Occupational Peripheral Neuropathies

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Neither clinical nor laboratory evaluation can distinguish occupational neuropathies from neuropathies due to other causes. A worker may suffer either from mechanical injury of individual nerves or from a toxic polyneuropathy that is usually axonal in type. A thorough occupational and environmental history and the recognition of clusters of cases are important in determining the diagnosis. Electrophysiologic studies are helpful in detecting neuropathies in patients who have been occupationally exposed to neurotoxins but have no symptoms. Prevention of occupational neuropathies depends on clinical vigilance, industrial hygiene surveys, biologic monitoring and periodic examination of workers exposed to neurotoxic chemicals. The development of more sophisticated methods of prevention and early detection of peripheral nerve involvement depend on understanding the mechanisms of action of toxins and the pathophysiology of the lesions they cause.

These then are the diseases that afflict men who handle lead when they work in the potter's shops. . . . Lead thought by nature chilly when pounded by that mass of stone, flares up into heat against its tormentors, sprinkles the potters with that cursed poison, carries numbness into their blood spirits, and crucifies their hands.

BERNARDINO RAMAZZINI
Diseases of Workers, 1713[1]

The risks associated with the use of lead are now well recognized, and the characteristic occupational peripheral neuropathy produced by lead is now fortunately extremely rare. Nevertheless, chronic lead exposure still represents an occupational hazard. Subtle changes in peripheral nerve function, detectable by means of electrophysiologic tests, have been found in subjects with very low levels of lead exposure.[2] The significance of these changes is debatable.[3]

Recent developments indicate that occupationally related neuropathies are still being seen by neurologists and general practitioners. New chemicals used in industrial environments may cause peripheral neuropathies to occur in clusters of exposed workers. In 1975, for example, a mysterious neurologic disorder was identified in workers at a chemical plant in Virginia[4] and traced to chlordecone (Kepone), a chlorinated insecticide. The severity of the symptoms was directly related to the dose and duration of exposure. Another example occurred in the fall of 1977, when workers at a polyurethane manufacturing plant began to have difficulty in urination.[5] The most severely affected workers had neurogenic bladders confirmed by cystometrograms and mild sensory peripheral neuropathy. A survey of the plant workers disclosed an increased incidence of urinary retention, muscle weakness, parethesias, insomnia and sexual dysfunction. Once the onset of the epidemic was recognized, a new catalyst, dimethylaminoproprionitrile, was identified as its cause.

When abused or used in a unique way, some chemicals generally regarded as harmless may cause occupational peripheral neuropathies. In 1978 three patients (two dentists and one technician) seen at the University of California, San Francisco, had sensorimotor polyneuropathy combined with signs of involvement of the posterior and lateral columns of the spinal cord.[6,7] Electrodiagnostic tests showed evidence of axonal polyneuropathy, but other laboratory tests showed no abnormalities. The only common factor in these cases was exposure to nitrous oxide. Ensuing publicity led to the recognition that a number of other patients had similar disorders. There is no proof that nitrous oxide was the

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cause of the myeloneuropathy in these patients, but indirect evidence strongly favored that conclusion.

Occupational neuropathies are often missed because the causal agent is overlooked in the formulation of the differential diagnosis. In January 1976 an outbreak of neurologic disease occurred in a chemical manufacturing plant in Texas[8] where a number of potentially injurious chemicals was used in the formation of a potent neurotoxic organophosphate, leptophos. Signs of peripheral and central nervous system toxicity were evident. Because blood cholinesterase levels were within normal limits, physicians did not initially appreciate the occupational origin of the symptoms, but attributed them to other disorders. Only retrospectively was this epidemic found to be related to exposure to leptophos and possibly to n-hexane.

Assessing peripheral nervous system function in workers may serve two purposes: to identify the chemicals that are neurotoxic to humans and to determine the level of exposure compatible with the safe handling of a potentially neurotoxic chemical.

Discovering the cause of a patient's peripheral neuropathy can be difficult. Alcoholism, diabetes mellitus, uremia and malignant disease, among other disorders, may cause peripheral neuropathy, but in approximately 25 percent to 50 percent of cases no specific cause can be found. For this reason it is important to appreciate that workplace exposure to some toxic substance may have injured the peripheral nerves. Common chemical substances that are known to be toxic to the peripheral nervous system in an occupational setting are listed in Table 1.

The purpose of this paper is to review the clinical and laboratory findings that may lead to a diagnosis of occupational peripheral neuropathy. Prevention of these neuropathies may be accomplished through the detection of workers at special risk, the monitoring of the environment, the biochemical and physiologic monitoring of exposed subjects, and the understanding of the mechanisms of toxicity.

