Toxic Neuropathy

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Author and Editor Disclosure

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Background

Lewis P. Rowland, in *Merritt's Textbook of Neurology,* defines the terms peripheral neuropathy and polyneuropathy as describing "the clinical syndrome of weakness, sensory loss and impairment of reflexes caused by diffuse lesions of peripheral nerves." The diagnosis most often is based on the clinical picture and is confirmed with electrodiagnostic techniques, most commonly electromyography (EMG) and nerve conduction studies. Facial nerve and blink reflex testing also are used commonly. Apparatuses, such as the neurometer, vibrometer, and sensory nerve perception threshold-testing device, often are used in research settings or to evaluate clusters of patients.

Patients with toxic etiologies for neuropathy are less common than patients with other neuropathies such as those due to hereditary, metabolic, or inflammatory causes. Drug-related neuropathies are among the most common toxic neuropathies. Neuropathies from industrial agents (either from occupational or environmental sources), presenting after either limited or long-term exposure, are insidious. Patients may present with subtle pain or weakness. Subclinical abnormalities found on electrodiagnostic testing may herald a progressive neuropathy if exposure continues at a similar dose. Attributing neuropathy to such an exposure often is difficult. In some patients, extensive search for an etiology may fail to uncover the exact cause of neuropathy.

Many chemicals are known to cause neuropathy in laboratory animals. Some of these have been associated with neuropathy in clinical epidemiologic studies, confirming their ability to injure the human peripheral nervous system (PNS). Other chemicals have been reported to be associated with PNS dysfunction and neuropathy on the basis of retrospective and cross-sectional epidemiologic studies. Designs for many of these studies have been criticized. Other associations have been made from many case reports and case series.

Human studies infrequently have associated exposure to environmental sources with peripheral neuropathy. As compared to nonexposed controls, exposed individuals have statistically significant differences in nerve conduction velocity (NCV) and EMG findings. Exposures have been estimated for duration and intensity based on point source extrapolation, a common method of environmental risk assessment. When reviewing the literature, a critical analysis of study designs and electrodiagnostic techniques is important.

An algorithm to assess patients with suspected neurotoxic illness is detailed in Medical/Legal Pitfalls. It describes occupational and environmental history as an important aspect of the medical history. In cases of positive occupational or environmental exposure, estimating dose and duration of exposure and level of protection afforded by personal protective equipment is emphasized. Government and professional organizations publish exposure limits for workers using various chemicals. Physicians may use this information to compare with industrial hygiene data. These are outlined in Table 1.

Table 1. Exposure Limits, Common Organic Solvents and Metals

Compound	OSHA PEL TWA: ppm (mg/m^3)	NIOSH REL TWA: ppm (mg/m^3), IDLH	ACGIH ppm (mg/m^3) TLV, STEL
Acrylamide	(0.3)	(0.03), 60 Ca	
Arsenic, inorganic	(0.01)	C (0.002)	(0.01), -
Arsenic, organic	0.5 mg/m^3		
Carbon disulfide	20, 30, 100 for 30 min	1 (3), 10 STEL (30), 500	10 (31)

Ethylene oxide		1 <0.1, <0.18, 5 C, 800	1 (1.8)
n-hexane	500 (1800)	50 (180), 1100	50, (176)
Lead	0.05 mg/m^3	0.100 mg/m^3	(0.05), -
Mercury, inorganic	C 0.1 mg/m^3	0.05 mg/m^3, C 0.01 mg/m^3, 10 mg/m^3	0.025 mg/m^3
Mercury, organic	0.01 mg/m^3, C 0.04 mg/m^3	0.01 mg/m^3, ST 0.03 mg/m^3, 2 mg/m^3	0.01 mg/m^3, 0.03 mg/m^3
Methyl *n*-butyl ketone	100 (410)		5 (20)
Perchloroethylene	100, 200 C, 300 for 5 min in 3 h	150 Ca	25 (170), 100 (685)
Styrene	100, 200 C, 600 for 5 min in 3 h	50 (215), 100 ST (425), 700	50 (213), 100 (428)
Thallium	0.1 mg/m^3 skin	0.1 mg/m^3, 15 mg/m^3	0.1 mg/m^3
Toluene	200, 300, 500 for 10 min	100 (375), 150 ST (560), 500	50 (188)
1,1,1 Trichloroethane (methyl chloroform)	350 (1900)	C 350(1900) for 15 min, 700	350 (1910), 450 (2460)
Trichloroethylene	100, 200 C, 300 for 5 min in 2 h	1000 Ca	50 (269), 100 (1070)
Vinyl chloride	1, 5 for 15 min	ND	
Xylene	100 (435)	100 (435), 150 ST (655)	100 (434), 150 (651)

Abbreviations: OSHA - Occupational Safety and Health Association; NIOSH - National Institute of Occupational Safety and Health; ACGIH - American Congress of Governmental Industrial Hygienists; TWA - time-weighted average; TLV - threshold limit value; PEL - permissible exposure limit; REL - recommended exposure limit; ppm - parts per million; STEL - short-term exposure limit; Ca - level for carcinogenicity; C - ceiling, should never be exceeded; ND - not determined

Utilizing neurophysiologic testing, neuropsychological testing, and neuroimaging to support a clinical suspicion is encouraged. When the exposure has ended, retesting also is appropriate after a period of time. Perform biological testing of serum and urine to assess absorbed dose. Values have been published for these data. These are outlined in Table 2.

Table 2. ATSDR Biological Exposure Indices (BEIs)

Compound	Urine	Blood	Expired Air	Other
Acrylamide				
Arsenic	Inorganic arsenic: end of work week, 50 µg/g monomethylarsonic acid, cacodylic acid (days)			Hair (ingestion chronic)
Carbon disulfide	2-TTCA 5 mg/g	Carbon disulfide	Carbon disulfide	
Ethylene oxide				
n-hexane	2-5 hexanediol: end of shift, 5 mg/g 2 hexanol, total metabolites	*n*-hexane	*n*-hexane	
Lead	Lead	Lead 30 mg/100 mL		Erythrocyte protoporphyrin
Mercury, inorganic	Mercury: start of shift, 35 µg/g	Mercury: end of shift at end of work week, 15 µg/L		
Methyl *n*-butyl				

Methyl n-butyl ketone		2,5 hexane dione		
Perchloroethylene	PERC, trichloroacetic acid	PERC 1 mg/L	PERC: before last shift of week, 10 ppm	
Styrene	MA: start of shift, 300 mg/g; end of shift, 800 mg/g PGA: start of shift, 100 mg/g; end of shift, 240 mg/g	Styrene: start of shift, 0.02 mg/L; end of shift, 0.55 mg/L		
Thallium	Thallium			
Toluene	Hippuric acid	Toluene	Toluene	
1,1,1 Trichloroethane (methyl chloroform)	Trichloroacetic acid: end of work week, 10 mg/L total trichloroethanol: end of shift at end of work week, 30 mg/L	Total trichloroethanol 1 mg/L	Methyl chloroform: prior to last shift of work week, 40 ppm	
Trichloroethylene	TCE, TCA: end of work week, 100 mg/g or TCA plus trichloroethanol, 300 mg/g	TCE: end of work week, 4 mg/L	TCE	
Vinyl chloride				
Xylene	Methylhippuric acid: end of shift, 1.5 mg/g	Xylene	Xylene	

Abbreviations: ATSDR - Agency for Toxic Substances and Disease Registry; 2-TTCA - 2-thiothiazolidine-4-carboxylic acid; ppm - parts per million; MA - mandelic acid; PGA - phenylglyoxylic acid; TCE - trichloroethylene; TCA - trichloroacetic acid; PERC - perchloroethylene

Use of the medical literature to associate an agent with an abnormality is important. Ascertain existence of supporting evidence that suggests exposure at a specific dose and duration that can cause such dysfunction and whether animal data are helpful to extrapolate an estimated dose that may lead to a health effect in humans.

Pathophysiology

Neuropathy may be categorized by presentation (ie, motor or sensory symptoms), electrodiagnostic features, and neuroanatomical location within the peripheral nerve (ie, demyelinating or axonal, neuronopathy, ion channel neuropathy, neuromuscular transmission) or location (ie, cranial or peripheral). Toxic neuropathy refers to those presentations that are caused by drug ingestion, drug or chemical abuse, or industrial chemical exposure from the workplace or from the environment. Kimura mentions that these may be divided into 3 groups based on the presumed site of cellular involvement: (1) neuropathy affecting the cell body, especially those of the dorsal root ganglion, (2) myelinopathy or schwannopathy with primary segmental demyelination, and (3) distal axonopathy causing dying back axonal degeneration. Although distal axonopathy is the most common form, a few agents have been associated with the first 2 types.

Antibiotic treatment or cisplatin or pyridoxine toxicity may cause sensory neuropathy, and segmental demyelination may result from the cardiac medications perhexiline or amiodarone, tetanus toxoid or diphtheria toxin administration, or exposure to lead or arsenic. In North America, sodium channel dysfunction may be the result of ciguatera toxin from reef fish or saxitoxin from shellfish. This often presents as an acute or subacute illness. Pufferfish may be intoxicated with tetrodotoxin in Japan. Neuromuscular transmission dysfunction is associated most commonly with organophosphate intoxication; however, envenomation from snake bites or botulism may be as serious a culprit. Cranial neuropathies affecting isolated nerves are uncommon. Trichloroethylene (TCE) has been associated with trigeminal neuropathy, and ethylene glycol may affect the facial nerve. The existence of these syndromes has been revealed by facial nerve and blink electrophysiologic studies (see Causes).

