Approach to Diagnosis of Peripheral Neuropathy

I - Definitions

The peripheral nervous system (PNS) is defined as that part of the nervous system where axons are surrounded by Schwann cells, as distinguished from the central nervous system, where axons are surrounded by oligodendrocytes.

Sensory cell bodies, found in the dorsal root ganglia, as well as their axons are part of the PNS. Anterior horn cells and autonomic cell bodies in the intermediolateral cell column are in the CNS, but their axons are in the PNS. Cranial nerves 3-12, but not their cell bodies, are also part of the PNS.

Peripheral neuropathy is a somewhat ambiguous term, implying a disorder of peripheral nerves. Clearly, a single focal compressive palsy (e.g. carpal tunnel syndrome) or a radiculopathy due to disc herniation should not be considered on equal grounds with something like CIDP or diabetic polyradiculoneuropathy. But that about plexopathy, when multiple nerves in the same region are affected? Clearly, the definitions are not always straightforward.

To further confuse the issue, some workers use the term "polyneuropathy" synonymously with peripheral neuropathy, while others regard "polyneuropathy" as a subset of peripheral neuropathy characterised by a symmetrical distally-predominant distribution of symptoms and signs.

To clarify matters, the following definitions are probably most often applied by workers in the field:

**Mononeuropathy:** a clinical syndrome in which all the manifestations can be explained by a single site of injury to a single nerve

**Mononeuropathy multiplex:** a clinical syndrome with evidence of dysfunction at multiple nerve trunks. The term "mononeuritis" should not be used because this implies an inflammatory basis which cannot be proven on clinical grounds alone. For example multiple intraneural hemorrhages or Hereditary Neuropathy with Liability to Pressure Palsies can present with this syndrome. Recall that a nerve roots and cranial nerves are also nerve trunks, so mononeuropathy can include radicular and cranial involvement

**Polyneuropathy:** a clinical syndrome characterised clinically by symmetrical and distally-predominant manifestations

**Polyradiculopathy:** a syndrome due to of involvement at multiple nerve roots. This diagnosis is sometimes not certain on clinical grounds alone and laboratory evidence should be obtained to support it.
Polyradiculoneuropathy: a process with elements of both polyradiculopathy and polyneuropathy. Clinical judgement has its limits. This diagnosis is basically a laboratory diagnosis.

Peripheral Neuropathy: a disorder characterised by dysfunction of at least two, and usually many, peripheral nerves. This would include mononeuropathy multiplex, polyneuropathy, polyradiculopathy, and polyradiculoneuropathy. Generally speaking, this definition excludes traumatic nerve injuries (compression, traction, trans-section, etc) unless there is an underlying peripheral nerve disorder which predisposes to such injuries, e.g. Hereditary Neuropathy with Liability to Pressure Palsies.

Strictly speaking, regional peripheral nerve syndromes such as plexopathies or cauda equina syndrome are peripheral neuropathies. However, these distinctive syndromes have a limited differential diagnosis compared to what we would consider in a truly diffuse disease of the peripheral nerves. Although some of the etiologies can overlap (for example, plexopathy due to vasculitis), it is best to consider regional peripheral nerve syndromes separately.

These definitions leave some unavoidable ambiguity, such as what degree of asymmetry, if any, is to be tolerated within the rubric of a polyneuropathy. Also, when multiple mononeuropathies become confluent, they can mimic a polyneuropathy. These issues will be discussed below.

Epidemiology of peripheral neuropathy

The incidence of peripheral neuropathy in the United States has been estimated to be comparable to that of epilepsy or parkinsonism – about 2%, and probably rises to 5-8% in older individuals. Since most patients are not investigated data regarding the frequency and etiology of peripheral neuropathies are hard to obtain. For example, Dyck estimated 20 years ago that only 10% of affected patients with hereditary motor and sensory neuropathy type 1 (CMT-1) present as a direct consequence of symptoms produced by this disease. Probably this is an considerable understatement in the modern era of more intensive medical scrutiny, but it remains true that patients are routinely found to have a generalized neuropathy as an incidental finding of another presentation or as part of a family assessment. Furthermore, many individuals with mild or subclinical neuropathy, whether genetically determined or acquired, do not require investigation or treatment. The largest and best documented peripheral neuropathy series originate from specialized centers or are selected from biopsy cases and so are not representative of neuropathy in the general population.

It is helpful to classify the major etiologies of peripheral neuropathy into four major groups:
• acquired toxic or metabolic
• inflammatory or infectious
• neoplasm- and paraprotein-associated
• genetically determined

Acquired toxic or metabolic factors probably account for the majority of neuropathies. Common etiologies include diabetes, renal failure, and pharmaceutical neurotoxins. These diagnoses are usually easy to make since the underlying medical disease is usually recognized before the neuropathy arises.

The most frequent inflammatory and infectious neuropathies are Guillain-Barre Syndrome (GBS), Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), vasculitic neuropathies, HIV associated neuropathies, and leprous neuritis.

Malignancy and paraproteinemia are associated with neuropathy through a variety of mechanisms, including autoimmunity, metabolic derangement, and infiltration of nerve.

The Charcot-Marie-Tooth type 1 and 2 syndromes are the best known familial neuropathies, and of these, CMT1A (Charcot-Marie-Tooth disease type 1A) - caused by a chromosome 17p11.2 duplication - is the most commonly proven genetic diagnosis. It may not be the most common genetic neuropathy, since CMT-2 probably is more common than CMT-1, but much harder to diagnose at the present time due to a lack of available genetic testing. In the modern literature, 10% to 20% of neuropathies remain cryptogenic – a substantial proportion of these may be genetically determined but if there is no way to prove such an etiology.

I estimate that in the developed world metabolic, toxic, and nutritional causes account for 50% or more of neuropathies coming to the attention of physicians, inflammatory neuropathies (mainly GBS, CIDP, and vasculitis) for 10% to 20%; genetically determined neuropathy for 10% to 20%; neoplasia associated neuropathy for 5% to 10%; and approximately 10% to 20% are cryptogenic. Most of the cryptogenic neuropathies are those coming on in older patients, relatively mild, and the more one looks for this, the more one sees it. A large variety of rare neuropathies make up the rest of the group (for details see Midroni & Bilbao, Biopsy Diagnosis of Peripheral Neuropathy, Butterworth Heinemann, 1995 chapter 1)

These figures represent the experience with adult patients in the developed world. In pediatric neuropathy the etiologic spectrum differs, with genetic neuropathies predominating. Moreover, geographic factors are pertinent in determining the relative frequency of neuropathies in a given population. Leprosy and nutritional neuropathies are dominant in the underdeveloped world, and genetically determined neuropathies that are extremely rare to us are commonplace elsewhere (e.g. porphyric neuropathy in South Africa).
Cryptogenic peripheral neuropathy

Despite widely variable selection criteria in different series, the proportion of neuropathies that remain cryptogenic is relatively constant in modern reports, ranging from 10% to 20%. When previously adequately assessed patients with a chronic idiopathic neuropathy are re-studied, an etiologic diagnosis often can be made; perhaps one third of such patients will be diagnosed after one year of follow up. The rest often have a relatively stereotyped syndrome of a relatively mild predominantly sensory, slowly progressive neuropathy in which pain may or may not play a prominent feature, and onset in later life. Several studies of undiagnosed neuropathies have emphasized the importance of careful history taking in diagnosis, especially for evidence of a familial neuropathy or of toxic exposure. Examination of family members, even if they are not known to be symptomatic, can prove extremely helpful. In other patients the etiology becomes clear with time, as malignancy or other systemic diseases emerge. It is quite unusual to fail to diagnose a severe neuropathy (causing significant weakness or sensory loss), but mild sensory predominant neuropathies are much more frequently idiopathic.

II - Clinical Approach

A number of questions must be systematically answered as the peripheral neuropathy is assessed:

1) Is a peripheral neuropathy present and is it the principal cause of the patient's symptoms?

In a 7 year review of 276 nerve biopsies referred to St. Michael’s hospital pathology, i.e. patients with a “neuropathy” severe enough to merit biopsy, a diagnosis other than peripheral neuropathy was ultimately made in about 5-10% (myopathy, neuromuscular junction disease, ALS, myelopathy, functional). Motor neuron disease, myopathies, and neuromuscular junction diseases can cause weakness in almost any distribution. Spinal cord disease can cause sensory and motor symptoms that may mimic a neuropathy (e.g. distal tingling in hands and feet with a foot drop due to MS or spinal cord compression). Also, there are some patients who complain of vague tingling in hands and feet, “weakness all over”, or cramps, raising the possibility of peripheral neuropathy - but whose symptoms remit when underlying depression or ongoing life stressors resolve. Such patients probably have a functional illness. Although the latter diagnosis should never be made lightly, it should always be considered prior to carrying out the aggressive investigations that are entailed in a complete peripheral neuropathy workup.

In general, the most common reason for misdiagnosis of peripheral neuropathy is an inadequate or misinterpreted NCS/EMG. The most common error,
especially in the elderly, is mistaking lumbosacral polyradiculopathy, or age related changes, for peripheral neuropathy - clinically these are often indistinguishable, and only a thorough EMG can make the difference.

Even if a neuropathy is present, the patient’s disability may be primarily due to another process. Consider an elderly patient with cervical spondylosis causing some sensory symptoms in the arms, some hand muscle atrophy, and a myelopathy with gait difficulty and dorsal column sensory deficits. If this patient also has a mild neuropathy (or “age related” changes) causing numbness in the feet with absent ankle jerks, one can be fooled into thinking that all of the symptoms and disability are due to a peripheral nerve process. Thus, the clinician must always be alert to the possibility of alternative or multiple diagnoses. Careful clinical examination is essential - in the patient described above, there will probably be important findings that are atypical for peripheral neuropathy, and suggest the presence of a cervical myelopathy (hands weaker than feet, possibly hip flexors weaker than distal leg muscles, pathological reflexes, presence of bladder dyscontrol, a Lhermitte’s symptom).

2) Is the distribution of disease most suggestive of a diffuse or a multifocal process?

The purpose of most of the general component of peripheral neuropathy history and physical is to determine whether the disease pattern is mostly that of a polyneuropathy (a fairly nonspecific pattern usually due to a diffuse process), or whether there are features suggesting of a multifocal process (syndromes of mononeuropathy multiplex, polyradiculopathy).