Clinical Aspects

The clinical manifestations of peripheral nerve pathology are well recognized. Involvement of sensory fibers may lead to pain, paresthesias, hyperpathia, numbness, loss of sensation or a sensory ataxia (or combinations of these), whereas disturbed function of motor fibers may cause weakness and wasting of muscles. The tendon reflexes may be lost with damage to either afferent or efferent fibers subserving the reflex arcs. Occupational neuropathies do not differ clinically from neuropathies of other origins, but occupational history and clusters of cases may help in suggesting the underlying cause. Early detection of a single case is important not only in order that the individual patient may be shielded from further exposure to the toxic environment but also so that neuropathy may be prevented in other workers.

An occupationally related peripheral nerve lesion may result from compression or other forms of physical injury to individual nerves. Clinical findings of weakness and sensory impairment depend on the affected nerve. Severe compression or nerve transection leads to Wallerian degeneration of axon and myelin distal to the lesion, and results in wasting as well as weakness of affected muscles. Recovery is likely to be slow and is often incomplete. Mild compression leads to segmen-

TABLE 1.—*Substances Causing Occupational Peripheral Neuropathies**

Substance	*Uses/Industry*	*Reference*†
Metals		
Lead	Smelting, paint, inks, ceramics, plastics, batteries	2,3
Arsenic	Pigment production, by-product of smelting, pesticide	9
Mercury (inorganic)	Mercury cell chlorine plants, electrical apparatus, dentistry	10
Solvents		
Hexacarbons (MBK, n-hexane)	Glues, inks, shoe industry	11
Trichloroethylene	Dry cleaning, rubber production, degreasing agent	12
Carbon disulfide	Viscose-rayon production, laboratory solvent	13
Gases		
Methyl bromide	Fire extinguishers, refrigerants, fumigants, insecticides	14
Nitrous oxide	Anesthetic	6,7
Pesticides/Herbicides		
Chlordecone	Pesticide	4
Some organophosphates	Pesticides (hydraulic fluids and plastificants)	8,15
2,4-Dichlorophenoxy acetic acid	Herbicide	16
Plastics		
Acrylamide (monomer)	Waterproofing polymers, production in paper manufacture	17
Dimethylaminoproprionitrile	Catalyst in polyurethane manufacturing	5
Styrene	Production of plastics and resins	18

MBK = methyl butyl ketone.

*Environmental chemicals and drugs with neurotoxicities that are not directly related to occupational exposures have been excluded.

†The most comprehensive reference is *Experimental and Clinical Neurotoxicology* by P. Spencer and H. H. Schaumburg, (Williams & Wilkins, Baltimore) 1980. The references listed here have been chosen because they are recent, comprehensive or useful.

tal demyelination. There is no wasting of weakened muscles and recovery is rapid once the compression is relieved. Examples of such occupationally related compressive neuropathies include the anterior interosseous nerve syndrome in manual workers, ulnar nerve palsy in sedentary workers who constantly lean on the elbow, ulnar nerve lesion in the hand after recurrent mechanical trauma to the palm (for example, in operators of pneumatic drills and in those who repeatedly use shears or bang on staplers or other appliances with the palm), digital neuropathy with repeated pressure from instruments such as scissors, sciatic nerve lesions in harvesters, and peroneal nerve palsy in those who sit with crossed legs for long periods or are required to squat, as when picking strawberries.

It is more common for occupationally related hazards to lead to a polyneuropathy—that is, the symmetrical involvement of a number of peripheral nerves. Polyneuropathies may result from pathologic involvement of neurons (axonal neuropathies) or Schwann's cells (demyelinating neuropathies). Occupational toxic neuropathies are usually of axonal type and are characterized by degeneration of either the axon or the entire cell. The clinical features will differ depending on whether the predominant involvement is of sensory or motor fibers or whether there is mixed involvement of different fibers. Autonomic function is usually not affected to any great extent in occupational neuropathy; however, abdominal pain is associated with lead poisoning and bladder problems have been reported with exposure to dimethylaminoproprionitrile.