Frequency

United States

In one study, 76% of 205 patients who presented with undiagnosed neuropathy had neuropathies that were classifiable. Thus, about 25% of all neuropathies have an unknown etiology. Environmental and occupational exposure may play a role in some of these undiagnosed neuropathies.

History

- Patients with neuropathy typically present with symptoms of pain, tingling, or numbness in their feet, consistent with dysfunction affecting the longest and largest fibers of the PNS.
    - In some cases, they may have weakness (distal more than proximal) or difficulty with gait.
    - In other cases, patients may also present with symptoms of pain. This may suggest a small fiber neuropathy, which exists when small myelinated and unmyelinated fibers are involved. Clinically, pain may be accompanied by restless leg syndrome, a condition in which disagreeable leg sensations and an irresistible urge to move occur prior to sleep onset.
    - Also, other forms of autonomic dysfunction may be present such as hypohidrosis or hyperhidrosis, diarrhea or constipation, urinary incontinence or retention, gastroparesis, sicca syndrome, blurry vision, facial flushes, orthostatic intolerance, or sexual dysfunction. Autonomic dysfunction may present as cramping. In these cases, the examination reveals normal proprioception, vibration, power or bulk, reflexes, and normal findings on electromyography (EMG) or nerve conduction studies (NCS) (Hoitsma, 2004).
- The clinician needs to exercise a high index of suspicion to uncover toxic etiologies. A patient beginning a new medication in the last few weeks or months should raise a red flag. Certainly, the search for an underlying chronic disease is the most common workup ordered; however, new medications are commonly a culprit.
- Toxic neuropathy due to recreational drug or chemical abuse may be more difficult to uncover than occupational or environmental exposures, since direct questioning of the patient may lead to incorrect information. In some cases, a dramatic systemic reaction leads to an emergency department (ED) visit because of an acute alteration of consciousness, heralding the diagnosis of drug abuse. The challenge for the ED clinician at this point is to uncover the agent of ingestion or inhalation. Neuropathy, in these cases, may present over a few days to weeks since the dose is often higher than in prescribed-medication settings.
- Occupationally induced neuropathies may be secondary to low-level, long-term exposures. The differential diagnosis may not include a work-related exposure, since physicians often are not trained to ask questions about patients' work practices or environment. The presentation may coincide with other lifestyle and medication changes and recent medical diagnoses. After a high-level acute exposure, an occupational etiology for toxic neuropathy may be easier to consider.
- Environmental exposure–induced neuropathies follow the same pattern as those from occupational exposures; however, they are omitted even more commonly from the differential diagnosis. For example, a physician is even less likely to ask questions about the patient's use of groundwater, proximity to pesticides, or household use of organic solvents than about occupational exposures. As with occupational exposure, environmental exposures often are very low level, but they are long term and more intensive than occupational exposures, lasting longer than a 40-hour workweek for the duration of employment. Patients who have had high-concentration acute exposure from an environmental accident may present with more obvious clinical symptoms. A differential diagnosis ruling out more common causes of neuropathy is mandatory to establish the cause of neuropathy.
- Prior to appearance of symptoms, subclinical findings on EMG or NCV studies may be apparent and consistent with axonal or demyelinating abnormalities. Occupational or environmental exposure at doses approaching regulatory levels for duration or intensity may warrant such an evaluation. Often these are performed in field studies with the use of portable apparatus. Dysfunction associated with environmental exposure to TCE, mainly subclinical, is revealed by electrodiagnostic techniques.
- Pain or numbness in the distribution of the trigeminal nerve suggests a disorder of that nerve.

Physical

- Kimura, in *Electrodiagnosis in Diseases of Nerve and Muscle,* notes that polyneuropathy presents clinically as a "triad of sensory changes in a glove and stocking distribution, distal weakness, and hyporeflexia." The sensory changes include sensory loss in a stocking-glove distribution. Often, progression is distal to proximal. This is consistent with the commencement of axonal degeneration. Early loss of symmetrical ankle jerk is noted. In severe cases, motor dysfunction such as abnormal gait and foot drop also may occur. In some patients with exclusively small fiber neuropathy, the motor and reflexes examination may be normal.

- Spencer and Schaumberg emphasized a gradual insidious onset, as well as slow recovery. Recovery proceeds at a rate of 2 mm/day and may take months or several years, or may never be complete. Function is restored in reverse order to the sequence of loss. Coasting may be noted, that is, intensification may occur for weeks before improvement. This often reflects continued axonal degeneration and reconstitution.

- Signs of CNS disease also may be present at examination. This occurs in some patients recovering from certain toxic neuropathies. Dorsal column or corticospinal tract degeneration may be present. These clinical signs of degeneration are not prominent early in the illness; however, the patient may manifest hyperreflexia, Babinski responses, and stiff-leg ataxic gait with corticospinal tract disease or diffusely decreased proprioceptive and vibratory sensations and gait ataxia with dorsal column degeneration.

- Autonomic neuropathy
    - Involvement of the autonomic nerves may lead to a different clinical presentation–miosis, anhydrosis, orthostatic hypotension, sphincter symptoms, impotence, and vasomotor abnormalities. These may occur with or without evidence of a peripheral neuropathy.

    - Tachycardia, rapid alterations in blood pressure, flushing and sweating, and abnormalities in gastrointestinal motility may be present.

- Sensory neuronopathy: Spencer and Schaumberg reported the association of sensory ganglion cell loss in pyridoxine-associated sensory neuropathy with 9 clinical features; they are as follows:
    - Rapid or subacute onset may occur following massive intravenous administration.

    - Initial sensory loss may occur anywhere; the gasserian ganglion often is affected simultaneously with the dorsal root ganglion, and thus facial numbness may be noted.

    - Diffuse sensory loss with ataxia and preservation of motor power may be present. Proprioceptive deficit is noted to be greater than the loss of pain or temperature sensation.

    - Tendon reflexes may be absent.

    - NCV results usually are normal; sensory nerve potentials may be abnormal or absent. Recovery is variable, reflecting the death of nerve cell bodies and consequent permanent loss of axons. Collateral sprouting from surviving axons may account for the extent of recovery in these conditions.

    - No signs of CNS disease are present.

    - Cholinergic symptoms follow (see Organophosphates and disorders of neuromuscular transmission).

Causes

- A variety of drugs and industrial chemicals cause distal axonopathy. In 1989, Kimura listed amiodarone, chloramphenicol, dapsone, diphenylhydantoin, disulfiram, gold, isoniazid, lithium, metronidazole, misonidazole, nitrofurantoin, nitrous oxide, perhexiline maleate, thalidomide, and vincristine as potential causes of toxic neuropathy.

- Industrial chemicals causing toxic axonal neuropathy also are listed by Kimura; they include acrylamide, carbon

disulfide, inorganic mercury, methyl *n*-butyl ketone, the organophosphate parathion, polychlorinated biphenyl, thallium, triorthocresyl phosphate, and vinyl chloride.

- In 1999, Feldman added the heavy metals arsenic and lead, as well as the solvents *n*-hexane, perchloroethylene (PERC), and TCE to this list.

- In 1995, Albers and Bromberg summarized the literature on toxic neuropathy caused by the solvents ethylene oxide (EtO), styrene, toluene, and mixed solvents.

- Spencer and Schaumberg listed agents that commonly are associated with peripheral neuropathy (see Table 2 in Schaumberg, 2000).

- Toxic neuropathy may be the result of exposure to numerous agents and is related to dose and duration of exposures and to host factors. Most syndromes are subacute, progressing to chronic as already described. Chemicals such as thallium, dimethylaminopropionitrile (DMAP), and organophosphates present with specific syndromes associated with peripheral neuropathy; however, all of these may lead to systemic abnormalities as well.
    - Thallium is used in glass and in metal alloys. It had been used therapeutically to treat venereal disease, tuberculosis, ringworm, and as a rodenticide. Accidental or homicidal abuse is a common reason for toxicity. Acute intoxication leads to pain and paresthesias in the distal extremities followed by weakness and eventual atrophy. Preservation of peripheral reflexes is a useful physical finding to differentiate thallium toxicity from Guillain-Barré syndrome. Alopecia is a clinical hallmark of thallium toxicity that may develop weeks after intoxication. Mee lines, nephropathy, anemia, and hepatotoxicity are systemic manifestations. Autonomic dysfunction also may be a part of the clinical syndrome. Thallium toxicity may be mistaken for porphyria, arsenic toxicity, or botulism. Serum thallium levels typically are elevated.

    - DMAP is used as a catalyst in the manufacture of polyurethane foam and in an acrylamide grouting compound. It is used as a waterproofing agent in tunnels and sewer lines. Industrial exposure has led to prominent urinary and sexual dysfunction as well as to distal sensory neuropathy.

