Toxic Neuropathies Associated with Pharmaceutic and Industrial Agents

Zachary London, MD, James W. Albers, MD, PhD*

*Department of Neurology, University of Michigan, 1324 Taubman Center,
Ann Arbor, MI 48109-0322, USA*

The diagnosis of peripheral neuropathy can be established readily on the basis of clinical and electrodiagnostic criteria. Clinicians generally think of neuropathy, as a manifestation of an underlying systemic disorder, such as diabetes mellitus, or as a hereditary disorder of myelination. Investigations aimed at identifying the source of a neuropathy are fueled appropriately by the desire to find a reversible cause or at least to provide information about prognosis. The most common causes of peripheral neuropathy are genetic, inflammatory, or systemic, and many of these conditions can be diagnosed with simple blood tests.

In up to 20% of cases of neuropathy, however, the standard battery of laboratory tests is unrevealing. In these instances, it is natural for patients and physicians to wonder whether or not an unsuspected toxicant could be responsible. This suspicion can be heightened when patients have

unexplained systemic manifestations or when other close contacts also have developed symptoms of neuropathy. In other cases, exposure to a specific agent is suspected as the cause of peripheral neuropathy. At times like this, it can be tempting to equate exposure (or opportunity for exposure) with causation. Patients may be anxious to know if they need to take steps to eliminate an ongoing industrial or environmental exposure, and in some cases litigation is involved. Perhaps an even more common situation is patients who have idiopathic neuropathy and who undergo exhaustive work-up and are found to have abnormal levels of an unsuspected toxicant. For example, routine screening for urine arsenic is a common practice, and elevated levels periodically are discovered in patients who do not have a known exposure. The physician then is left with the task of determining if these values represent true toxicity.

In all of these situations, it helpful to have an understanding of the clinical, laboratory, and electrodiagnostic features of specific toxic neuropathies. Whenever a toxic neuropathy is suspected, it also is essential to understand the scientific methodology necessary to verify or refute this suspicion. The purpose of this article is to discuss the clinical investigation of a suspected toxic neuropathy, to review some of the more common or representative toxicants, and to identify the methods for establishing causation.

The clinical evaluation of suspected toxic neuropathy

Perhaps the most compelling reason to be familiar with the various toxic neuropathies is that these conditions are, by nature, reversible with removal of the offending agent. Thus, even though these conditions are rare, there is an urgency to arrive at the correct diagnosis so measures can be taken to eliminate ongoing toxic exposure. Early diagnosis also can identify other individuals who may be at risk. Unfortunately, identifying a toxicant as the causative agent for a patient's neuropathy can be a difficult task, as there are no neurologic or electrodiagnostic features that distinguish toxic neuropathy from other causes of peripheral neuropathy reliably. Thus, toxic neuropathies always must be considered once a clinical diagnosis of neuropathy is established.

The first step in working up a suspected toxic neuropathy is to establish that a patient does, in fact, have clinical and electrodiagnostic evidence of peripheral neuropathy. The history should focus on sensory, motor, and autonomic complaints, including temporal profile, magnitude, and description of the symptoms. Most toxic neuropathies involve the longest and largest axons, causing numbness, paresthesias, or weakness in a stocking or stocking-glove distribution [1].

If a toxic neuropathy is suspected based on a patient's symptoms and signs and an apparent lack of a systemic or hereditary cause, the diagnostic yield can be increased by asking directed questions about potential

pharmaceutic, industrial, recreational, or environmental exposures. It is useful particularly to become familiar with common pharmaceutic agents that can be associated with neuropathy. Examples include amitriptyline, cimetidine, cisplatin, colchicine, dapsone, disulfiram, ethambutol, gold, hydralazine, isoniazid, lithium, paclitaxel, phenytoin, nitrofurantoin, metronidazole, thalidomide, and vincristine. It also is important to ask about over-the-counter preparations and vitamins, because some agents, such as the essential vitamin, pyridoxine, can be potent neurotoxicants at high doses. It is also worthwhile to ask about potential occupational exposures, including specific chemicals, whenever possible. Industrial exposures have become increasingly uncommon compared with their reported frequency in the early twentieth century. This almost certainly is the result of increased awareness of the neurotoxic properties of the chemicals used in manufacturing and the institution of preventive measures to reduce exposure. Exposures to known neurotoxicants still occur, however, often in epidemic form, and new industrial chemicals that may cause neuropathy periodically are introduced into society.

It is important, also, to solicit information about recreational exposures, such as use of chemicals in hobbies. Recreational drugs, such as alcohol, nitrous oxide, and n-hexane (from sniffing glue) are well-established causes of neuropathy. These causes of neuropathy easily can be missed, because patients may hesitate to volunteer information about recreational drug use. Even a negative response to direct questioning does not exclude such agents from further consideration.

Finally, it is important to take a thorough review of systems and perform a thorough general examination, because many neurotoxicants also cause systemic toxicity (Table 1). For example, arsenic poisoning can cause abnormal skin pigmentation and nail abnormalities (Mees' lines), and thallium intoxication can cause alopecia. Often, patients complain of nonspecific systems suggestive of gastrointestinal, cardiovascular, hepatic, or renal toxicity. These features should raise clinical suspicion for a toxic neuropathy, even though they may not suggest a specific toxicant.

Physical examination should focus foremost on findings that are suggestive of peripheral neuropathy. Objective findings, such as motor weakness and loss of reflexes, are more significant than subjective findings, such as sensory loss, without supportive evidence of impaired sensation (eg, a positive Romberg's sign). Examination of the skin, hair, and nails may help identify features of systemic toxicity. Most patients found to have toxic neuropathy do not exhibit any of these cardinal features. Furthermore, features that are believed the most suggestive of a toxic exposure, such as Mees' lines, often appear long after patients develop symptoms of neuropathy, limiting their initial diagnostic usefulness.

Electromyography (EMG) and nerve conduction studies are an essential part of the investigation for neuropathy, because they can confirm the diagnosis of peripheral neuropathy and give valuable information about

Table 1
Selected systemic clues associated with specific neurotoxicants

Neurotoxicant	Systemic feature
Acrylamide	Irritant dermatitis, palmar erythema, desquamation, hyperhydrosis, axonal swellings
Arsenic	Gastrointestinal symptoms, hyperpigmentation, hyperkeratosis, Mees' lines, cardiomyopathy, hepatomegaly, renal failure, anemia, basophilic stippling of red blood cells
Colchicine	Myopathy (neuromyopathy)
Dapsone	After decades of use, possibly slow acetylators
Ethyl alcohol	Nutritional factors, Wernicke's syndrome (dementia, ophthalmoplegia, and ataxia), midline cerebellar degeneration, abnormal liver function, cirrhosis
n-hexane	Irritant dermatitis, axonal swellings
Lead	Gastrointestinal symptoms, musculoskeletal complaints, weight loss, gum lead line, bone lead line, Mees' lines, renal failure, anemia, basophilic stippling of red blood cells
Lithium	Postural tremor
Mercury, elemental	Anorexia, gingivitis, hypersalivation, papular rash, hyperkeratosis, lens opacities, postural tremor, nephrotic syndrome, respiratory tract irritation, metal fume fever
Nitrofurantoin	Elderly with impaired renal function
Nitrous oxide	Myelopathy
Organophosphate pesticides	Irritant dermatitis, acute cholinergic effects, corticospinal tract residua, noncardiogenic pulmonary edema
Phenytoin	Gingival hyperplasia, cerebellar ataxia
Thallium	Gastrointestinal symptoms, irritant dermatitis, alopecia, noncardiogenic pulmonary edema
Trichloroethylene	Vasodilation with ethanol ingestion, irritant dermatitis, elevated liver function tests, cirrhosis
Toluene	Respiratory tract irritation, irritant dermatitis
L-tryptophan	Peau d'orange, eosinophilia

