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Occupational toxic neuropathies — An update

by Fengsheng He, MD¹

HE F. Occupational toxic neuropathies — An update. *Scand J Work Environ Health* 11 (1985) 321–330. Peripheral neuropathy is the commonest neurological syndrome produced by industrial and agricultural chemicals. A number of chemicals have been recently found to be neurotoxins; in addition some known occupational neurotoxic hazards more often produce subtle alterations in the peripheral nervous system. There have been problems of both evaluating neurotoxic effects and identifying toxic causes. This article reviews and discusses the current research and progress covering neurophysiological, neuropathological, biochemical, and epidemiologic approaches in clinical and experimental neurotoxicology, as related to the assessment and pathogenesis of occupational toxic neuropathies.

Key terms: assessment, clinical neurophysiological testing, distal axonopathy, epidemiologic investigation, identification, neuropathological approach, pathogenesis, toxic causes.

Along with the development of various chemical industries there has been a growing list of industrial chemicals which can cause damage to the peripheral nervous system. On the other hand, occupational exposure to low levels of known neurotoxins more often causes subtle alterations of peripheral nervous function. This occurrence raises problems in occupational health practice and stimulates research concerning the early diagnosis and prevention of occupational toxic neuropathies. In the meantime, modern techniques of neurophysiology, neuropathology, and biochemistry have been introduced and utilized to explore the mechanisms of some neurotoxic effects. All these methods lead to a substantial amount of progress in evaluating and understanding occupational toxic neuropathies, which have been reviewed in this article.

PROGRESS IN ASSESSMENT AND IDENTIFICATION

The diagnosis of chemically-induced neuropathies can be reasonably made in those subjects who have a verified history of exposure to neurotoxins and characteristic clinical evidence of neuropathy with exclusion of other causative factors. But there are some asymptomatic individuals under neurotoxicologic risk who may be suspected of having subclinical peripheral neuropathies and, on the other hand, a number of symptomatic patients having the presumptive diagnosis

of polyneuropathy without a known etiology. In these cases, the question of either the existence or the etiology of the peripheral neuropathies remains to be settled.

Detection of neurotoxic effects on the peripheral nervous system

In subjects exposed to potentially neurotoxic substances, it is of paramount importance to determine whether or not neurotoxic lesions have developed. Apart from evaluation of the clinical history and the neurological examination, recent advances in sensitive diagnostic electrophysiological tests and in the morphological approach by nerve biopsy permit improvement in the assessment of peripheral neuropathies in clinical neurotoxicology.

Nerve biopsy

Much of the present body of information regarding peripheral nerve disease has been gathered from detailed examinations of nerve biopsies. In order to obtain pathological information as an aid to the diagnosis of a peripheral nerve disorder, the sural nerve is commonly used. With the use of contemporary neuropathological techniques, including single nerve fiber teasing and thin plastic sections, it is possible to perform both qualitative and quantitative morphological assessments of nerves on the basis of both light and electron microscopy of nerve fibers and their connective tissues (94).

Some information about the nature of the pathological change in a variety of toxic neuropathies has been obtained from biopsies of peripheral nerves. The following two basic forms of damage to peripheral nerves have been identified as being responsible for the

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peripheral neuropathies associated with exposure to neurotoxins in humans (7):

1. Segmental demyelination and remyelination results from primary destruction of the myelin sheath and Schwann cells with relative sparing of the axon. This process begins at the nodes of Ranvier and results in the slowing of nerve conduction. Characteristically, there is no evidence of muscle denervation. As remyelination begins during the recovery phase, recovery is rapid and is usually complete in mild to moderate neuropathies.

2. Axonal degeneration and regeneration is associated with a direct attack on axons by a neurotoxin and is manifest by degeneration of the distal portion of the nerve fiber. Myelin sheath degeneration may occur secondarily, and the distal portion of the degenerated nerve fiber may undergo a condition referred to as Wallerian degeneration, which is a fragmentation and absorption of the axoplasm and the myelin sheath. Nerve conduction velocities are usually normal until the condition is relatively far advanced. Distal muscles show changes of denervation or atrophy. Recovery may occur by axonal regeneration but is very slow or incomplete (7, 62).

