies (HSANs) and idiopathic chronic anhidrosis (Javed et al, 2014).

G) Skin Biopsy

(See Lauria, 2007, 2008; Sommer, 2008 and Ebenezer et al., 2007 for reviews)

The skin and its receptors represent a complex environment with a variety of elements specialized for sensory (Zimmerman et al., 2014) and autonomic modalities. The use of skin biopsy to measure the density of intraepidermal nerve fibers has enabled small fiber sensory neuropathy to be examined in various conditions including HIV infection and the neurotoxicity resulting from antiretroviral and antineoplastic drugs, hypothyroidism, paraneoplastic neuropathies, Friedreich ataxia, SLE, Fabry disease, Sjogren syndrome, familial dysautonomia, congenital insensitivity to pain, CIDP and Guillain-Barré syndrome (GBS). Onion-bulb formation may be seen in the innervation of the skin in a variety of hereditary neuropathies. Skin biopsy may aid in the screening of patients with a familial neuropathy with characteristic features such as defects in myelin compaction in MPZ, numerous myelin outfoldings in MTMR2 gene mutations or MFN2 mutations with abnormal intraaxonal mitochondria. Although there is a role for skin biopsy in examining neuropathies, it may be limited in making the initial diagnosis of cases where sural remyelinative episodes.
nerve biopsy may provide more information (e.g., vasculitis, Guillain–Barré syndrome, amyloidosis, leprosy, sarcoidosis, lymphoma, CIDP or other atypical neuropathies). Large fiber neuropathies or mixed sensorimotor neuropathies may be difficult to interpret by focusing on small fiber rich skin innervation. In CIDP and GBS, patients with reduced IENF (Intra Epidermal Nerve Fiber) density are reported to have a poorer outcome and a higher risk of developing dysautonomia. Quantification of IENF density can better assess the diagnosis of small fiber sensory neuropathy than sural nerve biopsy.

Abnormal epidermal innervation may occur in the absence of changes in the sural nerve in diabetic sensory neuropathy, which reflects loss of the most distal sensory complement of axons. The ability for multiple biopsies to be performed in the essential absence of neuropathic residua is one of the assets of skin biopsy and can be used to follow the progress of treatment. After chemical denervation of the skin with topical capsaicin, diabetic patients show a slower rate of IENF regeneration compared with healthy subjects, suggesting the ability to identify incipient neuropathy by regenerative stress at the earliest stages in which it may be most amenable to therapy. The demonstration of distal preterminal nerve-fiber swellings in HIV neuropathy and diabetes are thought to represent a “pre-degenerative” change but do not apparently reflect a relationship to pain or clinical neuropathy severity in DPN (Cheung et al., 2015). Skin biopsies may also help distinguish neuropathies from radiculopathies, which typically do not produce epidermal nerve changes because the root damage is proximal to the DRG. Small, thinly myelinated A-\(\beta\) (A-delta) axons, which subserve cutaneous mechanoreceptors and thermal receptors, can also be identified in skin biopsies. Dermal nerve fibers innervate sensory receptors including Meissner corpuscles, Merkel cell complexes, Pacinian, Krause and Ruffini corpuscles.

The examination of the innervation of sweat glands, arrector pili and arterioles extends the usefulness of skin biopsies to the analysis of autonomic nerves which has been used to investigate diabetic autonomic neuropathy, autonomic changes accompanying Parkinson disease and familial dysautonomia. Sweat glands are innervated by different populations of autonomic fibers expressing multiple different neurotransmitters (e.g., VIP, CGRP, Substance P) or transmitter synthesizing enzymes (dopamine beta hydroxylase, choline acetyltransferase and neuronal nitric oxide synthase) and may be differentially susceptible to experimental and clinical insults. Skin biopsy correlates with sweat gland nerve fiber density, neuropathic symptoms, neurological deficits, and sweat production in diabetic patients. Similar approaches have been used to demonstrate abnormal innervation of the gastric mucosa in diabetic patients.

**IENF and Painful Neuropathy** Painful small fiber neuropathy (SFN) can be caused by diabetes, alcohol abuse, deficiency or increase of vitamins (B12,B6,B1), acute intermittent porphyria, familial amyloid polyneuropathies, systemic vasculitides, HIV, Hepatitis C, Lyme disease, leprosy, or be immune-mediated, idiopathic or age-related (Hoeijmakers et al, 2012). Painful peripheral neuropathy involving small-diameter nociceptive nerve fibers represents a significant public health challenge; in about one-half of cases, no cause can be identified. In studies of HIV-associated neuropathy patients with severe pain showed a non-significant trend toward a lower density of intraepidermal nerve fibers in the distal leg than those with lesser pain, but in diabetic painful neuropathy IENF density was reported to be lower or unchanged in patients with pain compared to those without pain and pain intensity did not correlate with IENF density (not all studies agree, See Kalliomäki et al, 2011). IENF density is reported to be lower in diabetic patients with early painful neuropathy and may be reversible with quick intervention. Nonetheless, patients with painful dysesthesias with a normal electrophysiologic exam often show loss of IENF. Skin biopsy may be most useful in the diagnosis of painful or small fiber neuropathy in which there is a differential diagnosis not involving neuropathy as a cause (e.g., ALS). Some neuropathic pain states may reflect the hyperexcitability of peripheral nerves following local up-regulation of a variety of Na\(^+\) and Ca\(^{2+}\) channels, altered function in response to increased release of cytokines/chemokines in the DRG, as well as alterations in microglia and central processing in the spinal cord, thalamus or at higher centers. Recent studies (reviewed in Hoeijmakers et al., 2012; Dib-Hajj et al, 2013) have described changes in a variety of ion channels in patients with painful small fiber neuropathies (Nav1.7, Nav1.8, SCN7A/Nax, Kv9.1 (kcns1), TRPA1, TRPV1). It is known that human acute and inflammatory pain requires the expression of voltage-gated sodium channel Nav1.7 and ablating the Nav1.7 gene (SCN9A) expression in all sensory neurons abolishes
mechanical pain, inflammatory pain and reflex withdrawal responses to heat. In the DRG, Nav1.7 is expressed in A- and C-fiber type neurons, but is more prominently expressed in small diameter neurons, with 85% of functionally-identified nociceptive neurons exhibiting Nav1.7 immunolabeling. Nav1.7 sequence variants associated with SFN are disease-causing mutations that impair slow inactivation of the channel and enhance neuronal excitability to produce neuropathic pain in young patients. Missense substitutions in SCN9A that encode functional Nav1.7 variants are common in patients with biopsy-confirmed small fiber neuropathy. Abnormal expression of TRPV1 in large myelinated axons may result in neuropathic hyperalgesia, dysesthesia and paresthesias. Spontaneous sensations after peripheral nerve lesions appear to be generated as a result of hyperexcitability in the primary sensory neuron, leading to ectopic action potential discharge at the site of injury and resultant neurona, but also at more proximal axonal sites, including the soma. Nav1.7 mutations have also been linked to inherited erythromelalgia and paroxysmal extreme pain disorder and cause inappropriate spontaneous firing and increased response to depolarization.

H) Corneal Confocal Microscopy (CCM) Another recent novel approach is the examination of corneal nerves using non-invasive in vivo confocal microscopy (Azmi et al., 2015). Findings using this technique have been correlated with the presence and severity of diabetic autonomic neuropathy and its improvement following combined pancreas/kidney transplantation, IENF loss or (in some studies, see below) the presence of painful diabetic neuropathy. Similar changes have been described in idiopathic small fiber neuropathy and Fabry disease. Use of CCM has demonstrated significant regenerative improvements in corneal nerve fiber density, branch density, and length at 12 months in diabetic patients after simultaneous pancreas-kidney transplantation (Tavakoli et al, 2013).

II. Basic Pathologic Mechanisms

A. Axonal Degeneration

A multitude of neuropathic conditions (diabetes, cancer chemotherapy, infectious and autoimmune diseases) result in degeneration of the axon and myelin and subsequent regeneration (see reviews by Zochodne, 2012; Conforti et al., 2014; Loreto et al 2015; DeFrancesco-Lisowitz et al., 2015; Cashman & Hoke, 2015) and reflect "a combination of just six primary mechanisms: altered metabolism, covalent modification, altered organelle function and reactive oxygen species formation, altered intracellular and inflammatory signaling, slowed axonal transport, and altered ion channel dynamics and expression dynamics" (Cashman and Hoke, 2015). Often the distal portions of the longest axons are preferentially involved (i.e., "distal axonopathy" or "dying-back neuropathy").

For years it was thought that Wallerian/axonal degeneration was the simple result of loss of neuronal cell body provided material as a passive process. However, studies with the WldS mouse, in which survival of the distal peripheral nerve segment may extend for several weeks after transection, have shown that axonal degeneration is an active, intrinsic process of self-destruction and protects against neuropathy in a variety of diseases (reviewed in Cashman and Hoke, 2015). Furthermore, these studies have established a protective role of a fusion protein that elevates nicotinamide mononucleotide adenylyltransferase (Nmnat), acting as a survival signal which decreases after axotomy, and protects axons through downstream effects on nicotinamide adenine dinucleotide (NAD) and SIRT1. The NAD-precursor NMN stimulates a Ca2+ rise in injured axons, which requires the proteogenerative protein SARM1 and precedes fragmentation (Gerdts et al., 2013;Loreto et al., 2015). NMN and SARM1 appear to act in a common pathway culminating in intraxonial Ca2+ increase and axonal fragmentation and dissociate mitochondrial dysfunctions from this pathway (Loreto et al., 2015). SARM1 initiates a local destruction program involving rapid breakdown of nicotinamide adenine dinucleotide (NAD(+)) after injury, a process which is dependent on dimerization of a Toll-interleukin receptor domain of SARM1, (Gerdts et al., 2013). Increase in free intracellular Ca2+, which is abolished by pharmacological or genetic reduction of NMN levels, is followed by the activation of calpains leading to a massive decrease of microtubules and neurofilaments. However, although the
inhibition of NMN synthesis and SARM1 deletion do block Ca2+ rise and preserve axonal integrity, they fail to prevent early mitochondrial dynamic changes. It is thought that NAD+ augmentation may have a therapeutic function in treatment of neuropathies (and other neurologic disorders (Gerdts et al., 2015).

Mitochondrial dysfunction is also thought to be a common cause of peripheral neuropathy, although not previously thought to involve a role for Schwann cell mitochondria. A mouse model of peripheral neuropathy secondary to Schwann cell mitochondrial dysfunction (Tfam-SCKOs) has been developed (Viader et al., 2013). Schwann cell mitochondrial dysfunction subsequently causes a shift in lipid metabolism resulting in depletion of important myelin lipid components as well as in accumulation of acylcarnitines. Acylcarnitines which are released from SCs and induce axonal degeneration.