Polyneuropathy is the commonest pattern, usually due to a metabolic problem, with a very wide differential diagnosis. Multifocal neuropathy has a far less broad differential diagnosis, and many of the possible etiologies are treatable. Thus, making this distinction is perhaps the most important step in diagnosis of a peripheral neuropathy.

In deciding about whether the neuropathy is multifocal or diffuse the principal considerations are symmetry and length-dependence.

2.i) Symmetry

As a general rule neuropathies due to toxic/metabolic/genetically determined causes are approximately symmetrical. The process affects nerves diffusely, hence right should equal left in terms of nerve dysfunction. In contrast, with processes causing multifocal injury to nerve, one side might well be expected be more severely affected than the other by chance. Symmetrical neuropathies are pretty common, and so this pattern does not really help in reaching a diagnosis. However,
a significantly asymmetrical degree of deficit, reaching its extreme example in the syndrome of mononeuropathy multiplex, should suggest alternative diagnostic possibilities:

### Multifocal neuropathies

**Axonal**
- Vasculitis syndromes (polyarteritis, RA, Wegener’s, isolated PNS vasculitis, SLE, Churg-Strauss, HIV, cryoglobulinemia, others)
- Diabetes
- Sarcoidosis
- Leprosy
- Lyme disease
- Sensory polyganglionopathy (idiopathic, paraneoplastic, Sjogren’s)
- some amyloid neuropathies (rare familial variants)
- Perineuritis
- Neoplastic nerve infiltration
- Bacterial endocarditis (multiple emboli to nerves)
- Multifocal primary nerve tumours (Neurofibromatosis)
- Hemorrhagic diathesis

**Demyelinating**
- Multiple compression palsies
- GBS / CIDP (idiopathic or secondary)
- Multifocal motor neuropathy / persistent conduction block neuropathy
- Hereditary neuropathy with liability to pressure palsies (HNPP)
- Castleman’s disease
- Radiation (multifocal plexopathy)
- ? Tangier disease (some cases allegedly – count me skeptical)

*this means that demyelination is an important element; a purely demyelinating neuropathy is extremely rare (see below)*

Notice that nearly all the causes of this syndrome are acquired (except for HNPP and Tangier disease), and involve a local pathogenic process affecting the nerve (vascular injury, hemorrhage, compression, or infiltration). Notice also that the two most common “multifocal neuropathies” seen in the real world are not mentioned in this table. First, there is polyradiculopathy due to multilevel degenerative spine disease, which is often mistaken for non-length dependent peripheral neuropathy, and which is probably more common than any single item noted above. Second, diabetics present with a sometimes confusing picture of multiple pathologies, including polyneuropathy, Carpal Tunnel Syndrome, ulnar neuropathy at the elbow, and sometimes cranial nerve palsies, thoracic radiculopathy, or lumbar radiculopathy (so called “diabetic amyotrophy”) that would lead to justifiable concern about mononeuropathy multiplex.
2.ii) Proximal-distal gradient

Nearly all diffuse neuropathies, and even some pathophysiologically multifocal, neuropathies show a length-dependent pattern of involvement, i.e. the longest and most distal fibers are most affected. In most metabolic/toxic/genetically determined neuropathies, the length dependence probably arises from the fact that distal axon segments farthest away from their cell body have the most tenuous supply line for transport of essential nutrients synthesized in the cell body. Thus, distal axons will be affected first if this supply mechanism is disrupted. This group of neuropathies have also been termed “distal axonopathies”. Moreover, some multifocal neuropathies present in a length-dependent pattern. The putative explanation is that tiny multifocal random nerve lesions will occur most frequently in the longest nerves, and thus summate to give the appearance of a distally predominant neuropathy.

2.iii) The clinical features of symmetrical distally predominant polyneuropathy

Symptoms begin with involvement of the longest axons in the body, the sensory fibers supplying the toes. Paraesthesiae usually herald the onset, affecting the toes, then spreading to the sole and top of the foot. These “positive” symptoms probably reflect pathological irritability and spontaneous activity of the diseased sensory axons. Sensory loss, a “negative” symptom which reflects a loss of axons, usually follows and affects the distal foot first. A helpful clue towards distinguishing between acquired and genetically determined peripheral neuropathies is the presence of positive sensory symptoms (pain, tingling, burning, etc). These are much less often seen with genetically determined neuropathies than with acquired neuropathies.

As the neuropathy progresses the sensory symptoms ascend up the lower extremities. The long fibers to the hands are approximately as long as those supplying the mid-leg, so when the sensory symptoms reach this level in the leg, paraesthesiae often start in the fingers. This pattern is termed the "glove and stocking" distribution of sensory symptoms. Rarely, one sees a length-dependent peripheral neuropathy of sufficient severity to affect the sensory fibers on the abdomen, manifesting as a diamond shaped region of dysesthesia or hypoesthesia on the lower abdomen, as this region is supplied by the longest intercostal nerves. If cranial nerves begin to become affected, the vertex of the head is supplied by the longest trigeminal fibers, and hence should be the first site of sensory symptoms. This is a very rare observation.

Motor symptoms usually follow the sensory symptoms. This is partly because (at least clinically) motor fiber irritability (manifesting as cramps and fasciculations) often seems to be a less prominent feature than sensory fiber irritation (manifesting as dysesthesia or paraesthesia). More importantly, the
longest motor fibers are those supplying the intrinsic foot muscles. These are several centimeters shorter than the longest sensory axons which supply the distal toes, and hence the sensory fibers would be affected first in a progressive length-dependent process. In addition, clinical detection of intrinsic foot muscle dysfunction is difficult. In a very slowly progressive process the earliest feature might be wasting of the extensor digitorum brevis, or a isolated foot deformity; the latter is common in genetically determined processes. In general, atrophy out of proportion to weakness indicates slow progression and favours a genetically determined etiology; the slow progression permits time for axonal terminal sprouting and reinnervation of denervated muscle fibers so that strength is relatively preserved until such time as re-innervation can no longer keep up.

In more rapidly progressive length-dependent processes the earliest definite motor sign is weakness of the toe extensors (the great toe is most reliable to examine), followed by weakness of foot dorsiflexion. Many neurologists rely on heel walking as a rapid and sensitive screening test of this function – it is not reliable! Similarly, ability to fan the toes is not always helpful as a test of foot muscle strength because some normal people cannot do this voluntarily. At about the time that foot dorsiflexion weakness becomes definite, the small muscles of the hands (which are much easier to examine than those of the foot) begin to show weakness. The most useful hand muscle to examine for subtle weakness is the first dorsal interosseous, which is supplied by the longest axons in the upper extremities, and which is much more reliably assessed than the thenar and hypothenar muscles. With continued progression muscles of the thigh and forearm are affected.

One should not forget that the recurrent laryngeal and phrenic nerves are actually quite long, and would be expected to become involved in a length-dependent process at around the point where weakness reaches the muscles of elbow flexion and extension. Otherwise, however, involvement of cranial nerve supplied muscles is very unusual in length-dependent processes unless the patient is totally paralysed elsewhere, and if present should suggest that underlying process is not truly length-dependent, i.e. more likely due to focal or multifocal nerve injury than a toxic/metabolic problem.

Regardless of etiology, certain muscle compartments will often seem weaker than others, probably relating to their intrinsic strength reserve. In a normal person the plantarflexors are far stronger than the dorsiflexors, the knee extensors are stronger than the knee flexors, the wrist, finger, and elbow extensors are weaker than the corresponding flexors. Hence even in a length-dependent process one may obtain a so-called "pseudo-pyramidal" distribution of weakness, which can mislead the unwary examiner.

Reflex changes also follow a length-dependent pattern. Typically the ankle jerks go first, followed by the knee jerks, brachioradialis, triceps, and biceps reflexes. The jaw-jerk is almost never affected in length-dependent processes, but
this sign would be difficult to interpret in any case, as it can be absent or very weak even in normal patients. As a general rule, in axonal neuropathies the level of reflex loss parallels the level of sensory and motor deficit (i.e. if only the distal legs are affected, only the ankle jerks and perhaps the knee jerks will be abnormal). In contrast, with demyelinating neuropathies there is often a more diffuse loss of deep tendon reflexes which is sometimes out of proportion to the motor and sensory deficits in the distribution of the spinal segment involved in the reflex. This reflects desynchronization of the afferent volley activated by a tendon tap, resulting in loss of a strong input to the spinal reflex arc. Such desynchronization, however, does not produce neurological deficit such as severe sensory loss or weakness, and a clinical discordance will be seen between normal strength and sensation, but absent reflexes. As a general rule, deficits such as sensory loss and weakness are due to axonal loss, although in demyelinating neuropathies (esp. GBS) deficits may also be due to **conduction block** (see below). Conduction slowing, however, does not cause significant deficit, and desynchronization of conduction may cause reflex loss and perhaps impairment of vibration sensation, but not weakness or significant sensory loss.

2. iv) Multifocal / asymmetrical neuropathy

The preceding sections describe the typical pattern of a length-dependent neuropathy, which is common and non-specific. Of greater interest diagnostically are those instances when this stereotyped pattern is violated. This occurs when the process affects nerve fibers in a multifocal patchy and random manner, which leads to the differential diagnosis listed above. Hence, much of the peripheral neuropathy history and physical examination is devoted to looking for hints that the process is NOT length-dependent or symmetrical. There are a number of important clues:

- **asymmetry at onset:** close questioning of patients who at first indicated that their symptoms were about the same on both sides sometimes reveals that one side was symptomatic for a few weeks before the other became involved. This may be indicative of a multifocal process which quickly became confluent (e.g. CIDP, vasculitis).

- **asymmetry or non-length dependence of findings:** careful examination may reveal that weakness or reflex changes are actually asymmetrical. A particular examination coup would be demonstration that sensory changes which sound length dependent are actually not (for example, sensory loss below the knee SPARING the medial aspect of the leg (saphenous nerve). This usually indicates L5 and S1 radiculopathy, or sciatic neuropathy. Another example is sparing of sensation between the toes in leprosy.
• On exam a bit of asymmetry is nonspecific and should not be over-interpreted, but significant asymmetry is important. Don’t get thrown off by common compression palsies.

• Early involvement of proximal or bulbar muscles. Polyradiculopathy or plexopathy often affect proximal muscles equally or even to a greater degree than distal muscles.