In most instances, occupational toxic neuropathies are of the axonal degeneration type, whereas segmental degeneration is much less common in chemically induced neuropathies.

Nerve biopsy has been applied to detect toxic neuropathy in several studies. Results of nerve biopsies obtained from individuals with moderate or severe n-hexane neuropathy have been very informative (67, 70, 87). In these cases, teased myelinated nerve fiber preparations have clearly illustrated paranodal giant axonal swellings accompanied by myelin retraction. Electron microscopy has revealed that the axonal swellings consist of accumulations of 10-nm neurofilaments. These pathological features are identical to the abnormalities observed in experimental hexacarbon neuropathy (87).

Sural nerve biopsies in patients with acrylamide (49), dipterex (92), parathion (23), and ethylene oxide (45) neuropathies all show axonal degeneration. Dimethylaminopropionitrile (DMAPN) neuropathy is also characterized by filamentous accumulations in biopsied sural nerve (64). In a patient with lead neuropathy with a blood lead level of more than 150 $\mu\text{g}/100\text{ ml}$ (7.2 $\mu\text{mol/l}$) a marked decrease in the number of large myelinated nerve fibers was found by sural nerve biopsy without any abnormalities in the teased fibers (17).

It must be recognized that nerve biopsy is of little aid to the etiology of toxic neuropathies. Moreover, it is invasive, though it produces only minor sequelae. Possibly therefore nerve biopsy is less often clinically applied to detect toxic neuropathies.

Clinical neurophysiological approaches

Electrophysiological tests provide sensitive and objective methods for detecting impairment of nerve and muscle function (53). However, each group of neurotoxic substances has its own particular effect on the peripheral nervous system and produces pathological lesions which are often distinctive in type and distribution and results in a characteristic pattern of electrophysiological abnormalities (48). Knowledge of the pathophysiology of a particular toxic peripheral nervous disorder is important when one must decide on the most sensitive test to apply when looking for mild or subclinical damage (40, 48). In instances where information is not available, standard electrophysiological screening procedures must be used for evaluating toxic peripheral nerve disease.

Electromyography. Electromyography (EMG) consists of an examination of the electrical activity of the muscle at rest and during contraction. It is an extremely useful method for detecting axonal degeneration of motor nerve fibers (53). Since the pathological change in the majority of toxic neuropathies is axonopathic in type, electromyography may be expected to provide evidence consistent with axonal and mixed neuropathies.

Seppäläinen & Haltia (76) found fibrillation potentials in 20 out of 38 patients with chronic carbon disulfide poisoning. In a reexamination of a group of patients with chronic carbon disulfide neuropathy, findings consistent with an irreversible axonal change were found (20). In delayed neuropathy of acute organophosphorous pesticide poisoning, electromyography reveals changes of denervation in nearly every case. These changes are confined to distal muscles in mild instances and generally involve proximal leg muscles in severe cases (92). Electromyography has also been extremely useful in the assessment of patients with toxic neuropathies induced by n-hexane (87), methyl n-butyl ketone (3), allyl chloride (33, 34), and ethylene oxide (28, 30).

In general, electromyography is sensitive to the denervation of muscle fiber groups, a condition which typically signifies a state of advanced axonal degeneration (12, 33, 34). If toxic axonopathies are longstanding, electromyography often shows signs of partial denervation with collateral reinnervation; these signs are more sensitive than purely clinical measurement (33). Follow-up studies with electromyography also may provide evidence implying prognosis (35, 75, 93).

Electroneurography. Measurements of motor and sensory nerve conduction velocities in peripheral nerves are standard procedures used for assessing toxic neuropathies. Loss of large diameter fibers may reduce the maximal motor nerve conduction velocity, even though smaller diameter fibers may be unaffected by the toxic agent. A profound slowing of motor or sensory con-

duction velocity is usually associated with marked demyelination, which is rare in occupational neuropathies.