    - Alcohol, by itself, is toxic to the PNS. Individuals who consume alcohol also may become nutritionally compromised. Studies have found that alcohol impairs axonal transport and that this can occur in the setting of normal nutrition. Since it may affect both the cerebellum and the autonomic nervous system, ataxia and other systemic symptoms may accompany symptoms of dysesthesia and weakness of the lower extremities. In the patient with occupational exposure to other peripheral neurotoxic agents, alcohol may act either to slow metabolism and increase toxicity or, in the case of a habitual alcohol user, promote metabolism and reduce toxicity from the agent. This is observed most clearly with toluene exposure.

- Other organic solvents have been associated with peripheral neuropathy on the basis of cross-sectional studies and animal data. Prospective data are unavailable. Solvent mixtures have been noted to be responsible for toxic neuropathies in many studies. Identifying the culpable agent has been difficult. Often, no chemical with a clear association with neuropathy is listed, suggesting that organic solvents themselves, either in mixture or individually, may cause neuropathy. Studies that have found subclinical abnormalities further support this hypothesis.

- Often study designs have been criticized for their definition of neuropathy. NCV and EMG findings in many of these studies are difficult to categorize. To ascertain whether a toxic etiology is a possibility for a patient, a clinician may need to search the literature for the agent as well as the industry. Many agents are used in many different industries. The industrial agents and some of the industries that utilize them are listed in Table 3. For information on toxic neuropathy caused by organophosphates, refer to the article Organophosphates.

- Carbon disulfide and peripheral neuropathy
    - Carbon disulfide is an agent used in the viscose rayon industry. Refer to Table 3 for its other uses.

    - Carbon disulfide has been deemed a peripheral neurotoxin in both animals and humans by the Agency for Toxic Substances and Disease Registry (ATSDR). Consistency has been established for effect (ie, neurophysiological impairment and pathologic changes) but not for dose. The pathophysiology for toxic neuropathy is an axonal neuropathy in a distal dying back pattern. Reduced or absent sensory nerve action potentials (SNAPs) are common. Conduction velocities are usually normal, but they may be borderline low owing to selective involvement of large fibers. Metabolic abnormalities from coexisting

diseases may be associated with reduced conduction velocities and may contribute to electrophysiologic abnormalities.

- In humans, neurophysiological effects have been demonstrated at low levels of occupational exposure. In 1974, Seppalainen and Tolonen demonstrated a decrease in maximal motor NCV in the median, ulnar, peroneal, and posterior tibial nerves in 118 viscose rayon workers who had exposure to an average of 10-20 parts per million (ppm) of carbon disulfide for an average of 15 years. No improvement was noted after removal from exposure, but a follow-up study by these authors demonstrated that fewer workers who had retired 10-15 years prior had decreased NCVs than those who had been removed from their work 0-4 years prior to the study. (These abnormalities were in workers who had no subjective complaints.) In 1990 and 1993, Ruitjen et al demonstrated that 44 viscose rayon workers exposed to 1-30 ppm of carbon disulfide for at least 10 years had somewhat slower slow motor fiber conduction velocities than 31 controls, based on the antidromic collision technique.

- Symptoms of clinical neuropathy related to cumulative exposures were absent in the patients in this study. This study revealed that a decrease in the conduction velocity occurs at low levels of exposure to carbon disulfide. Extrapolation of these results suggests that small effects may occur after a mean cumulative exposure of 165 ppm-years, which would be equivalent to a concentration of 4 ppm over an 8-hour time-weighted average (TWA). At this exposure level over a lifetime of employment, the observed effects would be expected. The authors explained that the significance of these effects on health would be that these observed changes might reduce reserve capacity to cope with other noxious influences. They concluded that these changes are undesirable until they are shown to be not detrimental to health in the long term.

- The second study to verify these findings reexamined these workers 4 years later and found a statistically significant decrease in velocities in the slow as well as the fast motor nerve fibers of the peroneal nerve. Weighted cumulative exposures correlated less well with the peripheral nerve indices and revealed no evidence that the effects were reversible. The authors reiterated their concerns for the neurotoxic effects of carbon disulfide at these exposure levels.

- In 1983, Johnson et al examined 189 workers from a viscose rayon plant; 245 workers in polyester-nylon filament and staple plants were used as controls.
  - Confounding exposures were hydrogen sulfide, tin oxide, zinc oxide and sulfate, sodium hydroxide, and sulfuric acid. At no point in time did hydrogen sulfide levels exceed 1 ppm.
  - Carbon disulfide exposure was divided into high (median >7.1 ppm), medium (median 3-7.1 ppm), and low (median <3 ppm). Exclusion criteria were alcohol consumption >35 U, blood glucose >110 mg/dL, or blood lead >40 mcg/L. Mean duration of exposure for all exposed subjects was 12.1 years; for the high-exposure group it was 13.6 years; for the medium-exposure group it was 12.3 years; and for the low-exposure group it was 10.5 years. The average age of exposed individuals was 38.5 years and of controls, 33.9 years.
  - The study assessed NCV of motor (ie, peroneal, ulnar) and sensory (ie, sural) nerves. A reduction in peroneal nerve mean conduction velocity (MCV) was found to be related, in a dose-response sense, to cumulative exposure to carbon disulfide.

Table 3. Industrial Uses of Common Organic Solvents and Metals

Compound	Industrial Uses
Acrylamide	Mining and tunneling, adhesives, waste treatment, ore processing, paper, pulp industry, photography, dyes
Arsenic	Pesticides, pigments, antifouling paint, electroplating, seafood, smelters, semiconductors, logging
Carbon disulfide	Viscose rayon, explosives, paints, preservatives, textiles, rubber cement, varnishes, electroplating
Ethylene oxide	Instrument sterilization, chemical precursor
n-hexane	Glues and vegetable extraction, components of naphtha, lacquers, metal-cleaning compounds
Lead	Solder, lead shot, illicit whiskey, insecticides, auto body shops, storage

Lead	batteries, foundries, smelters, lead-based paint, lead stained glass, lead pipes
Mercury	Scientific instruments, electrical equipment, amalgams, electroplating, photography, felt making, taxidermy, textiles, pigments, chloroalkali industry
Methyl *n*-butyl ketone	Paints, varnishes, quick-drying inks, lacquers, metal-cleaning compounds, paint removers
Organochlorine	Insecticides
Organophosphates	Insecticides
Perchloroethylene	Dry cleaning, degreaser, textile industry
Styrene	Fiberglass component, ship building, polyester resin
Thallium	Rodenticides, fungicides, mercury and silver alloys, lens manufacturing, photoelectric cells, infrared optical instruments
Toluene	Paint, fuel oil, cleaning agents, lacquers, paints and paint thinners
1,1,1 Trichloroethane(methyl chloroform)	Degreaser and propellant
Trichloroethylene	Cleaning agent, paint component, decaffeination, rubber solvents, varnish
Vinyl chloride	Intermediate for polyvinyl chloride (PVC) resins for plastics, floor coverings, upholstery, appliances, packaging
Xylene	Fixative for pathologic specimens, paint, lacquers, varnishes, inks, dyes, adhesives, cements

- Ethylene oxide and peripheral neuropathy

  - EtO is a sterilizing agent with an epoxide structure often used in hospital settings. Refer to Table 3 to review other industrial uses of EtO. Symptoms suggestive of neuropathy, such as numbness and weakness of extremities, leg cramps, and gait difficulties, are reported mostly after long-term EtO exposures. In 1978, Gross et al reported 4 cases of peripheral neuropathy caused by EtO resulting from a large EtO sterilizer leak that was not noticed for 2 months. These patients were working as sterilizer operators and had exposures of 3 weeks to 8 years. One operator was asymptomatic; 3 had headaches; and 2 developed fatigue, numbness, and muscle weakness in the extremities. In 1983, 5 of 6 sterilizer operators of a factory producing medical appliances were poisoned by EtO gas.

  - In 1986, Fukushima et al examined 4 operators who had exposures to the chemical ranging in duration from 20 days to 8 months. Gait disturbance was noted in all 4 operators. All 4 complained of numbness and muscle weakness in the feet and numbness of the fingers. Two operators had pain in the calf muscles and 3 had muscle weakness of the fingers. A 23-year-old man had been exposed 2-3 times a day for 5 months to high levels of EtO, up to 500 ppm, while working in a food and medical supply sterilization factory prior to his admission to a hospital. He complained of increasing weakness in his lower extremities.

  - Schroeder and Kuzuhara reported 2 patients with long-term EtO exposure. Both had difficulty in walking. One had been an operator of a sterilizer for 3 months before noting paresthesias and weakness in the distal limbs with staggering. After he returned to work, his symptoms worsened, and 3 months later he was admitted to a local hospital. His symptoms cleared entirely after 2 months. The second patient noted paresthesias in his feet 6 months after he had started to load and unload the sterilizers with medical supplies. Staggering followed the numbness and tingling of both hands and feet. Symptoms cleared 1 month later.

  - Finelli et al reported another case series of 3 males with toxicity from EtO. Two of these had been operators of sterilizers. One worked for a year and the other worked part-time for 1.5 years before developing symptoms. Both had difficulties with their gait after developing numbness and weakness in their lower extremities. One operator reported numbness in his feet and buckling of his right leg, and the other complained of cramps in his calf muscles. Both reported an odor; the part-time operator also reported headaches, burning eyes, and nausea.