• Predominance of motor symptoms or deficits (particularly common in CIDP)

• Disproportionate reflex loss (typical of demyelination)

• Symptom onset in the upper extremities

Clinically, the boundary between mononeuropathy multiplex and polyneuropathy is often unclear. If a multifocal process hits many nerves at many sites, deficits become confluent and the clinical picture may appear distally-predominant and symmetrical. On the other hand, a focal compression neuropathy (CTS, peroneal neuropathy) may become superimposed on a diffuse distally-predominant neuropathy, a situation that becomes particularly likely if one considers that abnormal nerves are unusually vulnerable to compression. Remember also that an additional or alternative diagnosis outside the peripheral nervous system may explain the unusual distribution of weakness, e.g. a myopathy or a proximal spinal muscular atrophy.

2.v) Polyradiculopathy / polyradiculoneuropathy

This is a spatial pattern seen with some peripheral neuropathies in which there is evidence of involvement at multiple nerve roots, with or without additional involvement at sites more distal in the peripheral nervous system. Strictly speaking, this is a subset of the multifocal neuropathies since it is practically never due to a metabolic or genetic problem, and much more often to inflammatory or infiltrative lesions, so many of the etiologies are similar to those causing multifocal neuropathies (as listed above). However, with prominent multiradicular involvement a number of additional diagnoses have to be considered, such as spinal cord lesions and diseases selectively affecting the subarachnoid space.

Clinically, this syndrome may show some distinctive features including roughly equivalent proximal and distal weakness, diffuse areflexia with relatively preserved strength (more to do with frequently associated demyelination than with the polyradiculopathy itself), and segmental sensory symptoms such as spontaneous or movement provoked shock-like pain in a dermatomal distribution (cervical, thoracic, or lumbosacral). More frequently, however, the diagnosis is
made using laboratory testing. EMG is critical, as this will show denervation of paraspinal muscles and perhaps prolonged F latencies if the process is demyelinating and the tested nerve segments are involved. CSF examination will usually show elevation of protein. MRI can show nerve root enhancement (lumbar roots are most reliable in this regard as they have a long well-visualized course).

The differential diagnosis is listed below, but the most common etiologies are lumbosacral polyradiculopathy due to spinal stenosis, diabetic polyradiculoneuropathy and CIDP.
Differential Diagnosis of polyradiculopathy / polyradiculoneuropathy

- Diabetes

Inflammatory
- GBS
- CIDP
  Systemic disease associated:
  - SLE, Sjogrens (may or may not be vasculitic)
  - sarcoidosis
  - other causes of vasculitic neuropathy
  - Inflammatory bowel disease
  - Associated with bone marrow transplant
- arachnoiditis

Infection associated
- Cytomegalovirus, Epstein-Barr virus
- Herpes Zoster
- Lyme disease
- Diphtheria
  Chronic meningitis
  - fungal
  - TB

Malignancy associated:
- paraprotein associated (basically CIDP-like)
- associated with osteosclerotic myeloma
  Leptomeningeal metastasis
  - Lymphoma, leukemia
  - other cancers less common
- Epidural metastasis
- Intramedullary tumour
- intravascular lymphoma
- lymphomatoid granulomatosis
- paraneoplastic (sensory ganglionopathy +/- motor neuronopathy)
  Treatment related:
  - Intrathecal ARA-C or methotrexate

Structural spinal lesion
- multifocal degenerative bone disease (* very common)
- syringomyelia
- AVM

Degenerative
- motor neuron disease
2.vi) The importance of EMG and NCS in topographic diagnosis

For making these distinctions, careful electrophysiological testing is the most important part of the assessment after the history and physical. Although beyond the scope of the present discussion, EMG may reveal asymmetry or multifocality, subclinical proximal involvement, radicular involvement, conduction block, extreme chronicity, and will do much to exclude muscle and neuromuscular junction disease.

3) Which fiber types are affected by the neuropathy?

3.i) Sensory neuropathy

The fundamental biology and vulnerability to injury of axons does not differ dramatically between sensory and motor axons or their Schwann cells. Thus, most neuropathies are sensorimotor. Truly pure sensory or motor neuropathies are rare. It is more helpful to think of the differential diagnosis of predominantly motor or predominantly sensory neuropathies.

Often, a neuropathy seems to be predominantly sensory because the sensory symptoms are much more severe than the motor problems. However, you don’t have to lose very many sensory axons to have severe pain: pain is function of fiber irritability not fiber loss. This is probably why many common neuropathies such as most mild diabetic neuropathies and HIV DSPN are thrown into the “sensory neuropathy” rubric. Also, in length-dependent processes the longest axons in the body, which are sensory to the toes, are affected first, and thus it is generally true that length dependent polyneuropathies are predominantly sensory in their early stages; normal progression will then reveal typical motor involvement.

While atypical presentations of fairly common neuropathies can always be seen (sensory CIDP, or even more rarely, sensory GBS), usually there has to be a good anatomic reason why a neuropathy would affect sensory fibers but not motor fibers. For example, most truly pure sensory "neuropathies" are actually a consequence of dorsal root ganglion injury (inflammatory polyganglionopathy, spinocerebellar degenerations, vitamin E deficiency, early amyloid neuropathy, some toxic exposures). The dorsal root ganglion is a vulnerable site of injury because of the absence of a blood nerve barrier at this location. As another example, in early lepromatous leprosy there is only sensory involvement because only superficial cutaneous nerve fibers are affected. Motor fibers run deeper than sensory fibers, and are thus spared. Another mechanism for pure sensory neuropathy is small fiber disease (early amyloid, diabetes, some hereditary sensory neuropathies), since there are no small fiber motor axons.
Predominantly sensory neuropathy

Inflammatory
- Idiopathic Inflammatory polyganglionopathy (IPG) not associated with malignancy
- Sjogren’s syndrome (can be associated with IPG)
- Predominantly sensory Guillain-Barre syndrome (extremely unusual)
- Predominantly sensory CIDP (unusual)
- Vasculitic neuropathy, “cutaneous vasculitis” (unusual)
- Sensory perineuritis (rare condition)

Neoplasia-associated
- Paraneoplastic sensory ganglionopathy
- Paraprotein associated
- Infiltration with lymphoma/leukemia
- Early amyloid neuropathy (small fiber)

Infection-associated
- HIV distal predominantly sensory neuropathy (DPSN)
- Leprosy (some)
- Lyme disease (some)

Metabolic
Endocrine
- Diabetes (small fiber, large fiber, or both)
- Hypothyroidism (some)

Organ disease
- Uremia (early)
- Liver disease (including primary biliary cirrhosis)

Nutritional
- B12 deficiency
- Pyridoxine excess
- Thiamine deficiency (atypical cases)
- Strachans Syndrome/Cuban neuropathy (multinutrient deficiency)
- Vitamin E deficiency
- Malabsorption associated with Celiac disease (without evident vitamin deficiency)

Toxins:
- Cis-Platinum
- Chloramphenicol
- Metronidazole, misonidazole
- Isoniazid, ethionamide
- Nitrous oxide (produces a B12 deficiency state)
- Thalidomide
- Ethylene oxide
- Chlorpyrifos (organophosphate insecticide)
- Taxol
- Vacor

Genetically determined
- Associated with spinocerebellar degeneration, especially Friedreich’s ataxia
- Hereditary sensory and autonomic neuropathies (several types)
- Fabry’s disease
- Tangier disease (pleomorphic clinical features)
- Familial amyloid neuropathy (early)
- Some mitochondrial diseases
3.ii) “Small Fiber Neuropathy”

Having identified a predominantly sensory neuropathy, the clinician must then decide whether there is predominant or exclusive involvement of small or large fibers. This is done through clinical assessment, and if available using quantitative sensory testing and electrophysiological tests of small and large sensory fiber function (see below). Small fiber neuropathies are characterised by disproportionate loss of pain and temperature sensation, with relative sparing of reflexes, vibration, and joint position sensation. It is permissible to have a bit of vibratory sensory reduction and Achilles’ reflex loss and still call the process “small fiber” if there is disproportionate pinprick loss and/or autonomic dysfunction. However, JP loss or absent vibration at the ankles normally would not be acceptable.

Painful paraesthesiae are often a feature of small fiber disease. “Burning” pain is what patients usually describe. Motor fibers derived from alpha motor neurons are all of large calibre, and thus are not affected by a pure small fiber neuropathy.

With involvement of small myelinated and unmyelinated fibers autonomic symptoms are sometimes. a prominent part of the clinical picture (orthostatic hypotension, abnormal heart-rate responses to various stimuli, impotence, constipation, anhydrosis, incontinence, etc).

Unfortunately, small fiber function is not assessed on standard nerve conduction studies (which examine the state of large fibers exclusively), and thus NCS/EMG may be entirely normal despite severe patient symptomatology. As an aside, the sympathetic skin response test which can be done in the EMG lab is very insensitive for detecting small fiber neuropathy, and tests of cardiac variability and blood pressure are not much better unless performed very rigorously. The best test for small fiber disease is probably quantitative assessment of sweating by acetylcholine iontophoresis or thermoregulatory sweat testing, but this is available at only a few sites in the world.

Skin biopsy with quantitative assessment of dermal unmyelinated fiber density has emerged as the gold standard in diagnosis of SFN. However, this is not available in Toronto, and it is not clear how reproducible and specific the findings are.

Small fiber neuropathies (SFN) are probably overdiagnosed. Some patients who come in with distal pain or orthostatic hypotension, but have no objective changes on any testing are sometimes labelled as having a “small fiber neuropathy” despite the absence of any evidence to support this. Moreover, some patients with an obvious sensorimotor polyneuropathy can have prominent autonomic symptoms. But, this does not make the process a “small-fiber neuropathy” - it simply means that small as well as large axons are affected. Thus, small fiber neuropathy is relatively uncommon, and has a limited differential diagnosis. After early amyloid
neuropathy and diabetic neuropathy are excluded, all other causes of SFN are vanishingly rare.

Unfortunately, in a substantial proportion of patients who present with an SFN syndrome, no diagnosis can be found despite debilitating symptoms of neuropathic pain. Actual neurological deficit is usually not the main issue, although in severe cases loss of nociception in the feet can produce serious foot damage.

