

HUMAN TOXIC NEUROPATHY DUE TO INDUSTRIAL AGENTS

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Identification of Toxic Peripheral Neuropathies

Despite widespread media attention to their rare epidemic occurrence, toxic polyneuropathies (TxPN) are relatively infrequent in North America. Most TxPN encountered in routine clinical practice are due to iatrogenic pharmaceutical intoxications; epidemic occupational exposure, as with large pharmaceutical companies, is unusual. The majority, and unfortunately the most difficult, cases of TxPN are individual intoxications due to small scale, often chance, occupational exposures, or intentional and homicidal ingestion.

The identification that a sporadic peripheral neuropathy results from toxin exposure in the occupational setting is often made difficult by an unclear exposure history. TxPN are usually distal axonopathies and clinically and electrophysiologically resemble neuropathies from metabolic abnormalities, nutritional deficiencies, or systemic illness. Clinically relevant and reliable toxicologic tests are often unavailable or unhelpful, either because the necessary laboratory tests are not available, or the substance is undetectable because of the delay between exposure and examination. Consequently, when a naturally occurring medical cause is not *readily* apparent, there is an unfortunate tendency for many peripheral neuropathies to be misdiagnosed as toxic in nature. As a result, cases of naturally occurring PN are more often misdiagnosed as being toxic in nature, than the reverse,

The underlying pathology of many TxPN is the central-peripheral axonopathy¹. Initial exposure results in degeneration of distal peripheral sensory and motor axons. With continued exposure and worsening of the neuropathy, similar changes occur in the distal segments of dorsal column, corticospinal and spinocerebellar tract axons. Initial clinical symptoms reflect dysfunction in peripheral axons. As the peripheral nerves recover however, signs of central nervous system impairment such as spasticity, mild ataxia, and persistent sensory loss may be evident. These latter deficits result from the lack of regeneration in central sensory and motor tracts.

Our limited knowledge of the biochemical and pathophysiologic mechanisms of most neurotoxins has led to a simplistic classification system according to compound class (e.g. solvents, metals). Such a classification is clinically unhelpful and potentially misleading. A compound cannot be presumed to be neurotoxic because of a superficial

resemblance to a related known toxin of similar class; all compounds within the same class are not neurotoxic (e.g. acrylamide monomer is capable of producing a devastating peripheral neuropathy, while the polymer is innocuous). Structure-toxicity relationships are clear for only a few classes of substances, such as organophosphates and hydrocarbons.

Cardinal Tenets of Neurotoxic Illness Affecting The Peripheral Nervous System

The identification of a neurotoxic illness should satisfy, or at least not be inconsistent, with the following basic principals of neurotoxic disease. The key to correctly recognizing the presence of a TxPN is not remembering the characteristics of the many potential neurotoxins, but in understanding and applying these basic tenets².

a. Strong Dose-Response Relationship

Most neurotoxins produce a consistent pattern of disease, commensurate with the dose and duration of exposure. Neurotoxins rarely cause focal or asymmetric deficits. Since most neurotoxins cause diffuse myelin and/or neuronal dysfunction, their related symptoms and signs are usually widespread and symmetric. In the case of TxPN, this usually means a relatively symmetric distal axonopathy with initial symptoms in the feet and proximal progression, with continued exposure, Only rarely does an occasional toxin cause strikingly asymmetric or focal dysfunction (e.g. trichloroethylene³)

b. Consistency of Response

All individuals with similar exposure to the same neurotoxin will invariably manifest similar signs and symptoms, if the chemical enters the circulation, and the agent, its metabolite or intermediate, has similar access to the nervous system. Although the same toxin may produce strikingly different clinical syndromes if the exposure dose or duration is different, a similar and consistent illness should result in patients with similar exposures. There is usually no individual susceptibility or idiosyncratic reactions, if dose and duration of exposure are similar. A neuropathy is unlikely to be neurotoxic if it occurs in only one member of a group with similar exposure history. Likewise, neurotoxicity should also be doubted when substantially different clinical manifestations occur in a group of individuals with identical chemical exposure.

c. Proximity of Symptoms to Exposure

Neurotoxic illness usually occurs concurrent with exposure or following a short latency. Neurologic symptoms do not begin months to years after exposure. The two most common exceptions are the 2-6 week delay following exposure to organophosphates and the occasional 2 month latency between cis-platin intoxication and neuropathic symptoms⁴.