A. 1 Histopathologic Changes of Axonal Degeneration

The earliest degenerative changes proceed independently of invading macrophages. Myelin destruction and its early catabolism occur in the Schwann cell, producing the myelin "ovoid" of teased fibers. Schwann cell loss of axonal contacts results in their upregulation of cytokines and chemokines that play a key role in attracting hematogenously- and endogenously-derived macrophages by synthesizing monocyte chemoattractant protein-1 and relaxing the blood nerve barrier. Mast cell histamine and chemokines are also released within hours of nerve injury, contributing to the recruitment of neutrophils and monocytes/macrophages, and encourage the development of hyperalgesia. Macrophages subsequently engulf the debris from Schwann cell cytoplasm in a poorly understood process. Macrophage recruitment rapidly clears myelin debris, which contains axon growth inhibitors, and thus facilitates nerve regeneration. Macrophages produce mitogenic factors for Schwann cells and fibroblasts. With time macrophages in the distal stump of injured nerve are eliminated by local apoptosis or by drainage into regional lymph nodes. There is also evidence that myelin constituents are locally metabolized and cholesterol reutilized to facilitate axonal regeneration. Recent studies suggest that a non-secreted protein is released from disintegrating axons to initiate the innate immune response using Toll-like receptor-4 which also contributes to Wallerian degeneration. Early regenerative events begin with the proliferation of Schwann cells and their processes which accumulate within the original basal lamina of the axon/Schwann cell unit as "bands of Büngner". Concomitantly, axonal regeneration begins, consisting of sprouting of the proximal viable portion of the axon and the proximodistal growth of regenerative sprouts within the bands of Büngner. Some axons project quickly and initially, and other axons follow. Inhibition of PTEN, a tumor suppressor molecule, in a geographically and temporal delineated fashion, may significantly augment axon outgrowth. Finally, supernumerary sprouts can be potentially problematic as it is estimated that individual parent axons elaborate 10–40 sprouts which must be maintained. By days 3–5 after a peripheral nerve injury, there is influx of macrophages and T lymphocytes into the proximal and distal stumps. This cellular influx is associated with expression of interleukins 1β, 6 and 10, IFNγ, TNF-α, RAGE (receptor for advanced glycation endproducts), LIF, MCP-1, MIP1α, MMPs, NO and likely many others. Delayed clearance of axon and particularly myelin debris impedes subsequent regrowth, possibly due to inhibition by myelin associated glycoprotein (MAG). Schwann cells comprising the band of Büngner decrease the synthesis of myelin related proteins (P0, MAG) and increase their synthesis of cytokines and growth factors as a trophic and tropic stimulus. Studies suggest that Schwann cells express different growth factor phenotypes in regenerating motor (pleiotrophin, GDNF) and sensory (IGF-1, VEGF, NGF, BDNF and hepatocyte growth factor) nerves (reviewed in Gordon, 2014). They have shown that sensory and motor Schwann cells promoted axon regeneration on a phenotypic-specific basis using a wide range expression pattern for 11 neurotrophic substances examined. There were differences in terms of motor versus sensory Schwann cells and also among sensory Schwann cell populations (cutaneous sensory versus muscle afferent) and between proximal (root) and distal sites (peripheral nerves). Motor and sensory Schwann cell responses to denervation differ and may play a role in pathway specification during regeneration. Schwann cells may transfer ribosomes to injured and regenerating axons. Eventually, newly generated Schwann cells of injured nerves are culled by apoptosis. Experimental interference with Schwann cell mitochondria can be sufficient to cause both demyelination and axonal degeneration; Schwann cell mitochondria help maintain the axoglial interactions required for the long-term support of axons. The role of mitochondria in axonal degeneration may include mitochondrial metabolic failure with increased ROS production, increased intra-axonal calcium
resulting in calpain activation and cytoskeletal degeneration and release of other prodegenerative molecules from swollen mitochondria.

Several axon sprouts within any Schwann cell tube begin to mature giving rise to small groups of thinly myelinated axons, i.e., regenerative clusters, which ultrastructurally are also confined within the basal lamina of the original Schwann cell. With time one axon emerges and the others regress. A plastic cross section of such a regenerated axon, which characteristically shows a myelin sheath relatively thin for its axon caliber, provides little evidence of its history; however, teased fiber measurements provide a glimpse of the fiber's past. In teased fibers of normal nerves internodal length varies directly with axonal diameter (i.e., longer internodal lengths for larger axons). Additionally, axons which have degenerated and regenerated demonstrate a uniform internodal length regardless of axon diameter. Schwann cells will myelinate or ensheath axons based on their expression of neuregulin; specifically, independent of axon size, axons that express low levels of neuregulin are ensheathed while those expressing high levels are myelinated. Eventually, following regeneration, functional recovery may occur. Alternatively, in the endstages of a chronic severe neuropathic process the nerve may consist of rare preserved axons accompanied by scattered fibroblasts and Schwann cells. Such an endstage nerve provides little detailed information concerning the process which preceded it. Loss of unmyelinated axons may result in the formation of numerous "collagen pockets" in which longitudinal bundles of collagen are held by Schwann cells in lieu of axons, a process which may be deceptively unimpressive by light microscopy.

What is the difference between axonal degeneration and Wallerian degeneration? Wallerian degeneration, strictly defined, represents the degenerative in vivo reaction of axons and Schwann cells distal to a site of mechanical axonal damage. Axonal degeneration, therefore, is more limited but uses many of the same processes as Wallerian degeneration and the terms are often used interchangeably. Points of difference include: i) Wallerian degeneration occurs simultaneously in many of the axons in a fascicle; and, ii) Wallerian degeneration is stereotyped in contrast with some axonal degenerations in which distinctive pathologic signatures (swollen axons containing collections of neurofilaments or tubulovesicular elements, neuroaxonal dystrophy, etc.) may occur. As mentioned, degeneration of the distal axonal segment is an active process rather than simply a loss of synthetic support normally provided by the perikaryon.

B) Segmental Demyelination

Segmental demyelination represents preferential damage to one or several internodes of the myelin sheath, directly to myelin or to its Schwann cell, with relative axonal sparing. Schwann cell proliferation with eventual remyelination of individual internodes is typical, which frequently results in the replacement of each lost myelin internode by several shorter internodes. Therefore, a plot of axonal diameter versus internodal length of teased fibers shows marked variation in internodal length from node to node along individual teased fibers compared with normal axons. Demyelination may induce the disruption of nodally restricted ion channels including dispersion of sodium channels which may permit the non-saltatory conduction of the action potential across the demyelinated segment.

C) Secondary Demyelination

Conceptually, secondary demyelination integrates both axonopathy and demyelination. Demyelinated segments are preferentially located along the course of selected axons and entirely spare others as opposed to the typical situation of random demyelination of axons. Targeted axons may exhibit degenerative alterations or atrophy. The mechanism appears to involve an abnormality in the relationship of the Schwann cell and myelin sheath to the underlying axon resulting in secondary myelin loss. The best worked out example is uremic neuropathy, although the process may be considerably more common.

III. Toxin-induced Neuropathies (includes Chemotherapy-induced peripheral neuropathy, CIPN) (see reviews in Manji, 2011; Farquhar-Smith, 2011; Jaggi & Singh, 2011; Argyriou et al., 2014; Karam & Dyck, 2015) Toxic neuropathies are induced by many of the widely used chemotherapy agents include platinum compounds (cisplatin, carboplatin, and oxaliplatin), proteasome inhibitors (bortezomib), vinca alkaloids
(vinblastine, vincristine), thalidomide and taxanes (taxol, paclitaxel, docetaxel).

A) Axonopathy

One group of axonal degenerations has a similar pathogenetic mechanism involving the effects of selected toxins on axonal transport. A variety of toxins target selective phases of transport or, even more selectively, the transport of discrete substances. Iminodiproprionitrile (IDPN), methyl-butyl ketone (MBK), 2,5 hexane-dione (2,5 HD), aluminum, and carbon disulfide are experimental or environmental toxins which target one phase or another of neurofilament transport resulting in neurofilamentous axonal swellings. The clinical chemotherapeutic agents vinblastine, vincristine, taxanes (paclitaxel and docetaxel) and colchicine interrupt microtubule function and, as expected, are potent inhibitors of axonal transport and produce neuropathy. Acrylamide, used in a variety of manufacturing processes and in the laboratory, can result in distinctive neurofilament and tubulovesicular aggregates involving distal portions of axons. Zinc pyridinethionine and bromophenylacetylurea (BPAU) preferentially target the “turnaround” axonal transport process in which proximodistal transport reverses polarity; predictably, these agents result in swellings at the nerve terminals. Similarly, diabetes appears to influence the turnaround process but involves other phases of orthograde and retrograde transport as well. In contrast to vincristine, which prevents polymerization of tubulin into microtubules, paclitaxel promotes the formation of an overabundance of rigid microtubules inhibiting axonal transport.

As in other inherited and HIV-related neuropathies a role for mitochondriopathy is developing in the dose-limiting and often painful sensory axonopathy which accompanies oncologic use of paclitaxel and oxaliplatin. Mitochondria in experimental neuropathies produced by these agents may be swollen and vacuolated, with accumulated mutations in mitochondrial DNA, decreased mitochondrial calcium, changes in ion channels and functional abnormalities. It is thought that chronic neuronal energy deficit results in degeneration of the terminal receptors and spontaneous nerve impulses (Bennett et al., 2014). Paclitaxel targets TRPV4 via oxygen radical formation and may play a significant role in inducing mechanical hyperalgesia in paclitaxel induced painful peripheral neuropathy. A possible defect in axonal transport or transport of abnormal mitochondria, may underlie the phenomenon of coating, i.e., continuing or transient worsening after discontinuation of administration of the agent. Inhibition of mitochondrial changes by the administration of acetyl-L-carnitine (an amino acid derivative with an important role in transporting long-chain free fatty acids into mitochondria) is associated with a reduction of paclitaxel-induced neuropathic pain. Bortezomib is a proteasome inhibitor used in the treatment of relapsed/refractory multiple myeloma, which produces a demyelinating small fiber sensory axonal polyneuropathy which may be characterized by pain in as many as half of patients developing neuropathy and, is accompanied to a lesser degree by autonomic symptoms. In a model of toxin-induced neuropathy caused by cisplatin, subcutaneous inoculation of HSV vectors constructed to express either NGF or NT-3 just prior to a 6-week course of cisplatin resulted in significant protection against the development of neuropathy.

B) Myelinopathies

Lead, diphtheria toxin, perhexiline, lycocleithin, tellurium and hexachlorophene are prominent toxins directed at the Schwann cell and/or its myelin sheath, although the precise targeted element differs between toxins.

C) Drug-Related

Isoniazid, hydralazine (probably related to pyridoxine deficiency), chloroquine, metronidazole, disulfiram, amiodarone, misonidazole, perhexiline, propafenone, allopurinol, dapsone, phenytoin, cloquinol, amitriptyline, nitrofurantoins and lithium. Thalidomide, used as an immunomodulatory agent in the treatment of myeloma, causes a length-dependent neuropathy in which sensory loss and painful paresthesias are characteristic.

D) Heavy Metals

Arsenic, mercury, thallium, gold are well known for their toxic effects on peripheral nerves.

E) Miscellaneous

Triorthocresyl phosphate (TOCP), mipafox, kepone, adulterated rapeseed oil, 1,1’-ethyldenebis L-tryptophan (eosinophilia-myalgia syndrome), buckthorn and carbon disulfide are known agents capable of producing peripheral neuropathy.
IV. Ischemic Neuropathies

The vascular supply to peripheral nerve (i.e., the "vasa nervorum") is typically rich and anastomotic and, therefore, a substantial decrease in nerve blood flow is needed to interrupt function. The vasculitides, defined as vasculopathies with angionecrosis, are frequently patchy or focal which underscores the necessity for thorough sampling of biopsied nerves.

Vasculitis - Clinical Presentation Patients experience an abrupt onset of pain, paraesthesia, and paralysis in the distribution of a single nerve trunk evolving over hours to days, with newly involved nerves appearing over days to months. The clinical pattern of asymmetric involvement of nerves (i.e., mononeuritis multiplex) is the classic manifestation of vasculitic neuropathy; however, this pattern of presentation is not confined to ischemic neuropathies and may include multiple myeloma, Waldenstrom macroglobulinemia, cryoglobulinemia, lymphoma, sarcoidosis and leprosy in which vascular participation is more problematic. Experimental studies have reported the improvement of hindlimb ischemia-induced neuropathy with local injection of DNA encoding vascular endothelial growth factor (VEGF) (Schratzberger et al., 2000). Although a pattern of central fascicular fiber degeneration has been considered characteristic of experimental nerve ischemia, clinical patterns of axon loss often show more patchy involvement rarely confined to the fascicular center.