**Small fiber neuropathy**
- Diabetic small fiber diabetic neuropathy (commonest etiology by far)
- Idiopathic small fiber neuropathy (particularly in elderly)
- Amyloidosis (primary or genetically determined)
- HIV associated neuropathy
- Idiopathic acute / chronic pandysautonomia
- Alcohol / nutritional
- Lepromatous (cutaneous) leprosy
- Hereditary sensory and autonomic neuropathies
- Fabry’s disease, Tangier disease
- Other obscure / unproven causes
  - toxins (propafenone, dimethylpropioaminonitrile)
  - extreme hypertriglyceridemia
  - primary biliary cirrhosis
  - vasculitis
  - sarcoidosis
  - paraproteinemia

3.iii) **Large fiber Sensory Neuropathy**

Large fiber involvement is identified by loss of reflexes, with disproportionate involvement of vibration and joint position sensation relative to pin and temperature sensation. In contrast to small fiber disease, loss of large fibers is detected readily on nerve conduction studies. Symptoms suggestive of large fiber sensory loss include ataxia, pseudoathetosis, and clumsiness out of proportion to the degree of weakness in the affected limb (assuming CNS involvement is absent). This is not a particularly specific pattern, but when very striking, a number of possibilities should be considered: CIDP, paraprotein associated neuropathy (especially an IgM paraprotein with activity against MAG), and sensory polyganglionopathy (with its various disease associations).

3.iv) **Motor dominant neuropathy**

If the neuropathy is exclusively motor a warning bell should go off, and diagnostic possibilities other than peripheral neuropathy should be considered including distal spinal muscular atrophy, ALS, distal myopathies, and Lambert-Eaton syndrome. Assuming that these are excluded, there are neuropathies characterised by pure, or more commonly predominant, motor involvement. A disproportionate number of these are demyelinating processes, of which CIDP is by far the most
common. Everyone always remembers multifocal motor neuropathy, but less common than almost any of the entities mentioned above.

**Predominantly motor neuropathy***

- Inflammatory/demyelinating
  - GBS or CIDP with motor predominance (common)
  - Multifocal neuropathy with persistent conduction block (includes multifocal motor neuropathy)

- Infection-associated
  - Diphtheria

- Metabolic
  - Porphyria
  - hypoglycaemia-associated neuropathy

- Toxic
  - lead, mercury
  - dapsone
  - delayed neurotoxicity after organophosphate poisoning

- Neoplasm-associated
  - Lymphoma-associated motor neuropathy
  - Paraprotein-associated motor neuropathy
  - POEMS syndrome

- Genetically determined
  - CMT-1, CMT-2 (sensory features often overshadowed by motor involvement)

*don’t forget to consider non-peripheral nerve disease

**Multifocal Motor Neuropathy**

A word about multifocal motor neuropathy is appropriate, since it seems to be very misunderstood. Contrary to the common statement that it can masquerade as ALS, the differential diagnosis of MMN usually is CIDP, and usually MMN is usually an easy diagnosis. The keys to diagnosis of MMN are

- marked focality of weakness in a peripheral nerve pattern (most commonly radial, ulnar/lower trunk, or median)
- extremely slow progression (5-10 years not uncommon)
- sparing of bulbar muscles
- relative sparing of muscle bulk compared to prominent weakness if conduction block is present (not as common as people think, nor easy to assess reliably)

The distinction from CIDP is based on:
- sparing of reflexes in MMN (except where weakness is present)
-much more diffuse and often symmetrical weakness in CIDP. Often involvement of shoulder/hip girdles in CIDP. CIDP also usually progresses more quickly, over weeks and months, than MMN which progresses over months and years.
-tingling and numbness are usually present in CIDP
-conduction velocity slowing is a much less significant feature in MMN compared to CIDP
-sensory conduction abnormalities can be seen in MMN, but are usually much more significant in CIDP
-high CSF protein and/or nerve root enhancement in CIDP

The distinction from ALS is based on:

- upper motor neuron signs in ALS
- bulbar involvement in ALS
- pseudobulbar involvement in ALS
- diffuseness of involvement in ALS
- more rapid progression of ALS (spread within limb over a few months, to other limbs within 1-2 years at most)
- true conduction block rules out ALS, but many EMGs do not assess this accurately. It is common to overdiagnose conduction block in ALS patients
- paraspinal denervation in ALS, especially thoracic

Fasciculations really are of no importance in sorting out any of these conditions – they occur in any of these conditions, and do not make the separation.

4) **What is the temporal evolution?**

It is important to note how long and how quickly the process has been evolving prior to coming to neurological attention, as this gives clues to the underlying etiology. An acute process evolves over fewer than two to four weeks, and the differential diagnosis of peripheral neuropathy evolving this rapidly is limited.

Similarly, a process that has been present for years, and progressed very slowly or imperceptibly, has a limited number of possible etiologies. The clues to an extremely chronic process are: lack of positive symptoms (tingling, neuropathic pain, cramping), and dominance of negative symptoms (loss of sensation, wasting, weakness, foot injury or deformity) at presentation. Another useful clue is patients who come in complaining of relatively minor symptoms, yet exam discloses very impressive deficits – because the patient has been so abnormal, for so long, progressing so slowly, that they weren’t aware of how weak or numb they were.
Most commonly, however, neuropathies evolve at an intermediate pace. The tables provided below are neither exhaustive, not absolute. They are guidelines only, and atypical presentations should always be considered.

Also, try to determine if the course has been relentlessly progressive, or characterised by stepwise worsening or relapses and remissions. Spontaneous remissions are sometimes seen in CIDP, and vasculitic neuropathies can progress in a stepwise course.

### Differential Diagnosis of Acutely Evolving Neuropathy

<table>
<thead>
<tr>
<th>Demyelinating</th>
<th>Axonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• GBS</td>
<td>• Axonal GBS</td>
</tr>
<tr>
<td>• Diphtheria (historical interest only)</td>
<td>• Porphyria</td>
</tr>
<tr>
<td></td>
<td>• Critical illness polyneuropathy</td>
</tr>
<tr>
<td></td>
<td>• Mononeuropathy Multiplex syndromes:</td>
</tr>
<tr>
<td></td>
<td>• Vasculitis</td>
</tr>
<tr>
<td></td>
<td>• Intraneural hemorrhagic diathesis</td>
</tr>
<tr>
<td></td>
<td>• Intraneural emboli (cholesterol, endocarditis)</td>
</tr>
<tr>
<td></td>
<td>• Toxic exposures</td>
</tr>
<tr>
<td></td>
<td>• Misonidazole, nitrofurantoin</td>
</tr>
<tr>
<td></td>
<td>• Arsenic*, thallium</td>
</tr>
<tr>
<td></td>
<td>• Alcohol/nutritional</td>
</tr>
<tr>
<td></td>
<td>• Anti GD2 antiserum (for Rx of Melanoma)</td>
</tr>
</tbody>
</table>

* alleged to sometimes show EMG features suggestive of demyelination

^ evolving over <4 weeks

### Differential Diagnosis of common subacute-chronic Neuropathies

<table>
<thead>
<tr>
<th>Axonal</th>
<th>Demyelinating</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diabetes</td>
<td>• CIDP</td>
</tr>
<tr>
<td>• Toxic exposures (alcohol, drugs, industrial)</td>
<td>• Paraprotein associated neuropathy</td>
</tr>
<tr>
<td>• Vasculitis syndromes</td>
<td>• Hereditary neuropathy with pressure palsies</td>
</tr>
<tr>
<td>• Collagen diseases without vasculitis</td>
<td>• Toxic exposure</td>
</tr>
<tr>
<td>• Nutritional defects (B12, B6, B1, vitamin E)</td>
<td>• perhexiline, amiodarone, chloroquin</td>
</tr>
<tr>
<td>• Uremia</td>
<td>• hexacarbon solvents / glues</td>
</tr>
<tr>
<td>• HIV-associated</td>
<td>• Lyme disease</td>
</tr>
<tr>
<td>• Paraproteinemia</td>
<td>• Paraneoplastic</td>
</tr>
<tr>
<td>• Paraneoplastic infiltration</td>
<td>• Neoplastic infiltration</td>
</tr>
</tbody>
</table>

^ evolving over 1 month to 1-2 years
5) Is the neuropathy “Axonal” or “Demyelinating”

Much has been made of this distinction, which rests mostly on electrophysiological studies, and to a lesser extent on nerve biopsy. History and examination are not reliable in this regard, although early and diffuse loss of reflexes out of proportion to deficits, and motor greater than sensory abnormalities favour a demyelinating neuropathy. A rare observation, but one which brings many kudos when made, is that of enlarged nerves: greater auricular over the sternomastoid, brachial plexus in the axilla, ulnar at the elbow, superficial radial at the anatomic snuffbox, and superficial peroneal at the ankle. This almost always indicates an “onion bulb” neuropathy, i.e. one in which recurrent demyelination and remyelination have occurred.

The majority of neuropathies are axonal. The remainder show features of both axonal degeneration and primary demyelination - these are best termed "mixed" axonal/demyelinating neuropathies. Despite the universal misuse of the term in the literature, “demyelinating” neuropathies are extremely rare - they are a mostly theoretical or experimental construct. Axon loss or muscle denervation / reinnervation (demonstrated on EMG or on biopsy studies) occur in essentially all of the so-called "demyelinating" processes such as CIDP, classic Guillain-Barre Syndrome, Hereditary Neuropathy with liability to Pressure Palsies (HNPP), and CMT-1. Indeed, disability is usually a consequence of axonal loss rather than demyelination, even in so called “demyelinating” neuropathies. Thus, a more accurate distinction is between “axonal” and "mixed" neuropathies. Still, to maintain consistency with common parlance, and to simplify discussion, I will refer to those neuropathies in which primary demyelination occurs as “demyelinating” neuropathies, regardless of the nearly invariable concurrent presence of axonal degeneration.
**Note:** primary demyelination should be distinguished from *secondary demyelination*; in the latter a primary axonal process (usually atrophy due to metabolic axonopathy) results in demyelination. For example, in the 1960’s a debate raged regarding whether uremic neuropathy was a predominantly axonal or a predominantly demyelinating process. As it turns out, the axonal change was primary, and the myelin change came secondarily. Indeed, secondary demyelination occurs frequently when the axon is sick, and this has misled inexperienced pathologists and electromyographers into diagnosing a demyelinating neuropathy where one does not exist. Strict criteria are required in order to accurately diagnose the presence of primary demyelination on nerve conduction studies: at the very least, motor conduction velocities should be reduced to 75% of the lower limit of normal, distal latencies and F latencies should be prolonged by at least 25% of the upper limit of normal, and some allowance must be made for a severe reduction in axon numbers which may leave behind a residual population of small (and hence slowly conducting) axons.