In addition, the extent and severity of neuropathy is usually commensurate with the degree of toxin exposure. It is unlikely that a single, brief, low-level exposure will result in a devastating peripheral neuropathy. Some lipid stored agents (e.g. chlorinated hydrocarbons) are detectable in fat biopsies years following exposure. Although this provides a valuable marker of previous exposure, there is no evidence that this state is associated with risk for future neurotoxicity, and attempts at removal or mobilizing the body burden are unnecessary.

d. **Improvement Usually Follows Cessation of Exposure**

TxPN generally plateau and then gradually improve after removal of the neurotoxic agent. Some degree of recovery is the rule, except in the most severely affected cases. A neuropathy that shows no improvement or continues to deteriorate, despite the cessation of exposure to a suspected neurotoxin, is unlikely to be neurotoxic in nature. The clinical picture may become somewhat murky however in certain toxic axonopathies in which cessation of exposure may be followed by worsening of symptoms (coasting) for several weeks before recovery commences⁵.

Confusing Aspects of Neurotoxic Illness

a. **Multiple clinical syndromes may result from different levels of exposure to a single toxin**

Different exposure levels to the same substance may produce dramatically different syndromes. Most confusing is the bizarre constellation of symptoms that may arise from intoxication with intermediate levels of the neurotoxin. Examples include the different clinical syndromes produced by acute high-level and intermediate-level exposure, and prolonged low-level acrylamide intoxication. Exposures to high-level acrylamide cause early CNS dysfunction with drowsiness, disorientation, hallucinations, seizures, and severe truncal ataxia, followed by neuropathy of variable severity. Prolonged, lower-level exposure causes little CNS dysfunction but a marked peripheral neuropathy. Exposure to intermediate levels of acrylamide causes hallucinations, mental confusion and cognitive dysfunction, followed by sensory complaints affecting the distal limbs.

Another example is organophosphate poisoning in which there may be early, severe cholinergic symptoms resulting from excessive muscarinic receptor stimulation. Within 1-3 days there may occur generalized paralysis with respiratory distress owing to nicotinic receptor blockade. After a few weeks, a distal axonopathy may be evident.

In some instances, a single compound may produce similar clinical symptoms at both high and low level-exposure, although different anatomic structures are affected. High dose pyridoxine intoxication produces widespread sensory loss due to dorsal root ganglion dysfunction; low-level exposure produces similar symptoms but due to a distal axonopathy.

b. **Asymptomatic Disease**

Prolonged, low-level exposure may occasionally produce widespread subclinical dysfunction. Clinical deficits may go unnoticed by the patient unless they perform an usually skilled job that requires fine-motor control or intact sensibility. Insidiously developing subclinical TxPN may occur in individuals who deny any disability.

c. **Enhancement by Bystander Chemicals**

An agent without known neurotoxic activity may enhance the toxicity of a known neurotoxin that is present at a “no effect” level. This disquieting notion has raised the general public’s fear that the combined effects of multiple chemicals in hazardous waste disposal sites may be more toxic than their separate effects. Such sites may contain low, presumably harmless levels of neurotoxic solvents, metals or pesticides, whose neurotoxic potency conceivably might be enhanced by one or the other chemicals present. Neurotoxic potentiation is illustrated by the epidemic of peripheral neuropathy which occurred in German youths who abused paint thinner containing n-hexane. Initially there were no instances of neuropathy, but when the paint thinner was reformulated by lowering the concentration of n-hexane and adding MEK, there resulted an epidemic of severe distal axonopathy⁶. Experimental evidence subsequently showed the while MEK by itself was not neurotoxic, the compound dramatically potentiated the neurotoxic effects of n-hexane.

d. **Chemical Formula May Not Predict Toxicity**

The neurotoxic potential of a compound cannot usually be predicted by its chemical formula. This is especially important to consider when evaluating cases of potential occupational exposure to chemicals that superficially resemble a known neurotoxin. An example is workers exposed to acrylamide polymer, an innocuous substance, who have been needlessly alarmed by physicians familiar only with the effects of acrylamide monomer, a potent neurotoxin. Unpredictability exists because the underlying biochemical mechanisms and active metabolites of most neurotoxins are unknown.

Identification of Toxic Peripheral Neuropathy

The presence of a toxic peripheral neuropathy is suggested by the following:

- a. suspicion raised by history and reinforced by compatible findings on physical exam;
- b. lack of naturally-occurring alternative explanation;
- c. consistency with basic principals of neurotoxic disease;
- d. compatible EDx;
- e. confirmation by demonstration of elevated body burdens if appropriate, or resolution of condition with removal of potential exposure.