Vasculitic Neuropathies (reviewed in Naddaf & Dyck, 2015; Collins et al) are often defined by the presence of fibrinoid angionecrosis but other findings may also permit a (possibly tentative) diagnosis of vasculitis including thrombosis, deposition of IgM, fibrinogen, asymmetric fascicle-to-fascicle or intrafascicular axon loss, perivascular or intramural hemorrhage, loss or fragmentation of the endothelium, internal elastic lamina, or intramural smooth muscle. Similarly, evidence of chronic vasculitic neuropathy includes asymmetrical medial fibrosis, hemosiderin deposition, iron deposition, and thrombosis with recanalization.

1) Isolated PNS vasculitis
2) Primary systemic vasculitis
   - Polyarteritis nodosa (PAN)
   - Churg-Strauss Syndrome
   - ANCA-Associated Microscopic Polyangiitis
   - Wegener granulomatosis (Granulomatosis with Polyangiitis)
   - Essential Mixed Cryoglobulinemia
   - Behçet disease
   - Henoch-Schölein Purpura
3) Secondary Systemic Vasculitides associated with:
   3-1 Collagen vascular diseases
      A) Rheumatoid arthritis
      B) Systemic Lupus Erythematosus (SLE)
      C) Sjögren Syndrome
      D) Scleroderma
   3-2 Other Vasculitis and vasculopathies
A) Giant cell arteritis
B) Paraneoplastic (Hematological or Solid Malignancy)
C) Hypersensitivity vasculitis
D) Sarcoidosis
E) Lymphomatoid granulomatosis

3-3 *Infection-associated vasculitis*

A) Leprosy in ENL reaction
B) HIV infection (Includes CMV-related
C) Lyme disease
D) Bacterial endocarditis
E) Tuberculosis

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**A) Non-systemic (isolated) Peripheral Nervous System Vasculitis (NSVN)**

Vasculitis involving the peripheral nerves can be seen in isolation, and results in a peripheral nerve syndrome indistinguishable from that of vasculitic neuropathy in multisystem disease. One study of 60 cases of NSVN showed the presentation was mostly asymmetric (80%), sensorimotor (75%), and painful (63%) (Üçeyler et al, 2015). That group found that the pathology of sural nerve was informative in all cases irrespective of neurophysiological findings and prior immunosuppression. After initial treatment with i.v. methylprednisolone, all patients reported overall improvement. Subclinical involvement of muscle and skin is regarded as compatible with the diagnosis (Üçeyler et al, 2015). The apparent selectivity of peripheral nerve involvement may reflect an increased vulnerability of this tissue to multifocal microvascular insults, and the presence of a milder disease sufficient to clinically affect nerve but no other tissues. Some authors have suggested that NSVN should be considered a low-grade systemic vasculitis that is symptomatic in nerves only.

**B) Primary systemic vasculitis - Polyarteritis nodosa (PAN)**

Approximately 25% of cases with vasculitis neuropathy are diagnosed with primary vasculitis neuropathy. These patients usually present with a subacute or chronic neuropathy, often with a mononeuritis multiplex, and have few or no systemic abnormalities on history, physical, or laboratory investigation. Polyarteritis nodosa is the prototypic ischemic neuropathy. Epineurial arteries may be entirely destroyed by an infiltrate containing polymorphonuclear leukocytes, macrophages, monocytes and fibrin which may occur in a patchy distribution. Axons in fascicles adjacent to the arteritis may be minimally involved or, much less frequently, completely infarcted. The clinical pattern of mononeuritis multiplex reflects the distribution of significant vasculitic hits on the vasa nervorum. Fibrotic vessels with recanalization mark previous sites of vasculitic damage. PAN commonly is associated with hepatitis B and may be more aggressive in these patients in comparison to PAN unassociated with Hepatitis B.

**C) Secondary Systemic Vasculitis - Collagen Vascular Diseases (SLE, Rheumatoid Arthritis, Progressive Systemic Sclerosis, Sjogren Syndrome)**

A variety of histopathologic findings have been described in the nerves of patients with collagen vascular diseases and more than one type of injury may occur in any given patient. Rheumatoid arthritis may result in a pattern of mononeuritis multiplex histologically comparable to that of polyarteritis nodosa. Alternatively, it may only exhibit "microvasculitis" in which the pathologic appearance of blood vessel damage is deceptively benign. Microvasculitis is characterized by T lymphocytes and histiocytes infiltrating the thin vessel walls in the absence of angionecrosis resembling the common picture of lymphocytic cuffing. Some investigators identify this pattern as microvasculitis or "non-necrotizing vasculitis" if it is associated
with regenerating small vessels, vascular deposits of IgM, C3, or fibrinogen by direct immunofluorescence, prominent active axonal degeneration, adjacent muscle necrosis or infarction, endoneurial hemorrhage (iron stains may help) and asymmetry of axon loss or axonal degeneration. This pattern may represent an early or mild vascular injury or represent an area adjacent to more substantial vascular pathology. Microvasculitis involving smaller arterioles (lacking an internal elastic lamina), microvessels and venules occurs in vasculitic neuropathy localized to nerve, immune sensorimotor polyneuropathies, Sjogren syndrome, paraneoplastic neuropathies, and virus-associated neuropathies. Epineurial perivascular aggregates of a few mononuclear cells are common in a variety of clinical nerve biopsies in which an ischemic pathogenesis is not expected and some authors consider them, in isolation, to be of little pathologic importance. Immunohistologic methods may demonstrate prominent deposition of immunoglobulins and complement within the vascular wall in collagen vascular diseases which reflects the presence of underlying circulating immune complexes which may not be specific for nerve.

C) Other Disease Entities

Vasculopathy with neuropathy is also seen in paraneoplastic neuropathies, hypersensitivity angiitis, cranial arteritis, AIDS, Lyme Disease, Kohlmeier-Degos disease, thromboangiitis obliterans (Buerger disease), diabetes, amyloid, hyperviscosity syndromes including macro- and cryo-globulinemia, polycythemia, sickle cell disease, thrombocytopenia, as well as a few other miscellaneous entities (cold exposure, entrapment, injection sites). Certain vascular targets correlate with clinical entity.

Large arterioles (75 to 200 microns) in the epineurium and perineurium are frequently associated with Churg-Strauss syndrome, in which eosinophilic infiltrates may be prominent, Wegener granulomatosis (a rare cause of vasculitic neuropathy), rheumatoid arthritis and polyarteritis nodosa. Fibrinoid necrosis of the tunica media often is prominent and characteristic in large vessel vasculitis but is not encountered in nerve microvasculitis.

V. Metabolic Neuropathies

The neuropathies which may accompany a variety of metabolic diseases are a pathogenetically heterogeneous group. Nerve injury may be primary in the disease or represent a variety of superimposed processes such as vasculopathy resulting in an ischemic pathogenesis.

A) Diabetes (see Zochodne, 2014; Izenberg et al, 2015 for recent review)

Studies support only a modest reduction in neuropathy in patients with type 2 diabetes in response to enhanced glucose control in comparison to the substantial effect in those with type 1 diabetes which may reflect a role for insulin resistance and dyslipidaemia in pathogenesis. There is a complex spectrum of neuropathies in diabetes (cranial nerve, symmetrical sensorimotor, autonomic, or lumbosacral plexus neuropathies) which may have different pathogenetic mechanisms (see Table 1).

<table>
<thead>
<tr>
<th>Presumed Pathophysiology</th>
<th>Subtype of Diabetic Neuropathies</th>
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<tbody>
<tr>
<td>Metabolic-microvascular-hypoxic</td>
<td>Diabetic polyneuropathy</td>
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<td></td>
<td>Diabetic autonomic neuropathy</td>
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<tr>
<td>Inflammatory immune</td>
<td>Diabetic lumbosacral radiculoplexus neuropathy</td>
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<td>Diabetic thoracic radiculoneuropathy</td>
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<td>Diabetic cervical radiculoplexus neuropathy</td>
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<td></td>
<td>Cranial neuropathies</td>
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<td></td>
<td>Painful neuropathy + weight loss, (diabetic cachexia)</td>
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<td></td>
<td>CIDP in diabetes</td>
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<tr>
<td>Compression and repetitive injury</td>
<td>Median neuropathy at the wrist</td>
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<td>Ulnar neuropathy at the elbow</td>
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<td>Peroneal neuropathy at the fibular head</td>
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<tr>
<td>Complications of diabetes</td>
<td>Neuropathy of ketoadidosis</td>
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<tr>
<td></td>
<td>Neuropathy of chronic renal failure</td>
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</table>
Neuropathy associated with large vessel ischemia
Insulin neuritis
Hyperinsulin neuropathy

(from Sinnreich et al., 2005)

1) Symmetrical Sensori(motor) Polyneuropathy
This is the most well known of the neuropathies of diabetes and presents with largely distal sensory problems which range from trivial electrophysiologic alterations to stocking-glove anesthesia. Motor problems may also occur, although they are typically less reproducibly involved. Patients may develop neuropathy after years of diabetes or present with neuropathic symptoms which prompt workup and result in the first-time diagnosis of diabetes. Pathologic findings are dominated by variable degrees of axon loss accentuated in the distalmost portions of the peripheral nerves as described in dying-back neuropathies. A detailed morphometric study by Dyck and colleagues (1986a,b) has been thought to provide evidence for involvement of the vasculature in the development of the neuropathy. Multiple ischemic hits on the proximal portions of the peripheral nerves running from root to distal limb nerves were thought to summate and produce a symmetrical and uniform axon loss distally. However, recently microvascular pathology has been variously interpreted as critical evidence for an ischemic pathogenesis in diabetic neuropathy or unrelated but parallel changes. In support of this position, Zochodne (2015) has pointed out that several rigorously conducted studies of nerve blood flow in experimental diabetes have not demonstrated consistent reductions and that vascular caliber is actually increased rather than reduced; improvement of nerve blood flow in some studies may not be specific; and that treatment and transgenic models which do not target microvessels can correct experimental DPN. In a human clinical trial Theriault et al. (1997) demonstrated that measurements of nerve blood flow in patients with mild DPN were not decreased. Current thinking (Zochodne, 2015) is that "microangiopathy contributes to DPN, especially in later disease, but that it is not its primary trigger" and that loss of neuronal plasticity is a more important pathogenetic mechanism. Others (Østergaard et al., 2015) suggest changes in endoneurial capillary morphology and vascular reactivity are early changes followed by reduction in nerve conduction velocity which correlate with the level of endoneurial hypoxia. Nonetheless, the idea that microvascular changes cause diabetic neuropathy is not supported by studies showing elevated endoneurial blood flow in early experimental diabetes, and absence of decreased blood flow at the time when early histological signs of neuropathy first develop in humans (Østergaard et al., 2015). Small axons are often involved during the initial phases, although large axons are not spared and typically all fiber sizes are eventually involved. Schwann and perineurial cells as well as endoneurial capillaries are enveloped by thickened basement membranes, which are related to the duration of disease and are thought to reflect resistance to degradation because of the formation of advanced glycation endproducts (AGEs); however, reduplication of the basement membrane of the endoneurial microvasculature is also described in aged patients. The microscopic picture also may include secondary segmental demyelination, proliferation of Schwann cell bands of Büngner and occasional onion-bulb formation.

1A) Painful Neuropathy
The prevalence of painful diabetic neuropathy is estimated to be 18% in type 2 diabetes and 6% in type 1 diabetes, and the incidence increases with age and diabetes duration. A patient with early damage to small axons may experience burning, dysesthetic pain, often accompanied by hyperalgesia, and allodynia, a pain different from that experienced due to large axon neuropathy. Although the definitive mechanism is not yet established a role for mitochondriopathy, upregulated cutaneous NGF with an effect on CGRP levels, NGF sensitization of peripheral terminals of nociceptors, increased membrane insertion of the heat-sensitive ion channel TRPV1 at peripheral terminals of nociceptors have all been proposed to play a role (see Lee-Kubli & Calcutt, 2014 for review). Central microglial contributions including purinergic receptor activation and a critical role for astrocytes in the spinal cord have also been proposed. As mentioned previously, gain-of-function variants of sodium channel Nav1.7 and mutations in Nav1.8, may contribute to the pathogenesis of painful neuropathy.