Adapted from Ford D. Exposure assessment. Continuum: lifelong learning in neurology neurotoxicology; 1999. p. 9–25.

pathophysiology and severity [2]. Nerve conduction studies, in particular, provide a degree of information that cannot be determined on a clinical basis alone. First, nerve conduction studies can determine whether or not the neuropathy involves sensory axons, motor axons, or both. Second, they can determine whether or not there is conduction slowing. Any neuropathy that causes loss of large-caliber myelinated axons can cause mildly reduced conduction velocities, but conduction slowing out of proportion to axonal loss can help focus the differential diagnosis significantly. Third, nerve conduction studies can identify the pattern of neuropathy, such as a typical stocking-glove polyneuropathy or a mononeuritis multiplex. Needle EMG is of

secondary importance in the evaluation of neuropathy. It is useful predominantly for identifying the degree of axonal involvement and ruling out polyradiculopathy, which can mimic peripheral neuropathy.

Many neurotoxicants cause similar clinical manifestations, but electrodiagnostic testing can be used to divide the neuropathies produced by neurotoxicants into broad categories. These categories are not exclusive, and some toxicants can cause more than one type of neuropathy, often depending on whether or not patients are subjected to a massive acute exposure or a low-dose chronic exposure. Nevertheless, this classification scheme is useful because it incorporates the suggested pathophysiology of the abnormality and can reduce an exhaustive list of potential neurotoxicants to a more manageable differential. These major categories include motor or motor greater than sensory neuropathy with or without conduction slowing, sensory neuropathy or neuronopathy, sensory greater than motor neuropathy with or without conduction slowing, and mononeuritis multiplex.

Discussion of every known toxic neuropathy is beyond the scope of this article. Rather, it focuses on selected examples that are the most common or most characteristic of each of the categories described.

Motor and motor greater than sensory neuropathy, with conduction slowing

Some neurotoxicants can mimic acute inflammatory demyelinating polyradiculoneuropathy (AIDP), with a motor or motor greater than sensory neuropathy with conduction slowing. Examples include arsenic (shortly after exposure), n-hexane, amiodarone, carbon disulfide, cytosine arabinoside, methyl n-butyl ketone, perhexiline, saxitoxin, and suramin.

Arsenic

Arsenic is a metalloid best known for its use as a poison in homicide and suicide. Industrial exposure may occur in lead and copper smelting, mining, and pesticide manufacturing [3]. Sources of environmental exposure include tainted well-water, wood preservatives, and arsenic-contaminated fossil fuels [4,5].

The neurotoxic effects of arsenic differ, depending on whether or not patients are subjected to an acute massive exposure or a chronic, low-level exposure. High-dose exposure can lead to a syndrome that can mimic AIDP [6]. Neuropathy begins 5 to 10 days after exposure and progresses over weeks. As with many toxic neuropathies, there may be a "coasting" effect, with continued progression of disease for a period of weeks after removal from exposure. Patients can develop flaccid areflexic quadriparesis, bifacial weakness, and even diaphragm paralysis, requiring ventilatory support [7,8].

Clinical manifestations can help distinguish arsenic toxicity from inflammatory demyelinating neuropathy, including a variety of systemic symptoms that may develop before the onset of neuropathy. Gastrointestinal

disturbance with abdominal pain and vomiting, tachycardia, and hypotension are common, although these symptoms also may be seen in AIDP [9]. Nonspecific systemic manifestations may follow, including hepatomegaly, renal failure, anemia, and cardiomyopathy, which are atypical for AIDP. Other systemic features are more specific to arsenic toxicity, such as brownish desquamation of the hands and feet (arsenical dermatitis) and Mees' lines on fingernails and toenails. Unfortunately, the skin and nail changes may not appear until a month or more after isolated ingestion of arsenic, by which time the diagnosis rarely is still in question.

If an initial EMG is performed within days, decreased motor unit recruitment may be the only finding. Over the first few weeks, EMG may show motor greater than sensory neuropathy with reduced amplitudes, borderline–low conduction velocities, prolonged F waves, and even partial conduction block in several motor nerves. The nerve conduction studies even may fulfill criteria for the diagnosis of an acquired demyelinating neuropathy [10]. Cases even are reported in which the sural sensory response is normal, but the median sensory response is absent, a finding often found in AIDP [11]. Follow-up studies are more consistent with a typical dying-back axonopathy, with absent sensory and motor responses and denervation/reinnervation changes on needle EMG.

Chronic exposure to low levels of arsenic, such as can be seen in industrial settings, often results in dermatologic manifestations first, including hyperpigmentation, hyperkeratosis, and mucosal irritation [12]. Ongoing exposure may lead to a painful length-dependent neuropathy with proportionally fewer motor symptoms [3].

Laboratory testing can aid in the diagnosis of arsenic poisoning in acute and chronic settings. Urine arsenic levels greater than 25 μg in a 24-hour specimen generally are considered abnormal, although levels may be elevated falsely by the ingestion of seafood, in particular bottom-feeding finfish. Small amounts of arsenic bind to keratin in growing tissues, allowing diagnosis to be made by measuring levels in hair and nails. This is useful particularly in the setting of chronic or low-level exposure or for detecting a remote exposure that has since ceased. Blood arsenic levels are not helpful, because serum arsenic is cleared within 2 to 4 hours [13].

Chelation with penicillamine or dimercaprol should be started as soon as possible after exposure [14,15]. The usefulness of chelation in preventing progression of acute arsenical neuropathy is unknown, however.

Hexacarbons

N-hexane and methyl-n-butyl ketone are hexacarbons used in industrial solvents and household glues. Most of the industrial exposures producing neuropathy occurred in the cabinet- and shoe-making industries, where hexacarbon solvents were used extensively until the 1970s. More recently, cases of n-hexane neuropathy were reported in automotive technicians using

degreasing solvents and cleansers. The most common source of n-hexane exposure today is the intentional inhalation of household glues for the purpose of intoxication [16,17].