In the case of a mixed sensorimotor polyneuropathy there is usually symmetrical sensory loss, weakness and depressed or absent tendon reflexes. The clinical deficit commences distally in the extremities. It is usually more severe in the legs than in the arms, presumably because the longest axons are affected first. In some toxic neuropathies, however, motor function is affected disproportionately as, for example, in lead neuropathy or the neuropathy due to gasoline sniffing.[19] Conversely, in other conditions it is the sensory deficit that is conspicuous. Pain may be especially troublesome, for example, in the neuropathy due to arsenic. Even mild toxic polyneuropathy may predispose a patient to secondary disease of the peripheral nervous system, such as to an entrapment neuropathy. Thus, patients with a toxic polyneuropathy may, for example, present the clinical features of a carpal tunnel syndrome with little clinical evidence of more widespread pathology. Cranial nerve involvement may be conspicuous in trichlorethylene-induced neuropathy,[12] whereas a myelopathy may be a pronounced additional feature of the neurologic disorder produced by nitrous oxide[6,7] or organophosphates such as triorthocresylphosphate.[15]

Laboratory investigations can exclude other known causes of peripheral neuropathy. Nerve biopsy is rarely necessary to make the diagnosis, but it may be helpful in defining the underlying pathologic condition, especially if a connective tissue or arteritic disorder is suspected. A biopsy can also quantitate any structural changes that are present.

Electrophysiologic evaluation of a patient in whom peripheral neuropathy is suspected requires expensive equipment and the expertise of a clinical neurophysiologist, but it does have certain specific advantages:

1. It can provide objective evidence of peripheral nerve involvement and indicate the extent and severity of such involvement. This is particularly useful when clinical examination is difficult or clinical findings are relatively inconspicuous. The findings may help in distinguishing weakness or sensory symptoms due to peripheral nerve dysfunction from those due to other causes.

2. Nerve conduction studies provide quantifiable data. Comparisons are possible between groups of subjects or between data obtained from the same subject at different times.

3. Such studies can be used to identify a focal lesion of an individual peripheral nerve. This is important because many focal entrapment neuropathies may be related to occupational factors.

4. In patients with a mononeuropathy, electrophysiologic studies can indicate whether or not there is an underlying subclinical polyneuropathy that has rendered the individual nerves more susceptible to pressure or other injuries.

5. The electrophysiologic findings may indicate whether or not the predominant pathologic disturbance is axonal degeneration or segmental demyelination.

6. Nerve conduction studies are useful in epidemiologic surveys as a means of detecting heterogenicity among cases that are clinically similar. Electrophysiologic abnormalities may be detected at a time when there is no clinical evidence of peripheral neuropathy.[9]

The principles underlying nerve conduction studies are simple. If a record is made of the electric response of the muscle—that is, the compound muscle action potential—to supramaximal stimulation of its motor nerve at two points along its course, terminal motor latency and maximal motor conduction velocity along the intervening segment of the nerve may be calculated. Similarly, maximal conduction velocity and amplitude of the action potential in sensory nerves can be measured by stimulating such nerves at one point and recording from them at another. Aminoff summarizes the technical details of these methods.[20] There is, as yet, no simple and convenient method for the routine study of conduction in the most slowly conducting fibers of nerves.

Conduction velocities are reduced to a pronounced degree in the Guillain-Barré syndrome and certain hereditary or familial disorders, whereas mild slowing of conduction is found in the neuropathies associated with diabetes, uremia and certain nutritional disorders. Conduction velocity is normal or only minimally reduced when the predominant pathology is axonal degeneration rather than segmental demyelination; consequently it is usually normal in the toxic neuropathies. In such circumstances, however, the compound muscle action potential or the sensory action potential may be abnormally small because of the reduction in the number of

functional axons. If results of nerve conduction studies are completely normal, the sole electrophysiologic evidence of peripheral nerve damage may be that derived from needle electromyography. This technique will show signs of denervation in muscles supplied by affected nerves if axonal degeneration has occurred. In resting muscle, abnormal spontaneous activity, consisting of fibrillation, positive sharp waves and bizarre high frequency potentials, is found, and fasciculation potentials are occasionally encountered. During active contraction of the muscle, the number of motor units is reduced and when reinnervation of muscle fibers has occurred by collateral sprouting from surviving axons, an increased number of long duration, high amplitude and polyphasic motor units may be found.

In patients with a simple focal or entrapment neuropathy, the electrophysiologic findings are confined to the distribution of the affected nerve. There may be disproportionate slowing of nerve conduction velocity across the site of the lesion and a drop in size of the compound muscle action potential elicited by stimulating the nerve proximal to the lesion. Such findings may be superimposed on more diffuse abnormalities in those persons with clinical or subclinical polyneuropathy.