The initial step is a suspicion raised by a thorough occupational history. Unfortunately, because most toxic polyneuropathies are insidious in onset, many patents are unable to

discern a relationship between their symptoms and chronic, low-level, toxin intoxication. Inquiry should focus on potential occupational, environmental, and iatrogenic exposures. The individual habits of a patient should be inquired about. Are protective devices worn and clothes changed before coming home? Do they eat in the workplace and are hands washed prior to eating? What is the health of their peers? Do symptoms improve when they are away from the potential toxin, such as on weekends or holidays? Do workplace conditions (ventilation, drainage) predispose to an unacceptably high risk of toxin exposure? Answers may only be available after a visit to the home or workplace itself. In cases of suspected domestic poisoning or substance abuse, home visits may be needed to check hobby workshops, medicine cabinets, and food and water sources. Inquiry should be made about recent pesticide applications, a similar illnesses in neighbors may prove helpful in identifying a neurotoxin.

The nature of the suspected toxin should focus the physical examination to relevant deficits. Thus a suspicion of mercury poisoning should prompt a careful examination for tremor and mild cerebellar dysfunction. The function of the neurologic exam is to demonstrate that neurologic deficits are in a pattern and of a severity that is consistent with neurotoxic illness. Since the clinical deficits resulting from a TxPN should be symmetric in distribution, the presence of multifocal deficits should suggest a diagnosis other than neurotoxic disease. In addition, since most TxPN affect mixed nerve function, finding a purely small fiber neuropathy makes neurotoxic disease unlikely.

Occasionally the nature of the neurologic deficit gives some clue to etiology:

Motor > Sensory Toxic Neuropathies:

1. dapsona
2. disulfiram
3. nitrofurantoin
4. organophosphates
5. lead
6. vincristine

Sensory > Motor Toxic Neuropathies:

1. cisplatin
2. pyridoxine
3. thalidomide
4. thallium
5. arsenic
6. polychlorinated biphenyls

Determination of Body Burdens

In the usual scenario, screening levels for heavy metals are not fruitful. In many cases this is because the toxin exposure was too remote, allowing time for the offending agent to be cleared from the serum. In cases of prolonged exposure, the neurotoxin may be

sequestered in various tissues and therefore not available to laboratory identification. With some chemicals, the safe level has not been established.

Caution must be taken when interpreting body burden results. An example is arsenic levels which are frequently of little clinical value and may be raised by recent shell food ingestion. In some cases of prolonged exposures, like thallium or lead, finding elevated levels either in slow growing tissues such as hair, or in urine or serum after chelation, is often diagnostic.

Electrodiagnostic Assessment

Electrophysiologic findings should be consistent with a distal axonopathy or mixed axonal, demyelinating neuropathy. Only a few rare neuropathies, such as n-hexane, perihexiline, amiodarone, and early arsenic poisoning, have predominant slowing of conduction velocities.

Quantitative Sensory Testing

Quantitative thresholds for thermal and vibration appreciation have proven extremely useful in documenting objective evidence of sensory impairment and monitoring the course of recovery or deterioration. These procedures are non-invasive and reproducible and can be performed by a trained technician.

Systemic Features Suggestive of Neurotoxic Disease

The neuropathies resulting from most neurotoxins are remarkably similar in both their clinical and electrophysiologic characteristics. Occasionally, there may be systemic complaints or signs which suggest the nature of the neurotoxic insult. Usually these symptoms/signs are apparent with either acute high-level, or chronic low-level intoxication. The following clinical characteristics may be the identifying feature that suggests a TxPN:

- **acrylamide** - dermal contact associated with contact dermatitis, excessive sweating of hands and feet.
- **carbon disulfide** - chronic low-level exposure associated with a variety of behavioral and psychiatric abnormalities along with peripheral neuropathy.
- **ethyl oxide** - cognitive impairment and neuropathy with prolonged low-level exposure.
- **hexacarbons** - acute, high-level exposure may mimic AIDP with prominent autonomic dysfunction.
- **lead** - Mee's lines, blood abnormalities (basophilic stippling, anemia), GI abnormalities, and predominantly a motor neuropathy.
- **mercury** - tremor and ataxia with a predominantly sensory neuropathy.
- **methyl bromide** - corticospinal and cerebellar dysfunction along with an axonal neuropathy.

- **organophosphate intoxication** - early cholinergic symptoms, may have intermediate syndrome preceding neuropathy, late emergence of corticospinal tract dysfunction as the peripheral neuropathy resolves.
- **polychlorinated biphenyls** - symmetric sensory neuropathy associated with brown acneiform skin eruption and brown pigmented nails.
- **thallium** - prominent GI distress with high-level exposure, alopecia, Mee's lines, hyperkeratosis with more prolonged exposure, sensory greater than motor neuropathy.