The differential diagnosis of axonal neuropathies is nearly endless. In contrast, the differential diagnosis of neuropathies with primary demyelination is limited, and should be memorised by every neurologist (see table). Note that most of the so-called demyelinating neuropathies can occasionally manifest with electrophysiological or biopsy features indicative of axonal degeneration only, mostly due to the limitations of these diagnostic techniques. This probably occurs most often in CIDP, where the disease can be very focused on the nerve roots - i.e. a *polyradiculopathy*. Biopsy and electrophysiological tests do not assess this region very well, and may show only the consequences of nerve fiber degeneration distal to the site of disease activity.

It is no coincidence that the demyelinating neuropathies are often more responsive to treatment than axonal neuropathies: myelin injury is repaired much more rapidly than axonal damage. Thus, as a general rule, demyelinating neuropathies have a better prognosis.
Demyelinating Neuropathies

Acquired (often non-uniform NCS abnormalities)
- Guillain Barre Syndrome
- CIDP
  - Idiopathic
  - Secondary:
    - paraprotein
    - collagen disease
    - HIV
    - Malignancy
- Paraprotein Associated Neuropathies, esp. IgM anti-MAG paraprotein
- POEMS syndrome, Castleman’s disease
- Diabetes (generally predominantly axonal)
- Toxins:
  - amiodarone, perhexilene, chloroquin
  - hexacarbons (actually very prominent secondary demyelination)
  - Diphtheria

Genetically Determined (generally uniform NCS abnormalities)
- CMT-1, CMT-X in males
- Congenital dysmyelinating neuropathies
- Leukodystrophies
  - Metachromatic leukodystrophy
  - Globoid cell leukodystrophy (Krabbe’s)
  - Adrenomyeloneuropathy (more often axonal pattern)
- Mitochondrial disease (esp. MNGIE Syndrome)
- Refsum’s disease
- Cerebrotendinous Xanthomatosis
- Niemann Pick Disease
- Oxalosis (some cases)
- Cockayne disease
- Tangier Disease (some cases)

In clinical practice, the differential diagnosis of a demyelinating neuropathy usually quickly comes down to GBS for acutely evolving neuropathies, and CIDP (idiopathic or secondary), paraprotein-associated neuropathy, or CMT-1 for more slowly evolving processes. All the others are rare birds that most neurologists never see. Diabetes sometimes causes a problem. This is usually an axonal neuropathy. However, there is still controversy regarding whether or not primary demyelination occurs in diabetes, and any practising electromyographer will know that a minority of diabetics show a degree of conduction slowing which is out of proportion to that seen in other axonal neuropathies of equal severity; this suggests the presence of some primary demyelination. Some workers would argue that many of these demyelinating diabetic neuropathies represent the co-occurrence of diabetic neuropathy and CIDP, and increasingly such patients are being treated with immune modulating agents as though they had CIDP.
III - Etiological Classification of Neuropathy

The following table is a comprehensive listing, organised according to etiology, of the known causes of neuropathy. Asterisks indicate neuropathies for which the literature evidence is not absolutely conclusive. Some of the listings are not really etiologies, but syndromes which may have multiple causes (e.g. GBS and CIDP). Toxic and genetically determined neuropathies are listed in more detail in separate tables subsequently. Ultimately, despite intensive investigation and adequate follow-up, about 10-20% of neuropathies remain undiagnosed.
Acquired demyelinating neuropathies

• Guillain-Barre syndrome
• Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
  • Idiopathic
  • Secondary
    • paraprotein
    • systemic inflammatory disease
    • malignancy
    • HIV
• Multifocal neuropathy with persistent conduction block (? CIDP variant)
• Multifocal motor neuropathy

Metabolic neuropathies

Endocrine disease

• Diabetes
  • symmetrical distal predominant neuropathy
  • polyradiculoneuropathy
  • small fiber neuropathy
  • others (truncal radiculopathy, cranial neuropathy...)
• Hypothyroidism
• *Hyperthyroidism
• Acromegaly
• *Hyperlipidemia

Organ disease

• renal failure
• respiratory failure
• liver disease
  • cirrhosis (any etiology)
  • *primary biliary cirrhosis
  • *hepatitis B
• intestinal disease
  • Celiac disease
  • Crohn’s disease

Nutritional deficits

• B12
• B1 (Thiamine)
• B5 (pyridoxine)
• Vitamin E (tocopherol)
• *Folate

Exogenous toxins (see separate table below)

Drugs
Metals
Occupational exposures
Biological toxins

Infectious and infection-associated neuropathies

• Leprous neuropathy
• HIV-associated neuropathies
  • Distal Predominantly Sensory Neuropathy
• Vasculitic neuropathy
• HIV associated GBS or CIDP*
• CMV neuritis in immunosuppressed patients (usually HIV infected)
• *HTLV-1-associated neuropathy
• Lyme neuritis
• Diphtheric neuropathy
• Chagas’ disease
• *Neuropathy in Jakob-Creutzfeldt disease

Vasculitic Neuropathies

Primary vasculitides
• “Isolated” peripheral nerve vasculitis
• Polyarteritis nodosa (PAN)
• Churg-Strauss allergic angiitis and granulomatosis (CSA)
• Overlap syndromes
• Giant cell arteritis
• Hypersensitivity type vasculitis
  • amphetamine exposure
  • serum sickness

Multisystem diseases
• Rheumatoid arthritis
• Systemic lupus erythematosus (SLE)
• Sjogren’s syndrome (primary or secondary)
• Wegener’s granulomatosis
• Undifferentiated connective tissue disease
• Cryoglobulinemia
• Scleroderma A
• Sarcoidosis A
• Behcet’s disease A
• Lymphomatoid granulomatosis
• Neoplasm associated
  • paraprotein associated
  • hematological or solid malignancy
• Cholesterol embolus syndrome

Infection-associated vasculitis
• Leprosy reaction (ENL)
• HIV infection
• CMV infection
Non vasculitic neuropathy associated with systemic inflammatory / collagen disease

• Sarcoidosis
• rheumatoid arthritis
• SLE
• Sjogren’s syndrome
  • inflammatory polyganglionopathy syndrome
  • sensorimotor polyneuropathy
• scleroderma
• cryoglobulinemia

Dysproteinemia-associated neuropathy

• Primary amyloidosis
• IgM paraprotein (MGUS, Waldenstrom’s macroglobulinemia, lymphoma)
• IgG or IgA MGUS or multiple myeloma
• Immunoglobulin deposition disease
• POEMS syndrome and osteosclerotic myeloma
• Cryoglobulinemia

Neuropathy associated with neoplasia (excluding paraproteins)

• Paraneoplastic neuropathy
• Infiltrative neuropathy
  • lymphoma
  • leukemia
  • plasmacytoma
• Castleman’s disease-associated neuropathy
• *Neuropathy in angioimmunoblastic lymphadenopathy

Genetically determined neuropathies - see separate table

Other Neuropathies

• Critical illness polyneuropathy
• Acute motor axonal neuropathy (axonal Guillain-Barre syndrome)
• Neuropathy of the hypereosinophilic syndrome
• Neuropathy in Madelung’s disease
• Adult polyglucosan body disease

A proven vasculitis very rare, neuropathy usually on a different basis
Genetically Determined Neuropathies

**Unknown Genetic Basis***

- CMT-1 (not in known defects)
  - Autosomal dominant (small fraction)
  - Autosomal recessive

- CMT-2 (neuronal)
  - Autosomal dominant
  - Autosomal recessive

- X-linked CMT (some)
- Dejerine Sottas Syndrome (DSS) (some)

- Congenital dysmyelinating neuropathies (some)
- Rare CMT variants and complex forms

- Some hereditary sensory and autonomic neuropathies

- Neuropathies in hereditary ataxias (non Friedreich, none SCA)

- Others
  - Neuroaxonal dystrophy
  - Familial Neuralgic Amyotrophy (types I-III)

**Known metabolic or genetic defects causing neuropathy**

- Charcot-Marie-Tooth syndromes- see table below

- Familial amyloid polyneuropathies:
  - TTR mutations (> 40 types)
  - Apolipoprotein A mutations
  - Gelsolin mutations

- Neuropathies in hereditary ataxias
  - Friedreich’s ataxia
  - SCAs (1-4,8,12)

**Hereditary Sensory neuropathies**

- HSN1 – serinepalmitoyltransferase
- HSN4 ( congenital insensitivity to pain with anhydrosis – trkA/NGF receptor

**Neuropathies with defects in lipid metabolism**

- Sphingolipidoses
  - Metachromatic leukodystrophy
  - Globoid cell leukodystrophy (Krabbe’s disease)
  - Fabry’s disease
  - Niemann-Pick disease
  - Farber’s disease

- Other defects in lipid metabolism
  - Abetalipoproteinemia (Bassen-Kornzweig)
  - Adrenoleukodystrophy
  - Refsum’s disease (CMT-4)
  - Cerebrotendinous xanthomatosis

**Other genetic defects**

- Abnormal porphyrin metabolism
  - Acute intermittent porphyria
  - Variegate porphyria
  - Hereditary coproporphyria
  - ALA dehydratase deficiency
  - Hereditary tyrosinemia

- Defects of DNA repair
  - Ataxia telangiectasia
  - Xeroderma pigmentosum
  - Cockayne’s syndrome

- Neuropathy in Mitochondrial diseases
  - MNGIE (100%)
  - MELAS

- Others
• Glycogen storage diseases (types II, III)
• Primary hyperoxaluria
• Myotonic dystrophy
• Neuroacanthocytosis
• Tangier disease (analphalipoproteinemia, due to mutant ATP binding cassette transporter)
• Some familial CJD
• Giant axonal neuropathy (Gigaxonin)
• Chediak Higashi

*some of these have known chromosomal locations, but actual gene not YET known.
Charcot-Marie-Tooth disease

- Type I – autosomal dominant, demyelinating
  - 1A – most common, 70% of type I, chr 17p11.2, PMP-22 duplication
  - 1B, 1E – chr 1q22, P0 protein
  - 1C – chr 16p13, LITAF (Lipopolysaccharide induced TNF-a)
  - 1D – chr 10q21 EGR2 (Early Growth Response 2)
  - 1F – NFEL, 8p21, neurofilament light chain