Both n-hexane and methyl-n-butyl ketone are metabolized to 2,5-hexanedione in the liver, which probably is the neurotoxic agent [18]. Substantial n-hexane toxicity causes central nervous system depression and narcosis, but with repeated exposures, peripheral neurotoxicity can develop. Specifically, n-hexane causes a neuropathy consisting of length-dependent distal sensory loss, weakness, atrophy, reduced or absent distal reflexes, and autonomic dysfunction. Among "huffers," who inhale massive quantities of n-hexane volitionally, motor and cranial nerve symptoms may predominate. Furthermore, nerve conduction studies often demonstrate reduced amplitudes with conduction velocities in the range of a primary demyelinating disorder [19]. As with arsenic, n-hexane can create a clinical picture that mimics AIDP. Chronic, low-level exposures are associated with a more typical dying-back sensorimotor neuropathy with sensory loss, distal weakness, and absent ankle reflexes [20,21]. Chronic occupational and recreational exposures also are associated with degeneration of distal corticospinal and dorsal column pathway and impairment of color vision [22].

The classic neuropathologic finding in n-hexane neuropathy is giant axonal swellings, which consist of neurofilamentous aggregates that accumulate secondary to abnormalities of axonal transport. The slow conduction velocities found on nerve conduction studies are believed to represent secondary myelin sheath damage from these focal axonal swellings [17,23–27].

Cessation of exposure is the primary means of treatment, and in one large case series, all 102 patients who had identified cases of n-hexane intoxication recovered completely without other intervention [28].

Amiodarone

Amiodarone is a di-iodinated benzofuran derivative used for refractory or life-threatening ventricular arrhythmias. Amiodarone is associated with several neurotoxic effects, including peripheral neuropathy, action tremor, myopathy, optic neuropathy, basal ganglia dysfunction, encephalopathy, and pseudotumor cerebri.

The neuropathy associated with chronic amiodarone use varies in various reports. The clinical presentation may be a symmetric, subacute to chronic sensorimotor polyneuropathy with distal predominance [29–37]. Other investigators have reported a rapidly evolving motor-predominant neuropathy that can be difficult to distinguish from AIDP [38].

Reports of nerve conduction studies vary from a sensory-predominant axonopathy with reduced amplitudes to a demyelinating picture with prominent conduction slowing [39]. The findings in sural nerve biopsies also vary, with some specimens demonstrating axonal loss and others showing almost pure demyelination [40]. Amiodarone is highly lipophilic and forms intralysosomal

lipid complexes, leading to inclusions in multiple tissues. These inclusions are seen in neural structures, suggesting a possible mechanism of toxicity.

There is no specific treatment for amiodarone-induced neuropathy other than lowering or discontinuing the drug. Recovery can be slow after removal of the exposure, because amiodarone has a long half-life (25–100 days).

Motor and motor greater than sensory neuropathy, without conduction slowing

Some neurotoxicants are known to produce a motor-predominant neuropathy without conduction slowing, including certain organophosphates, vincristine and other vinca alkaloids, nitrofurantoin, cimetidine, dapsone, and possibly lead.

Organophosphates

Unlike most chemicals that cause neuropathy, organophosphates have been used widely because they are poisonous, rather than in spite of it. The neurotoxic properties of organophosphate compounds have led to their use as insecticides and ''nerve'' gases. Less toxic forms also have been used in hydraulic fluids, lubricants, fuel additives, plastic modifiers, and flame retardants. Today, most cases of acute neurotoxicity are in the setting of intentional ingestion of insecticides as a suicide attempt.

One of the most remarkable illustrations of large-scale organophosphate poisoning was the jake leg epidemic of 1930. Jamaica ginger, or jake, was an alcohol-based patent medicine that was popular among poor city-dwellers trying to circumvent Prohibition laws. To fool Prohibition chemists into thinking the medicine had a higher percentage of solids, one supplier contaminated Jamaica ginger with triorthocresyl phosphate (TOCP), an organophosphate that was believed harmless. By the time the source of the contamination was identified and removed, tens of thousands of Americans had developed disabling neuropathy [41–43].

Organophosphates exert their primary neurotoxic effect by inactivating acetylcholinesterase. This leads to an accumulation of acetylcholine in muscarinic and nicotinic receptors. Symptoms of cholinergic excess include bradycardia, salivation, nausea, bronchospasm, miosis, diarrhea, sweating, central nervous system dysfunction, muscle weakness, and fasciculations. After 1 to 4 days, an intermediate syndrome develops, characterized by weakness of proximal limb, neck, extraocular, bulbar, and respiratory muscles. This syndrome resembles myasthenia gravis and most likely represents a depolarizing blockade of neuromuscular transmission. A subacute motor greater than sensory neuropathy develops as the symptoms of the acute and intermediate syndromes resolve. Organophosphate-induced delayed neurotoxicity (OPIDN), as it has been called, occurs 7 to 21 days after exposure

and occurs only with certain exposure to certain organophosphates. Weakness follows a length-dependent pattern, with early foot drop and weakness of hand intrinsic muscles followed by more proximal weakness. Some patients go on to develop spasticity and upper motor neuron signs, indicative of superimposed distal corticospinal tract dysfunction [44]. TOCP, the agent implicated in jake leg, is a unique organophosphate that causes OPIDN without causing overt cholinergic symptoms first [45,46].

OPIDN is a distal axonopathy that affects the peripheral nerves and the long tracts in the spinal cord. Nerve conduction studies show evidence of sensorimotor neuropathy without conduction slowing [47,48]. The pathophysiology of OPIDN is believed the result of organophosphate-induced modification of a neuronal membrane protein called neuropathy target esterase, although the exact mechanism is unknown [49,50].

Vincristine

Vincristine is a vinca alkaloid chemotherapeutic agent used for treatment of solid tumors, lymphoma, and leukemia. Peripheral neuropathy is the dose-limiting side effect of all vinca alkaloids, with vincristine the most neurotoxic [51]. The mechanism of vincristine neuropathy is believed related to impairment of the function of microtubules involved in axonal transport [52].

Pain and small-fiber sensory loss predominate early, usually occurring at 4 to 5 weeks [53]. Autonomic dysfunction also may occur early, with constipation, orthostatic hypotension, and impotence. Distal symmetric weakness invariably occurs with continued exposure, and in some patients, these symptoms may develop fulminantly [54]. There also are cases of vincristine therapy leading to a severe acute neuropathy by unmasking a subclinical inherited neuropathy, such as Charcot-Marie-Tooth disease type 1 or hereditary neuropathy with liability to pressure palsies [55–57]. Patients who have these neuropathies may be susceptible to developing severe weakness with low or even single doses of vincristine.

In vincristine neuropathy, the EMG demonstrates axonal neuropathy, with decreased sensory and motor amplitudes on nerve conduction studies. The presence of motor involvement on electrodiagnostic testing correlates with the degree of clinical weakness.