There has been an unusual degree of slowing of motor nerve conduction for an axonal polyneuropathy in hexacarbon neuropathy (73, 87). This phenomenon has been attributed to the paranodal demyelination that accompanies the early swelling of the affected axon. In chronic carbon disulfide poisoning, the conduction velocity of the slow fibers of the ulnar and peroneal nerves was reported to be the most sensitive test for peripheral nerve involvement (96). It has been observed that measurement of sensory nerve potentials provides the most sensitive electrophysiological test of peripheral nerve function in patients poisoned by acrylamide and in cases of organophosphorus-delayed neuropathy (48, 50).

Because electroneurography (ENG) is thought to be noninvasive, reproducible, and easy to implement and quantify, it is useful in follow-up studies on toxic neuropathies, as reported in cases of subacute arsenic neuropathy (57). A correlation between abnormal nerve conduction velocities and exposure levels in patients of organic solvent poisoning has also been reported (79). Moreover, electroneurography has been increasingly applied in recent epidemiologic studies to

screen exposed populations and to determine subclinical neurotoxic effects on peripheral nerves. Statistically significant differences between exposed and reference groups have been reported for some electro-neurographic parameters in a number of studies related to mercury (2, 51, 90), carbon disulfide (9, 38, 96), hexacarbon (55, 58, 59, 60, 69), arsenic (27), organophosphate (40), 2,4,5-trichlorophenoxy acetic acid (80), and lead (10, 21) exposures. A summary of selected results is shown in table 1.

However, the results of electroneurographic studies of lead-exposed workers have been controversial. It has been reported that motor nerve conduction velocity is often reduced even in symptomless lead workers (6, 8, 13, 47, 66, 77, 78, 91). An exposure-response relationship has also been demonstrated between time-weighted blood lead levels and abnormalities of nerve conduction (77, 78). Some authors have also confirmed these findings by demonstrating that impairment in nerve conduction indeed starts at blood lead levels lower than formerly believed to be safe, ie, 70–80 $\mu\text{g}/100\text{ ml}$ (3.4–3.9 $\mu\text{mol/l}$) (3, 13). Recently some results (66, 74, 78) showed that the lead effects in the peripheral nerves start at a very low exposure level, namely, at blood lead levels just exceeding 30 $\mu\text{g}/100\text{ ml}$ (1.4 $\mu\text{mol/l}$), and indicated that nervous system lesions

Table 1. Nerve conduction changes (D = decrease and I = increase) with statistically significant differences ($p < 0.05$) in asymptomatic neurotoxin-exposed groups when compared with reference groups, listed according to the neurotoxic chemical and the authors of the study.

	Mercury		Lead						Carbon disulfide		Hexa-carbon
Nerve ^a	Levine et al (51)	Triebig et al (90)	Ashby (6)	Buchthal & Behse (16)	Seppäläinen & Hemberg (77)	Bordo et al (19)	Triebig et al (91)	Baker et al (8)	World Health Organization (96)	Johnson et al (38)	Mutti et al (58)
	(N = 18)	(N = 21)	(N = 94)	(N = 20)	(N = 61)	(N = 62)	(N = 148)	(N = 99)	(N = 118)	(N = 156)	(N = 95)
Median											
MCV	.	.	D	D	.	D	.	.	.	.	D
DML	.	.	.	I	I	.	.	.	I	.	.
MAP	.	.	.	.	.	.	.	.	.	.	D
SCV	.	D	.	D	D	D	D	.	.	.	.
SAP	.	.	.	I	.	D	.	.	.	.	.
Ulnar											
MCV	.	.	D	.	.	.	D	.	.	.	.
DML	I	.	.	.	.	.	.	.	I	.	.
MAP	D	.	.	.	.	.	.	.	.	.	D
SCV	D	D	.	.	.	.	D	.	.	.	.
DSL	I	.	.	.	.	.	.	.	.	.	.
CVSF	.	.	.	.	D	.	.	.	D	.	.
Peroneal											
MCV	.	.	D	.	.	.	.	.	D	D	D
DML	.	.	.	I	.	I	.	.	.	.	.
MAP	.	.	.	.	.	.	.	.	.	.	D
SCV	.	.	.	D	.	.	.	.	.	.	.
DSL	.	.	.	I	.	.	.	.	.	.	.
CVSF	.	.	.	.	.	.	.	.	D	.	.
Sural											
SCV	.	.	.	.	.	.	.	D	.	D	.
Dose-response	Yes	No	No	No	Yes	No	Yes	Yes		Yes	Yes