- Type II – axonal, autosomal dominant
  - 2A – chr 1p: 2 mutations
    » Kinesin (!) motor protein (KIF1B)
    » MFN2 (mitofuscin 2, a nuclear encoded mitochondrial gene) may account for as many as 20% of all CMT-2 cases
  - 2B – 3q13, RAB 7 (with ulcerations, overlaps HSAN type I)
  - 2C – with vocal cord and diaphragm involvement
  - 2D – 7p14, Glycyl tRNA Synthetase (disproportionate hand weakness)
  - 2E – 8p21, neurofilament light chain protein
  - 2F – 7q11. HSP27 (heat shock protein 27, overlaps hereditary motor neuropathy 1, which is often classified with the distal spinal muscular atrophies)
  - CMT-2G: 12q12 link
  - CMT-2I, 2J: P0 mutation (same myelin gene in CMT-1B, yet causes axonal neuropathy depending on site of mutation)
  - CMT-2L: heat shock protein 8, 12q24. (same gene as causes Hereditary Distal Motor Neuropathy type II, viewed as a distal spinal muscular atrophy)

- Autosomal recessive forms (CMT-4):
  - Can be axonal or demyelinating
    » 4A – 4F known causes of recessive demyelinating neuropathies, often present at birth (congenital)
    » arCMT-2A, 2B
  - Many single families with unique features

- X-linked CMT
  - Connexin32 (Gap Junction Beta 1, GJB1 is emerging as preferred name) mutations
  - Mutations in coding region mostly, rarely in regions which control expression of gene
What happened to CMT-3? Currently this term is not in use. It used to be part of Dejerine Sottas Syndrome, which has multiple genetic causes, most often just a “severe” CMT-1 (autosomal dominant demyelinating). The rest are part of CMT-4 (recessive demyelinating)

» Point mutations in PMP-22
» Point mutations in EGR2 (Early growth response 2)
» Point mutations in P0 protein
» mutations in NDRG1 (n-myc downstream regular gene 1)
» Mutations in MTMR2 (myotubularin-related protein 2)
» Others not yet identified
### Toxic Neuropathies caused by Pharmaceutical Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Used for:</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almitrine</td>
<td>COPD</td>
<td>Axonal, mild</td>
</tr>
<tr>
<td><em>Allopurinol</em></td>
<td>Gout</td>
<td>Axonal, ? some demyelination</td>
</tr>
<tr>
<td>AntiGD2 antibody</td>
<td>Melanoma</td>
<td>Acute sensorimotor polyradiculopathy</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Antiarrhythmic</td>
<td>Neuromyopathy, Mixed axonal/demyelination, characteristic inclusions on biopsy</td>
</tr>
<tr>
<td><em>Amitriptyline</em></td>
<td>Antidepressant</td>
<td>Neuropathy described after acute massive intoxication</td>
</tr>
<tr>
<td><em>Chloramphenicol</em></td>
<td>Antibiotic</td>
<td>Sensory - no human data</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Antimalarial, antiinflammatory</td>
<td>Neuromyopathy, mixed axonal/demyelinating with characteristic inclusions</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Gout, FMF</td>
<td>Neuromyopathy, axonal</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Leprosy, dermatologic</td>
<td>Axonal, motor &gt; sensory</td>
</tr>
<tr>
<td>ddI/ddC</td>
<td>HIV infection</td>
<td>Axonal, sensorimotor</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Alcoholism</td>
<td>Axonal, sensorimotor, may show axonal swelling on biopsy</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Antineoplastic</td>
<td>Sensory ganglionopathy in animal modesl</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Antibiotic</td>
<td>Axonal, sensorimotor</td>
</tr>
<tr>
<td><em>FK506</em></td>
<td>Immune suppressant</td>
<td>CIDP-like picture (one report only)</td>
</tr>
<tr>
<td>Gold</td>
<td>Rheumatoid Arthritis</td>
<td>Axonal, subacute sensorimotor, myokymia</td>
</tr>
<tr>
<td><em>Hydralazine</em></td>
<td>Antihypertensive</td>
<td>Axonal, sensorimotor, ? d/t pyridoxine deficiency</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Antibiotic</td>
<td>Axonal, sensorimotor, ? d/t pyridoxine deficiency</td>
</tr>
<tr>
<td>Interferon (alpha)</td>
<td>Immune modulator</td>
<td>Isolated reports of multiple or diffuse axonal neuropathy</td>
</tr>
<tr>
<td>Lithium</td>
<td>Psychiatric</td>
<td>Acute-subacute axonal, sensorimotor. ? only after acute massive intoxication</td>
</tr>
<tr>
<td>L-Tryptophan</td>
<td>Hypnotic</td>
<td>Neuromyopathy, axonal sensorimotor</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Antibiotic</td>
<td>Axonal, sensorimotor</td>
</tr>
<tr>
<td>Misonidazole</td>
<td>Sensitizing agent</td>
<td>Acute-subacute axonal, sensorimotor</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Urinary antibiotic</td>
<td>Acute-subacute axonal sensorimotor</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Anaesthetic abuse</td>
<td>Axonal sensorimotor myeloneuropathy (B12 defect)</td>
</tr>
<tr>
<td>Perhexilene</td>
<td>Antianginal</td>
<td>Neuromyopathy, mixed axonal / demyelinating, characteristic inclusions</td>
</tr>
<tr>
<td><em>Phenytoin</em></td>
<td>Anticonvulsant</td>
<td>Axonal, subclinical, after chronic use</td>
</tr>
<tr>
<td>cis-Platinum</td>
<td>Antineoplastic</td>
<td>Axonal large &gt; small fiber sensory</td>
</tr>
<tr>
<td>Podophyllin</td>
<td>Herbal remedy</td>
<td>Acute-subacute sensorimotor, interferes with microtubule function</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Vitamin abuse</td>
<td>Axonal, sensory, large &gt; small fiber</td>
</tr>
<tr>
<td>Sodium cyanate</td>
<td>Sickle cell anemia</td>
<td>Axonal, sensorimotor</td>
</tr>
<tr>
<td>Suramin</td>
<td>Antineoplastic</td>
<td>Severe axonal/demyelinating, sensorimotor</td>
</tr>
<tr>
<td>Taxol</td>
<td>Antineoplastic</td>
<td>Axonal, sensorimotor</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Immune modulating agent</td>
<td>Axonal, sensorimotor</td>
</tr>
<tr>
<td>Thiophenicol</td>
<td>Antibiotic</td>
<td>Subacute sensory</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Antineoplastic</td>
<td>Axonal, sensorimotor</td>
</tr>
</tbody>
</table>

* Existence of neuropathy not completely proven
## Neuropathies caused by metals/occupational/biological toxins

<table>
<thead>
<tr>
<th>Substance</th>
<th>Exposure</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrylamide</td>
<td>mining, paper industries</td>
<td>axonal sensorimotor, mild giant axonopathy</td>
</tr>
<tr>
<td>Arsenic</td>
<td>murder, antimicrobial</td>
<td>axonal sensorimotor</td>
</tr>
<tr>
<td>Buckthorn</td>
<td>Shrub in SW North America</td>
<td>acute axonal/mixed sensorimotor</td>
</tr>
<tr>
<td>Carbon disulfide</td>
<td>Rayon manufacture</td>
<td>axonal sensorimotor (giant axonal change)</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Cassava, sorghum, laetrile</td>
<td>axonal/mixed sensorimotor</td>
</tr>
<tr>
<td>Dimethylaminopropionitril</td>
<td>Grouting</td>
<td>axonal sensorimotor ? small fiber</td>
</tr>
<tr>
<td>Diphtheria toxin</td>
<td>infection</td>
<td>demyelinating sensorimotor</td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td>cool sterilization, chemical</td>
<td>axonal sensorimotor</td>
</tr>
<tr>
<td>Lead</td>
<td>plumbing, battery, paint</td>
<td>axonal sensorimotor</td>
</tr>
<tr>
<td>Mercury</td>
<td>pollutant</td>
<td>axonal sensory motor neuropathy +/- neuronopathy</td>
</tr>
<tr>
<td>Methyl Methacrylate</td>
<td>resin (dental, ortho</td>
<td>axonal sensorimotor</td>
</tr>
<tr>
<td>Methyl n-butyl ketone</td>
<td>resins, inhalant abuse</td>
<td>axonal/mixed sensorimotor, giant axonal change</td>
</tr>
<tr>
<td>n-Hexane</td>
<td>resins, inhalant abuse</td>
<td>axonal/mixed sensorimotor, giant axonal change</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>insecticides, plastics</td>
<td>axonal acute/subacute sensorimotor</td>
</tr>
<tr>
<td>*Styrene</td>
<td>paint/dye industry</td>
<td>chronic sensorimotor</td>
</tr>
<tr>
<td>Thallium</td>
<td>Rat poison, depilatory agent</td>
<td>axonal acute/subacute sensorimotor</td>
</tr>
<tr>
<td>Vacor</td>
<td>Rat poison</td>
<td>acute axonal sensorimotor</td>
</tr>
</tbody>
</table>

### IV - Laboratory Testing in Peripheral Neuropathy

Laboratory investigations are guided by the history and physical findings. When possible and clinically reasonable, examination of family members should be done in any patient who might have a genetically determined neuropathy.

Electrophysiological testing is mandatory. This quantifies severity, serves as an objective basis for comparison in the future, and may reveal critical clues to the etiological diagnosis, such as radicular involvement, demyelination, conduction block, etc.

Laboratory testing should be carried out in several stages. After the initial assessment, if a peripheral neuropathy is being seriously considered or is definitely present, the patient should undergo the following as a minimal assessment.

- NCS/EMG
- CBC, ESR
- creatinine
- Glycosylated hemoglobin or glucose tolerance test (fasting glucose not good enough)
- TSH
- ANA, RF
• Serum B12
• Serum immunoelectrophoresis (IEP)

If one is not certain that a neuropathy is present, it may be worthwhile holding off on the more expensive components of this battery (especially the IEP) until after the presence of the neuropathy is confirmed by NCS. While normal NCS do not entirely exclude a peripheral neuropathy, if the NCS are normal the neuropathy must be very mild or involve small fibers only, and in such instances a specific etiologic diagnosis is rarely made and treatment is rarely offered.