  - The third patient worked for 6 days a week at a plastic manufacturing company, where several times a

day he worked in a sterilizing tank for about 40 minutes; he also unloaded materials in a decontamination area for half an hour each day. His chief complaints were leg cramps and a sense of heaviness of the feet. He first noted difficulty with sleeping, nervousness, and cramps in his hands and calf muscles. One month later, he noted poor balance and repeated stumbling. He also was aware of odd tingling sensations in both feet that had been present for longer than 3 months.

- Two women workers developed symptoms referred to the PNS after chronic EtO exposure. Both had been part of a group of 12 sterilizer workers in a hospital in Italy who were tested 2 years after the commencement of this exposure. Four of these 12 women complained of paresthesias and fatigue. Two were found to have peripheral neuropathy. Complete remission of these symptoms was reported for most of these women approximately 6 months after removal from exposure.

- Mercury (inorganic and organic) and peripheral neuropathy

  - Inorganic mercury is used in the chloralkali industry. Other uses are noted in Table 3. Neuropathy and PNS dysfunction, often motor more than sensory, were noted in the cases summarized here.

  - Albers et al reported 138 chloralkali plant workers with long-term exposure to inorganic mercury vapor who were found to have elevated urine mercury levels and reduced sensation on quantitative testing. Subjects exposed to mercury for 20-35 years who had urine mercury levels greater than 0.6 mg/L demonstrated significantly less strength, poorer coordination, more severe tremor, more impaired sensation, and higher prevalence of Babinski and snout reflexes than controls. Subjects with polyneuropathy had higher peak levels of mercury than healthy subjects.

  - In another study by Anderson et al, chloralkali workers exposed to inorganic mercury vapor for an average of 12.3 years revealed a higher prevalence of reduced distal sensation, postural tremor, and impaired coordination than controls. Barber reported 2 employees of a chloralkali plant who had findings suggestive of amyotrophic lateral sclerosis (ALS). Signs, symptoms, and laboratory findings returned to normal 3 months after withdrawal from exposure. Adams et al (1983) reported a 54-year-old man with a brief but intense exposure to mercury vapor, which led to a syndrome resembling ALS that resolved as urinary mercury levels fell. Ross reported that prolonged application of an ammoniated ointment to the skin was a cause of motor polyneuropathy, with cerebrospinal fluid (CSF) findings suggestive of Guillain-Barré syndrome.

  - Warkany and Hubbard reported the association of acrodynia and symmetrical flaccid paralysis with mercury toxicity.

  - Organic mercury was deemed the culprit in a number of historic environmental accidents. One noted catastrophe, reported by Yoshida et al, occurred in Minimata Bay, Japan, and involved organic mercury. The majority of Minimata patients with methylmercury intoxication had elevated pain thresholds but suffered from glove and stocking hyperesthesia in the extremities.

- Xylene and neuropathy

  - Xylene often is a component of paints and other industrial processes (see Table 3 for other uses of xylene). A literature search using Medline uncovered 11 epidemiologic studies of painters or other subjects with occupational exposure to organic solvents, including xylene, that found positive associations between exposure and PNS dysfunction. Two studies reported that vibration sensation was significantly less acute in 102 painters than in 102 age- and sex-matched controls. Four studies utilized quantitative sensory test (QST) methods.

  - In 1991, Bleeker found a correlation between increasing exposure dose and elevated vibration sensation thresholds in 187 workers from 2 paint-manufacturing plants. A second study noted higher vibration thresholds in 80 exposed painters than in controls. Demers et al noted statistically significant differences in vibrotactile measurements by QST of upper and lower extremities between 28 painters and 20 nonexposed controls. In 1989, Bove et al compared 93 painters to a nonexposed control population of 105 construction workers. Subjects were tested by 2 QST devices, a vibrometer and a temperature sensitivity tester.

Painters had significantly higher temperature sensation thresholds, and exposure intensity and cumulative exposure over the past month and year were associated positively with vibration thresholds.

- In 1989, Padilla et al performed an important animal study in which axonal transport was noted to be decreased by 30-50% in the rat optic nerve system immediately and 13 hours after inhalation exposure to xylene. Exposure was subacute; 800 and 1600 ppm for 6 hours/day, 5 days a week for 8 days led to these abnormalities. The authors concluded that the decreased supply of cellular materials to the axon and nerve-ending regions could initiate the neuronal malfunction reported in solvent-exposed animals and humans. As axonal transport is a process common to all nerves, any perturbation in these processes may disrupt the structure and functional integrity of the neuron. This mechanism has been used to explain both the CNS and PNS toxicity from organic solvents.

- Seven men aged 17-22 years developed severe distal symmetrical polyneuropathy after repeatedly inhaling a commercially available brand of lacquer thinner that was composed predominantly of xylene. All 7 were disabled permanently with motor weakness. One man died, 3 remained wheelchair bound, and 3 could walk but demonstrated varying degrees of weakness. Pathologic specimens revealed evidence of peripheral neuropathy.

- Perchloroethylene and neuropathy

  - PERC is an agent used in the dry-cleaning industry. Its various other uses are listed in Table 3. Peripheral neuropathy is a clinical diagnosis that is listed as secondary to chronic PERC exposure by Feldman (1991, 1995). Neither article refers to specific study results. Spencer and Schaumberg list neuropathy with a question mark as an effect of tetrachloroethylene (ie, perchloroethylene) toxicity. This article refers to 2 articles by Anti Poika and Juntunen et al that reported sensory trigeminal (fifth cranial nerve) defects in those exposed to mixed solvents. A 1978 National Institute for Occupational Safety and Health (NIOSH) publication on PERC remarked that "various disturbances of the peripheral nervous system such as tremors and numbness have also been associated with exposure to tetrachloroethylene."

  - Juntunen et al studied 87 patients from Finland diagnosed as having chronic intoxication caused by exposure to a mixture of solvents or to TCE and PERC between 1970 and 1974. Of these, 14 had been exposed to TCE or PERC alone, 53 to solvent mixtures, and 13 to all of them. Disturbances of cutaneous sensation and the sense of vibration were encountered frequently as clinical signs.

  - The Anti Poika article of the same year (ie, 1982) discussed the EMG findings of this same group. Electroneuromyography ([ENMG], including NCV and EMG) revealed 64 patients with signs positive for PNS disease and 34 patients with subjective symptoms. Signs of polyneuropathy were reported in 13 subjects. In the discussion, the author remarked that the number of patients with clinical polyneuropathy was so small that a trend could not be evaluated definitively.

  - A publication the following year (ie, 1983) by Seppalainen and Anti Poika categorized the specific ENMG findings of each of the 3 groups in the previously mentioned 2 studies. Of 18 patients in the group exposed to either TCE or PERC alone, 9 (50%) were deemed to have neuropathy on the first ENMG examination. On the second ENMG, 15 of 21 (71%) patients had this diagnosis. For those exposed to TCE or PERC or a mixture, 10 of 11 (91%) patients and 11 of 13 (85%) patients had this diagnosis, as opposed to 26 of 44 (59%) and then 38 of 53 (72%) of those exposed only to a mixture excluding chlorinated hydrocarbons (ie, TCE or PERC). The authors concluded that those patients with exposure to a mixture of solvents and to TCE or PERC tended to have neuropathic findings more often than patients exposed to either TCE or PERC alone or to a solvent mixture that did not include TCE or PERC. Findings on ENMG in these patients suggested axonal changes rather than segmental demyelination.

  - One toxicology text remarked that neuropathy may present following solvent exposures because the solvent (ie, PERC) often is mixed with amines, epoxides, and esters to protect it from moisture and light. Some of these compounds are known to cause neuropathy. Two European articles report PERC as being associated with neuropathy. In 1989, Herruzo-Perez et al described one case in which the authors suspected that a sensitive painful polyneuropathy probably was caused by poisoning with PERC. In 1989, Muller et al found slight derangements in neural functions in 130 dry-cleaning workers with long-term exposure to PERC during a 5-year follow-up study.

- Baker reported in a review from 1994 that recent studies suggested that mild subclinical disruption of PNS function does occur in workers exposed to solvent mixtures. In 1988, Orbaek et al studied patients with long-term exposures to organic solvents and found evidence of PNS dysfunction and slowing of the median nerve that was more pronounced in follow-up testing 22-72 months later. Slowing in the peroneal nerve was observed only at the follow-up NCV examination. Sensory conduction studies showed substantially reduced amplitudes in median and sural nerves with a prolongation of the distal latency in comparison with a control group; sensory conduction velocity in the median nerve also was slowed in the follow-up examination.

- Whether this and other studies of mixed organic solvent exposures suggesting neuropathy with various neurophysiological tests can implicate PERC is not clear, since PERC, its metabolites, or chemicals of similar structure may or may not have been a component of the solvent mixture. Maizlich et al refer to chlorinated aliphatic and chlorinated hydrocarbon solvents as components of paint vehicles and glues to which their subject population was exposed; other authors do not specify the composition of the substances to which their subjects were exposed.

- Trichloroethylene and neuropathy

  - TCE is used as degreaser in many industrial processes (refer to Table 3 to review its other industrial uses). Bernad et al evaluated 22 persons in a cohort of Michigan residents exposed for 5-20 years to well water with a low level of TCE contamination; 8-14 ppm of TCE was measured in the well water. Questionnaire, examination, and computer current perception-threshold testing (CPT) was performed. Results revealed hyperesthesia in 21 of 22 persons by CPT. Fatigue, lack of energy, somnolence, numbness, and tingling were reported by all 10 adults.