Muscle weakness usually recovers rapidly after the drug is discontinued. Up to two thirds of patients continue to have residual sensory symptoms and absent deep tendon reflexes, however. Electrodiagnostic measures of neuropathy may persist indefinitely, with low or absent sensory nerve action potentials.

Sensory neuropathy or neuronopathy, without conduction slowing

Cisplatin, pyridoxine, thallium, metronidazole, ethyl alcohol, nitrofurantoin, and thalidomide are shown to induce a pure sensory neuropathy or neuronopathy without conduction slowing.

Cisplatin

Cisplatin is a chemotherapeutic agent used for ovarian and small cell lung cancers that causes a cumulative dose-limiting axonal sensory neuropathy. The primary site of damage is the dorsal root ganglion (sensory neuronopathy), but the large myelinated sensory axons also may be affected [58,59]. Manifestations include numbness, paresthesias, and occasionally pain in the distal extremities, with loss of deep tendon reflexes and position sense. The most important condition to consider in the differential diagnosis is paraneoplastic sensory neuronopathy, which can present identically. Paraneoplastic neuropathies may be associated with autoantibodies in the serum and may continue to progress despite discontinuation of the cisplatin. In cisplatin neuropathy, nerve conduction studies show decreased sensory nerve action potential amplitudes and prolonged sensory latencies.

The toxicity of cisplatin can persist long after the medication is discontinued. In one study of patients who had been treated with cisplatin 13 or more years prior, 38% were found to have nonsymptomatic neuropathy, 28% symptomatic neuropathy, and 6% disabling polyneuropathy [60].

The mechanism of cisplatin neurotoxicity is unknown, but it is believed to relate to disruption of fast axonal transport and induction of apoptosis in dorsal root ganglion cells [61,62].

Pyridoxine

Pyridoxine, or vitamin B_6, is an essential vitamin that has neuroprotective effects when used to treat isoniazid overdose, Gyromitra mushroom or false morel (monomethylhydrazine) poisoning, and hydrazine exposure [63]. Pyridoxine also is a potent neurotoxicant, however, with low-dose, chronic exposure and with acute massive exposure. Pyridoxine toxicity produces a pure sensory neuropathy, with numbness and loss of position sense but no dysfunction of motor nerves or the central nervous system [64]. In most cases, the neuropathy is slowly reversible with discontinuation of the pyridoxine, but large acute doses may be associated with permanent profound sensory loss and pseudoathetosis [65].

Thallium

Thallium is a neurotoxic metal that has been used in the manufacture of optical lenses, semiconductors, scintillation counters, some fireworks, insecticides, and rodenticides [66]. The most common causes of thallium poisoning are homicidal, suicidal, or accidental ingestion of rat poison, although the number of cases has declined substantially since thallium was banned in the United States as a rodent poison in 1972 [67–70].

Thallium causes a predominantly small-fiber neuropathy, with painful dysesthesias in the distal lower extremities. Dysautonomia often is present and may precede neuropathy [71]. Reflexes often are preserved, a feature

that helps localize the lesion to the small-fiber nerve and differentiate thallium poisoning from AIDP and other toxic neuropathies. Although most cases of thallium poisoning cause sensory symptoms only, there also are reports of motor manifestations [72].

Early signs of systemic toxicity include gastrointestinal symptoms, cardiac and respiratory failure, encephalopathy, and renal insufficiency [73]. The most pathognomonic manifestation of thallium poisoning is alopecia, which appears 15 to 39 days after intoxication and, therefore, is not useful in the acute setting [74]. Mees' lines (white stria of the nails) also may develop as a late sign.

Early in the course of the disease, there may be involvement only of the small nerve fibers. At this point, nerve conduction studies may be normal or show only mild abnormalities, such as absent plantar sensory responses. In more severe cases, evidence of axonal loss is found on electrodiagnostic testing and sural nerve biopsy [75,76].

The exact mechanism of thallium toxicity is unknown. Thallium enters cells through potassium channels and may compete with potassium in intracellular reactions and interfere with energy metabolism in the Kreb's cycle, oxidative phosphorylation, and glycolysis [77].

Sensory greater than motor (sensorimotor) neuropathy, with conduction slowing

Saxitoxin and tetrodotoxin, although not pharmaceutic agents, are biologic neurotoxicants that produce a sensory greater than motor neuropathy with conduction slowing.

Saxitoxin

Saxitoxin, otherwise known as red tide, is the neurotoxicant implicated in paralytic shellfish poisoning. The most common source of saxitoxin poisoning is the consumption of bivalve mollusks, in particular those harvested in the months of May, June, and July [78,79]. Clinical manifestations include gastrointestinal symptoms, cerebellar ataxia, and a sensorimotor neuropathy, which may be severe enough to cause respiratory depression.

Saxitoxin exerts its effects by blocking sodium channels, reducing the local currents associated with propagation of the action potential [80]. Nerve conduction studies show prolonged distal sensory and motor latencies with slowed conduction velocities and moderately diminished response amplitudes [81].

Tetrodotoxin

Tetrodotoxin is a poison derived from puffer fish, where it is found in various concentrations in the liver, ovaries, intestines, and skin [82]. Fugu, or puffer fish fillet, is a delicacy in Japan, where it is the most common cause

of fatal food poisoning [83]. Clinical manifestations depend on the dose of the exposure, but neurologic symptoms and signs may range from perioral numbness to flaccid paralysis, dilated pupils, and respiratory failure without loss of consciousness. Symptoms may begin within 1 hour after ingestion of the contaminated fish and generally abate after 5 days [84].

Like saxitoxin, tetrodotoxin causes blockade of voltage-sensitive sodium channels, leading to conduction failure. Nerve conduction studies show prolongation of sensory and motor latencies, prolongation of F waves, slowing of conduction velocities, and reduced sensory and motor amplitudes [85].

Sensory greater than motor (sensorimotor) neuropathy, without conduction slowing

The majority of peripheral neurotoxicants produce a length-dependent sensorimotor neuropathy without conduction slowing. Some examples of neurotoxicants known to fit this pattern include acrylamide, amitriptyline, arsenic (chronic), carbon monoxide, ethambutol, ethyl alcohol, ethylene oxide, gold, hydralazine, isoniazid, lithium, elemental mercury, metronidazole, nitrofurantoin, nitrous oxide, paclitaxel, perhexiline, phenytoin, thallium, and vincristine.

Acrylamide

Acrylamide is a vinyl polymer used to synthesize polyacrylamide, which has many applications as a soil conditioner, flocculator, and waterproofing agent and in the cosmetic, paper, and textile industries. Although polyacrylamide is nontoxic, it can be contaminated with the toxic acrylamide, especially when it is used as a flocculator [86,87].

Acrylamide causes a typical axonal neuropathy with weakness, sensory loss, and areflexia involving primarily large axons. Systemic symptoms include irritant dermatitis, palmar erythema, and encephalopathy. Nerve conduction abnormalities generally are mild and show low amplitude sensory responses, and, to a lesser extent, low amplitude motor responses without significant conduction slowing [88]. Subclinical neuropathy also is detected in patients who have low-level industrial exposures [89,90].