In screening patients with subclinical or minimal involvement of peripheral nerves, the most sensitive electrophysiologic means for showing any involvement will depend on the nature of the underlying disorder. Maximal motor conduction velocity is easy to determine but is often normal even in patients with clinically evident toxic neuropathy because the usual pathologic basis of the neuropathy is axonal degeneration. However, in the toxic neuropathy produced by methyl butyl ketone and some hexacarbon solvents, motor conduction velocity may be greatly reduced. Thus, in a case of n-hexane neuropathy due to glue sniffing, Korobkin and associates found delayed motor conduction velocity in the median, ulnar and peroneal nerves.[21] Nevertheless, a finding of motor conduction velocities within the normal range does not exclude the possibility of a mild neuropathy even in patients exposed to methyl butyl ketone.[22]

In neuropathy caused by exposure to acrylamide, maximal motor conduction velocity is usually within normal limits,[23] but sensory nerve action potential may be small or absent when recorded at the wrist in response to stimulation of the digital fibers of the median nerve. In cases of organophosphate neuropathy, measurement of the amplitude of sensory nerve action potential is also a very sensitive electrophysiologic screening test, although in the established neuropathy a motor deficit is conspicuous clinically while sensory findings may be minimal.[24]

Roberts[25] suggested that variation in size of the compound muscle action potential is a sensitive indicator of exposure to organophosphate compounds, but other investigators have not been able to confirm this finding.[26-28]

The prognosis for recovery from a toxic axonal neuropathy depends on the underlying cause. If exposure to the toxic substance is discontinued, further progression of the neuropathy may be halted, but any recovery is usually slow and often incomplete. Moreover, as recovery occurs in the peripheral nervous system, previously masked evidence of central involvement, such as pyramidal (corticospinal) signs, may become apparent.

Methods of Prevention

Studies in Animals

The prevention of peripheral neuropathies of occupational origin is accomplished by setting a "no adverse effect" threshold level of exposure. These thresholds are set after animal testing and are then subject to continuous revision on the basis of clinical and toxicologic observations in humans.[29] Neurotoxicology studies in animals are particularly difficult to interpret because the choice of an appropriate animal model is more critical than in other toxicity studies. Some chemicals—for example, arsenic—may cause peripheral neuropathy only in humans,[30] whereas others—such as cadmium—produce peripheral neuropathy only in animals.[31] Certain chemicals are toxic to humans and only to certain species of animals. For example, organophosphates cause peripheral neuropathy in humans and hens but not in rodents.[15] Finally, certain metals like lead cause neuropathy both in animals and humans, but its pathologic basis in experimental animals differs from that in humans.[32]

The observation of humans exposed to potential toxins is difficult. Peripheral neuropathy is a disease with an insidious onset and with clinical features that do not differentiate the cause of the disease. Underlying disease and other chemicals may also affect the pathogenesis of occupational neuropathy caused by low and prolonged exposure to toxic substances in the workplace. Animal studies of neurotoxicity are therefore necessary not only for defining any toxic effect but also for determining its mechanisms; in this way it may be possible to set no-effect levels of exposure in a more rational way.

Studies using animals provide key information about the metabolism of a chemical and about the mechanism of its action. Two examples of the successful application of findings from animals to occupational medicine are of note. Two hexacarbon solvents that have been used in many industries are n-hexane and methyl butyl ketone. In the early 1960's, outbreaks of neuropathies in Japan and Italy were related to n-hexane. Studies noted the structural similarity between n-hexane and methyl butyl ketone, suggesting the possibility of a common neurotoxic metabolite. Experimental studies in animals on the metabolism of methyl butyl ketone and n-hexane showed several intermediate metabolites with a common toxic metabolite, 2,5-hexanedione. Later, researchers using closely related compounds in which the carbonyl groups occupied different positions on the six carbon chain were unable to induce neuropathy; the neurotoxic property of 2,5-hexanedione is associated with the 1-4 spacing of the ketone groups. Because 2,5-heptanedione and 2,5-octanedione were also shown to induce the same type of experimental

neuropathy, it was suggested that the term "diketone neuropathy" be used to describe this type of neurotoxicity.[11] Similar patterns of n-hexane metabolites have been detected in the urine of workers exposed to commercial n-hexane. Thus 2-hexanol, 2,5-hexanedione, 2,5-dimethylfuran and γ-valerolactone were found as n-hexane metabolites in urine: the first two of these metabolites were positively correlated with the intensity of the exposure.[33] These results suggest that urinary excretion of hexane metabolites may be used for monitoring occupational exposure to n-hexane; the urinary level of the metabolites that is associated with a neurotoxic effect is unknown.

Two general principles emerge from these metabolism studies. First, primary prevention—that is, prevention of exposure—can be accomplished by understanding structure-activity relationships. Second, secondary prevention—prevention of toxicity by minimizing exposure—can be facilitated by the use of methods for detecting metabolites in human urine.