  - Feldman et al evaluated 21 residents of a Massachusetts community with alleged long-term exposure to TCE through drinking water and laboratory controls. The wells in question had 256 and 111 parts per billion (ppb) mean concentrations of TCE (maximum contaminant level [MCL] recommended by the Environment Protection Agency [EPA] is 0.5 ppb) and 26 and 24 ppb mean concentrations of PERC; duration of exposures was less than 1 to 12 years. Blink reflexes revealed differences in conduction latency of the reflex for the exposed population versus the controls, suggesting a subclinical alteration in the function of the fifth cranial nerve.

  - In 1994, Feldman et al published a study that compared this population to 2 other populations that had been exposed to environments contaminated with TCE and PERC and included more details of the population's neurologic examinations. The Massachusetts group was found to have sensory impairment and reflex abnormalities as evidence of peripheral neuropathy. The second group was 12 residents from an Ohio community who had been exposed to well water contaminated by wastewater deposited in a nearby creek by a company that fabricated sheet metal and precision-formed metal tubes. Their exposure was 3.3-330 ppb of TCE for 5-17 years. PERC also was found in the contaminated water. Nerve conduction studies (including blink reflexes) were performed. Reflex abnormalities were the most prevalent examination finding. Abnormal ulnar sensory latencies were noted in 81% of the group.

  - The third group comprised 14 residents from a Minnesota community who had been exposed to well water contaminated by a nearby army ammunitions plant. Exposure to TCE was between 261 and 2440 ppb in wells. 1,1-dichloroethane (DCE), 1,2-DCE, and 1,2-*trans*-DCE were identified in some wells. Questionnaires, examinations, and nerve conduction studies (including blink reflexes) were performed. Reflex abnormalities were the most common finding on neurologic examination. Approximately 70.6% had abnormal ulnar sensory latency, while 21% had abnormal blink reflex studies.

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DIFFERENTIALS

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Acute Inflammatory Demyelinating Polyradiculoneuropathy

Alcohol (Ethanol) Related Neuropathy
Amyotrophic Lateral Sclerosis
Chronic Inflammatory Demyelinating Polyradiculoneuropathy
Diabetic Neuropathy
Lambert-Eaton Myasthenic Syndrome
Metabolic Neuropathy
Myasthenia Gravis
Neuropathy of Leprosy
Nutritional Neuropathy
Paraneoplastic Autonomic Neuropathy
Uremic Neuropathy
Vitamin B-12 Associated Neurological Diseases

Other Problems to be Considered

Peripheral neuropathy
Small fiber neuropathy
Infectious neuropathy
Autoimmune neuropathy
Chronic disease polyneuropathy
Carcinogenic neuropathy
Vitamin B-6 deficiency
Vitamin B-12 deficiency
Connective tissue disorder
Glucose intolerance

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WORKUP

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Lab Studies

- See other eMedicine articles on neuropathy for workup to rule out common causes of neuropathy.
- Quantitative sensory testing includes vibration threshold testing, thermal threshold testing, portable motor and sensory latency tests, and current perception threshold (CPT) testing. These tests are often portable gadgets useful in the field. Each has its limitations, but some may be able to measure functions pertaining to small fiber neuropathy, such as the CPT and thermal testing devices. Others are simple versions of the NCV. The vibration testing device measures large fiber function and may be useful if NCV is not available.
- Other techniques that help prove the presence of neuropathy include skin biopsy and intraepidermal nerve fiber density (IENF) testing. This is well reviewed in the article by Smith et al (2005).
- The sympathetic skin reflex is performed with EMG machinery, where the absence of one side's testing suggests an abnormality. This test is technically difficult. A sural nerve biopsy is invasive but may be useful. Laser evoked potential and Quantitative Sudomotor Axon Reflex Test (QSART) have been useful in research. QSART measures sweat volume.
- IENF testing is relatively easy since it is a small punch biopsy of skin (6 mm). It has a reliable method of measuring small fiber neuropathy and has good interrater reliability. It measures intraepidermal nerve fibers, crossing the dermal, epidermal junction. It is being used in clinical trials for pharmaceuticals.
- For patients with cryogenic neuropathies, glucose tolerance testing makes sense because impaired glucose tolerance is prevalent in 14% of those aged 50-65 years. This is well reviewed by Sumner et al (2003). It is associated with a syndrome of insulin resistance, and 25-40% of patients progress to frank diabetes. An abnormal oral glucose tolerance test result is defined as a glucose level of 140-200, 2 hours after a 75-g

anhydrous load. Clinically, 86% of patients had exclusively sensory symptoms with pain and one third had otherwise idiopathic neuropathy. Oral glucose tolerance testing is more sensitive than glycosylated hemoglobin HbA1C testing.

- For cryptogenic neuropathy, the glucose tolerance test result is abnormal in 33-61% of patients. Other important laboratory tests to consider are tests for vitamin B-12, monoclonal gammopathy of unknown significance (3% of those >70 y), axonal neuropathy (1-5%), cryoglobins and hepatitis C evaluation, and immunofixation for paraneoplastic neuropathy.

- CSF protein level in toxic neuropathy is usually normal.

- Consider performing serum, urine, or blood testing to assess for evidence of absorption (see Table 2). If evaluating a patient weeks or months after the exposure ceased, biological data may not yield useful information. In the case of arsenic, for example, separating inorganic from organic arsenic is important, since organic arsenic is a component of seafood and may contaminate and confuse clinicians. Patients need to refrain from seafood for 24 hour prior to urine testing. Furthermore, labs need to be instructed to perform testing for inorganic, not organic, arsenic. Some agents do not have indices that can be tested. Most need to be performed relatively soon after exposure.

Other Tests

- Electromyography and nerve conduction studies
    - Normal to mildly slow motor NCVs
    - Sensory amplitudes frequently diminished
    - EMG evidence of denervation characterized by symmetrical fibrillation potentials in distal muscles
    - EMG helpful to establish the duration of the disorder and identify ongoing reinnervation
- Neurophysiologic abnormalities in workers exposed to ethylene oxide
    - In 1993, Ohnishi and Murai reviewed polyneuropathy cases caused by EtO. Needle EMG revealed neurogenic changes in 8 of 11 patients. Conduction studies of limb nerves were abnormal in 8 of 10 patients. Relatively mild decreases of motor and sensory NCVs with decreases in the amplitudes of nerve and muscle action potentials indicated axonal degeneration of both motor and sensory nerve fibers.
    - In 1983, Kuzuhara et al reported 2 patients with occupationally induced EtO polyneuropathy and their EMG and NCV results. In one patient, EMG of the limb muscles was normal except for long-duration and high-amplitude units recorded from the triceps. Motor NCVs were relatively well preserved. In the second patient, only an EMG was performed, which revealed denervation patterns in distal limb muscles.
    - Finelli et al reported electrophysiological findings in 3 patients with EtO-induced neuropathy; they demonstrated mild slowing of motor conduction with positive sharp waves and fibrillation potentials on EMG during the active disease state, indicating axonal neuropathy.
        - In patient 1, nerve conduction studies showed no response to stimulation of the left peroneal nerve, slowing of motor conduction over the right peroneal and the right posterior tibial nerves, and absence of the right tibial H reflex and the right sural nerve sensory potential. The EMG showed scattered positive sharp waves and fibrillation potentials with increased polyphasic activity in the intrinsic foot muscles and, to a lesser extent, in the leg muscles. Repeated examinations 5 weeks and 7 months later showed return of normal conduction velocity and disappearance of denervation potentials and the recording of giant potentials as signs of reinnervation. The left H reflex remained suppressed.
        - In patient 2, the EMG initially showed positive sharp-wave fibrillation potentials and small-amplitude motor unit potentials in leg and foot muscles. Follow-up studies showed the disappearance of the denervation potentials and the appearance of giant potentials indicating reinnervation.

        - Patient 3 showed absent potentials from the extensor digitorum brevis muscle on stimulation of the right peroneal nerve. Right tibial conduction was slowed, and the tibial H reflex was absent on the right and delayed on the left. The right sural nerve sensory potential amplitude was normal but delayed. Leg and foot muscle EMG studies showed denervation potentials. Repeat studies 7 months later showed mild slowing and active denervation on EMG with some polyphasic giant potentials.

    - In 1979, Gross et al reported 4 patients with EtO neurotoxicity and results of their nerve conduction studies. One patient had acute CNS symptoms and normal NCV. Another 2 had milder CNS symptoms with symptoms of a generalized sensorimotor polyneuropathy with fibrillations in the intrinsic muscles of the feet and abnormal NCVs (patient 2), and decreased numbers and increased amplitude and duration of motor unit potentials in the distal muscles (patient 3). Patient 4 was asymptomatic. Patients 2, 3, and 4 had decreased amplitudes of motor action potentials, moderately decreased NCVs, and signs of denervation compatible with axonal degeneration as the cause of neuropathy.

    - In 1985, Schroeder et al also reported a case of EtO-induced polyneuropathy. This patient had nerve conduction study findings that showed slowed NCVs; the mean tibial NCV was 26 m/s, with normal amplitudes, 2.5 mV.