^a MCV = motor nerve conduction velocity, DML = distal motor nerve latency, MAP = motor action potential, SCV = sensory nerve conduction velocity, SAP = sensory action potential, DSL = distal sensory latency, CVSF = conduction velocity of slow fibers.

can be detected in lead workers in whom available methods cannot detect impairment of the heme synthesis (74). But some of the investigators were unable to demonstrate any nerve conduction change in lead workers with blood lead levels predominantly between 60 and 80 $\mu\text{g}/100\text{ ml}$ (2.9–3.9 $\mu\text{mol/l}$) (61, 63, 88), nor could they find any correlation between a reduction in nerve conduction velocity and a number of biochemical measurements (blood lead, zinc protoporphyrin, aminolevulinic acid dehydratase, delta-aminolevulinic acid) (6). Buchthal found that, in individual lead smelter workers with blood lead levels at 70–144 $\mu\text{g}/100\text{ ml}$ (3.4–6.9 $\mu\text{mol/l}$), motor and sensory nerve conduction and the amplitude of sensory and motor responses were normal or borderline, while, in the group as a whole, the motor latency was longer and the average maximal sensory and motor conduction was slightly slower than in referents. There was neither a dose-effect relationship for the electroneurographic abnormalities nor any nerve fiber degeneration in teased sural nerve fibers. The slowing of nerve conduction seems to be due to a slight change in the properties of the nodal membrane that might prolong the rise time of the transmembrane potential (17). This possibility was supported by the observation that marked improvement in the motor nerve conduction velocity occurred in lead workers in a month following calcium-ethylenediaminetetraacetate injections (4). Whether the slowing of nerve conduction velocities in lead-exposed workers should be regarded as a warning sign of incipient neuropathy is still an open question.

Apart from the controversy on the effect of lead on nerve conduction, there has been some disagreement about the sensitivity of nerve conduction measurement at the early stage of toxic distal axonopathies. Because more than 50 % of the nerve fibers must be blocked or lost before the amplitude of the evoked action potential is outside normal limits. On the other hand, due to interindividual variation, the normal range of each electroneurographic parameter is wide. Therefore, in mild cases of toxic neuropathy, all such parameters might be below normal mean values but still within the normal range. The sensitivity of electroneurography as a screening tool is problematic (12, 95). In association with this problem Wennberg proposed a polyneuropathy index based upon ten different electroneurographic parameters of the median, peroneal, and sural nerves and found it more sensitive than a single parameter in the early diagnosis of axonopathy (95). The analysis of the response to pairs of stimuli also seems to be a more sensitive measure of axonal conduction deficit than is the determination of the single action potential, and it has been demonstrated to be sensitive in both segmental and axonal degeneration (12, 81).

H reflex velocity of the tibial nerve. Lukás used a two-point stimulation technique to investigate the conduction velocity of the H reflex, which is a classified

example of afferent fibers of the lower extremities. In two groups of patients exposed to carbon disulfide, the slowing of H reflex velocity appeared earlier than the decrease in the conduction velocity of motor nerve fibers, and it correlated with the exposure levels and the frequency of hyporeflexia or areflexia in the L5-S2 reflexes (54).

Quantitative sensory testing. Efforts are being directed towards developing a portable instrument for quantitative sensory testing to be used for screening for early evidence of dysfunction in the peripheral nervous system (5, 11). The modified Optacon, a simple battery-powered device which measures tactile and vibration threshold at the fingertip, has been used successfully in screening for some types of toxic neuropathy, such as acrylamide-induced polyneuropathy. When individuals are found to have a decreased perception of vibration, further study through the recording of sensory action potentials evoked by a probe designed to stimulate Pacinian corpuscles is recommended as a second level examination (12).