Another example of the relevance of animal studies to the prevention of occupational neuropathies is the case of the organophosphorus esters. Organophosphorus esters vary in their toxicity to the nervous system. The most extensively studied effect is acute toxicity, which is related to inhibition of acetylcholinesterase. However, another form of toxicity that is not related to cholinesterase inhibition is caused by some organophosphates and is called organophosphorus-induced delayed neuropathy. The primary molecular target of this form of toxicity has been identified as another esterase in nervous tissue called neurotoxic esterase. The mechanism of organophosphorus-induced delayed neuropathy is complicated, and inhibition of neurotoxic esterase is only the first step in its production.[15] These studies made possible the distinction of organophosphates with high neurotoxic potential from those with a negligible one on the basis of their affinity for neurotoxic esterase.

Organophosphates are commonly used as pesticides and their potency as anticholinesterase agents is an absolute requirement for their pesticide action, whereas an ability to phosphorylate neurotoxic esterase is not. Appreciation of the molecular targets allows accurate studies of the relationship of structure to activity and the development of organophosphates with restricted toxicity to humans.[34] Recently, in a study of this enzyme in tissues of experimental animals, neurotoxic esterase was discovered in lymphatic tissue and in circulating peripheral lymphocytes.[35] This observation suggests the possibility of monitoring exposure to neurotoxic organophosphates by measuring neurotoxic esterase in peripheral lymphocytes. Because lymphocyte neurotoxic esterase correlates with the level of inhibition in the target organ, such measurements may provide a clinical test that will reflect the interaction of a chemical with its molecular targets. Such a study was recently performed and the results indicate that the test is feasible in humans but not yet proved to be of immediate use in the setting of clinical or occupational medicine.[28]

Industrial Hygiene and Toxicology

Measurement of environmental levels of toxic chemicals and maintenance of these chemicals at safe levels are essential in preventing occupational neuropathies. Workers can also be monitored directly.

Recognition of high-risk workers. There is a debate on the emphasis that should be put on tests for identifying subjects who might be at particular risk in occupational exposures.[36] The main concern in developing such an approach is that it may lead to excluding hypersusceptible subjects from the workplace rather than attempting to clean up the environment. In general, diabetic and alcoholic workers and those with other disorders known to affect the peripheral nerves could conceivably be more susceptible to the development of a toxic peripheral neuropathy than normal workers.

Tests of exposure. These tests are based on empiric correlation between the level of certain toxins in blood or urine and the toxic effect. One of the chemicals most frequently studied is lead, the blood concentration usually being taken to indicate the severity of exposure of industrial workers. However, the blood level of a chemical does not differentiate workers with peripheral neuropathy from those without. Recently, Seppäläinen and associates[2] suggested that subclinical changes can be detected electrophysiologically in workers with blood levels of lead below 50 μg per dl, which has previously been considered a "safe" level. These results have, however, been questioned by Buchthal and Behse.[3]

Exposure tests such as the blood concentration of lead may therefore not be accurate in predicting the likelihood of developing peripheral neuropathy. They may be useful in establishing a dose-effect relationship in exposed workers when accurate and early biochemical or physiologic changes are available as an endpoint.

Tests of target response. Another series of tests are based on studies concerning interaction of the chemical with its molecular target; unfortunately, these tests of neurotoxicity are not available as they are for other target systems (for example, porphyrins for lead toxicity to the heme). If the neurotoxic esterase test for orthophosphorus-induced delayed neuropathy proves to be clinically useful, it will represent the first response test available in occupational medicine for studying peripheral neuropathies.

Methods for detection. A fourth group includes tests for early or subclinical diagnosis of the neuropathy by means of the electrophysiologic techniques described earlier.

Future advances in the comprehension of the pathophysiologic basis of peripheral neuropathies may well lead to the development of other more sophisticated measures of early detection at a subclinical level.

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New Training Opportunities in Occupational Health

Approved residency training in occupational medicine is offered at several institutions in the western states: In Northern California (a collaborative effort of the University of California School of Public Health at Berkeley and the School of Medicine at San Francisco), in Southern California (a collaboration of the University of California College of Medicine at Irvine and the UCLA School of Public Health), at Salt Lake City (University of Utah Medical Center) and at Tucson (University of Arizona Health Sciences Center). A new program is under review at the University of Washington School of Public Health and Community Medicine at Seattle. All of these are supported in part by the National Institute of Occupational Safety and Health through Educational Research Center grants.

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