    - Fukushima et al reported a 19-year-old patient with 20 days of EtO exposure who had numbness and weakness of his extremities and was noted to have a steppage gait on examination at the time of admission 1 month later. Nerve conduction study findings were abnormal; mean peroneal and tibial NCVs were 37.7 and 37.1 m/s (no normals were included), respectively. No latency potential was demonstrable for the right peroneal nerve. Neurogenic changes were demonstrated on EMG in the anterior tibial muscles.

    - Deschamps et al reported a case of persistent asthma after accidental EtO exposure. They performed EMG and NCVs after an examination of the patient's lower extremities revealed abnormal findings. EMG and NCV findings were normal, but maximum amplitudes of the right and left H reflex responses were reduced significantly (ie, 6% and 2% of the maximum amplitude elicited from the direct response) without a decrease in the proximal conduction velocity. These results suggested axonal neuropathy.

- Neurophysiologic abnormalities associated with mercury exposure (inorganic and organic)
    - Inorganic mercury is noted to produce a sensory or sensorimotor polyneuropathy similar to that produced by arsenic. Chloralkali plant workers (n=138) with long-term inorganic mercury vapor exposure were noted to have elevated urine mercury levels and reduced sensation on quantitative testing, prolonged distal latencies with reduced sensory-evoked response amplitudes, and increased likelihood of abnormal needle EMG findings. Factory workers exposed to elemental mercury vapor with elevated urine mercury concentrations had prolonged motor and sensory ulnar distal latencies. Slowing of the median motor NCV was found to correlate with both increased levels of mercury in blood and urine and with increased numbers of neurological symptoms. Sensory deficits found with short-term exposure to mercury vapor, whereas motor nerve impairment occurred with longer periods of exposure.

    - Chloralkali workers exposed to inorganic mercury vapors for an average of 12.3 years were found to have median motor and sensory NCVs that were slightly reduced among the highly exposed subjects. Seventeen thermometer factory workers had high urine and blood mercury levels but no symptoms; 88% had subclinical neuropathy, mainly distal and axonal neuropathy. In another study, a sensory polyneuropathy was found in 11% of workers exposed to inorganic mercury, while a sensorimotor polyneuropathy was found in 27% of workers.

    - Chloralkali workers who were exposed to inorganic mercury for an average of 7.9 years and had ceased working in that environment an average of 12.3 years prior to the study were found to have both median sensory NCV and amplitude of the sural nerve associated with measures of cumulative exposure to mercury. A study reviewing the relationship between exposure-related indices and neurological and neurophysiological effects in workers previously exposed to mercury vapor revealed that, of 298 dentists with long-term exposure to mercury amalgam vapor evaluated for peripheral neuropathy, 30% had polyneuropathies. Another paper reported that one dentist apparently had an unelicitable sensory superficial peroneal nerve action potential that returned to normal following penicillamine treatment.

- Industrial workers with long-term exposure to mercury were found to have performance decrements in neuromuscular functions that were reversible and correlated with blood and urine mercury levels.

- Neurophysiological abnormalities in workers exposed to xylene
  - Nerve conduction testing was utilized in 8 studies evaluating the PNS in workers with occupational exposure to mixed organic solvents including xylene. One of these noted a prolonged refractory period in lower extremity motor and sensory nerves of 28 exposed painters compared with age-matched controls. In 1980, Elofsson found a slight decrease in NCV in the distal sensory nerves of the lower extremities of an exposed population. He concluded that these findings were consistent with an axonal polyneuropathy.

  - In 1978, Seppalainen noted that 12 of 59 car painters had abnormally slow motor and sensory NCVs, while none of the controls had slowing. In 1980, Seppalainen reported that at least one abnormally slow NCV was noted in 48 of 107 subjects with a diagnosis of solvent poisoning. A third publication by the same author reported a different cross-sectional study and noted that 26 of 44 (59%) subjects with a diagnosis of organic solvent intoxication, who had been exposed exclusively to mixed solvents including dimethyl benzene, were diagnosed with peripheral neuropathy by EMG. Follow-up questionnaires of all subjects of the previous study, including those with mixed solvent exposure, noted that 57 of 87 subjects had symptoms referred to the PNS.

  - EMG revealed sensorimotor neuropathy in 5 of 7 painters tested in a study by Linz. Four of these 5 painters had evidence of mild distal neuropathy with reduced 2-point discrimination on neurologic examination. Temporal dispersion noted in sural SNAPs was a statistically significant finding in 50 male painters compared with controls.

Histologic Findings

Muscle and nerve pathology findings associated with ethylene oxide or mercury exposure include the following:

- Muscle and nerve biopsies were carried out by Kuzuhara et al on 2 patients who developed distal symmetrical polyneuropathies after being exposed to EtO while working as employees of a factory that produced medical supplies. The nerve biopsies of both patients implied axonal degeneration and regeneration. Swollen Schwann cell processes with numerous filaments, myelin figures, debris, and vacuoles with and without granules were seen on the electromicrogram of the sural nerve of patient 1. Growth cones of damaged axons were seen on the sural nerve of patient 2.

- Muscle biopsies revealed smearing and distortion of the Z bands. Some revealed absence of mitochondria and target or targetoid structures. Transverse sections showed atrophic fibers, scattered or grouped with many target fibers. Enzyme histochemistry of muscle from patient 2 revealed atrophy of both type 1 and type 2 fibers in the myosin adenosine triphosphatase (ATPase) reaction and dark angulated fibers, target, targetoid, and moth-eaten fibers on nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR) reaction.

- In 1993, Ohnishi and Murai reported that histologic studies of the sural nerves biopsied in 3 patients revealed decreased density of large myelinated fibers, reduction of the cross-sectional area of axons, reduction of axonal circularity, and presence of myelin ovoid and Bunger bands, which are compatible with a mild degree of axonal degeneration.

- Experimental EtO neuropathy was produced by Ohnishi in rats exposed to a one-time dose of 500 ppm for 6 hours or 5 doses of 250 ppm for 6 hours at a time over a week. In both experiments, distal axonal degeneration was found both in peripheral and central myelinated axons of lumbar primary sensory neurons of rats. In hind leg nerves and in the fasciculus gracilis, myelinated fibers showed axonal degeneration sparing the nerve cell body of the lumbar dorsal root ganglion and myelinated fibers of lumbar dorsal and ventral roots. The rats exposed to 250 ppm also showed a retardation of growth and maturation of myelinated fibers in the presence of mild axonal degeneration.

- In a patient with EtO polyneuropathy after 5 months of exposure, Schroder et al performed a sural nerve biopsy that revealed nerve fiber degeneration of the wallerian type associated with reduction of axonal cross-sectional areas and some degree of nerve fiber regeneration. Conspicuous paranodal vesicular disintegration of individual myelin lamella also was present. Unusual cisternae with introverted hemidesmosomes were noted in endoneural fibroblasts.

- Nerve pathology was investigated in those exposed to organic mercury. Miyakawa et al reported selective swelling and degeneration of the Schwann cells, noticeable changes of both myelin sheaths and the axon. Pathologic changes began at the nodes of Ranvier. Primary site of damage was noted to be in the cell bodies of the sensory ganglion cells, with axonal degeneration occurring later in rats poisoned by methylmercury hydroxide. The largest myelinated fibers were affected to a greater extent than the smaller caliber fibers in the dorsal root.

- An autopsy performed on a descendant of a woman exposed to mercury at Minimata Bay demonstrated segmental demyelination of the PNS. In both humans and animals, the major pathologic effect of methylmercury appears to be on the dorsal root ganglion cells. Similar data are not available for inorganic or metallic mercury poisoning.

Medical Care

- Advise removal from occupational or environmental exposure.

- Advise discontinuation of medication or recreational drug habit. Also provide information regarding how alcohols affect those with exposures.

- Acute care for those intoxicated with recreational, industrial, or other agents is discussed in other articles on this web site.

- Preventive care and supportive care should include consideration of life stressors, diet, and overall behavior modifications.

- Treatment options also include the following:
    - Nonpharmacologic options include cool soaks, heat, massage, elevation or lowering of the limbs, shoe tightness, and/or exercise.

    - Pharmacological options include tricyclic antidepressants, anticonvulsants, opiates, or topical capsaicin cream. Other options include intravenous gamma globulin, aldose reductase inhibitors, nerve growth factor, anti–tumor necrosis factor-a; these are mainly research ideas. Three that may be helpful presently include lipoic acid, evening primrose, and vitamin E.

        - Alpha lipoic acid is well reviewed by Halat and Dennehy (2003). Thiolic acid is a free radical scavenger and chelator. It is approved for use in Germany for neuropathy. The best studies suggest parenteral use followed by oral use relieves symptoms and improves nerve blood flow. Oral preparations are available in United States. Two studies suggest increased nerve conduction (600/1200 mg for 2 y, oral) and reduced symptoms (1800 mg/d for 3 wk, oral). The mechanism of action includes chelation and, thus, a concern for mineral shortage exists. Monitoring iron levels is suggested, and persons with alcoholism need to take vitamin B.