The pathologic hallmark of acrylamide neurotoxicity, like that of n-hexane, is giant axonal swellings. Classically, acrylamide is believed to exert its toxicity through disruption of anterograde and retrograde axonal transport [91]. Some studies suggest, however, that the nerve terminal may be the primary site of neurotoxicity rather than the axon itself [92,93].

Nitrofurantoin

Nitrofurantoin is an antibacterial agent specific for urinary tract infections. Nitrofurantoin is implicated in the development of axonal sensorimotor

neuropathy, with sensory-predominant (common) and motor-predominant (less common and typically developing after onset of the sensory neuropathy) neuropathies reported. Patients who have pre-existing renal dysfunction or diabetes mellitus are at greater risk for developing nitrofurantoin-induced neuropathy, but neuropathy also is described in otherwise healthy patients taking standard doses of this medication. [94,95]. The pathologic changes in nitrofurantoin-induced neuropathy are those of acute, severe axonal degeneration [95]. It is hypothesized that nitrofurantoin exerts its toxic effects through dose-dependent depletion of glutathione [96].

Phenytoin

Peripheral neuropathy long has been recognized as a side effect of chronic phenytoin use, especially at higher doses [97,98]. Although it is not well studied in prospective trials, most reports of phenytoin toxicity suggest that it probably does not live up to its reputation as a serious peripheral neurotoxicant. With standard doses and close monitoring of levels, phenytoin-induced neuropathy is rare. When present, patients usually are asymptomatic and the neuropathy can be detected only by physical examination or electrophysiologic studies [99–101].

Mononeuritis multiplex

Rarely, neurotoxicants can present with a clinical picture suggestive of multiple mononeuropathies, rather than a symmetric, length-dependent peripheral neuropathy. Examples include trichloroethylene, dapsone, lead, and L-tryptophan.

Trichloroethylene

Trichloroethylene is a chlorinated hydrocarbon that has been used as a cleaner, solvent, degreasing agent, and surgical anesthetic. It is unusual among neurotoxicants in that it is associated with a cranial mononeuritis multiplex with little evidence of sensory or sensorimotor neuropathy [102]. Patients develop ptosis, extraocular muscle dysfunction, facial and bulbar weakness, and signs of trigeminal dysfunction [103]. Like other neurotoxicants, trichloroethylene also is a systemic poison. It is shown to cause irritant dermatitis, cirrhosis, and cardiac failure [104].

In association with a trichloroethylene cranial mononeuritis multiplex, facial motor nerve distal latencies and blink reflex R1 latencies are prolonged. Blink reflexes also are used to suggest the presence of a subclinical trigeminal neuropathy in patients who have chronic, low-dose exposure to trichloroethylene through contaminated well water [105,106].

It is controversial whether or not trichloroethylene is directly toxic to nerves or if neurologic symptoms actually are the result of toxicity from

dichloroacetylene, a metabolite of trichloroethylene that is formed only in certain conditions, such as high heat or extreme alkalinity [107]. It also is hypothesized that trichloroethylene does not actually cause a toxic neuropathy but rather triggers the reactivation of a latent herpes virus [108]. Necropsy examination of one patient showed degeneration of the brainstem nuclei and tracts, the trigeminal nerve, and cranial sensory roots [103].

Dapsone

Dapsone is an antiparasitic and antimycobacterial agent used to treat leprosy, toxoplasmosis, malaria, and the skin condition, dermatitis herpetiformis. Most descriptions of dapsone neuropathy are those of a motor-predominant neuropathy, often with an asymmetric presentation, suggesting a mononeuritis multiplex [109–112]. Mixed sensorimotor neuropathy and mild, sensory neuropathies also are described [113,114].

Neuropathy generally is seen only in patients who have been taking dapsone for several years, with most cases developing within 5 years of initiation. Ironically, dapsone has been used widely to treat leprosy, an infectious cause of peripheral neuropathy. In spite of this, most cases in the literature occur when patients are taking dapsone for dermatitis herpetiformis. Slow acetylators of dapsone likely are at additional risk for developing neuropathy [110,115].

Electrophysiologic and pathologic studies suggest a distal motor axonopathy without features of demyelination [116]. Most patients recover completely over the course of many months after the drug is withdrawn [115].

Methodology used to establish causation

The most important tenet of establishing a neurotoxic cause of any neurologic problem is that the opportunity for exposure does not prove that the symptoms were caused by the exposure. Given the widespread prevalence of peripheral neuropathy, a patient who works with industrial chemicals or takes a medication known to cause neuropathy still could develop neuropathy from a different cause. In fact, in many situations, the alternative explanation is more likely. Knowledge of the biologic effects of the toxicant and the circumstances of the exposure can help differentiate causation from mere association.

Most clinicians apply general scientific principals in the formulation of differential diagnosis without giving thought to the process, but formal criteria exist for evaluating the role of a suspected toxin in a specific case [117]. The purported effect of the toxicant needs to be biologically plausible. The relative risk of neuropathy varies significantly between neurotoxicants, and large epidemiologic studies, in particular cohort or case control studies, that demonstrate a strong association between the toxicant and neuropathy confer more support for the hypothesis than isolated case reports or

cross-sectional studies. The existence of a well-studied animal model also can be helpful in identifying potential mechanisms of neurotoxicity.

The circumstances of the exposure can provide additional information. For instance, the temporal nature of the exposure is important in establishing causation. Obviously, the neuropathy cannot precede the exposure. Conversely, a neuropathy that develops months or years after a single acute exposure is not consistent with causation.

In almost all toxic neuropathies, there should be a dose-response relationship between the level of toxicant exposure and the severity of the neuropathy. For many toxicants, biologic markers can be measured in the blood, urine, or hair. Established reference levels can be used to suggest whether or not the degree of exposure is substantial enough to account for a patient's symptoms. Resolution of the neuropathy and normalization of the biologic markers after removal of the exposure provide some of the strongest evidence of causation. Some toxic neuropathies, however, continue to progress for a few weeks after removal of exposure before stabilizing and eventually improving, a phenomenon known as ''coasting.''

The most difficult task in establishing causation is eliminating other causes from the differential diagnosis. Although a patient's symptoms, signs, and electrodiagnostic findings may be ''consistent with'' a toxic neuropathy, it is likely that the same findings are ''consistent with'' several other causes also. Eliminating all competing causes from the differential diagnosis requires a working knowledge of systemic, genetic, inflammatory, infectious, and nutritional causes of neuropathy and other neurotoxicants that could produce a similar form of neuropathy.

Industrial, environmental, and pharmacologic causes of neuropathy are uncommon, and may account for only a small fraction of neuropathies in which no underlying cause is identified with routine tests. Most likely, physicians who attribute a neuropathy to a toxic cause as a diagnosis of exclusion simply are not generating an accurate or complete differential diagnosis. Nevertheless, it is important to become familiar with the most common and representative neurotoxicants, because toxic neuropathies are among the most treatable forms of peripheral nervous system dysfunction.