Individual Toxic Compounds

ACRYLAMIDE {CH₂=CHCONH₂}

Use and Sources of Exposure

Acrylamide is a man-made vinyl monomer compound synthesized by the hydration of acrylonitrile with sulfuric acid monohydrate. The principal use of acrylamide has been the commercial polymerization of the neurotoxic monomer into nontoxic polymers, which have been used as flocculents in the treatment of waste waters, as grouting agents in waterproofing, and in electrophoresis chromatography. Acrylamide neurotoxicity is most often seen in the setting of involved workers physically handling the monomer in preparation for polymerisation. Skin contact appears to have been a greater industrial hazard than inhalation, both in the factory and in grouting. Instances of acrylamide neurotoxicity are now rare since the monomer is no longer a commercial product in North America.

Toxicity and Metabolism

The monomer is an odorless, white, crystalline solid which is very water soluble. It is readily absorbed by all tissues, including skin, and is distributed throughout body water within minutes following intravenous administration. Acrylamide disappears rapidly from the serum and only minute amounts persist in nervous tissue for 14 days. Less than 1% is bound to nervous system tissues. The monomer undergoes oxidation at the double bond, which is required for neurotoxicity⁶⁹. Detoxification is *via* epoxy hydratase to 2,3-dihydroxy propenamide¹⁶⁵. Elimination is rapid *via* glutathione conjugation, although significant amounts persist in rats for 14 days after injection¹⁵⁶. Attempts to monitor acrylamide exposure in workers by urine measurements have been unsuccessful. One report suggests that hemoglobin adducts may be an accurate measure of industrial exposure¹⁶⁹.

The nervous system is the principal toxic target organ for acrylamide in humans. Human peripheral neuropathy results from repeated neurotoxin exposure⁵⁸. Aside from fatigue and weight loss, acrylamide produces little other systemic dysfunction. Acrylamide, in large doses is carcinogenic and genotoxic in rats and mice.

Clinical Features

Extremely high exposures, in suicidal attempts, are associated with generalized seizures. Moderately high exposure, 40 ppm acrylamide daily for several months in well water, cause an encephalopathy (memory loss, hallucinations) and cerebellar signs followed by peripheral neuropathy⁷⁹.

Chronic low-level exposure can cause a distal, symmetric peripheral neuropathy. Initial complaints are numbness and increased sweating in the hands and feet and an unsteady gait^{51, 54, 71, 121, 155}. Positive sensory symptoms, such as paresthesias, are rare. Difficulty in walking and performing coordinated sequential tasks, such as climbing ladders, is disproportionate to weakness or sensory loss. Objective signs are present in all symptomatic individuals and reflect peripheral nerve and, possibly, cerebellar dysfunction.

Repetitive exposure to toxic doses of acrylamide results in weakness of foot dorsiflexion and intrinsic hand muscles, along with a diffuse loss of tendon reflexes. A consistent finding is vibration loss in the feet and hands. Muscle tenderness occasionally occurs but, in general, acrylamide neuropathy is not an overly painful condition. Clumsiness and occasional intention tremor may be present in the arms and a broad based, swaying gait is often an early finding. Autonomic dysfunction, prominent in some experimental studies, is not a feature of human acrylamide neuropathy. There are neither postmortem studies in acrylamide neuropathy nor nerve biopsies during the active phase of the illness. Sural nerve biopsies from two recovering patients displayed diminished numbers of large diameter fibers.

Sensory nerve action potential amplitudes usually are markedly reduced in the arms and legs; this has been suggested as a sensitive electrophysiological test for the detection of early cases^{95A}. Motor and sensory nerve conduction velocities are usually fairly well preserved in cases of acrylamide neuropathy.

There is no known treatment for acrylamide neuropathy. Removal from exposure in the early stages of neuropathy results in gradual and, eventually, complete symptomatic recovery. Careful examination may demonstrate persistent abnormalities of vibration sense as the sole deficit. In more severely affected individuals, improvement continues for several months, but frequently there is residual distal weakness, gait ataxia, and impaired vibration sense. Persistent sensory dysfunction may stem from degeneration of axons in dorsal columns, and ataxia from changes in cerebellar efferent and afferent fibers.

There is considerable interest in detecting subclinical acrylamide neuropathy in exposed workers. Estimation of sensory nerve action potential amplitude appears to be a sensitive electrophysiological measurement. Quantitative assessment of distal extremity vibration sense is also a useful measure, an idea supported by studies of vibration sense and of degeneration in pacinian corpuscles in acrylamide-dosed monkeys^{109,141}.