1B) Impaired glucose tolerance (IGT)
A significant number of patients with IGT may have
neuropathy (Azmi et al., 2015), which tends to involve small fibers and may be painful, although others have not found an increase in small fiber sensory DPN in prediabetes (Kassardjian et al., 2015).

2) Asymmetric Neuropathies
Patients with this form of neuropathy are typically older type 2 diabetics who develop motor involvement, often accompanied by constant pain, after a period of unexplained weight loss and often recover spontaneously (although incompletely). This category includes diabetic lumbosacral radiculoplexus neuropathy (see review, Laughlin & Dyck, 2014) ("diabetic amyotrophy"), truncal radiculopathy, upper limb mononeuropathy and cranial nerve (chiefly III nerve in which the pupillary reflex is relatively spared) palsies. The pathologic characterization of this group of neuropathies may involve an autoimmune component resulting in an inflammatory microvasculitis involving the vasa nervorum and/or perineuritis with thickening, neovascularization, possible immune complex and complement deposition, prior bleeding, and an axonopathy which ranges from scattered degenerating axons to the formation of an “injury neuroma”.

The pathogenesis of DRPLN is still unclear, although immune-mediated epineurial microvasculitis is thought to be the culprit in some cases. A recent study of lumbosacral and cervical radiculoplexus neuropathy (Massie et al., 2012) found ischemic patterns of injury, i.e., axonal degeneration, multifocal fiber loss, focal perineurial thickening, injury neuroma, inflammation, epineural perivascular inflammation, hemosiderin deposition, vessel wall inflammation and microvasculitis to support an ischemic origin. This study concluded that diabetic cervical radiculoplexus neuropathy is a focal (evolving into multifocal), predominantly monophasic, upper limb diabetic neuropathy with pain followed by weakness and involves motor, sensory and autonomic fibers sharing many of the clinical and pathological features of diabetic lumbosacral radiculoplexus neuropathy. Immunosuppressive therapy is recommended using high-dose steroids or intravenous immunoglobulin. Diabetic truncal radiculoneuropathy affects middle-aged to elderly patients, especially males with pain developing uni- or bilaterally in the lower thoracic or abdominal wall.

3) Diabetic Autonomic Neuropathy
Although dysfunction of the autonomic nervous system may complicate and shorten the lives of patients with diabetes, relatively little is known of the pathologic abnormalities which underlie its development. The pathogenesis of all the myriad symptoms of diabetic neuropathies may not involve the same mechanism and may involve different portions of the sympathetic, parasympathetic, enteric and visceral sensory nervous systems. Autonomic axons may also be involved in somatic nerves as part of symmetrical sensorimotor polyneuropathy. In the parasympathetic nervous system, significant loss of axons and neurons has been described. In experimental animals, subpopulations of autonomic fibers in the gut, bladder, penis and other organs may show preferential damage to, or sparing of, subpopulations of nerves. In a series of studies of autonomic neuropathy in the streptozotocin diabetic rat and various mouse models, preterminal axons and synapses in prevertebral (celiac, superior mesenteric) sympathetic ganglia are markedly enlarged and exhibit the ultrastructural features of neuroaxonal dystrophy. Similar dystrophic findings are reported in intrinsic cardiac nervous system in experimental diabetic autonomic neuropathy (Menard et al, 2014). Studies of human diabetics show similar changes in prevertebral sympathetic autonomic ganglia. Cholinergic dysfunction in diabetic mouse heart may be caused by a defect of preganglionic cholinergic nerves and/or neurotransmission at the intrinsic cardiac ganglia which may reflect sprouting and remodeling of cholinergic cardiac terminals, increasing the potential for arrhythmogenesis. Autonomic dysfunction is thought to underlie the development of Charcot joints. Selective dysfunction of populations of autonomic neurons have been described including phased degeneration of nitricergic enteric and urogenital axons (and even more specialized, involved nNOS-immunoreactive neurons that did not contain heme oxygenase-2). Conversely, electrophysiologic studies have shown that although hyperglycemia depresses synaptic transmission on sympathetic neurons and adrenal chromaffin cells it has little effect on synaptic transmission at synapses on parasympathetic neurons (Rudchenko et al. 2014). Corneal nerve damage can be deployed to diagnose subclinical and overt diabetic autonomic neuropathy (Tavakoli et al., 2015).
4) “Insulin Neuritis” (Treatment Induced Neuropathy, reviewed Hwang & Davies, 2015) Patients, both types 1 and 2 diabetes, developed reversible length-dependent severe pain within 8 weeks of the initiation of intensive glucose control, often accompanied by autonomic cardiovascular, gastrointestinal, genitourinary, and sudomotor symptoms. Reduced intra-epidermal nerve fiber density (IENFD) may be accompanied by swellings of cutaneous fibers. Continued insulin treatment usually results in the improvement of signs and symptoms. Patients who intentionally withhold insulin for weight loss may be at particularly high risk.

5) "Diabetic neuropathic cachexia" is a rare disorder in poorly controlled types 1 & 2 diabetic patients who develop significant unintentional weight loss associated with an acute symmetrical painful burning peripheral neuropathy without weakness, often with predominant lower limb involvement and allodynia. Various autonomic symptoms can be involved. Typically monophasic, it may recur. Diabetic neuropathic cachexia is usually reversible over weeks to months after adequate diabetic control (Knopp et al., 2013).

5) Skin Biopsies (see Kennedy et al., 2005; Sommer, 2008; Ehmke et al., 2015) Quantification of skin innervation demonstrates loss of IENF with duration of hyperglycemia, and may be used either for the early detection of diabetic neuropathy or for assessing its progression in clinical practice and trials. Demonstration of small fiber pathology by skin biopsy and non-invasive corneal confocal microscopy have shown decreased nerve fiber lengths in painful vs. painless diabetic neuropathy, although there is not complete agreement and changes in the receptive properties of nociceptors may also contribute. Axon loss is distally accentuated, may occur in asymptomatic patients, and often is accompanied by axonal swellings containing mitochondria and neurofilaments, even in areas in which axon density is near normal. These findings are interpreted as predegenerative changes resulting from altered axonal transport. Capsaicin application to the skin is followed by regeneration of axons; however, in diabetics there is a slower rate of IENF regeneration, even in the absence of overt neuropathy (i.e., during periods of impaired glucose tolerance alone) and may be corrected with treatment. The rate of IENF regeneration following capsaicin chemical denervation showed that it is slower in patients with diabetes or HIV without signs or symptoms of neuropathy compared to healthy subjects.

A recent study of a number of patients with painful sensory neuropathy with predominant small-fiber dysfunction (with exclusion of motor signs or sensory large fiber involvement), as verified by abnormality of thermal thresholds or IENF density, has demonstrated that diabetes mellitus, chronic alcoholism and high serum cholesterol levels were associated with most cases leaving a group (22.6%) without established etiology (Bednarik et al., 2009). Thus, there are currently no consistent differences in peripheral nerve morphology between painful and painless diabetic peripheral neuropathy. IENF loss is an early feature of diabetes, progresses with increasing neuropathic severity and may improve with appropriate intervention. Three recent studies in humans-- functional studies in rare genetic disorders, and a third study showing a role for Na(V)1.9 in painful peripheral neuropathy--have demonstrated that Na(V)1.9 plays an important part in regulating sensory neuron excitability and in pain signaling. (Dib-Hajj et al. 2015).

Pathogenetic Mechanisms of Diabetic Neuropathy (see Tomlinson and Gardiner, 2008; Stavniichuk et al., 2011; Zochodne, 2015; Fernyhough, 2015)
Investigation of several rodent models of diabetic neuropathy has suggested a variety of pathogenetic mechanisms including:

A) Oxidative/Nitrosative stress contributed by a variety of normal and pathologic pathways in excess of normal protective mechanisms resulting in subcellular damage and activating repair processes.

B) Advanced Glycation/Glycoxidation thought to operate through increased production of reactive oxygen species.
C) Polyol Pathway in which significantly elevated intraaxonal glucose is metabolized along minor pathways producing increased amounts of an impermeable sugar alcohol, sorbitol, and abnormal phosphoinositide metabolism resulting in oxidative stress, deficient sodium pump operation and diminished nerve conduction velocity.

D) Axonal Transport Dysfunction involving a variety of materials

E) Vasculopathy

F) Neurotrophic Factor Dysfunction of neurotrophic factors (NGF, CNTF, IGFs, C-peptide), their receptors or axonal transport (Verge et al., 2014). Recent studies have suggested that insulin and IGF-I, in doses which do not affect glycemic status, may produce salutary effects on diabetic sensory and autonomic neuropathies, presumably acting as neurotrophic substances.

G) Protein kinase C and p38 MAPK Activation

H) Mitochondriopathy-Based Pathway and Calcium Dyshomeostasis

Studies of DRG neurons in experimental diabetic neuropathy show changes in bioenergetics of peripheral nerve. Depression of respiratory complex activity correlates with increased depolarization of the mitochondrial inner membrane, suppression of expression of proteins of respiratory chain complexes, decreased mitochondrial proteins, impaired mitochondrial biogenesis, loss of calcium homeostasis and defective signaling of the adenosine monophosphate-activated protein kinase/PGC-1α pathway resulting in inability to respond to peaks of ATP demand in the distal axon (Chowdhury et al., 2010, 2012; Fernyhough & Jonathan, 2014; Fernyhough, 2015). Diabetes-induced loss of NF-κB may be the result of loss of insulin signaling (Saleh et al., 2012). Defective PGC-1α signaling leads to suboptimal TFAM and NRF2 expression and drives mitochondrial dysfunction. The loss of efficient energy production via OXPHOS by the mitochondria in diabetic peripheral nerve is maladaptive leading to energy failure under stress and an inability to support high-energy consuming neurons (Fernyhough, 2015).

Viader and colleagues (2013) using mice with TFAM knocked out in Schwann cells (TFAM SCKO) demonstrated that crippled mitochondria activated a stress response in the Schwann cells resulting in metabolically inefficient burning of fatty acids and, over time, a buildup of acylcarnitines, a toxic substance, in the Schwann cells. Eventually, the fatty acid derived toxin leaks out of the Schwann cells and onto the nerve axons thought to result in pain, numbness, tingling and other symptoms.

In summary, data suggest that diabetic sensory neurons are unable to produce enough energy to meet the demand. Energy deficits result in spontaneous sensory afferent discharges due to membrane depolarization secondary to inadequate Na+/K+ pumping, and degeneration that first appears in the most distal regions of neurons with the highest energy demands. Accordingly, mitotoxicity may represent a mechanism underlying the development of distal symmetrical sensory peripheral neuropathy (Bennett et al., 2014).

I) Insulin Resistance It was recently proposed (Callaghan et al., 2012) that neurons develop insulin resistance and cannot respond to the neurotrophic properties of insulin, resulting in neuronal injury and dysfunction, proposed to involve PI3K/Akt signaling and effects on mitochondrial function in neurons with increased oxidative stress and an imbalance in mitochondrial biogenesis and fission.

J) Regenerative Defects Studies by Zochodne and colleagues have found an unexpected role for PTEN upregulation in diabetic mouse peripheral neurons in attenuating axon regrowth. In chronic diabetic neuropathy models in mice, we identified significant PTEN upregulation in peripheral sensory neurons of messenger RNA and protein (Singh et al., 2014).
**K) ER Stress** Endoplasmic reticulum stress (unfolded protein response) has been identified in the CNS and PNS of streptozotocin diabetic rats and mice. A chemical chaperone, trimethylamine oxide, administered in a prevention paradigm attenuated endoplasmic reticulum stress, peripheral nerve dysfunction, intraepidermal nerve fiber loss, and sciatic nerve and spinal cord oxidative-nitrative stress in streptozotocin diabetic rats (Lupachyk et al., 2013).