Biochemical testing

Delayed neuropathy induced by organophosphorous compounds results from inhibition of a neurotoxic esterase and is distinct from the acute effect. It has been proved that the inhibition of a neurotoxic esterase in the brain, spinal cord, and peripheral nerve in hens is dose-related. A neurotoxic esterase showing biochemical characteristics similar to brain neurotoxic esterase has been detected in peripheral lymphocytes in hens (39). This understanding permits the assessment of delayed neuropathic potential in terms of a quantitative measurement of the inhibition of neurotoxic esterase in human peripheral lymphocytes. Recently Lotti et al (52) used the measure of neurotoxic esterase inhibition in lymphocytes as a monitor for occupational exposure to the cotton defoliants S,S,S-triethylphosphorotriothioate (DEF) and merphos and found the neurotoxic esterase in lymphocytes of the exposed group inhibited at about 50 % of the preexposure value without any detectable electrophysiological effects. It appears that measurement of neurotoxic esterase in lymphocytes in workers exposed to organophosphate represents a rational biological monitoring method for organophosphates capable of producing delayed neuropathy.

Searching for toxic causes

The identification of a previously unknown neurotoxin in relation to toxic neuropathy is often based on the physician's vigilance in identifying occupationally related diseases, followed by an epidemiologic investigation giving clues of a possible causative agent and animal studies confirming the neurotoxic effects of the potential chemical.

There have been several outbreaks of occupational toxic neuropathies caused by, namely, methyl n-butyl ketone (3), n-hexane (87), allyl chloride (33), and DMAPN (43) in the last decade. Both epidemiologic investigations of humans and experimental studies of animals have greatly contributed to the identification of the etiology.

Role of epidemiologic investigation

A number of industrial chemicals were discovered to be neurotoxic in workplace epidemics. Through the characterization of the epidemic in terms of the latency period, the clinical syndrome, case attack rates, the identity, intensity, duration and scope of exposure, and a description of the natural history of the disease, etiologic hypotheses have been successfully derived (3, 18, 34, 43). Epidemiologic studies can also provide information concerning who should be protected first and what intervention schemes should be taken (46, 56, 71, 72). The following examples demonstrate the importance and effectiveness of the implementation of epidemiologic methods in the analysis of the outbreaks and the identification of major causal factors.

Methyl n-butyl ketone. An extensive neurotoxic outbreak resulted from the exposure of workers of a coated fabrics plant to the industrial solvent methyl n-butyl ketone in the United States in 1973 (3). The first case of polyneuropathy produced a list of five fellow workers with a similar condition from the same printing department. The factory was soon investigated. Through the screening of 1 157 employees with standardized diagnostic procedures, a total of 86 verified cases of a distal polyneuropathy was ultimately identified, including 37 subclinical cases. The results indicated that the printing area of the factory showed a high prevalence of polyneuropathy among the workers, and there was a strong correlation to the amount of exposure of the involved workers to the solvents. Further study revealed that the outbreak had occurred only after methyl n-butyl ketone had been introduced into the printing process. After elimination of the compound from the workplace, improvement was noted in the majority of cases. The techniques utilized in this investigation are generally held as a paradigm for the evaluation of an outbreak of neurotoxic disease.

Allyl chloride. Allyl chloride is a volatile chlorinated hydrocarbon liquid at room temperature and is commercially used as a raw material for manufacturing epichlorohydrin, epoxy resin, glycerin, pesticides such as Cartap (Parden), and sodium allyl sulfonate, which is one of the monomers of polyacrylonitrile (33, 34). No neurotoxic effect had been reported until two outbreaks of polyneuropathy due to exposure to allyl chloride in China in the early 1970s. Both groups of patients, one exposed to allyl chloride in a factory pro-

ducing sodium allyl sulfonate and the other in a plant manufacturing epichlorohydrin, showed distal and sensory polyneuropathy without liver or kidney dysfunction. Electromyographic abnormalities gave evidence of neuropathy in 10 of 19 examined subjects at a prevalence of 52.6 % in the former factory. Five patients who returned to work after apparent recovery had a relapse of polyneuropathy. Possible etiologic factors were excluded, except heavy exposure to allyl chloride. All the evidence obtained by the epidemiologic study indicated that allyl chloride was the causative agent of the polyneuropathy. The neurotoxicity of allyl chloride on the peripheral nervous system was further confirmed by neuropathological studies in rabbits and mice (32, 33).