Following the completion of these initial studies, if no diagnosis is made, or specific etiologic possibilities need to be pursued, further non-invasive or minimally invasive tests may follow. These may include the following:

• Chest x-ray, abdominal US (sarcoid, occult malignancy, systemic disease)
• Cauda equina MRI with contrast (root enlargement and enhancement suggests CIDP)
• CSF examination (malignant cells, lymphocytes, increased protein)
• Skeletal survey (may show solitary, sclerotic, or multiple plasmacytoma despite negative immunoelectrophoresis - should be done in all patients with demyelinating neuropathy)
• Lyme serology (in endemic areas or if clinical picture suggestive)
• HIV testing (if high risk group or suggestive features)
• Hepatitis C serology
• Cholesterol and lipid assays, lipoprotein electrophoresis (Tangier disease, abetalipoproteinemia, hyperlipidemic neuropathy)
• Vitamin E levels (malabsorption syndromes, abetalipoproteinemia)
• Testing for malabsorption (vitamin deficiencies)
• Schirmer’s and Rose Bengal testing (Sjogren’s)
• Hair or urine heavy metal analysis (if suspect metal exposure)
• Anti-ganglioside (GM1, sulfatide), anti-MAG serum activity
• Anti-RO, anti-LA antibodies (if suspect Sjogren’s syndrome)
• Anti-neutrophil cytoplasm antibodies-ANCA (Wegener’s granulomatosis or microvasculitis)
• Anti-Hu antibodies (paraneoplastic sensory ganglionopathy)
• Serum cryoglobulins
• DNA testing (see section below)

A few words about some of these tests are in order:
• a chest Xray is a quick and cheap screening test for many systemic diseases that can cause neuropathy. Same is true for ESR.
• the CSF examination can be useful, especially when the diagnosis of CIDP is considered. A normal CSF protein is strong evidence AGAINST the diagnosis, as the CSF protein is elevated in 90-95% of these patients. However, the problem with CSF exam is nonspecificity. Many neuropathies, some of which
fall into the differential of CIDP, raise CSF protein, including diabetes, uremia, vasculitis, and neoplasia, and lumbar root compression.

• when seriously looking for a paraproteinemia, don’t forget to do a urine immunoelectrophoresis; the first morning specimen is OK, although a concentrated 24 hour collection is best. If initial tests are negative and clinical suspicion is high, repeating the test in several months may be worthwhile.

Also, a circulating paraprotein is absent in up to 20% of patients with plasma cell dyscrasia, primary amyloidosis, or osteosclerotic myeloma; a skeletal survey will pick up some of these otherwise missed diagnoses.

In contrast, too much emphasis is placed in the recent literature on various antibodies: e.g. anti-MAG, anti GM1, anti GQ1b, etc. As a general rule, these tests are not particularly useful, and some are downright useless (e.g. anti-sulfatide antibodies). For example, the anti GM1 antibody titre is mildly to moderately elevated in several patient groups, including multifocal motor neuropathy, motor neuron disease, and motor dominant CIDP; therefore it is likely to be unhelpful in distinguishing between these possibilities when the clinician is uncertain. It is suggestive of MMN when extremely high, but in those cases the diagnosis is usually obvious. When the clinical situation is obvious and the clinician is certain - who needs the test! Never diagnose MMN only on the basis of this antibody if the picture does not fit.

Similar considerations apply to anti-MAG antibodies, which usually occur in a very clinically and electrically stereotyped peripheral neuropathy. An IgM paraprotein is practically always present, and usually the diagnosis is obvious. The test can be obtained, but costs 300$ US (in 2003). It is nice to have this information, but it rarely impacts on clinical management.

Another example involves serum phytanic acid assays. The syndrome associated with Refsum’s disease is sufficiently characteristic that serum phytanic acid levels should not be required except to confirm a highly probable clinical diagnosis. Don’t order phytanic acid levels on every chronic demyelinating neuropathy.

Anti-GQ1b antibodies are usually present in Miller-Fisher syndrome. They can be helpful diagnostically in these patients who can be challenging to diagnose, but generally the result cannot be obtained in time to materially impact patient management.

There is an extreme rare syndrome of anti-GD1b antibody associated neuropathy the “CANOMAD” syndrome of Chronic Ataxic Neuropathy with Ophthalmoplegia M-protein, Aggulitation, and Diasialosyl antibodies. Antibodies can be helpful, but should not be sent on every sensory neuropathy patient.

Antisulfatide antibodies are discussed a lot in the literature for sensory neuropathies. I am not convinced that this has any validity.
Genetic testing

Huge advances have been made in the understanding of genetically determined neuropathies. Most of these relate to the understanding of Charcot-Marie-Tooth disease, but other advances have been made. See the table above for a current listing of CMT subtypes.

The mutations for which testing is now available include (list is not comprehensive as cannot keep up with advances)

- Charcot-Marie-Tooth disease
  - PMP duplication (CMT-1A) or deletion (HNPP) – readily available
  - P0 mutation (CMT-1B, some CMT-2) (available through US only)
  - EGR2 mutation (CMT 1, or Dejerine Sottas) (available through US only)
  - Connexin mutation (CMT-X) (available through US only)
  - Neurofilament light chain (CMT2) (US only)
  - Periaxin mutation (Dejerine Sottas) (US only)

- DNA testing for familial amyloid polyneuropathy (TTR mutations)
- DNA testing for mitochondrial disease
- DNA testing for the SCA syndromes, nearly all of which have an associated sensory neuropathy of varying severity
- Testing for defect of lipid metabolism (if clinical suspicion)
  - serum or leukocyte arylsulfatase (metachromatic leukodystrophy)
  - quantitated urinary sulfatide excretion (metachromatic leukodystrophy)
  - serum or leukocyte beta-galactosidase activity (Krabbe’s leukodystrophy)
  - serum or leukocyte alpha-galactosidase A (Fabry’s disease)
  - serum or cell culture sphingomyelinase activity (type I Niemann-Pick)
  - serum very long chain fatty acids (adrenoleukodystrophy)
  - serum phytanic acid (Refsum’s disease)

Most useful are the recently available genetic tests for CMT-1A and for HNPP, available for free, although some slight hassle to arrange, with the testing done in Ottawa.

For the uncommon cases of CMT-1 which are not due to the PMP-duplication (P0, EGR2) it is possible to get further testing through the US (Athena Diagnostics). Remember also that CMT-X looks like CMT-1 in men, so workup of a genetic neuropathy with significant conduction velocity slowing (<40 m/sec in nerves with decent amplitudes) may include this assessment also. In women, assessment for axonal CMT may include CMT-X, because this X-linked condition is milder in woman.

The Ministry of Health may approve funding for the tests in the US, but it hard to make the case for this expense unless in the information will in some way alter management, which generally it does not. It is also a lot of trouble for the physician to order these tests, and in general it has not yet (as of Sept 2003)
become the standard to check for anything other than that for CMT-1A/HNPP, which is reasonably easy to get.

**When to biopsy the nerve**

Before considering nerve biopsy, one should exhaust all reasonable non-invasive or minimally invasive diagnostic modalities. Furthermore, recall that nerve biopsy is associated with more short- and long-term sequellae than biopsy of skin, bone marrow, salivary gland (for diagnosis of Sjogren’s syndrome), muscle, or abdominal fat pad.

Nerve biopsy can be very helpful in providing an etiologic diagnosis. As a rough rule, for fully investigated cryptogenic neuropathies, it is diagnostic in 20%, helpful in patient management in another 20%, and not particularly useful in 60%. The following table lists the specific diagnoses that can be made by nerve biopsy. Note, however, that some of these are usually obvious on clinical or laboratory grounds, or can be made by biopsy of another organ.
Specific diagnoses that can be made by nerve biopsy

Inflammatory/infectious
- Neuropathy with macrophage mediated demyelination (CIDP, GBS)
- Vasculitic neuropathy
- Leprous neuropathy, especially primary neuritic leprosy
- Sarcoidosis or granulomatous neuropathy
- CMV neuritis in immune suppressed patients

Neoplasm/paraprotein associated
- Non-amyloid paraprotein associated neuropathies
  - IgM anti-MAG paraprotein (widely spaced myelin)
  - The POEMS syndrome (uncompacted myelin)
  - Cryoglobulin neuropathy with intravascular cryoglobulinemia
- Immunoglobulin deposition disease
- Primary amyloidosis
- Neoplastic infiltrative neuropathy
- Lymphomatoid granulomatosis

Toxic neuropathies
- Amiodarone/Perhexiline/Chloroquine neuropathy
- Hexacarbon neuropathy

Genetically determined Neuropathies
- Hereditary neuropathy with liability to pressure palsies*
- Familial Amyloid neuropathy
- Giant axonal neuropathy
- Neuroaxonal dystrophy
- Polyglucosan body disease
- Hereditary sensory and autonomic neuropathies
- Lipid metabolism diseases
  - Metachromatic leukodystrophy
  - Adrenoleukodystrophy
  - Globoid cell leukodystrophy
  - Niemann-Pick disease
  - Fabry’s disease
  - Tangier disease
  - Neuronal ceroid lipofuscinosis

As a general rule, biopsy should be seriously considered in any patient with a cryptogenic peripheral neuropathy, subject to these important caveats:

- The patient has been fully and correctly investigated by non-invasive means and less-invasive means
- A specific diagnosis would impact on management. In practice, this means that the neuropathy is sufficiently severe, or is progressing rapidly, so that one can justify immune modulating treatment.
• The patient understands the implications of treatment. Thus, the clinician must discuss the risks and benefit of the possible treatment (usually prednisone, cytotoxic agents, plasma exchange or IVIg) before the biopsy is performed. It serves no purpose to prove a diagnosis of CIDP or vasculitis by biopsy, if the patient then refuses the treatment.

• The biopsy will be examined by a pathologist with extensive experience in the examination of nerve specimens. This is essential both for satisfactory preparation of the specimen, and for an accurate tissue interpretation.

In practice, careful consideration of these issues results in nerve biopsy for only a tiny minority of patients with cryptogenic peripheral neuropathy. In nearly all cases, the majority actually, the neuropathic process is either so mild or minimally progressive that biopsy is not justified. In such cases, it is generally better to observe the patient and assess the process over time than to rush to nerve biopsy after the first assessment.

Much has been said, but little useful documented, regarding the yield of biopsy in various types of neuropathies, axonal vs demyelinating, symmetrical vs asymmetrical, etc. Clearly, in rapidly progressive multifocal neuropathies biopsy yield is very high (vasculitis, usually). Just as clearly, the yield would be very low in a patient with a 5 year history of minimally progressive sensory neuropathy affecting both feet.