These pathogenetic mechanisms are not mutually exclusive, i.e., one mechanism may be tied into several others and interplay. The currently favored mechanism involves diabetes-induced oxidative stress resulting from a variety of deranged metabolic pathways in diabetic nerve (polyol pathway, advanced glycation endproducts, deficiencies in protective enzymes, etc.) and, most recently, abnormal mitochondrial structure and function with increased generation of superoxide. Correction of sorbitol and phosphoinositide metabolism with aldose reductase inhibitors, i.e., drugs which inhibit the formation of sorbitol and have a salutary effect on phosphoinositide metabolism, are thought to partially or completely normalize measures of oxidative stress, nerve conduction velocity, axonal transport abnormalities and some vascular alterations. Initially in animal studies and subsequently in humans, an unusual alteration of the perinodal junctional apparatus ("axoglial dysjunction") of myelinated axons has been described which may result in myelinopathy at those sites and eventually nerve conduction deficits. Although studies concerning the existence of this entity have been contentious, a number of diabetes-altered proteins localized to the paranodal and nodal apparatus have been identified. It has been suggested that axoglial dysjunction may be more characteristic of patients with Type 1 diabetes ("IDDM") and ischemic neuropathy with axonal degeneration in Type 2 "NIDDM" patients. Recent work has suggested that the APO e4 allele is associated with an increased risk for diabetic neuropathy and a faster rate of its progression. Comparison of genes between patients with progressing or non-progressing diabetic neuropathy showed differentially expressed genes in progressors were enriched with defense and inflammatory responses. Carpal tunnel syndrome occurs three times as frequently in patients with diabetes compared with healthy populations.

**B) Uremia**

The neuropathy which accompanies chronic uremia is characterized by demyelination; however, teased fiber analysis shows concentration of demyelinated segments on some axons with complete sparing of others. Detailed analysis shows the demyelinated axon is relatively atrophic, and, therefore, the process represents secondary demyelination.

**C) Vitamin Deficiencies**

Deficiencies of pyridoxine; thiamine; vitamin E (found in abetalipoproteinemia, cystic fibrosis, and biliary atresia); niacin; cobalamin; and multiple nutritional deficiencies resulting in an epidemic in Cuba are associated with several forms of neuropathy.

**D) Others**

Hypothyroidism, acute intermittent porphyria, galactosemia, hepatic failure, acromegaly, chronic respiratory insufficiency and critical illness may be associated with neuropathy.

**VI. Neuropathies with an Immune-mediated Mechanism** With the parallel rise in neurobiology and immunobiology, much has been learned and much applied to the study and treatment of neuropathies with immune-mediated mechanisms (see recent reviews in Bourque et al., 2015; Martini & Willison, 2015; Allen & Parry, 2015; Feldman et al., 2015). Plasma exchange is known to remove autoantibodies, cytokines and complement and as yet undiscovered humoral factors. The ability to target selected portions of the immune system with a series of monoclonal antibodies promises to provide therapy without the sledgehammer approach of the past, although no therapy is without risk.

**Nodo-paranodopathy (NPN)** Detailed analysis of the node of Ranvier reveals a remarkable group of constituents organized for its structure and functional maintenance (Armati & Mathey, 2014). Although
immune-mediated neuropathies were previously considered demyelinating or axonal, recent work has identified a group of diseases with microstructural changes restricted to the nodal/paranodal region (Uncini & Kuwabara, 2015). NPN has different etiologies (dysimmune, inflammatory, ischemic, nutritional, toxic). Different techniques useful in characterizing NPN include nerve conduction, excitability studies, pathology and animal models. Uncini and Kuwabara (2015) proposed this new category with features including: (1) a pathophysiological continuum from transitory nerve conduction block to axonal degeneration; (2) conduction block due to paranodal myelin detachment, node lengthening, dysfunction or disruption of Na(+) channels, altered homeostasis of water and ions, or abnormal polarization of the axolemma; (3) conduction block which may be promptly reversible without development of excessive temporal dispersion; and, (4) axonal degeneration, depending on the specific disorder and its severity, eventually follows the conduction block. NPN entities identified by Uncini and Kuwabara (2015) include acute motor axonal neuropathy (AMAN), multifocal motor neuropathy (MMN), certain antiganglioside antibody driven entities, critical illness neuropathy, various ischemic neuropathies, beriberi and tetrodotoxin-intoxication.

A) Guillain-Barré syndrome (GBS)
   1) acute inflammatory demyelinating polyneuropathy (AIDP)
   2) acute motor axonal neuropathy (AMAN)
   3) acute motor sensory axonal neuropathy (AMSAN)
   4) Miller Fisher Variant

B) Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

C) Experimental Allergic Neuritis (EAN)

Guillain-Barré syndrome (GBS, see Vucic et al., 2009 for recent review)

Guillain-Barré syndrome is an acute onset polyneuropathy which may rapidly progress to paralysis in the absence of changes in the sensorium and currently occurs at a yearly rate of 2 cases per 100,000 population. A number of different subtypes have been identified including its classic form acute inflammatory demyelinating polyradiculoneuropathy (ADIP), the pattern resulting in 90% of the cases in the Western world. Acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN) are axonal forms of GBS which constitute 30-47% of GBS cases in Asia, South and Central America, and are often preceded by infection by Campylobacter jejuni. Rarer subtypes include (Miller) Fisher syndrome, acute sensory neuronopathy and acute pandysautonomia which present with a somewhat stereotyped clinical picture and, in some cases, autoantibody signature. The majority of GBS cases have an antecedent infection within 6 weeks of onset, most typically an upper respiratory tract infection or gastroenteritis including but not limited to Epstein-Barr virus, Mycoplasma pneumoniae, Campylobacter jejuni and cytomegalovirus. The axonal forms of GBS have a more acute and severe course, which may include more frequent respiratory, cranial nerve and autonomic involvement. Use of skin biopsy in GBS and its variants showed a substantial loss of IENFD which was greater in patients who experienced pain; patients with the pure motor variant of GBS, surprisingly, also showed decreased IENFD. The IENFD may predict long-term disability. In samples from GBS patients during the acute phase, most dermal nerve fibers showed segmental demyelination with adjacent T lymphocytes and macrophages.

Acute Inflammatory Demyelinating Polyneuropathy (AIDP)

ADIP, the acute inflammatory demyelinating form of Guillain-Barré syndrome, CIDP and EAN involve a cell-mediated autoimmune pathogenesis coupled with the participation of a humoral component, and have a number of pathologic findings in common. There may be a prominent perivascular epineurial and endoneurial lymphocytic infiltrate, mostly consisting of T cells and macrophages. Plastic sections demonstrate various stages of demyelination and remyelination coupled with macrophages containing myelin debris. The pathology is distinctive and characterized by macrophages which penetrate the Schwann
cell basal lamina, displace a rim of Schwann cell cytoplasm and strip away otherwise normal appearing myelin. Activated T cells and macrophages in the nerve liberate pro-inflammatory cytokines, proteases and toxic oxygen species. The number and proportion of CD4⁺CD25⁺ regulatory T cells are reduced in acute-stage GBS. Circulating antibodies directed against targets within the endoneurium may secondarily gain access through a damaged blood nerve barrier and contribute to nerve dysfunction. The adoptive transfer of pure P2 protein-specific CD4⁺ T cells derived from rats with EAN into recipient naïve rats results in axonal degeneration with mild demyelination; however, the same T cells administered with anti-myelin antibodies induces a more demyelinating pattern of injury which may reflect opening the blood nerve barrier. In other studies the addition of anti-myelin antibodies increases the extent of demyelination with the participation of fewer T cells. Thus, circulating antibodies may gain access to the endoneurium through an abnormally permeable blood nerve barrier or, potentially, be synthesized locally by invading or residing endoneurial elements, which may explain the positive clinical effects of plasmapheresis in some cases of CIDP as well as in GBS. A variety of cell adhesion molecules at nodes or paranodes (gliomedin, neurofascin, and contactin) are recognized by IgG antibodies in patients with GBS or CIDP. Recent studies have shown that intravenous immunoglobulins also neutralize neuromuscular blocking antibodies in GBS. Disruption of ion channels in demyelinated axons may contribute to functional changes. Eventually, Schwann cells proliferate and remyelinate the denuded internode. Axonal loss or axonopathy is seen, probably because of a noxious endoneurial environment due to liberated cytokines.

Axonal GBS [acute motor axonal neuropathy (AMAN) and acute motor sensory axonal neuropathy (AMSAN)]

An "axonal form" of GBS has been described in which the axon appears to be the primary target, rather than myelin. It is characterized by pure motor involvement, frequent antecedent infection by Campylobacter jejuni, association with anti-GM1 or anti-GD1a immunoglobulin G antibodies, and electrophysiological evidence of axonal degeneration and reversible conduction block. Although this pattern of GBS is rare in Europe and North America (<10% of GBS cases), it is predominant in China and Japan and forms approximately 50% of Indian cases. The axonal form consists of acute motor axonal neuropathy (AMAN), acute sensory ataxic neuropathy (ASAN) and acute motor and sensory axonal neuropathy (AMSAN). Pathologically, macrophages may be found immediately adjacent to nodes of Ranvier or extending their processes through the Schwann cell basement membrane at the level of the node which culminates in their entry into the periaxonal space. Substantial numbers of degenerating axons may be demonstrated in some cases; in others, only denervated neuromuscular junctions and loss of intramuscular axons have been reported. Studies of passively-transmitted experimental T cell mediated inflammatory peripheral neuropathy in rats have demonstrated that differences in the extent of demyelination vs. Wallerian degeneration may reflect the number of injected T cells. It has been proposed in studies of axonal GBS that antibody (anti-GM1 or GD1a) may target a constituent of the node of Ranvier to which it binds, fixes complement forming a membrane attack complex, recruits macrophages and results eventually in axonal degeneration, possibly by activating calpain at the nodes with subsequent loss of nodal complex proteins including Na⁺ channels. Clinical axonal GBS may be associated with a more aggressive course with poorer outcome, electrophysiologic and pathologic evidence of prominent axonopathy, relatively increased incidence of enteric Campylobacter jejuni infection (less frequently AIDP may be preceded by C. jejuni infection) and a role for antibody directed against GM1 ganglioside (the possible antibody target at the node of Ranvier) has been implicated in its pathogenesis, although polyclonal antibodies against GM1 have been described in a variety of motor neuron disorders and motor neuropathies. Thus, nodal disruption with autoantibodies to gangliosides GM1, GD1a, or GD1b, provide an explanation for the continuum of AMAN, AMSAN, and ASAN. Seropositivity for GM1 has been associated with evidence of C. jejuni infection and may be associated with severe neuropathy with increased axonal degeneration. IgG anti-GD1a antibodies have been found in 60% of Chinese patients with AMAN but only 4% with the demyelinating form of GBS. Autoantibodies to gangliosides may disrupt Nav channels concomitant with the deposition of complement, alterations in nodal cytoskeleton and Schwann cell processes as reproduced in animal models. Autoantibodies against gangliosides GM1 or GD1a are
associated with AMAN and AMSAN, whereas antibodies to GD1b ganglioside are detected in ASAN (Susuki et al., 2012). Complement activation and membrane attack complex formation result in loss of Na+ channels and terminal myelin loops. Different patterns of nerve injury seen in GBS may reflect the strain of infecting organism or host HLA alleles. It has been recently proposed that serum GFAP levels may be used in GBS as a diagnostic marker of the axonal variant where GFAP levels are increased compared to AIDP and predict outcome. Pathological changes in rabbits sensitized with ganglioside GM1 or C. jejuni are identical to those in human AMAN, accompany induction of anti-GM1 IgG antibodies and result in flaccid paralysis. In addition, there is loss of nodal sodium channel clusters and detachment of paranodal myelin terminal loops, thought to reduce the safety factor for impulse transmission and produce rapidly reversible functional conduction block. IgG antibodies to GM1, GalNAc-GD1a or GD1a from the sera of AMAN patients also blocked the Cav2.1 voltage-gated Ca channel current in cerebellar Purkinje cells, but those from AIDP patients did not. Rapid recovery of muscle action potentials is more suggestive of reversal of anti-ganglioside antibodies resulting in dysfunction of NaV at the nodes of Ranvier than structural axonal regeneration. The presence of IgG1 anti-ganglioside antibodies is associated with diarrhea, anti-Campylobacter antibodies, and poor prognosis; however, the presence of antibodies more related to upper respiratory tract infections such as Hemophilus influenzae were associated with a better outcome. It remains unclear why symptomatology differs between motor and sensory nerves since similar amounts of GD1a and GM1 are found in both.