Dimethylaminopropionitrile. Outbreaks of neurogenic dysfunction of the bladder occurred in two polyurethane foam factories in the United States in 1978 (41, 43). In one of the factories a neurogenic bladder dysfunction characterized by hesitancy, need to strain, decreased stream, and increased duration of urination developed in 104 (63 %) of 166 employees, the highest rate of illness (69 %) occurring among production workers and no case in office or warehouse workers. The onset of the epidemic coincided with the introduction of a catalyst, DMAPN, and monthly case incidence rates increased as DMAPN use increased. The outbreak ceased abruptly when DMAPN use was stopped. DMAPN has been added to the list of neurotoxins and is unique in producing urinary symptoms among known neurotoxins (42, 43).

Experimental investigations

Morphological approach. In contrast to the limitations of nerve biopsy and postmortem techniques in determining human toxic neuropathies, it is possible to detect the neurotoxicity of suspected chemicals and find morphological evidence in experimental animal studies. The findings from the animal studies with most neurotoxins, except arsenic and thallium, often correlate closely with the human clinical phenomenon. In some instances, such as in lead and methylmercury poisonings, species differences lead to important differences in the way nerves of humans behave from those of some experimental animals.

In addition to acrylamide (49), n-hexane (36, 87), methyl n-butyl ketone (3), allyl chloride (32), carbon disulfide (9, 31), and DMAPN (64) have been confirmed to be neurotoxins by neuropathological studies of experimental animals, and they have been identified as occupational hazards to the peripheral nervous system in the last decade. These animal models show similar clinicopathological correlations and provide a clear picture of a central-peripheral distal axonopathy as described by Spencer & Schaumburg (83, 84). This phenomenon is due largely to the use of contemporary morphological techniques (perfusion fixation with

buffered glutaraldehyde, postfixation in osmium tetroxide, thin plastic sections, etc) to identify the primary lesion site from the spatial temporal sequence of neuropathological events.

Electrophysiological investigation. Electrophysiological techniques have been used with varying degrees of success to detect the neurotoxicity of industrial chemicals in experimental animals. These tests can then be correlated with detailed pathological studies and therefore help in the interpretation of similar tests in humans. He et al (32, 33) dosed rabbits with allyl chloride and found a peripheral neuropathy with electromyographic abnormalities consisting of positive waves, fibrillation potentials, and pseudomyotonic potentials at the fifth or sixth week of dosing. These findings are consistent with the electromyographic changes observed in workers exposed to allyl chloride and the pathological changes of axonopathy seen in both rabbits and mice (32, 33). However, the use of electromyographic methods for evaluating neurotoxicity in experimental animals has not been great because it is difficult to control the degree of muscle contraction in some animals. On the other hand, maximal motor nerve conduction velocity has been more often applied either in short-term investigations to obtain useful information on peripheral nerves prior to any histological evidence of damage (65) or in long-term investigations to show the time of onset of any incidence of neurotoxicity and a correlation with histological changes (37).

Responsible neurotoxic metabolites. The discovery of the neurotoxic metabolites responsible for the toxic neuropathy produced by industrial chemicals can be well illustrated by the good example of hexacarbon metabolism. On the basis of data obtained from animal experimentation, it is clear that n-hexane and methyl n-butyl ketone share the common neurotoxic metabolites 2-hexanol and 2,5-hexanedione, etc (22, 36, 87). These metabolites, particularly 2,5-hexanedione, appear to mediate the neurotoxic syndrome of the central-peripheral distal axonopathy caused by hexacarbon. This phenomenon could well explain the resemblance of the clinical syndrome produced by n-hexane and methyl n-butyl ketone and the similarity of the pathological process induced in the peripheral nervous system (22, 36, 87).

Biochemical methods for detecting neurotoxicity. The measurement of beta-glucuronidase and beta-galactosidase in posterior tibial nerves appears to offer a useful method for detecting chemically induced degeneration in the peripheral nervous system, as the increase of the enzyme activity is related to the dose of the methylmercuric chloride or acrylamide administered. But it is unlikely that biochemical methods can play a major role in the first detection of unknown transient neurotoxicologic effects (24).