References

[1] Schaumburg HH, Spencer PS. Recognizing neurotoxic disease. Neurology 1987;37:276–8.
[2] Albers JW. Clinical neurophysiology of generalized polyneuropathy. J Clin Neurophysiol 1993;10:149–66.
[3] Feldman RG, Niles CA, Kelly-Hayes M, et al. Peripheral neuropathy in arsenic smelter workers. Neurology 1979;29:939–44.
[4] Kreiss K, Zack MM, Landrigan PJ, et al. Neurologic evaluation of a population exposed to arsenic in Alaskan well water. Arch Environ Health 1983;38:116–21.
[5] Mukherjee SC, Rahman MM, Chowdhury UK, et al. Neuropathy in arsenic toxicity from groundwater arsenic contamination in West Bengal, India. J Environ Sci Health [A] 2003; 38:165–83.

[6] Greenberg SA. Acute demyelinating polyneuropathy with arsenic ingestion. Muscle Nerve 1996;19:1611–3.

[7] Jenkins RB. Inorganic arsenic and the nervous system. Brain 1966;89:479–98.

[8] Chhuttani PN, Chawla LS, Sharma TD. Arsenical neuropathy. Neurology 1967;17:269–74.

[9] Ghariani M, Adrien ML, Raucoules M, et al [Subacute arsenic poisoning]. Ann Fr Anesth Reanim 1991;10:304–7 [in French].

[10] Donofrio PD, Wilbourn AJ, Albers JW, et al. Acute arsenic intoxication presenting as Guillain-Barre-like syndrome. Muscle Nerve 1987;10:114–20.

[11] Bromberg MB, Albers JW. Patterns of sensory nerve conduction abnormalities in demyelinating and axonal peripheral nerve disorders. Muscle Nerve 1993;16:262–6.

[12] Landrigan PJ. Arsenic—state of the art. Am J Ind Med 1981;2:5–14.

[13] Valenzuela OL, Borja-Aburto VH, Garcia-Vargas GG, et al. Urinary trivalent methylated arsenic species in a population chronically exposed to inorganic arsenic. Environ Health Perspect 2005;113:250–4.

[14] Wax PM, Thornton CA. Recovery from severe arsenic-induced peripheral neuropathy with 2,3-dimercapto-1-propanesulphonic acid. J Toxicol Clin Toxicol 2000;38:777–80.

[15] Heyman A, Pfeiffer JB Jr, Willett RW, et al. Peripheral neuropathy caused by arsenical intoxication; a study of 41 cases with observations on the effects of BAL (2, 3, dimercapto-propanol). N Engl J Med 1956;254:401–9.

[16] Kuwabara S, Kai MR, Nagase H, et al. n-Hexane neuropathy caused by addictive inhalation: clinical and electrophysiological features. Eur Neurol 1999;41:163–7.

[17] Kuwabara S, Nakajima M, Tsuboi Y, et al. Multifocal conduction block in n-hexane neuropathy. Muscle Nerve 1993;16:1416–7.

[18] Krasavage WJ, O'Donoghue JL, DiVincenzo GD, et al. The relative neurotoxicity of methyl-n-butyl ketone, n-hexane and their metabolites. Toxicol Appl Pharmacol 1980; 52:433–41.

[19] Smith AG, Albers JW. n-Hexane neuropathy due to rubber cement sniffing. Muscle Nerve 1997;20:1445–50.

[20] Paulson GW, Waylonis GW. Polyneuropathy due to n-hexane. Arch Intern Med 1976;136: 880–2.

[21] Ruff RL, Petito CK, Acheson LS. Neuropathy associated with chronic low level exposure to n-hexane. Clin Toxicol 1981;18:515–9.

[22] Issever H, Malat G, Sabuncu HH, et al. Impairment of colour vision in patients with n-hexane exposure-dependent toxic polyneuropathy. Occup Med (Lond) 2002;52:183–6.

[23] Korobkin R, Asbury AK, Sumner AJ, et al. Glue-sniffing neuropathy. Arch Neurol 1975; 32:158–62.

[24] Spencer PS, Schaumburg HH. Organic solvent neurotoxicity. Facts and research needs. Scand J Work Environ Health 1985;11(Suppl 1):53–60.

[25] Griffin JW. Hexacarbon neurotoxicity. Neurobehav Toxicol Teratol 1981;3:437–44.

[26] Yokoyama K, Feldman RG, Sax DS, et al. Relation of distribution of conduction velocities to nerve biopsy findings in n-hexane poisoning. Muscle Nerve 1990;13:314–20.

[27] Chang CM, Yu CW, Fong KY, et al. N-hexane neuropathy in offset printers. J Neurol Neurosurg Psychiatry 1993;56:538–42.

[28] Kuang S, Huang H, Liu H, et al. [A clinical analysis of 102 cases of chronic n-hexane intoxication]. Zhonghua Nei Ke Za Zhi 2001;40:329–31 [in Chinese].

[29] Besser R, Treese N, Bohl J, et al. [Clinical, neurophysiologic and biopsy findings in neurotoxic amiodarone syndrome]. Med Klin 1994;89:367–72 [in German].

[30] Meier C, Kauer B, Muller U, et al. Neuromyopathy during chronic amiodarone treatment. A case report. J Neurol 1979;220:231–9.

[31] Lemaire JF, Autret A, Biziere K, et al. Amiodaron neuropathy: further arguments for human drug-induced neurolipidosis. Eur Neurol 1982;21:65–8.

[32] Martinez-Arizala A, Sobol SM, McCarty GE, et al. Amiodarone neuropathy. Neurology 1983;33:643–5.

[33] Charness ME, Morady F, Scheinman MM. Frequent neurologic toxicity associated with amiodarone therapy. Neurology 1984;34:669–71.

[34] Pellissier JF, Pouget J, Cros D, et al. Peripheral neuropathy induced by amiodarone chlorhydrate. A clinicopathological study. J Neurol Sci 1984;63:251–66.

[35] Anderson NE, Lynch NM, O'Brien KP. Disabling neurological complications of amiodarone. Aust N Z J Med 1985;15:300–4.

[36] Abarbanel JM, Osiman A, Frisher S, et al. Peripheral neuropathy and cerebellar syndrome associated with amiodarone therapy. Isr J Med Sci 1987;23:893–5.

[37] Fernando Roth R, Itabashi H, Louie J, et al. Amiodarone toxicity: myopathy and neuropathy. Am Heart J 1990;119:1223–5.

[38] Pulipaka ULD, Omalu B. Amiodarone-induced neuromyopathy: three cases and a review of the literature. J Clin Neuromusc Dis 2002;3:97–105.

[39] Palakurthy PR, Iyer V, Meckler RJ. Unusual neurotoxicity associated with amiodarone therapy. Arch Intern Med 1987;147:881–4.