Routine diagnostic laboratory tests, including cerebrospinal fluid examination, are usually unremarkable. The diagnosis of acrylamide neuropathy is not difficult in an individual with proven industrial or occupational exposure. The presence of gait ataxia, moist peeling hands, and peripheral neuropathy leave little room for doubt. A detailed occupational history is the most important diagnostic procedure because acrylamide neuropathy almost never stems from environmental exposure.

Experimental Studies

Morphology

The development of acrylamide distal axonopathy requires repeated exposures to the neurotoxin. Experimental animal studies in several mammalian species have generally utilized either short term (up to 14 days), high level daily administration (25-90 mg/kg) or prolonged (6 weeks to 3 years), low-level (90.5-10 mg/kg) dosing. Each of these two regimens results in distinct spatiotemporal patterns of dysfunction and fiber degeneration, especially in the central nervous system.

Low Doses-The initial ultrastructural change in rats, cats and monkeys is an accumulation of 10nm neurofilaments, most marked at distal ends of peripheral nerves^{21, 141, 136}. Neurofilament accumulation within the paranodal region causes axonal swelling and retraction of myelin. In general, neurofilaments initially accumulate at multiple paranodal sites in the distal ends of the longest and largest-diameter axons. Early changes in feline pacinian corpuscles and annulospiral endings correlate with the profound loss of vibration sense and depressed tendon reflexes in the human neuropathy^{141,157}. Unmyelinated fibers in somatic nerves and in sympathetic nerve trunks degenerate in advanced stages of acrylamide intoxication¹¹⁹. There is evidence of axonal regeneration during low-level intoxication of all species.

Widespread, tract-oriented distal axonal degeneration in the central nervous system accompanies the peripheral nerve changes¹⁶⁷. Preterminal axonal degeneration in the gracile nucleus is an early occurrence and has been reported in one study that utilized unusually low-level dosing for a prolonged interval¹⁴⁴. Other vulnerable areas are the rostral regions of the dorsal spinocerebellar tracts and caudal regions of the long descending motor pathways in the lumbar spinal cord. Axonal swellings in shorter tracts, such as the optic nerve terminals in the lateral geniculate body have been observed in rats and monkeys dosed for longer durations.

High Doses-Administration of 30 mg/kg daily causes chromatolytic change in dorsal root ganglion cells and degeneration of Purkinje cells within one week. These findings are followed, in about two weeks, by widespread swellings of peripheral motor and sensory nerve endings, and multifocal terminal swellings in spinal cord, brainstem, and cerebellum.

Several studies have reported impaired axonal regeneration in rats exposed to high levels of acrylamide. Nerve ligation together with acrylamide dosing causes retrograde axonal

degeneration from the point of ligation, even extending into proximal sites in the nerve that are usually spared in distal axonopathies²⁶.

A single dose of 75 mg/kg caused swelling in dorsal and ventral roots, suggesting impaired transport of all slow component proteins⁵⁶. Repeated doses of 30 mg/kg cause diffuse, proximal axonal atrophy that progresses in a distal direction at a time when there is little distal terminal change; this suggests that repeated high doses cause an axotomy – like reaction in the nerve cell body.

Treatment for 5 days with levels of 30-50 mg/ kg causes subcellular reorganization in sensory ganglia, autonomic ganglia, and Purkinje cells prior to peripheral axonal degeneration. It is suggested that this type of cellular reorganization represents a direct toxic effect of high level administration of acrylamide^{27,162,163}.

Electrophysiology

There have been many electrophysiologic studies of experimental acrylamide-intoxicated animals. Early reports showed reduced peripheral nerve conduction in rats, cats, and primates^{52,164}. Single sensory nerve fiber conduction studies demonstrated the earliest change to be a failure of response of muscle stretch receptors. Studies of the responses of primary and secondary endings of muscle spindles revealed that the earliest abnormalities are elevated threshold and diminished response of spindle endings. It is suggested that the attenuated dynamic response of primary muscle spindles may be the basis for depressed tendon reflexes in the human neuropathy. It also seems likely that disordered peripheral sensory mechanisms, in combination with cerebellum dysfunction, may contribute to the severe gait ataxia that characterizes chronic neurotoxicity in humans. The spinal cord component of the monosynaptic stretch reflex is also clearly abnormal. One report of serial conduction measurements of central and peripheral projections of dorsal root ganglion cells describes persistent central slowing even after recovery of clinical abnormalities.