**Miller Fisher GBS Variant (MFS)**

The (Miller) Fisher variant of GBS is distinguished from AIDP and AMAN by a distinctive clinical syndrome in which ataxia, areflexia and ophthalmoplegia are prominent. These patients frequently exhibit antibodies against the ganglioside GQ1b (Koga et al, 1998) which appears to be concentrated at the nodes of Ranvier, particularly those of the oculomotor, trochlear and abducens nerves. Recent studies have demonstrated features in common with Bickerstaff brainstem encephalitis and acute ophthalmoparesis. Some investigators have separated off other subvariants (e.g., ataxic GBS, cranial nerve variant of GBS) which may represent forme frustes of MFS. MFS appears to be more common among eastern Asian GBS patients, some of whom had C. jejuni infection.

**CIDP**

CIDP is a clinical syndrome characterized by a chronic progressive or relapsing/remitting, symmetric sensory and motor polyradiculoneuropathy which progresses for more than 8 weeks (reviewed in Hughes et al., 2006). Proximal and motor nerves appear more affected than the typically biopsied sural nerve. The pathologic findings in CIDP include axon loss and chronic inflammation in the perineurium and onion-bulbs, not seen in all cases, and reflect the chronicity of the process. The histopathologic diagnostic criteria of the American Academy of Neurology for CIDP require the detection of more than 5 demyelinated fibers. Some investigators have proposed that CIDP is a chronic form of GBS. Its autoimmune pathogenesis involves T-cells (both CD4+ and CD8+) and antibodies. Myelin protein antigens, P0, P2 and PMP22 may be targets, particularly P0, against which antibodies are found in 20% of CIDP patients. The occasional coexistence of melanoma and CIDP also suggests the possibility of cross reaction of melanoma cell antigens with Schwann cells or myelin itself. Some HLA subtype frequencies (e.g., HLA-DR2) differ between GBS and CIDP. In CIDP there may be failure of regulatory T-cells to suppress and terminate the typically monophasic attack of GBS. This process is supported by the reported development of an autoimmune neuropathy due to a deficiency of numbers or function of regulatory T cells and the reduction of the number and suppressive function of CD4 CD25+ T regulatory cells in patients with CIDP compared with healthy controls. During the progressive or the relapsing phases of CIDP, the number of T regulatory cells was reduced, and the suppressive function of them decreased. Some investigators suggest CIDP belongs to a heterogeneous group of chronic immune-mediated demyelinating polyneuropathies which also include more poorly understood distal acquired demyelinating sensory polyneuropathy (DADS), multifocal acquired demyelinating sensory and motor polyneuropathy (MADSAM)/Lewis-Sumner syndrome, and, possibly,
multifocal motor neuropathy (MMN, see later), although the relationship of these entities is still unresolved. The presence of sensory involvement helps to distinguish CIDP from MMN, in which only motor nerves are involved. CIDP may occur with increased incidence in patients with diabetes, although this has also been disputed. CIDP is treated by steroids, intravenous immunoglobulin and plasmapheresis. Several studies have established that immunosuppressive agents TNF-α antagonists such as infliximab and etanercept may trigger the development of CIDP, GBS, Fisher syndrome or MMN. Recent data demonstrates that cytotoxic CD8+ T cells exhibit a much broader activation than CD4+ T cells, indicating a potentially crucial role of CD8+ T cells in the immunopathogenesis of CIDP (Mausberg et al., 2013). The profound oligoclonal response in T-cell activation suggests multiple peptides may induce and propagate CIDP (Mausberg et al., 2013).

D) Anti-Myelin Associated Glycoprotein (MAG) Neuropathy
A number of patients with a slowly progressive demyelinating neuropathy have been found to have an associated IgM monoclonal gammopathy ("monoclonal gammopathy of unknown significance", MGUS) which in some patients is associated with multiple myeloma, Waldenström macroglobulinaemia (WM) or amyloidosis. In about 50% of patients with neuropathy and IgM MGUS the M protein reacts with myelin-associated glycoprotein (MAG) a molecule which has properties that affect myelin integrity. "Anti-MAG" antibody may also cross react with other myelin proteins including 3-sulfated glucuronyl paragloboside (SGPG) and sulfated glucuronyl lactosaminylparagloboside, which share an antigenic carbohydrate determinant with MAG. Pathologic investigations have illustrated the deposition of anti-MAG on portions of the myelin sheaths of peripheral nerve axons. Ultrastructural studies have demonstrated the insinuation of anti-MAG antibody between the densely packed layers of myelin lamellae (accompanied by complement) which result in areas of altered myelin periodicity ("wide spaced myelin") which may eventually result in demyelination. This myelin modification corresponds to portions of the mesaxon that are neither flattened nor compacted and that are visible at least around 1 semicircumference of the axon on 3 or more consecutive lamellae. Axonal degeneration, however, may also occur in this syndrome. Immunosuppression and plasmapheresis have resulted in transient improvement. Anti-MAG IgM antibodies have been demonstrated involving sensory nerves in the skin. Injection of serum antibodies from MGUS patients into the endoneurium of experimental animals has been reported to produce an abnormality of conduction velocity. Recent studies with Rituximab, a mouse-human chimeric antibody against the B cell surface marker CD20 which results in a rapid and sustained depletion of B cells, are reported to benefit clinical status, although two recent randomized controlled trials with rituximab failed to provide evidence of efficacy in primary outcome measures, despite reduction in antibody levels. A population of MGUS patients eventually develops multiple myeloma, Waldenstrom macroglobulinemia, primary amyloidosis or lymphoproliferative disease. The pathogenic mechanism of myelin changes in anti-MAG neuropathy may target terminal myelin loops, subsequently leading to demyelination. Widening of the myelin lamellae have also been observed in nerve biopsy with ultrastructural examination several years before the monoclonal dysglobulinemia was detected in the serum. Nonetheless, a variety of neuropathic findings are described suggesting that the polyneuropathy associated with anti-MAG antibodies is less homogeneous pathologically and possibly pathophysiologically (Magy et al., 2015).

E) Other Paraproteinemic Neuropathies
Paraproteinemic neuropathies are a heterogeneous group of neuropathies that are most frequently associated with monoclonal gammopathies, which are caused by a proliferation of monoclonal plasma cells or B lymphocytes that result in M proteins or paraproteins formed from a single heavy chain and a light chain. As mentioned above, they include subclinical monoclonal gammopathy of undetermined significance (MGUS) as well as malignant systemic disorders such as multiple myeloma, amyloidosis, Waldenström macroglobulinemia, and POEMS syndrome. In addition, recent studies have identified a number of patients whose sera contain a variety of other (non-MAG) antibodies which may underlie several motor or sensory neuropathies including multifocal motor neuropathy. Antibodies to more than 20 different glycolipids have been associated with a wide range of clinically identifiable acute and chronic neuropathy syndromes. As in anti-MAG neuropathy, detection of IgM deposits may even precede the detection of IgM gammopathy in
serum.

**F) Antibody Mediated Paraneoplastic Neuropathies**

The antibody anti-Hu (also called ANNA-1 or type 1 antineuronal nuclear antibody) is associated with paraneoplastic subacute sensory neuropathy which may reflect development of antibodies against shared antigens of small cell lung carcinoma (most typically, but also breast and kidney carcinoma, lymphoma, etc.) and nervous system tissues, particularly dorsal root ganglion neurons but including myenteric plexus (25% of patients with anti-Hu antibody have GI motility problems) and CNS neurons. Ganglia typically show an inflammatory infiltrate which consists mostly of CD8+ T cells. A variety of other antibodies (directed against collapsing response-mediator proteins-3 and -5, amphiphysin, or anti-Yo antibodies) have been described associated with other paraneoplastic syndromes.

**G) Autoimmune Autonomic Neuropathy**

A clinical syndrome resulting in subacute autonomic failure has been identified, typically following a viral illness, in which circulating antibodies against ganglionic nicotine acetylcholine receptor have been identified (Low et al., 2003).

**H) Multifocal Motor Neuropathy (MMN)**

MMN is a rare inflammatory neuropathy characterized by slowly progressive, asymmetric distal limb weakness without sensory loss which is associated in 20-85% of patients with IgM anti-ganglioside GM1 antibodies and differs from vasculitic neuropathy because it is slow and painless and affects only motor nerve fibers. In a series of 40 MMN cases and controls, the assay sensitivity varies from 50% for GM1 alone to 75% for the GM1:GalC complex. (Willison et al, 2014). Intravenous immunoglobulin (IVIg) remains the only therapeutic option in MMN although there may be a role for eculizumab that binds and neutralizes human complement factor C5. Pathologic findings in MMN are poorly characterized and demyelination, axonal degeneration and perivascular lymphocytic infiltrates have been described.

**I) POEMS** (Crow-Fukase syndrome)

POEMS is an acronym for Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein and Skin changes and represents a demyelinating neuropathy with abnormality of myelin compaction (“uncompacted myelin lamellae” which is seen in 80% of the cases) and secondary axonal loss. In addition, patients have a monoclonal plasma cell disorder and may have sclerotic bone lesions, Castleman disease and serum VEGF elevation which represents a useful diagnostic marker. Patients may also have organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema or thrombocytosis/polycythemia. It is a rare paraneoplastic syndrome that usually occurs in the setting of osteosclerotic myeloma although some patients have Waldenstrom macroglobulinemia or plasmacytoma, and others do not have a malignancy.

**VII. Genetic Neuropathies**

The rise of molecular genetics has rapidly expanded the number of genetic neuropathies and provided insights into their possible pathogenetic mechanisms (Fridman & Reilly, 2015). The largest group of inherited peripheral neuropathies are separable electrophysiologically into 3 groups (see Rautenstrauss, 2011): 1) Hereditary Motor Sensory Neuropathy (Charcot Marie Tooth CMT); 2) Hereditary Sensory and Autonomic neuropathy (HSAN); and 3) distal Hereditary Motor Neuropathy. CMT has been divided into demyelinating forms (CMT 1) and axonal forms (CMT type 2) and intermediate forms on the basis of nerve conduction velocity. These entities are characterized by demyelination, axonal loss or both. Thus far, approximately 40 causative genes (see http://www.molgen.ua.ac.be/CMTMutations/) have been associated with CMT and distal HNM, and the pattern of inheritance can be autosomal dominant, autosomal recessive or X-linked. The major CMT2 gene is MFN2 (CMT2A), which encodes the mitochondrial membrane protein mitofusin 2. MFN2 is mutated in CMT2A patients, who represent around 20% of all CMT2 cases and show abnormal intraaxonal mitochondria of unusual shapes with abnormal cristae and focal aggregation.
A) Hypertrophic (Onion-bulb) Neuropathies (Table 2, http://www.molgen.ua.ac.be/CMTMutations/)

The concentric proliferation of Schwann cells in response to multiple episodes of demyelination and subsequent remyelination results in distinctive structures, onion-bulbs, which are the hallmark of hypertrophic neuropathy. Although onion-bulbs may be seen in small numbers in almost any chronic demyelinating condition, in onion-bulb or hypertrophic neuropathies they dominate the pathologic picture. The origin of onion bulbs as the result of impaired axonal regeneration has also been described. Nerves may be palpably enlarged and conduction velocities markedly decreased. Many of these neuropathies involve selective alterations in various myelin proteins. Targets include compact myelin constituents P0 protein (MPZ), peripheral myelin protein 22 (PMP22) and myelin basic protein as well as proteins localized to non-compact myelin near the paranode including the Schwann cell proteins MAG, connexin 32, neurofascin 155 and the axonal proteins Caspr and contactin. Many neonatal peripheral neuropathies belong to the congenital hypomyelinating neuropathy syndrome, in which defective synthesis and maintenance of myelin results in near complete absence of peripheral myelin. A similar process may present in infancy as Dejerine–Sottas neuropathy. Typically, de novo mutations in myelin protein zero (MPZ), peripheral myelin protein 22 (PMP22) and early growth response 2 (EGR2) are described as the cause of congenital hypomyelinating neuropathy and Dejerine–Sottas neuropathy (see below).