However, a review of experience from the St. Michael’s Hospital peripheral nerve pathology laboratory (Dr. J. Bilbao) suggested that the diagnostic yield was the same for axonal and demyelinating peripheral neuropathies. Many of the “diagnostic” biopsies were performed in patients who had a symmetrical, distally predominant process. A reading of the literature, as well as personal experience, indicate that there is no clinical feature of a neuropathy that excludes the possibility that biopsy will reveal a treatable problem.

**Alternative biopsy sites**

In ordering a nerve biopsy the clinician must take into account the morbidity of the procedure and the likelihood of a positive diagnosis in the different polyneuropathies. In amyloid neuropathy biopsy of skin or abdominal fat pad often allows detection of amyloid and characterization of its major protein. For familial amyloidosis, skin biopsy is probably a higher yield procedure than nerve biopsy, and similar considerations apply to abdominal fat pad aspiration in primary amyloidosis. In a patient suspected of having leprosy, examination of skin lesions should be performed first, although nerve biopsy is indispensable in primary neuritic leprosy.
Similarly, skin or conjunctival specimens might readily show characteristic findings in storage and axonal dystrophy states, including Giant Axonal Neuropathy, Neuroaxonal Dystrophy, Neuronal Ceroid-Lipofuscinosis, Fabry's and Niemann-Pick disease.

A combined nerve and muscle biopsy is best if a diagnosis of vasculitis or amyloidosis is suspected; these are two of the most common indications for nerve biopsy. In systemic vasculitis, the addition of muscle biopsy to nerve biopsy may increase the diagnostic yield an additional 15% to 45%. Muscle biopsy can also prove helpful in a search for sarcoidosis. Thus, the combined procedure is advocated when the clinician is considering these possibilities. The combined biopsy can usually be done through a single incision at midcalf between the heads of the gastrocnemius muscle, where the sural nerve can be found as it emerges through the fascia. An alternative method is biopsy of the superficial peroneal nerve and some of the underlying peroneus brevis muscle, but there is no experience with study of this nerve in Toronto.

Nerve biopsies performed for diagnostic purposes should comprise the entire thickness of the nerve trunk. A technique for fascicular biopsy was described in the 1960’s and enjoyed some popularity as it was thought to lower the rate of post-operative sensory loss and pain. However, most workers now reject this approach. Fascicular biopsy reduces the already small amount of tissue available to make a diagnosis. In diseases where involvement is multifocal, such as vasculitis, amyloidosis, leprosy or malignant infiltration, the diagnostic yield is undoubtedly reduced. Peripheral nerve vasculitis is usually predominantly epineurial, and fascicular biopsy provides little or no epineurium. While fascicular biopsy of normal nerves is not problematic, the technique becomes more difficult when there is marked neural atrophy, inflammation, or fibrosis. The fascicle is handled intimately, increasing the opportunity for producing artifacts. Finally, some workers have not observed a reduced rate of post-biopsy complications with this method as compared to whole nerve biopsy. Thus, there is essentially no role for fascicular biopsy in clinical neurology.

**Sequelae of Nerve Biopsy**

Some sensory loss in the area innervated by the sural nerve is likely if a whole nerve biopsy is performed. This result in itself is not ordinarily a problem. Some patients fully recover sensation in the territory of the sural nerve, especially if the biopsy is fascicular. In most the anaesthetic area shrinks over months and years to a small region.

Major complications, such as severe wound infections or neuroma formation requiring resection, are said to occur in 1% of patients. This is undoubtedly an underestimate - I suspect the figure is more like 5-10%. Patients with severe
wound infections or delayed healing often suffer from systemic vasculitis and are being treated with steroids. Thirty percent to 50% of patients experience immediate postoperative pain, and Dyck and colleagues reported that 36% of patients experienced discomfort of various types at three months. The occurrence of lasting paraesthesiae, dysesthesia, or pain varies in different series. Studies report that 10-40% of patients complain of persistent discomfort (usually unpleasant paraesthesiae) at 1 year after biopsy. In most cases this is mild and intermittent, and will improve with time, but up to 10% may be quite disturbed by their symptoms.

The bottom line on nerve biopsy is this: In the years 1999-2000 I saw several hundred patients with peripheral neuropathy in whom no diagnosis was evident. I have ordered 3 nerve biopsies in that interval. I can recall another in which I recommended the biopsy be done. Only 2 of the 4 biopsies were really useful in the final analysis.

In the same interval I have seen dozens of patients with relatively mild neuropathies who had biopsies before they were referred to me, in whom no diagnosis was made, and who indicated that the nerve biopsy they had was actually the worst aspect of their condition.
V – Treatment of Peripheral Neuropathy

There are two components to treatment of neuropathy – specific, and supportive.

Specific measures are those which alter the course of the disease so as to reverse or stop progression. These include immune modulating agents, specific supplements or drug/dietary changes. The ability to find these measures is limited in most cases. We always look for those neuropathies where we can truly treat the disease. Remember, however, that even if a “treatable” disease is found, like CIDP or vasculitis, the treatment can be worse than the disease, and that the severity and progression of the disease should justify the risks of the treatment.

Nonspecific measures are much more generally applicable, to reduce pain, to improve function, to improve ability to cope with the disease, physically or psychologically.

The discussion below applies only to the nonspecific aspects of peripheral neuropathy treatment. In the real world, this is the only thing we can do for most patients with peripheral neuropathy.

1) Education

Perhaps the most useful thing to do is to explain to the patient what is wrong with them. In particular patients are concerned about prognosis – fearing severe disability or pain as their condition evolves. In most cases they can be reassured that this will not ensue. Family physicians know little or nothing about neuropathy, and tend to increase patient anxiety in proportion to their own anxiety about the lack of understanding of the problem.

In patients with CMT in particular, it is important to emphasise that life expectancy is not reduced, most patients who have the disease do not even know it, and that the most important preventative measure is to protect the feet against unnecessary trauma, as musculoskeletal foot pain is the single problem most likely to seriously disable CMT patients.

2) Pain management

Symptoms such as numbness, “coldness”, “deadness”, etc cannot be treated. They are negative symptoms due to loss of sensory input. However, “burning”, “jabbing”, lancinating, “stabbing” and “electric shock” pains often respond to treatment. Although there are many drugs available for treatment, in the real world the approach is as follows:
i) If something simply like Tylenol (without codeine) works, or cold water soaks several times a day provide sufficient relief, even if there is residual pain, one may not need more. The goal of treatment is not to abolish neuropathic pain, but to reduce to a manageable level.

ii) As a next line, try gabapentin (Neurontin) for paroxysmal pains, and amitriptylline for burning pains. The latter is particularly effective if there is a sleep disturbance, which is often the case especially with the burning night time pain that many patients with small fiber neuropathy describe.

For Neurontin, the starting dose is 300 mg tid. This is usually well tolerated, but in frail patients it can be started at 300 qHS. The dose is then increased by 300 mg every 4-7 days, maintaining a TID schedule, until there is good pain relief or intolerable side-effects. Anything less than 1800 mg daily is not an adequate trial. A dose of 3000 mg/day is not unusual, and probably up to 4500 mg/day can be tried.

“Son of Gabapentin”, Pregabalin, is now starting to be marked by Pfizer. It seems to be about as effective as Gabapentin, have the same side-effects as Gabapentin, and the main advantage seems to be easier dosing (initial dose 75 mg bid, increasing to 150 bid if necessary). Time will tell if this drug will supplant Gabapentin.

For amitriptylline, the starting dose is 10-25 mg qHS, increasing by 10-25 mg every 1-2 weeks as tolerated, to a maximum dose of 150 mg qHS, or less if a good benefit is achieved. Side-effects are more of a problem than with Neurontin. If the main problem is excessive sedation, Nortriptylline (10-100 mg qHS) can be tried. However, usually the drowsiness side-effect of amitriptylline is in part what makes it desireable.

If these fail, usually nothing much worse. They can be used in combination with no significant interaction. If further attempts are desired, or if a drug is not available (Neurontin is not covered by the Ontario Drug Benefit Formulary for this indication), one can also consider carbamazepine or phenytoin at standard anticonvulsant doses. For burning pain mexiletine has been advocated, but it is rarely helpful if the others fail.

Topiramate is being advocated now, mostly by the company which makes it, for neuropathic pain. This is based on anecdote only. My attempts with the drug have been disappointing, with patient unable to tolerate the sedation, confusion, and ataxia it causes. The regimen is 25 od, increasing as high as 100 mg bid very very slowly (over many weeks).

Based on personal experience, capsaicin cream (Zostrix) appears to be useless for neuropathic pain.
IVIg and prednisone are both potentially of benefit for neuropathic pain. However, this is a situation where the treatment may be worse than the problem can justify.

3) Optimization of function and protection against secondary injury

Patients with less than grade 3 dorsiflexion usually benefit significantly from ankle-foot orthoses, although initially they may dislike them. They are important not only for more stable walking, but to help reduce formation of Achilles’ tendon shortening due to a chronically plantarflexed foot.

In patients with hand weakness causing “clawing”, splints should be worn, at least at night, to prevent finger flexion deformities.

Patients who have severe sensory loss in the feet need to be educated about the risk of painless injury, and need to have in place an active program of daily foot inspection (for unsensed trauma) and foot care. Needless amputations can result if this is not done proactively.

Standard foot orthotics (usually made for the benefit of the vendor, not the patient) are generally useless for neuropathic foot deformity.

For patients with Charcot-Marie-Tooth disease (or with foot deformity of any cause) it is essential to wear well padded shoes, with ankle support depending on the severity of weakness. There is no need for “orthopedic shoes” – a concept from dark ages which is no longer valid in the modern era of hi-tech sporting footwear. The patient should buy the best running/training shoes they can afford, and get a new pair every 6-12 months as the padding is worn out.

4) Role of activity

A regular program of stretching is useful for optimising joint mobility and prevention of contractures – which would just make a bad situation worse.

Physiotherapy does not offer much specific benefit in patients with chronic neuropathy, but the regular contact with a health professional, and the patient’s focus on maintaining physical function, are psychologically beneficial for coping with a chronic condition. It is important to set realistic and functionally useful goals.

Encourage patients to continue to walk, and be as active as their disease will safely permit. Many patients restrict themselves unnecessarily. The only exception to the rule is in patients with severe foot deformity who should avoid (within reason) high foot impact physical activity. Walking, however, and activities such as swimming or cycling, are always to be encouraged.
5) Genetic assessments

Family assessments are a common part of working up neuropathies. They will often yield affected family members. Depending on comfort level this may be dealt with by the neurologist, or referred for genetic counselling.