Electrophysiologic studies of the autonomic system have revealed no changes in unmyelinated fiber conduction but slowed conduction in myelinated sympathetic nerve fibers^{133,134}. One study demonstrated impairment of neuronal control of the mesenteric vascular bed in severely affected animals, and it was concluded that both preganglionic myelinated and postganglionic unmyelinated fibers were damaged.

Several studies support the view that physiologic changes antedate nerve fiber degeneration and behavioral dysfunction. One such study of pacinian corpuscles in the mesentery of cats treated with acrylamide demonstrated loss of detectable generator potentials prior to appearance of terminal axon changes as monitored by electron microscopic examination of chemically fixed or freeze-fractured, physiologically tested corpuscles¹⁵⁹. One study of somatosensory evoked potential from the lower extremities in intoxicated primates revealed changes in the short-latency (gracile) components at a time when peripheral conduction and behavior were normal and clinical signs of neuropathy were absent¹⁴⁴. No morphologic changes were detected in the PNS or CNS of these monkeys. The potentials returned to normal within 2 months of cessation of

intoxication. Some monkeys, dosed at levels of 1.0, 2.0, and 2.0 mg/kg/d (below the reported no-effect level), displayed onset of dysfunction only after extreme delay (940 days). This finding suggests that the current permissible levels of human exposure to toxins of this type should be reassessed.

Pathogenesis

The primary biochemical lesion responsible for the development of acrylamide neuropathy is unknown, as are its relationships to the disorders of axonal transport and metabolism described in the many experimental studies of the past two decades. Initial studies on the mechanism by which acrylamide produces its neurotoxicity focused on the role of energy metabolism. However, subsequent studies reporting the failure of acrylamide to inhibit adenosine triphosphate production *in vitro* or to impair brain mitochondrial metabolism *in vitro*, do not support the energy hypothesis^{152,110}.

Acrylamide axonopathy is associated with impairment of both fast and slow axonal transport systems^{56, 81, 113, 114, 153}. The impairment in slow transport observed following a single injection most likely underlies the pathogenesis of the formation of the accumulations of neurofilamentous axonal swellings. Changes in axonal transport following repeated exposures, in contrast, reproduce those following axotomy and are likely to arise secondary to axonal injury and/or a defect in delivery to the nerve cell body's response to a lost trophic support.

Impaired fast axonal transport is the earliest known physiological alteration following administration of acrylamide. The accumulation of tubovesicular profiles most likely is the morphologic correlate of early impairment of fast transport³². The reduction in both retrograde and anterograde fast transport occurs within hours following a single intraperitoneal injection of acrylamide. There is considerable speculation that acrylamide impairs the function of microtubular-based bidirectional axonal movement, and that the microtubular-based fast anterograde transport is the specific neuronal target underlying the development of acrylamide-induced axonal degeneration^{58, 68, 168}.

It is unclear how the axon undergoes degeneration in acrylamide neuropathy. Electron microprobe x-ray studies suggest that ion regulation in distal paranodal axon regions is impaired by diminished axolemmal sodium/potassium ATPase activity^{98, 99, 100}. It is alleged that this decreased ATPase activity is the result of aberrant cell body processing or deficient axonal transport. Subsequent membrane depolarization and accumulation of axoplasmic sodium favors the reverse influx of calcium and eventual axonal degeneration. It is uncertain whether these changes in distal axon elemental composition are a primary cause or reflect nonspecific secondary/compensatory responses to injury.

ALLYL CHLORIDE

(3-Chlorophene, CH₂CHCH₂Cl)

Allyl chloride is a colorless, chlorinated hydrocarbon which is liquid at room temperature, volatile and flammable. It has an irritating, unpleasant odor. Allyl chloride is primarily used in the manufacture of epichlorohydrin and glycerin pesticides, epoxy

resins, monomers of polyacrylonitrile, and allyl compounds such as sodium allyl sulfonate. The TLV in the United States is 1 ppm. Allyl chloride may be absorbed via the oral or inhalation route.

Neurotoxic effects of allyl chloride intoxication include a distal axonopathy. Several outbreaks have been reported in Chinese workers who developed distal lower limb numbness, paresthesias, and weakness⁷¹. Sensory loss is in a stocking-glove distribution, with early loss of the Achilles tendon reflexes⁷⁰. Electrophysiology showed denervation in distal leg muscles and delayed motor latencies. Recovery is usual after removal from exposure. Experimental animal studies demonstrated multifocal accumulations of axonal neurofilaments with motor, greater than sensory fiber degeneration in distal segments of the peripheral nerves and dorsolateral spinal cord tracts. Diagnosis of allyl chloride neuropathy is suggested by historical evidence of toxic exposure along with clinical and electrophysiologic evidence of a distal sensorimotor neuropathy.