Table 2

<table>
<thead>
<tr>
<th>Designation</th>
<th>Inheritance</th>
<th>Gene Defect</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT1A</td>
<td>AD</td>
<td>PMP22</td>
<td>Onion-bulbs (OB)</td>
</tr>
<tr>
<td>CMT1B</td>
<td>AD</td>
<td>P0</td>
<td>OB</td>
</tr>
<tr>
<td>CMT1C</td>
<td>AD</td>
<td>EGR2</td>
<td>OB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LITAF/SIMPLE</td>
<td>OB</td>
</tr>
<tr>
<td>CMT1X</td>
<td>XD</td>
<td>Connexin 32</td>
<td>Axonal/OB</td>
</tr>
<tr>
<td>CMT2A</td>
<td>AD or AR</td>
<td>Kinesin Family Member IB</td>
<td>Axonal/+OB</td>
</tr>
<tr>
<td>CMT2B</td>
<td>AD (rarer AR)</td>
<td>Mitofusin 2</td>
<td>OB</td>
</tr>
<tr>
<td>CMT2D</td>
<td>AD</td>
<td>RAB-7</td>
<td>Axonal/+OB</td>
</tr>
<tr>
<td>CMT2E</td>
<td>AD</td>
<td>glycyyl tRNA synthetase</td>
<td>Axonal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurofilament-L</td>
<td>Axonal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMP22, Po, Connexin 32</td>
<td>Axonal</td>
</tr>
<tr>
<td>CMT3 (DSS)</td>
<td>AD or AR (or de novo)</td>
<td>PMP22, P0, EGR2, Periaxin, GDAP1</td>
<td>OB</td>
</tr>
<tr>
<td>CMT4A</td>
<td>AR</td>
<td>GDAP1</td>
<td>OB</td>
</tr>
<tr>
<td>CMT4B.1</td>
<td>AR</td>
<td>myotubulin related protein 2</td>
<td>Demyel +folds</td>
</tr>
<tr>
<td>CMT4B.2</td>
<td>AR</td>
<td>set binding factor-2</td>
<td>OB + focal thickening</td>
</tr>
<tr>
<td>CMT4C</td>
<td>AR</td>
<td>SH3 &amp; tetratricopeptide repeat domain 2</td>
<td>OB + focal thickening</td>
</tr>
<tr>
<td>CMT4D</td>
<td>AR</td>
<td>N-myc downstream</td>
<td>OB</td>
</tr>
</tbody>
</table>

Table 2 continues...
1) **Hypertrophic Charcot-Marie-Tooth Disease (CMT1)**

Inherited as an autosomal dominant condition and initially thought to represent a primary axonopathy with secondary demyelination; studies of some forms of CMT have identified a duplication or point mutation in the gene for PMP-22, an integral myelin glycoprotein required for myelin compaction, a point mutation in P0 myelin protein, which is also needed for proper myelin compaction, a defect in the early growth response 2 gene (EGR2) and, most recently, mutations of periaxin (a cytoskeleton-associated Schwann cell protein which may regulate Schwann cell shape and relationship to its axon). Overexpression of PMP-22 in transgenic rodents results in hypomyelination and onion bulb formation and may induce defects in the metabolism of other proteins due to the development of an endoplasmic reticulum retention phenotype. Mice heterozygous for a null mutation in P0 also develop progressive demyelination and onion bulb formation. Studies with mouse models of CMT using P0+/− transgenic mice have surprisingly identified a role for macrophage and lymphocytic infiltration in the pathogenesis of genetically mediated demyelination. Cases of X-linked CMT demonstrate a defect in the gene for connexin-32. CNTF production by Schwann cells is markedly reduced in CMT1A and, in a mouse model of CMT1A characterized by early overexpression of PMP22, there is a strong up-regulation of CXCL14, which may play a novel regulatory role in Schwann cell differentiation.

2) **Other types** (Table 2) include CMT associated with neurofilament light chain abnormality, ganglioside-induced differentiation-association protein 1 and myotubularin-related protein 2 gene as well as Dejerine-Sottas disease (DSS, includes HMSN-III) beginning in early life, some cases of which have a demonstrable genetic defect in PMP-22, periaxin, GDAP1, EGR2 or myelin protein P0. P0 deficient mice develop peripheral neuropathy characterized by hypomyelination, demyelination, onion bulb formation and impaired nerve conduction. Refsum disease, caused by phytanic acid oxidase deficiency, also results in an onion bulb neuropathy. Mutations in mitofuscin 2 which underlie some cases of CMT2A have lead to burgeoning interest in genes controlling mitochondrial fusion and fission in peripheral neuropathy as well as central nervous system diseases.

B) **Hereditary Neuropathy with Pressure Palsies (HNPP)**

Teased fiber preparations of this dominantly inherited neuropathy demonstrate marked focal hypermyelination ("tomacula") characterized by redundant myelin folds, demyelination and remyelination. Experimental evidence suggests deletion of a region including the PMP-22 gene underlies this neuropathy; patients are thus monosomic for the region of chromosome 17 which includes the PMP-22 gene. Mice with diminished or absent PMP-22 gene product are reported to develop hypermyelinating tomacula, demyelination and functional impairment as well as structures resembling onion bulbs. Similarly, mice which lack PTEN selectively in Schwann cells causes focal hypermyelination and tomaculae; which is ameliorated by the mTOR antagonist rapamycin, evidence for a role for dysregulated phosphoinositide metabolism.

C) **Hereditary Giant Axonal Neuropathy (Johnson-Kenner et al., 2014)**

Axons are typically distended by aggregates of neurofilaments, and show thinned myelin sheaths which are accompanied by "kinky hair", and a variety of CNS symptoms. Schwann cells and endothelial cells may also have aggregates of intermediate filaments. The gene responsible for giant axonal neuropathy codes for the synthesis of gigaxonin. Recent work with an animal model proposes that the disruption of gigaxonin results in an impaired ubiquitin-proteosomal process leading to the accumulation of the microtubule

<table>
<thead>
<tr>
<th>(CMT-LOM)</th>
<th>regulated gene 1 (NDRG1)</th>
<th>Severe Myelin Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT4E</td>
<td>AR/AD</td>
<td>EGR-2, P0</td>
</tr>
<tr>
<td>CMT4F</td>
<td>AR/AD</td>
<td>Periaxin, PMP22, P0, EGR2</td>
</tr>
<tr>
<td>HNPP</td>
<td>AD</td>
<td>PMP22</td>
</tr>
</tbody>
</table>
associated protein MAP8. Similarly, giant axonal neuropathy-associated gigaxonin mutations impair intermediate filament protein degradation (Mahammad et al, 2013). Accumulated MAP8 is thought to subsequently alter the microtubule network, trapping the dynein motor of retrograde axonal transport as an insoluble structure, leading to neuronal death (Ding et al., 2006).

D) Hereditary Sensory and Autonomic Neuropathies (HSANs) (reviewed in Verpoorten et al, 2006; Dineen & Freeman, 2015; Rothier et al., 2012)

Disease associated mutations in a number of genes have been identified including two genes for autosomal dominant (SPTLC1 and RAB7) and five for autosomal recessive forms of HSAN (WNK1/HSN2, NTRK1, NGFB, CCT5 and IKBKAP). Included in this group are:

**HSAN I** Acral sensory neuropathy, dominant inheritance, due to a mutation in the serine palmitoyltransferase, long chain base subunit 1 (SPTLC1) gene and abnormality of glycolipid metabolism. Motor axons are typically involved and autonomic relatively spared in HSAN1. It is thought that deoxysphingolipids cause the clinical phenotype of HSAN1 because they can neither be converted into complex sphingolipids nor degraded by the classical catabolic pathways and deoxysphingolipids accumulate in cells. Causative mutations in five genes (SPTLC1, SPTLC2, ATL1, RAB7A and DNMT1) have been described (Rothier et al., 2012).

**HSAN II** Acral sensory neuropathy, recessive inheritance, a congenital neuropathy with prominent loss of myelinated axons and relative sparing of unmyelinated axons. Genetic studies show a defect in the WNK lysine deficient protein kinase 1 (WNK1) gene Mutations in WNK1, FAM134B, and KIF1A have all been associated with HSAN type 2 (Rothier et al., 2012). It is proposed that the kinase activity of WNK1/HSN2 regulates the unloading of KIF1A cargos at axonal tips of neurons.

**HSAN III** Familial Dysautonomia (Riley Day Syndrome), resulting in neuron loss in sensory and sympathetic ganglia with variable involvement of parasympathetic ganglia. Although the pattern of involvement suggested the potential for generalized deficiency of NGF in its pathogenesis, a mutation in the IKBKAP gene has been identified, specifically a splice variant resulting in a prematurely truncated IKBKAP protein product. Recent work describes the effect of a plant cytokinin kinetin on the prevention of a splice variant which might have a therapeutic role.

**HSAN IV** Congenital sensory neuropathy with anhidrosis. Marked neuron loss is found in sensory and sympathetic ganglia and, as expected, absence of unmyelinated axons and reduction of small myelinated axons in peripheral nerves. Skin biopsies show decreased C and Aδ fibers in the epidermis and absent or hypoplastic sweat glands lacking innervation. Genetic studies have identified mutations in the trkA (high affinity NGF receptor) gene.

**HSAN V** This entity is an AR childhood onset disorder with loss of deep pain and temperature sense. The current thought is that defects in the NGF-β gene results in inhibition only of p75 (low affinity neurotrophin receptor)-promoted NGF activities.

E) Distal Hereditary Motor Neuropathies (dHMN, see Rossor et al., 2012) are represented by a group of diseases with the common feature of a length-dependent predominantly motor neuropathy, although minor sensory abnormalities or an upper motor neuron contribution may be demonstrated. Multiple causative genes have been identified with AD, AR and X-linked patterns of inheritance. Patients develop a very slowly progressive length-dependent condition often starting in the first two decades of life. ATP7A mutations in dHMN have been recently discovered.

F) Others Ataxia Telangiectasia, mitochondrial diseases, infantile neuroaxonal dystrophy, multisystem degeneration, hereditary ataxias, leukodystrophies, and Fabry disease give rise to other inherited
neuropathies.