ADVANCES IN THE UNDERSTANDING OF THE PATHOGENESIS

Cellular targets and central-peripheral distal axonopathy

Experimental studies with laboratory species have demonstrated that most toxic neuropathies involve a distal axonal degeneration that advances in a centripetal or "dying back" manner. Despite the observation that neuronal perikarya commonly remain intact in these examples of toxic neuropathy, it was widely believed that the nerve cell body would be the site of vulnerability to toxic attack and that the effect of metabolic derangement of the neuron perikaryon would occur first in the regions most remote from the cell body. In other words, it was believed that degeneration would commence in the nerve terminal and march steadily up affected fibers with the degree of neuronal impairment (19, 85).

Spencer & Schaumburg (83) have demonstrated that for hexacarbon neuropathy this phenomenon takes the form of a progressive multifocal preterminal axonal degeneration. Focal accumulations of neurofilaments are observed on the proximal sites of the nodes of Ranvier, associated with which there is secondary demyelination. Affected axons may undergo regeneration after distal Wallerian-like degeneration. No metabolic compromise of the neuronal perikaryon has been seen. All these observations raise the possibility that these toxins selectively affect the distal parts of the axons and induce distal axonopathy.

Neuropathies induced by carbon disulfide (9, 31), allyl chloride (32), and acrylamide (49) are also characterized by a similar distal multifocal pattern of axonal degeneration with axonal filamentous accumulations. The axonopathies produced by organophosphorus (tri-o-cresylphosphate, di-isopropylfluorophosphate) are distal and multifocal too. Ultrastructurally distal axons contain an accumulation or proliferation of smooth-walled endoplasmic reticulum (14, 15). These toxic distal axonopathies commonly give rise to a simultaneous degeneration that affects both the peripheral nervous system and central long tracts. In relation to the primary sensory neurons, there is a distal degeneration of the distal portions of both the centrally and peripherally directed axons. This phenomenon has been termed central-peripheral distal axonopathy by Spencer & Schaumburg (83, 84, 89). The explanation for this selective effect is so far obscure.

On the basis of the cellular or subcellular target sites, Spencer & Schaumburg (84, 86) have suggested a new approach to defining and classifying neurotoxic disease. Some examples of the primary structural changes occur in the nerve cell body (followed by axonal degeneration or loss of the whole neuron) (neuronopathy), in the ensheathing cell and myelin sheath (myelinopathy), or in the vasculature (neurovasculopathy). Those that directly affect the axons produce

axonopathies, which can be classified as proximal, central-distal, or central-peripheral distal axonopathy on the basis of topographical relationships. As previously described, the commonest type of toxic neuropathy is central-peripheral distal axonopathy, which can be subdivided into the filamentous or tubulovesicular types based on the early ultrastructural changes that occur in the axon. A selected list of industrial and agricultural chemicals affecting different cell targets and producing damage to the peripheral nervous system is shown in table 2.

Axonal transport and distal axonopathy

Clinically many chemically unrelated neurotoxic compounds cause a strikingly similar pattern of distal symmetrical polyneuropathy in humans and animals. Structurally many toxic agents cause distal axonopathies with a selective accumulation of neurofilaments in the distal axons. The mechanism of the distal degeneration in distal axonopathies with filamentous accumulation is still uncertain. It has been demonstrated that slow antegrade transport of protein through the axoplasm with migration rates at 0.6—2.5 mm/d is associated with microtubules and microfilaments. Glycoproteins and phospholipids, which are transported with fast antegrade transport through the axoplasm at rates of 200—400 mm/d, are mainly associated with membranes of the smooth endoplasmic reticulum of the axons. Retrograde axonal transport drives membrane-associated macromolecules, which are distinct from the smooth endoplasmic reticulum, from the presynaptic nerve endings at rates of 150—250 mm/d (25, 26, 44).

Investigations on the axonal flow of labeled protein in hexacarbon neuropathy show that slow axonal transport is impaired with a secondary focal slowing of fast axonal transport (82). In acrylamide intoxication the slow transport components appear not to be affected, while there are local disturbances of the fast transport in distal parts of the axon. A slow axoplasmic flow of proteins also persists in cats intoxicated with tri-*o*-cresylphosphate, and there are marked focal accumulations of membranes of endoplasmic reticulum along the axon (25, 26, 44).