CARBAMATES

Use and Source of Exposure

The underlying structure of carbamates consists of either carbamic acid, the monoamide of carbon dioxide, or dithiocarbamic acid, the monoamide of carbon disulfide. Carbamates are highly unstable compounds that decompose rapidly. The salts and esters of carbamic and dithiocarbamic acids are widely used as insecticides, herbicides, and fungicides. The compound disulfiram is used in treating alcoholism. Many of these compounds are neurotoxic, with exposure through occupational, accidental, or suicidal intoxication. Most carbamate insecticides are N-monomethyl carbamate esters, which vary in their degree of lipid solubility, species specificity, and potency as an anticholinesterase. More recently developed carbamate insecticides are derivatives of aliphatic oximes and resemble aldehydes or ketones in structure. Carbamate insecticides are efficiently absorbed from the gastrointestinal tract. The degree to which carbamates are distributed to various organs depends on their lipophilicity. Although there is little body storage of carbamates, there are several case reports of episodic or prolonged effects, raising the question of organ storage with intermittent release into the bloodstream. Excretion of the biotransformed or degradation products is predominantly through the urine and feces.

Toxicity and Metabolism

The predominant effect of carbamates is to inhibit acetylcholinesterase (AChE), resulting in the accumulation of the unmetabolized neurotransmitter, acetylcholine (ACh). The result is excessive ACh accumulation at nerve endings of parasympathetic and sympathetic ganglia, CNS ganglia (nicotinic actions), postganglionic parasympathetic nerve endings (muscarinic actions), and at the neuromuscular junction of somatic motor nerves. Inhibition involves both true AChE and pseudocholinesterase. Clinical symptoms do not last beyond 3-6 hours, since there is a rapid, spontaneous reactivation of the inhibited enzyme, with destruction of accumulated ACh.

Clinical Features

Acute high-level exposure to carbamates produces immediate neurologic dysfunction. Occasionally, there are unusual neurologic signs of a delayed and/or prolonged nature⁴³. Early reports of carbamate intoxication with aldicarb-induced poisoning were reported in the United States and Canada in the 1970s and 1980s^{43,59}. Subjects ingesting Aldicarb contaminated fruit and vegetables exhibited rapid onset bradycardia, hypotension, vomiting, diarrhea, lacrimation, salivation, and muscular twitchings. An incident in Jamaica was reported in which methomyl was substituted for common salt in unleavened bread. Three of the five exposed individuals died. Two subjects displayed the muscarinic and nicotinic signs of carbamate toxicity⁴³. Neurotoxic symptoms appear rapidly, and tend to dissipate within a short time, due to reactivation of AChE. The widespread availability of carbaryl has resulted in numerous reports of intoxication³⁷. The severity of symptoms is dose related with early onset nausea, vomiting, lacrimation, blurred vision, salivation, and headache. High dose poisoning may be fatal; lower dose intoxication begins with early-appearing muscarinic and nicotinic signs, reaching peak severity within 2-3 hours of exposure.

There have been reports of carbamate neurotoxicity which was either delayed in onset, or had prolonged effects, following a severe, single exposure to carbamate insecticides⁴³. Early symptoms were as described above. Approximately 3-4 weeks later there appeared limb weakness and paresthesias, diffuse areflexia, limb incoordination, gait ataxia, and generalized fatigue. Unusual persistent neurologic signs included intense headache, poor anger control, mood swings, impaired recent memory, and syncopal episodes⁴³. Neurotoxicity due to chronic carbamate exposure is rare. One such case, in which there was exposure over a 6-8 month period, displayed typical early symptoms of carbamate toxicity. Persistent neurologic symptoms, after exposure was terminated, included a peripheral neuropathy with distal limb sensory loss and mild muscle weakness, disrupted sleep patterns, cognitive changes, tinnitus, and headache¹⁸. Carbamates rarely cause a severe, delayed peripheral neuropathy, similar to that from organophosphate esters. This may be because of their inability to age the inhibited neuropathy target esterase compound. (see Organophosphate Neuropathy)

There are fewer reports of human neurotoxicity with carbamates used as fungicides; the most common group of neurotoxic carbamate fungicides is the dithiocarbamates. Most carbamate fungicides are not readily absorbed through the skin or gastrointestinal tract. The usual route of intoxication is pulmonary, from inhaled powder or dusts. The most common metabolite is carbon disulfide, most of which is unexhaled. A degradation product of carbon disulfide, carbonyl sulfide may also contribute to neurotoxicity. Carbamate fungicides are very irritating to mucous membranes and skin, causing contact dermatitis and allergic hypersensitivity in exposed workers. These chemicals also cause thyroid dysfunction via the formation of ethylene urea with the release of atomic sulfur which binds to thyroid molecules, diminishes iodine uptake, and iodine tyrosine.⁷⁸ Goiters can occur with repeated exposures.