[40] Jacobs JM, Costa-Jussa FR. The pathology of amiodarone neurotoxicity. II. Peripheral neuropathy in man. Brain 1985;108(Pt 3):753–69.

[41] Morgan JP. The Jamaica ginger paralysis. JAMA 1982;248:1864–7.

[42] Morgan JP, Penovich P. Jamaica ginger paralysis. Forty-seven-year follow-up. Arch Neurol 1978;35:530–2.

[43] Woolf AD. Ginger Jake and the blues: a tragic song of poisoning. Vet Hum Toxicol 1995; 37:252–4.

[44] Eyer P. Neuropsychopathological changes by organophosphorus compounds—a review. Hum Exp Toxicol 1995;14:857–64.

[45] Konno N. [Neurotoxicity of organophosphorus and dithiocarbamate compounds]. Nippon Eiseigaku Zasshi 2003;57:645–54 [in Japanese].

[46] Barrett DS, Oehme FW. The effect of a single oral dose of tri-o-cresyl phosphate on neurotoxic esterase and acetylcholinesterase activities in the central nervous system, erythrocytes and plasma. Vet Hum Toxicol 1994;36:1–4.

[47] Senanayake N, Johnson MK. Acute polyneuropathy after poisoning by a new organophosphate insecticide. N Engl J Med 1982;306:155–7.

[48] Van den Neucker K, Vanderstraeten G, De Muynck M, et al. The neurophysiologic examination in organophosphate ester poisoning. Case report and review of the literature. Electromyogr Clin Neurophysiol 1991;31:507–11.

[49] McConnell R, Delgado-Tellez E, Cuadra R, et al. Organophosphate neuropathy due to methamidophos: biochemical and neurophysiological markers. Arch Toxicol 1999;73: 296–300.

[50] Akassoglou K, Malester B, Xu J, et al. Brain-specific deletion of neuropathy target esterase/swisscheese results in neurodegeneration. Proc Natl Acad Sci U S A 2004; 101:5075–80.

[51] Pace A, Bove L, Nistico C, et al. Vinorelbine neurotoxicity: clinical and neurophysiological findings in 23 patients. J Neurol Neurosurg Psychiatry 1996;61:409–11.

[52] Topp KS, Tanner KD, Levine JD. Damage to the cytoskeleton of large diameter sensory neurons and myelinated axons in vincristine-induced painful peripheral neuropathy in the rat. J Comp Neurol 2000;424:563–76.

[53] Nozaki-Taguchi N, Chaplan SR, Higuera ES, et al. Vincristine-induced allodynia in the rat. Pain 2001;93:69–76.

[54] Moudgil SS, Riggs JE. Fulminant peripheral neuropathy with severe quadriparesis associated with vincristine therapy. Ann Pharmacother 2000;34):1136–8.

[55] Chauvenet AR, Shashi V, Selsky C, et al. Vincristine-induced neuropathy as the initial presentation of charcot-marie-tooth disease in acute lymphoblastic leukemia: a Pediatric Oncology Group study. J Pediatr Hematol Oncol 2003;25:316–20.

[56] Mercuri E, Poulton J, Buck J, et al. Vincristine treatment revealing asymptomatic hereditary motor sensory neuropathy type 1A. Arch Dis Child 1999;81:442–3.

[57] Orejana-Garcia AM, Pascual-Huerta J, Perez-Melero A. Charcot-Marie-Tooth disease and vincristine. J Am Podiatr Med Assoc 2003;93:229–33.

[58] Roelofs RI, Hrushesky W, Rogin J, et al. Peripheral sensory neuropathy and cisplatin chemotherapy. Neurology 1984;34:934–8.

[59] Thompson SW, Davis LE, Kornfeld M, et al. Cisplatin neuropathy. Clinical, electrophysiologic, morphologic, and toxicologic studies. Cancer 1984;54:1269–75.

[60] Strumberg D, Brugge S, Korn MW, et al. Evaluation of long-term toxicity in patients after cisplatin-based chemotherapy for non-seminomatous testicular cancer. Ann Oncol 2002; 13:229–36.

[61] Russell JW, Windebank AJ, McNiven MA, et al. Effect of cisplatin and ACTH4–9 on neural transport in cisplatin induced neurotoxicity. Brain Res 1995;676:258–67.

[62] McDonald ES, Windebank AJ. Cisplatin-induced apoptosis of DRG neurons involves bax redistribution and cytochrome c release but not fas receptor signaling. Neurobiol Dis 2002; 9:220–33.

[63] Lheureux P, Penaloza A, Gris M. Pyridoxine in clinical toxicology: a review. Eur J Emerg Med 2005;12:78–85.

[64] Schaumberg H, Kaplan J, Windebank A, et al. Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome. N Engl J Med 1983;309:445–8.

[65] Albin RL, Albers JW, Greenberg HS, et al. Acute sensory neuropathy-neuronopathy from pyridoxine overdose. Neurology 1987;37:1729–32.

[66] Moore D, House I, Dixon A. Thallium poisoning. Diagnosis may be elusive but alopecia is the clue. BMJ 1993;306:1527–9.

[67] Rangel-Guerra R, Martinez HR, Villarreal HJ. [Thallium poisoning. Experience with 50 patients]. Gac Med Mex 1990;126:487–94 [in Spanish].

[68] Meggs WJ, Hoffman RS, Shih RD, et al. Thallium poisoning from maliciously contaminated food. J Toxicol Clin Toxicol 1994;32:723–30.

[69] Kubis N, Talamon C, Smadja D, et al. [Peripheral neuropathy caused by thallium poisoning]. Rev Neurol (Paris) 1997;153:599–601.

[70] Desenclos JC, Wilder MH, Coppenger GW, et al. Thallium poisoning: an outbreak in Florida, 1988. South Med J 1992;85:1203–6.

[71] Herrero F, Fernandez E, Gomez J, et al. Thallium poisoning presenting with abdominal colic, paresthesia, and irritability. J Toxicol Clin Toxicol 1995;33:261–4.

[72] Andersen O. Clinical evidence and therapeutic indications in neurotoxicology, exemplified by thallotoxicosis. Acta Neurol Scand Suppl 1984;100:185–92.

[73] Sharma AN, Nelson LS, Hoffman RS. Cerebrospinal fluid analysis in fatal thallium poisoning: evidence for delayed distribution into the central nervous system. Am J Forensic Med Pathol 2004;25:156–8.

[74] Pau PW. Management of thallium poisoning. Hong Kong Med J 2000;6:316–8.

[75] Kuo HC, Huang CC, Tsai YT, et al. Acute painful neuropathy in thallium poisoning. Neurology 2005;65:302–4.

[76] Dumitru D, Kalantri A. Electrophysiologic investigation of thallium poisoning. Muscle Nerve 1990;13:433–7.

[77] Hoffman RS. Thallium toxicity and the role of Prussian blue in therapy. Toxicol Rev 2003; 22:29–40.