Spencer et al (82) postulated that an interference with glycolysis through an inhibition of the enzymes glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and phosphofructokinase (PEK) might be involved and related to an impairment of axonal transport, as the activity of these enzymes is reduced in neuropathies induced by hexacarbon, acrylamide, and carbon disulfide. This possibility points to a common metabolic basis for many distal axonopathies, ie, that neurotoxic compounds deplete energy supplies in the axon by inhibiting nerve fiber enzymes required for the maintenance of energy synthesis and lead to a local blockade of energy-dependent axonal transport (68,

Table 2. Selected list of industrial toxic chemicals producing structural damage in the peripheral nervous system (32, 45, 83, 84, 86).

Structural lesion	Industrial and agricultural chemicals
Neuronopathy	
Cytoplasmic	Organic mercury
Axonopathy	Arsenic
	Thallium
	Ethylene oxide
Central-peripheral	
Filamentous	Acrylamide
	Allyl chloride
	Carbon disulfide
	Dimethylaminopropionitrile (DMAPN)
	n-Hexane
	Methyl n-butyl ketone (MnBK)
	Organophosphate (tri- <i>o</i> -cresylphosphate, leptophos)
Tubulovesicular	Lead?
Myelinopathy	Lead?
Neurovasculopathy	Lead?

82). However it is not known whether the delay of axonal transport is the primary defect, as it develops at the same time as the appearance of the morphological lesions in hexacarbon-induced neuropathy (44). A further possibility of axonal filamentous accumulation is cross-linking between neurofilaments so that they form adherent masses that become plugged on the proximal sides of the nodes of Ranvier and, in this manner, lead to degeneration more distally (29). One explanation for a selective effect on large fibers in these neuropathies could therefore be the relatively greater degree of axonal narrowing at the nodes of Ranvier on such fibers (89).

Neurotoxic esterase and delayed organophosphorous neuropathy

Some organophosphorous esters produce delayed neuropathy, which is a different toxic effect entirely unrelated to the inhibition of acetylcholinesterase at nerve endings. The neurotoxic effects are not seen until 8—14 d after exposure to the toxic agent. Cases of delayed neurotoxicity in humans have been reported for several organophosphorous compounds (52) including tri-*o*-cresylphosphate, mipofox, trichlorphon, trichlorate, *o*-ethyl-*o*-*p*-nitrophenyl benzene thio-phosphonate, leptophos, tamaron, and divipan (93). Some of these cases resulted from accidental exposure, others from occupational exposure (52).

The molecular mechanism of the initiation of organophosphorus-induced neuropathy has been extensively studied and recently reviewed (1, 39). Johnson (39) indicated that the initial biochemical steps in the development of delayed neurotoxicity involve another esterase in the brain, spinal cord, and peripheral nerves, one that is distinct from acetylcholinesterase. But the inhibition of this enzyme, known as neurotoxic protein or neurotoxic esterase (NTE) is not alone sufficient to initiate the biological changes leading to the axonal degeneration. A further obliga-

tory step, ageing, must take place, leaving a negatively charged phosphorus group attached to the esterase, which is itself tightly bound to membranous material in the nervous system.

Studies on the relationship between the chemical structure of organophosphorous esters and their neurotoxic potencies suggest that two hydrophobic areas may be present in the vicinity of the active site of the neurotoxic protein (1). Abou-Donia (1) postulated that delayed neurotoxic organophosphorous esters phosphorylate the active center of neurotoxic target proteins in the axon. The proteins have functions related to energy supplies for normal axoplasmic transport. Such phosphorylation would result in a localized disruption of axoplasmic transport and the accumulation of mitochondria at the distal parts of the axons. Broken down mitochondria will release calcium ion into the axoplasm. This occurrence disrupts the membrane control mechanism regulating intracellular-extracellular ionic gradients and leads to focal swelling in internodes followed by focal degeneration that spreads somatofugally to involve the entire distal axon.

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