        - Evening primrose is also well summarized by Halat and Dennehy (2003). It includes omega 6 essential fatty acids: gamma linoleic acid (GLA) and linoleic acid. It is an essential component of myelin and the neuronal cell membrane. Dosages ranging from 360-480 mg/d for 6 months to 1 year improved nerve function measurements. It has mild side effects including inhibition of platelet aggregation. Concern also exists for those with seizure disorders.

        - Vitamin E is discussed in the article Aargyrio et al (2005). Vitamin E has been administered to patients on chemotherapy for prevention of neuropathy at doses of 600 mg/d during treatment and then for 3 months after treatment. A reduced peripheral neuropathy score has been noted.

A neuroprotective effect has been described.

Consultations

- Occupational therapist
- Environmental medicine specialist

Diet

Although diet does not play a specific role in reparation of the PNS, a balanced diet is important for various reasons related to general health. Since various B vitamins have been implicated in the development of neuropathies, some physicians suggest supplementation.

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FOLLOW-UP

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Further Outpatient Care

- Consistent follow-up care with a neurologist is necessary to monitor the progress of neurological findings.
- Follow-up with an occupational medicine specialist may be important to assist with return to work and reduction of exposure. This clinician may be able to work with the company supervisors or management to improve the work environment. This may occur if the company chooses to substitute the neuropathy-causing agent with a less-toxic agent in the workplace, to change the schedules of workers so that their exposure is less during a period of time, or to promote safer personal protective equipment. Communication between health care provider and management is essential for this individual's health as well as his or her status for disability or ability return to work.

Prognosis

- Each patient's prognosis depends on the severity of the neuropathy when exposure is ceased or reduced to

levels that will not affect health negatively.

Patient Education

- Inform patients about aspects of dose, diet, and nutrition that may increase risk of toxicity when taking a medication. Since many solvents are metabolized in the liver, concomitant use of medications with similar metabolism may lead to increased toxicity.
- Workers, by law, need to be informed of chemicals in the workplace and their potential health hazards. Material safety data sheets (MSDS), per order of Occupational Safety and Health Administration (OSHA), are available to all workers in the workplace.
- The Emergency Planning and Community Right to Know Act (EPCRA) requires that facilities using, storing, or manufacturing hazardous chemicals make public inventory and report every release to public officials and health personnel. These facilities must cooperate with health personnel who are treating victims of exposure.

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MISCELLANEOUS

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Medical/Legal Pitfalls

- Consider the following algorithm to assess whether a toxic etiology satisfies a rigorous method of scrutiny.
- Algorithm for clinical assessment of neurotoxic disease
  - Begin the evaluation by noting chief complaint or complaints. Consider when they began and how they relate to an exposure.
  - Take a thorough medical history that includes an occupational and environmental history to consider all sources of exposure to all possible agents. List details of all jobs and job tasks within the jobs and what symptoms and medical problems began when.
  - Consider review of systems and how eating, bowel movements, sexual activity, sleep, and emotional status varied during exposure incidents.
  - List medical complaints on a timeline and relate each to exposure dates, duration, and intensity. Consider other occupational, environmental, and drug exposures. Include vitamin supplements, hobbies, and traditional practices.
  - Include birth history, pregnancy, and extensive family history to uncover any genetic or congenital diseases.
  - Consider how symptoms change as they relate to exposures. How often do flare-ups occur? Are the symptoms persistent or do they improve?
  - Do colleagues or co-workers have similar complaints?
  - List all potential sources of exposure: from where, what form, and how they are used.
  - Obtain MSDSs and scientific data on each chemical agent.
  - Perform neurologic examination. A general medical examination including an assessment of the autonomic

system, hair, teeth, nails, skin color, and lymph system is important. Are any objective neurological signs or other systemic findings noted?

- Arrange for confirmatory neurophysiological, neuropsychological, and imaging tests.
- Arrange for serum and biological monitoring when appropriate (see Table 2).
- Review regulatory information for this chemical. What have OSHA, EPA, NIOSH, American Conference of Governmental Industrial Hygienists (ACGIH), and other international organizations published as a safe level? See Table 1.
- Consider contacting an industrial hygienist for air and water sampling.
- Consider removal from exposure.
- Consider whether exposure and medical problem may be consistent chronologically. First, did the exposure precede the complaint or dysfunction?
- Exclude all other common causes of the diagnosis. Are the findings consistent with a primary neurological or other medical condition? Are the findings explained by other historical or familial factors? Other exposures, illnesses, or stressors?
- Search literature for epidemiologic and case studies and series that describe an association between exposure and dysfunction.
- Is dose and duration of exposure consistent with the described dysfunction? Focus on details of the literature.
- What is the proposed mechanism for this exposure-induced dysfunction?
- Estimate functional status and medical treatment options and consultation necessary for support.
- Reevaluate by examination and neurological and neuropsychological tests. Do the results remain consistent?

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REFERENCES

Authors and Editors Introduction Clinical Differentials Workup Treatment Follow-up Miscellaneous References

- ATSDR. Toxicological profile for carbon disulphide. US Department of Health and Human Services;1994.
- Adams CR, Ziegler DK, Lin JT. Mercury intoxication simulating amyotrophic lateral sclerosis. *JAMA*. Aug 5 1983;250(5):642-3. [Medline].
- Adams RD, Victor M, Ropper AH. Principles of Neurology. 6th ed. *New York: McGraw-Hill;*. 1997:1278-1369.
- Albers J, Bromberg MB. Chemically induced toxic neuropathy. In: Rosenberg NL, ed. Occupational and Environmental Neurology. *Boston: Butterworth-Heinemann;*. 1995:175-234.
- Albers JW, Cavender GD, Levine SP, Langolf GD. Asymptomatic sensorimotor polyneuropathy in workers exposed to elemental mercury. *Neurology*. Oct 1982;32(10):1168-74. [Medline].
- Albers JW, Kallenbach LR, Fine LJ, et al. Neurological abnormalities associated with remote occupational elemental mercury exposure. *Ann Neurol*. Nov 1988;24(5):651-9. [Medline].
- American Conference of Governmental Industrial Hygienist. Threshold Limit Values and Biological Exposure Indices. 1999.
- Andersen A, Ellingsen DG, Morland T, Kjuus H. A neurological and neurophysiological study of chloralkali workers previously exposed to mercury vapour. *Acta Neurol Scand*. Dec 1993;88(6):427-33. [Medline].
- Angotzi G, Battistini N, Carboncini F, et al. Impairment of nervous system in workers exposed to inorganic