[78] Lehane L. Paralytic shellfish poisoning: a potential public health problem. Med J Aust 2001;175:29–31.

[79] Wu JY, Zheng L, Wang JH. Contamination of shellfish from Shanghai seafood markets with paralytic shellfish poisoning and diarrhetic shellfish poisoning toxins determined by mouse bioassay and HPLC. Food Addit Contam 2005;22:647–51.

[80] de Carvalho M, Jacinto J, Ramos N, et al. Paralytic shellfish poisoning: clinical and electrophysiological observations. J Neurol 1998;245:551–4.

[81] Long RR, Sargent JC, Hammer K. Paralytic shellfish poisoning: a case report and serial electrophysiologic observations. Neurology 1990;40:1310–2.

[82] Isbister GK, Kiernan MC. Neurotoxic marine poisoning. Lancet Neurol 2005;4:219–28.
[83] Kanchanapongkul J. Puffer fish poisoning: clinical features and management experience in 25 cases. J Med Assoc Thai 2001;84:385–9.
[84] Isbister GK, Son J, Wang F, et al. Puffer fish poisoning: a potentially life-threatening condition. Med J Aust 2002;177:650–3.
[85] Oda K, Araki K, Totoki T, et al. Nerve conduction study of human tetrodotoxication. Neurology 1989;39:743–5.
[86] Friedman M. Chemistry, biochemistry, and safety of acrylamide. A review. J Agric Food Chem 2003;51:4504–26.
[87] Mulloy KB. Two case reports of neurological disease in coal mine preparation plant workers. Am J Ind Med 1996;30:56–61.
[88] Kjuus H, Goffeng LO, Heier MS, et al. Effects on the peripheral nervous system of tunnel workers exposed to acrylamide and N-methylolacrylamide. Scand J Work Environ Health 2004;30:21–9.
[89] Myers JE, Macun I. Acrylamide neuropathy in a South African factory: an epidemiologic investigation. Am J Ind Med 1991;19:487–93.
[90] Deng H, He F, Zhang S, Calleman CJ, et al. Quantitative measurements of vibration threshold in healthy adults and acrylamide workers. Int Arch Occup Environ Health 1993;65:53–6.
[91] Harris CH, Gulati AK, Friedman MA, et al. Toxic neurofilamentous axonopathies and fast axonal transport. V. Reduced bidirectional vesicle transport in cultured neurons by acrylamide and glycidamide. J Toxicol Environ Health 1994;42:343–56.
[92] LoPachin RM, Ross JF, Lehning EJ. Nerve terminals as the primary site of acrylamide action: a hypothesis. Neurotoxicology 2002;23:43–59.
[93] LoPachin RM. Acrylamide neurotoxicity: neurological, morhological and molecular endpoints in animal models. Adv Exp Med Biol 2005;561:21–37.
[94] Jacknowitz AI, Le Frock JL, Prince RA. Nitrofurantoin polyneuropathy: report of two cases. Am J Hosp Pharm 1977;34:759–62.
[95] Yiannikas C, Pollard JD, McLeod JG. Nitrofurantoin neuropathy. Aust N Z J Med 1981;11:400–5.
[96] Spielberg SP, Gordon GB. Nitrofurantoin cytotoxicity. In vitro assessment of risk based on glutathione metabolism. J Clin Invest 1981;67:37–41.
[97] Lovelace RE, Horwitz SJ. Peripheral neuropathy in long-term diphenylhydantoin therapy. Trans Am Neurol Assoc 1967;92:262–4.
[98] Eisen AA, Woods JF, Sherwin AL. Peripheral nerve function in long-term therapy with diphenylhydantoin. A clinical and electrophysiologic correlation. Neurology 1974;24:411–7.
[99] Shorvon SD, Reynolds EH. Anticonvulsant peripheral neuropathy: a clinical and electrophysiological study of patients on single drug treatment with phenytoin, carbamazepine or barbiturates. J Neurol Neurosurg Psychiatry 1982;45:620–6.
[100] Taylor JW, Murphy MJ, Rivey MP. Clinical and electrophysiologic evaluation of peripheral nerve function in chronic phenytoin therapy. Epilepsia 1985;26:416–20.
[101] Swift TR, Gross JA, Ward LC, et al. Peripheral neuropathy in epileptic patients. Neurology 1981;31:826–31.
[102] Bauer M, Rabens SF. Trichloroethylene toxicity. Int J Dermatol 1977;16:113–6.
[103] Buxton PH, Hayward M. Polyneuritis cranialis associated with industrial trichloroethylene poisoning. J Neurol Neurosurg Psychiatry 1967;30:511–8.
[104] Annau Z. The neurobehavioral toxicity of trichloroethylene. Neurobehav Toxicol Teratol 1981;3:417–24.
[105] Feldman RG. Facial nerve latency studies in man: effects of trichlorethylene intoxication. Electromyography 1970;10:93–100.
[106] Feldman RG, Chirico-Post J, Proctor SP. Blink reflex latency after exposure to trichloroethylene in well water. Arch Environ Health 1988;43:143–8.

[107] Laureno R. Trichloroethylene does not cause trigeminal neuropathy. Muscle Nerve 1993;
       16:217.

[108] Cavanagh JB, Buxton PH. Trichloroethylene cranial neuropathy: is it really a toxic neurop-
       athy or does it activate latent herpes virus? J Neurol Neurosurg Psychiatry 1989;52:
       297–303.

[109] Rhodes LE, Coleman MD, Lewis-Jones MS. Dapsone-induced motor peripheral neurop-
       athy in pemphigus foliaceus. Clin Exp Dermatol 1995;20:155–6.

[110] Rosen I, Sornas R. Peripheral motor neuropathy caused by excessive intake of dapsone
       (Avlosulfon). Arch Psychiatr Nervenkr 1982;232:63–9.

[111] Koller WC, Gehlmann LK, Malkinson FD, et al. Dapsone-induced peripheral neuropathy.
       Arch Neurol 1977;34:644–6.

[112] Gutmann L, Martin JD, Welton W. Dapsone motor neuropathy—an axonal disease. Neu-
       rology 1976;26(6 PT 1):514–6.

[113] Mery L, Dega H, Prost C, Dubertret L. [Dapsone-induced sensory peripheral neuropathy].
       Ann Dermatol Venereol 2003;130:447–9 [in French].

[114] Ahrens EM, Meckler RJ, Callen JP. Dapsone-induced peripheral neuropathy. Int J Derma-
       tol 1986;25:314–6.

[115] Waldinger TP, Siegle RJ, Weber W, et al. Dapsone-induced peripheral neuropathy. Case
       report and review. Arch Dermatol 1984;120:356–9.

[116] Sirsat AM, Lalitha VS, Pandya SS. Dapsone neuropathy–report of three cases and patho-
       logic features of a motor nerve. Int J Lepr Other Mycobact Dis 1987;55:23–9.

[117] Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:
       295–300.