VIII. Amyloid and Related Neuropathies

Amyloid is not a single biochemically defined substance; rather, it represents an extracellular deposit of proteins arranged in a beta pleated sheet conformation. Amyloid is characterized by 10-20 nm unbranched filaments which stain with Congo Red dye and polarize with a characteristic apple green color. Amyloid may arise from fragments of immunoglobulin light chains, mutant transthyretin (TTR, the transport thyroxin and retinol-binding protein) or other proteins. Amyloid neuropathy occurs in i) primary (non-hereditary) amyloidosis; ii) amyloidosis associated with dysglobulinemia (both i and ii composed of immunoglobulin derived amyloid); and, iii) selected hereditary amyloidoses (such as Andrade disease) in which the deposited amyloid is derived from TTR or other materials (e.g., lysozyme, gelsolin, apolipoprotein-A1). The mechanism of amyloid damage is unclear. Transthyretin amyloidosis is treated with liver transplantation, which eliminates the mutated transthyretin from the blood; however, some patients continue to deposit amyloid derived from normal TTR. Other treatment regimens include chemotherapeutic agents, corticosteroids, stem cell transplantation, iododeoxydoxorubicin (an agent which causes amyloid resorption), tafamidis meglumine and colchicine. Tafamidis meglumine, used in the treatment of Transthyretin Type Familial Amyloid Polyneuropathy (TTR-FAP), occupies TTR’s thyroxine binding sites and stabilizes both normal and mutated TTR tetramers shifting the monomer-tetramer equilibrium away from the amyloidogenic monomers.

Amyloid may be deposited within the endoneurium, in the endoneurial and epineurial vasculature or within epineurial connective tissue. Although amyloid neuropathy often preferentially involves small myelinated and unmyelinated axons, the mechanism is unestablished. One proposed mechanism in familial amyloid polyneuropathy involves transthyretin-derived amyloid fibril interaction with advanced glycosylation endproduct receptors (RAGE) with resultant upregulation of increased TNF$\alpha$, IL-1$\beta$ and NOS levels. Immunohistochemistry can be used to identify the source material of the amyloid, e.g., as in a patient with a plasma cell dyscrasia demonstrating immunofluorescence for altered immunoglobulin kappa light chains.

IX. Infectious Neuropathies

The perineurium provides a protective sheath to axons running through an area of infection and can usually withstand direct damage within a significant inflammatory infiltrate.

A) Herpes Zoster The disease presents as a painful vesicular rash corresponding to a dermatome innervated by a dorsal root or trigeminal ganglion. It represents the emergence of varicella virus from latency, having initially gained access to ganglia by parasitizing the cutaneous nerves at the time of childhood chickenpox infection. Latent virus is not visible by EM but its genome can be demonstrated as well as a lymphocytic infiltrate. At times of immune status alteration or for unknown reasons, the virus may emerge from latency and be transported to the skin, resulting in the cutaneous eruption of "shingles". At the time of cutaneous eruption the dorsal root or trigeminal ganglia may show hemorrhagic ganglioradiculitis. Necrotic neurons and satellite cells are admixed with angionecrosis, hemorrhage, and an inflammatory mononuclear cell infiltrate involving dorsal root ganglia and adjacent dorsal roots. Cowdry type A inclusions are seen in neurons, and, more frequently, within the nuclei of satellite cells. Occasional spread of the process along dorsal roots to the spinal cord is a recorded, but relatively rare, complication. The persisting lymphocytic cell infiltration and the elevated CD8$^+$ T cells and cytokine/chemokine expression in the trigeminal ganglia during viral latency is surprisingly not accompanied by neuronal degeneration. Varicella may reactivate without a rash (zoster sine herpete). Ramsay Hunt syndrome is characterized by a herpetic eruption in the external auditory canal accompanied by facial nerve palsy and ear pain.

B) Leprosy This infectious disorder results in loss of cutaneous sensation and motor function in patients with leprosy. Nerves routinely become infected with Mycobacterium leprae during the initial phases of the disease. Two patterns of involvement are seen which reflect the immune status of the host.
Patients with intact immune function react by producing a granulomatous reaction that involves skin and adjacent nerves ("tuberculoid" leprosy) in which few organisms are found. In this form destruction of the nerve is mediated by CD4+ T-helper cells interacting with M. leprae antigens presented in the endoneurium by macrophages and possibly IFN-γ stimulated Schwann cells. In patients with a compromised immune response to the organism, endoneurial fibrosis is accompanied by numerous organisms which can be demonstrated within Schwann cells (particularly those of unmyelinated axons), perineurial cells, endothelium, fibroblasts and endoneurial macrophages ("lepra cells"). Recent investigation has demonstrated that the organism colonizes Schwann cells by binding to laminin-α2 resulting in MAPKinase-cascade pathway induced de-myelination and de-differentiation of myelinated axons which, as a result, generate non-myelinated Schwann cells which are more susceptible to further parasitization by the organism. Adult Schwann cells are reprogrammed to stem cell-like cells by leprosy bacilli which promotes dissemination of infection (Masaki et al., 2013). Nerves are often expanded in size and may be palpable through the skin. Many leprosy cases in the southern USA involve infection with the same unique strain of M. leprae that occurs naturally among wild armadillos in the region. Although the prevalence of leprosy is declining worldwide, it is still among the common causes of neuropathy in parts of the developing world, particularly India, Brazil, parts of Africa, and Nepal.

C) AIDS Several different types of neuropathy may develop in patients infected with HIV. HIV-associated neuropathies include immune-mediated forms such as Guillain-Barre syndrome or CIDP (relatively early in the disease), vasculitic patterns, painful progressive distal sensory polyneuropathy (DSP, detected commonly in patients dying with AIDS), autonomic neuropathy with largely uncharacterized neuropathology, and lumbosacral radiculopathy associated with local CMV infection. DSP shows prominent activated HIV-infected macrophage activation and lymphocytic (CD8>CD4+) infiltration with local release of proinflammatory cytokines (IFN-γ, TNF-α and IL-6) in the vicinity of axonal degeneration and within the dorsal root ganglia in the presence of increased numbers of nodules of Nageotte (tombstones of prior neuronal loss). The viral protein gp120 may also exert a toxic effect mediated via CCL5 (a chemotactic cytokine which attracts T cells, eosinophils, basophils) and with the help of IL-2 and IFN-γ induces the proliferation and activation of NK cells. It has been reported that gp120 exerts its effects via an indirect insult to cell bodies resulting in apoptosis and a direct local toxicity on axons through activation of mitochondrial caspase pathway, a local effect mediated through gp120 binding to axonal chemokine receptors. The immunophilin ligand GPI-1046 is thought to protect DRG neurons from gp120-induced axonal damage by decreasing the entry of calcium. Neuropathy induced by anti-retroviral treatment may produce a clinical picture which closely resembles and exaggerates DSP. The pathogenesis of antiretroviral drugs is thought to reflect inhibition of DNA polymerase-γ and an interruption of bioenergetic function due to direct mitochondrial toxicity resulting from loss of the mitochondrial transmembrane potential differential. It is likely that HIV-proteins such as gp120 may result in increased vulnerability to dideoxynucleoside induced neurotoxicity as suggested in animal models. Skin biopsy is developing as a sensitive and early monitor of the development of DSP, producing loss of epidermal axons and development of swellings in residual axons often in the absence of neuropathic changes in the sural nerve. HIV related sensory neuropathy may show a distal axonopathy in which damaged mitochondrial DNA and decreased expression levels of mitochondrial respiratory chain complexes accumulate distally.

The varied patterns of AIDS Neuropathy are summarized in Table 3 modified from Pardo et al:

<table>
<thead>
<tr>
<th>Subtype of Neuropathy (NP)</th>
<th>Clinical Stage</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Distal Sensory NP</td>
<td>AIDS (CDC C)</td>
<td>Macrophage Mediated Axonopathy</td>
</tr>
<tr>
<td>2. Toxic Anti-retroviral Drug NP</td>
<td>Any (CDC A-C)</td>
<td>Mitochondrial DNA Synthesis</td>
</tr>
<tr>
<td>3. Mononeuritis Multiplex</td>
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<td></td>
</tr>
<tr>
<td>Vasculitic Form</td>
<td>CDC B</td>
<td>Immune Complex Deposition</td>
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<td>-------------------------------------</td>
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<tr>
<td>CMV Multiple MonoNP</td>
<td>AIDS</td>
<td>CMV Infection Schwann Cells, Vessels</td>
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<td>(CDC C)</td>
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<td>4. Inflammatory Demyelinating NP</td>
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<tr>
<td>GBS (demyelinating or axonal)</td>
<td>Pre-AIDS</td>
<td>Immune Dysfunction</td>
</tr>
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<td>CIDP</td>
<td>Pre-AIDS</td>
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<tr>
<td></td>
<td>or AIDS</td>
<td></td>
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<tr>
<td>5. Opportunistic Infectious NP</td>
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<tr>
<td>CMV Polyradiculopathy</td>
<td>AIDS</td>
<td>CMV Necrotizing NP</td>
</tr>
<tr>
<td>Herpes Zoster Radiculopathy</td>
<td>AIDS</td>
<td>VZV: Schwann cells and Endothelium</td>
</tr>
<tr>
<td>6. Neoplastic (Lymphoma)</td>
<td>AIDS</td>
<td>Endoneurial Infiltration</td>
</tr>
<tr>
<td>7. Other</td>
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<tr>
<td>8. Sensory NP/dorsal radiculopathy</td>
<td>Pre-AIDS</td>
<td>Immune Dysfunction</td>
</tr>
<tr>
<td></td>
<td>or AIDS</td>
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<tr>
<td>9. Diffuse Infiltrative lymphocytosis</td>
<td>AIDS</td>
<td>CD8 Lymphocytosis/Vasculopathy</td>
</tr>
</tbody>
</table>

**D) Lyme Disease**  A multifocal neuropathy accompanied by macules and papules on the trunk and abdomen is caused by the tick-borne spirochete Borrelia burgdorferi and is endemic to the northeastern United States and parts of Europe. Cranial and peripheral nerve involvement may show an epineurial or perineurial perivasculatory lymphocytic/plasmacytic infiltrate ("perivasculitis") and axonal degeneration. The histopathology is reported to differ from typical vasculitic neuropathies by the presence of perineurial thickening and infiltration with inflammatory cells as well as increased perineurial immunoreactivity for TNF and ICAM-1 in sural nerve biopsies. Organisms are not typically seen in involved nerves.

**E) Chagas' Disease**  Infection with Trypanosoma cruzi produces cardiac and gastrointestinal symptoms resulting from inflammatory damage to autonomic ganglia and nerves as well as muscle.

**F) Elsberg Syndrome**  Genital infection with Herpes simplex virus type 2 (HSV-2) has been associated with sacral polyradiculitis resulting in sacral paresthesias and pain followed by hypoesthesia, decreased anal sphincter tone, urinary retention and obstipation.

**XII. Traumatic Neuropathy**

Several forms of traumatic injury to nerve result in different histopathologic findings. Chronic compression of nerve, as might occur in an entrapment neuropathy, is characterized by focal loss of myelin and often the production of Renaut bodies, collections of perineurial cells, spidery fibroblasts and an extracellular matrix containing disoriented collagen fibers and elastin precursors. Traumatic damage to peripheral nerve with loss of continuity of the nerve may result in the development of a traumatic neuroma which represents a combination of degenerative and regenerative responses resulting in a disorganized aggregate of collagen and minifascicles of axons. Neuroma tissue has been found to have increased levels of the chemorepulsive protein semaphorin 3A, which may increase fasciculation and inhibit neurite outgrowth. The participation of alterations in sodium channel in neuromas may be followed by targeted blockade of NaV1.7 or ERK1/2 may represent a therapeutic strategy for amelioration of chronic pain that often follows nerve injury and formation of neuromas. Resection and apposition of proximal and distal stumps or transplantation of a nerve graft may be curative. Chronic compression may produce fibrosis of the underlying nerve accompanied by endoneurial edema, demyelination with remyelination and axon loss. Renaut bodies with fibroblast-like cells surrounded by mucoid extracellular matrix may be seen in significant numbers at nerve compression sites.
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