mercury. *Toxicol Eur Res*. Nov 1981;3(6):275-8. [Medline].
- Antti-Poika M. Overall prognosis of patients with diagnosed chronic organic solvent intoxication. *Int Arch Occup Environ Health*. 1982;51(2):127-38. [Medline].
- Argyriou AA, Chroni E, Koutras A, et al. Vitamin E for prophylaxis against chemotherapy-induced neuropathy: a randomized controlled trial. *Neurology*. Jan 11 2005;64(1):26-31. [Medline].
- Baker EL. A review of recent research on health effects of human occupational exposure to organic solvents. A critical review. *J Occup Med*. Oct 1994;36(10):1079-92. [Medline].
- Barber TE. Inorganic mercury intoxication reminiscent of amyotrophic lateral sclerosis. *J Occup Med*. Oct 1978;20(10):667-9. [Medline].
- Berger AR, Schaumberg HH. Disorders of the peripheral nervous system. In: Rosenstock L, Cullen MR, eds. Textbook of Clinical Occupational and Environmental Medicine. *Philadelphia: Saunders;*. 1994:482-513.
- Bernad PG, Newell S, Spyker DA. Neurotoxicity and behavior abnormalities in a cohort chronologically exposed to trichloroethylene. *Vet Hum Toxicol*. 1987;29:475.
- Bleeker ML. Clinical presentations of selected neurotoxic compounds. In: Bleeker ML, Hansen JA, eds. Occupational Neurology and Clinical Neurotoxicology. Baltimore: Williams & Wilkins;1994:207-234.
- Bove FJ, Letz R, Baker EL. Sensory thresholds among construction trade painters: a cross-sectional study using new methods for measuring temperature and vibration sensitivity. *J Occup Med*. Apr 1989;31(4):320-5. [Medline].
- Demers RY, Markell BL, Wabeke R. Peripheral vibratory sense deficits in solvent-exposed painters. *J Occup Med*. Oct 1991;33(10):1051-4. [Medline].
- Dyck PJ. Diabetic Neuropathy. *Philadelphia:*. WB Saunders Co;1998.
- Dyck PJ. Peripheral Neuropathy. *Philadelphia:*. WB Saunders Co;1993.
- Ellingsen DG, MÃ¸rland T, Andersen A, Kjuus H. Relation between exposure related indices and neurological and neurophysiological effects in workers previously exposed to mercury vapour. *Br J Ind Med*. Aug 1993;50(8):736-44. [Medline].
- Elofsson SA, Gamberale F, Hindmarsh T, et al. Exposure to organic solvents. A cross-sectional epidemiologic investigation on occupationally exposed care and industrial spray painters with special reference to the nervous system. *Scand J Work Environ Health*. Dec 1980;6(4):239-73. [Medline].
- Eto K, Oyanagi S, Itai Y, et al. A fetal type of Minamata disease. An autopsy case report with special reference to the nervous system. *Mol Chem Neuropathol*. Feb-Apr 1992;16(1-2):171-86. [Medline].
- Feldman RG. Occupational and Environmental Neurotoxicology. Philadelphia: Lippincott-Raven;1999.
- Feldman RG, White RF. Role of the neurologist in hazard identification and risk assessment. *Environ Health Perspect*. Apr 1996;104 Suppl 2:227-37. [Medline].
- Feldman RG. Effect of toxins and physical agents on the nervous system. In: Bradley WG et al, eds. Neurology in Clinical Practice. Boston: Butterworth-Heinemann;1991:1185-207.
- Feldman RG. The recognition and differentiation of neurotoxic and non-neurotoxic syndromes. In: Chang LW, Slikker W, eds. Neurotoxicology: Approaches and Methods. *San Diego: Academic Press*. 1995:689-694.
- Feldman RG. Neurotoxic effects of trichloroethylene in drinking water. In: Isaacson RL, Jensen KF, eds. The Vulnerable Brain and Environmental Risks: Toxins in Air and Water. Vol 3. *Plenum Press;*. 1994.
- Finelli PF, Morgan TF, Yaar I, Granger CV. Ethylene oxide-induced polyneuropathy. A clinical and electrophysiologic study. *Arch Neurol*. Jul 1983;40(7):419-21. [Medline].
- Fukushima T, Abe K, Nakagawa A, et al. Chronic ethylene oxide poisoning in a factory manufacturing medical appliances. *J Soc Occup Med*. 1986;36(4):118-23. [Medline].
- Gilioli R, et al. In: Horvath M, ed. Adverse Effects of Environmental Chemicals and Psychotropic Drugs. *Vol 2. Amsterdam:*. Elsevier Science;1976:157-164.
- Gross JA, Haas ML, Swift TR. Ethylene oxide neurotoxicity: report of four cases and review of the literature. *Neurology*. Jul 1979;29(7):978-83. [Medline].
- Halat KM, Dennehy CE. Botanicals and dietary supplements in diabetic peripheral neuropathy. *J Am Board Fam Pract*. Jan-Feb 2003;16(1):47-57. [Medline].
- Hoitsma E, Reulen JP, de Baets M, et al. Small fiber neuropathy: a common and important clinical disorder. *J Neurol Sci*. Dec 15 2004;227(1):119-30. [Medline].
- Iyer K, Goodgold J, Eberstein A, Berg P. Mercury poisoning in a dentist. *Arch Neurol*. Nov 1976;33(11):788-90. [Medline].
- Johnson BL, Boyd J, Burg JR, et al. Effects on the peripheral nervous system of workers' exposure to carbon disulfide. *Neurotoxicology*. 1983;4(1):53-65. [Medline].
- Juntunen J. Neurotoxic syndromes and occupational exposure to solvents. *Environ Res*. Jan 1993;60(1):98-111. [Medline].
- Juntunen J, Antti-Poika M, Tola S, Partanen T. Clinical prognosis of patients with diagnosed chronic solvent intoxication. *Acta Neurol Scand*. May 1982;65(5):488-503. [Medline].
- Kimura J. Polyneuropathies. In: Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice. *2nd ed*. Philadelphia: FA Davis;1989:462-81.
- Kimura J. Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice. *2nd ed*. Philadelphia: FA Davis;1989:149-162.
- Kuzuhara S, Kanazawa I, Nakanishi T, Egashira T. Ethylene oxide polyneuropathy. *Neurology*. Mar 1983;33(3):377-80. [Medline].

- Levine SP, Cavender GD, Langolf GD, Albers JW. Elemental mercury exposure: peripheral neurotoxicity. *Br J Ind Med*. May 1982;39(2):136-9. [Medline].
- Linz DH, de Garmo PL, Morton WE, et al. Organic solvent-induced encephalopathy in industrial painters. *J Occup Med*. Feb 1986;28(2):119-25. [Medline].
- Miller JM, Chaffin DB, Smith RG. Subclinical psychomotor and neuromuscular changes in workers exposed to inorganic mercury. *Am Ind Hyg Assoc J*. Oct 1975;36(10):725-33. [Medline].
- Miyakawa T, Deshimaru M, Sumiyoshi S, et al. Experimental organic mercury poisoning--pathological changes in peripheral nerves. *Acta Neuropathol (Berl)*. 1970;15(1):45-55. [Medline].
- National Institute for Occupational Safety and Health (NIOSH). Tetrachloroethylene. Current Intelligence Bulletin; January 1978;number 20.
- Ohnishi A, Murai Y. Polyneuropathy due to ethylene oxide, propylene oxide, and butylene oxide. *Environ Res*. Feb 1993;60(2):242-7. [Medline].
- Padilla SS, Lyerly DP. Effects of p-xylene inhalation on axonal transport in the rat retinal ganglion cells. *Toxicol Appl Pharmacol*. Dec 1989;101(3):390-8. [Medline].
- Pleasure DE, Schotland DL. Peripheral neuropathies. In: Rowland LP, ed. Merritt's Textbook of Neurology. *8th ed*. Philadelphia: Lea & Febiger;1989:601-26.
- Ross AT. Mercuric polyneuropathy with albumino-cytologic dissociation and eosinophilia. *JAMA*. Jun 1 1964;188:830-1. [Medline].
- Rowland LP, ed. Merritt's Textbook of Neurology. 8th ed. *Philadelphia: Lea & Febiger;*. 1989.
- Ruijten MW, SallÃ© HJ, Verberk MM, Muijser H. Special nerve functions and colour discrimination in workers with long term low level exposure to carbon disulphide. *Br J Ind Med*. Sep 1990;47(9):589-95. [Medline].
- Ruijten MW, Salle HJ, Verberk MM. Verification of effects on the nervous system of low level occupational exposure to CS2. *Br J Ind Med*. Apr 1993;50(4):301-7. [Medline].
- Schaumberg HH. Human neurotoxic disease. In: Spencer P, Schaumberg HH, eds. Experimental and Clinical Neurotoxicology. *2nd ed*. New York: Oxford University Press;2000.
- Schaumberg HH, Spencer PS. Clinical and experimental studies of distal axonopathy- A frequent form of brain and nerve damage produced by environmental chemical hazards. *Ann NY Acad Sci*. 1979;14-29.
- Schaumburg HH, Spencer PS. The neurology and neuropathology of the occupational neuropathies. *J Occup Med*. Nov 1976;18(11):739-42. [Medline].
- Schroder JM, Hoheneck M, Weis J, Deist H. Ethylene oxide polyneuropathy: clinical follow-up study with morphometric and electron microscopic findings in a sural nerve biopsy. *J Neurol*. 1985;232(2):83-90. [Medline].
- Seppalainen AM, Tolonen E. Neurotoxicity of long term effects of carbon disulfide in the viscose rayon industry. *Scand J Work Environ Health*. 1974;1:145-153.
- Seppalainen AM, Lindstrom K, Martelin T. Neurophysiological and psychological picture of solvent poisoning. *Am J Ind Med*. 1980;1(1):31-42. [Medline].
- Seppalainen AM, Antti-Poika M. Time course of electrophysiological findings for patients with solvent poisoning. A descriptive study. *Scand J Work Environ Health*. Feb 1983;9(1):15-24. [Medline].
- Seppalainen AM, Husman K, Martenson C. Neurophysiological effects of long-term exposure to a mixture of organic solvents. *Scand J Work Environ Health*. Dec 1978;4(4):304-14. [Medline].
- Shapiro IM, Cornblath DR, Sumner AJ, et al. Neurophysiological and neuropsychological function in mercury-exposed dentists. *Lancet*. May 22 1982;1(8282):1147-50. [Medline].
- Singer R, Valciukas JA, Rosenman KD. Peripheral neurotoxicity in workers exposed to inorganic mercury compounds. *Arch Environ Health*. Jul-Aug 1987;42(4):181-4. [Medline].
- Smith AG, Howard JR, Kroll R, et al. The reliability of skin biopsy with measurement of intraepidermal nerve fiber density. *J Neurol Sci*. Jan 15 2005;228(1):65-9. [Medline].
- Somjen S, Mercury. In: Schaumberg HH and Spencer PS, eds. Clinical Neurotoxicology. *Baltimore:*. Lippincott Williams & Wilkins;1980.
- Sumner CJ, Sheth S, Griffin JW, et al. The spectrum of neuropathy in diabetes and impaired glucose tolerance. *Neurology*. Jan 14 2003;60(1):108-11. [Medline].
- Wang MS, Fang G, Culver DG, et al. The WldS protein protects against axonal degeneration: a model of gene therapy for peripheral neuropathy. *Ann Neurol*. Dec 2001;50(6):773-9. [Medline].
- Warkany J, Hubbard DM. Acrodynia and mercury. *J Pediatr*. 1953;42:365-386.
- Yoshida Y, Kamitsuchibashi H, Hamada R, et al. Truncal hypesthesia in patients with Minamata disease. *Intern Med*. Feb 1992;31(2):204-7. [Medline].
- Zampollo A, Baruffini A, Cirla AM, et al. Subclinical inorganic mercury neuropathy: neurophysiological investigations in 17 occupationally exposed subjects. *Ital J Neurol Sci*. Jun 1987;8(3):249-54. [Medline].

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