There are two well documented cases of carbamate fungicide toxicity. One involved workers exposed to a commercial mixture of maeb and zineb who initially exhibited behavioral changes, dizziness, fatigue and weakness. A second exposure led to the rapid appearance of muscle weakness, limb ataxia, disorientation, dysarthria, depressed mental status, and seizures⁸⁰. The patient eventually completely recovered by the fourth day. A second report documented Parkinsonian-like signs and symptoms in two agricultural workers chronically exposed to maneb over 4-5 years.⁴⁸ Dysfunction included tremor, rigidity, gait difficulties, shuffling steps, postural tremor, bradykinesia, hyperreflexia, and emotional lability. A subsequent study of 50 workers exposed to maneb revealed similar, but less severe findings. It is suggested that the Parkinsonian-like symptoms are the result of carbon disulfide, a common breakdown product of most dithiocarbamates.¹⁶⁰

Atropine can counteract the muscarinic symptoms.⁴³ Atropine may also have a beneficial central effect, from a direct action on the respiratory system. Care should be taken regarding the amount of atropine given so as to avoid atropine toxicity, which may occur if there is reactivation of inhibited acetylcholinesterase. Treatment with diazepam can diminish muscle fasciculations, relieve anxiety, and counteract some CNS symptoms not affected by atropine. Pralidoxime, an axime reactivator, should be avoided in most case of carbamate poisonings, particularly with carbaryl in which the agent enhances toxicity. Intoxication with aldicarb may however, be treated with pralidoxime; in this setting, it may enhance the beneficial effects of atropine.⁴³

CARBON DISULFIDE NEUROPATHY

Use and Source of Exposure

Carbon disulfide is most commonly employed in the production of cellophane films¹⁴⁷ and viscose rayon fibers¹⁷³. Other sources of carbon disulfide are dithiocarbamates used in cancer chemotherapy, as well as those employed in agriculture. Carbon disulfide is a major metabolite of the drug disulfiram (antabuse), which is used as a deterrent for alcohol abuse⁸⁸. Most human intoxications result from inhalation exposure. Carbon disulfide intoxication has been a persistent problem in Scandinavia, Japan, and southern Europe³⁶.

Toxicology and Metabolism

Carbon disulfide is a colorless liquid that rapidly evaporates at room temperature. It is readily absorbed through the lungs and gastrointestinal tract; it passes less well through skin. Its high fat solubility of carbon disulfide results in rapid disappearance from blood and greater concentrations in brain and liver. Toxicity is attributed to its reactivity with amine, sulfhydryl, and hydroxyl groups in biologic systems⁶³. Reactive sulfur atoms form and suppress the activity of cytochrome P-450 enzymes. Di- and trithiocarbamates can chelate copper, and inactivate metalloenzymes such as dopamine *B*-hydroxylase, vital to norepinephrine production. These compounds are also metabolized to isothiocyanates that can covalently bind and cross-link with cytoskeletal proteins. This may account for the giant axonal swellings in experimental studies. Carbon disulfide can be transformed through reaction with amino groups and can also be converted to carbon dioxide in a two-stage desulfuration reaction⁴³. Human studies have shown that only 1 percentage of

absorbed carbon disulfide is eliminated in the urine; approximately 90 percent is subject to biotransformation. Urinary levels of 2-triothiazolidine-4-carboxylic acid (TTCA) are a sensitive measure of carbon disulfide exposure¹¹².

Clinical Manifestations

Acute or subacute high-level exposures cause signs of CNS dysfunction: confusion, hallucinations, memory impairment, and emotional lability⁶⁰⁻⁹⁶. Chronic, low-level exposure causes a combination of peripheral neuropathy and CNS abnormalities⁷. The neuropathy may be asymptomatic and detected only by electrophysiologic testing when exposure is low (10-40 ppm). As the concentration increases (20-60 ppm), a progressive sensorimotor, distal, asymmetric polyneuropathy emerges. Clinical findings initially include leg weakness, loss of ankle and patellar reflexes, and diminished pain, touch and vibration sensation in the distal lower limbs. Upper limb dysfunction appears following continued exposure. In some, recovery may be slow and incomplete, possibly because of residual CNS axonal damage^{36,149}. This notion is supported by experimental animal studies that demonstrate tract-oriented distal axonal degeneration in the spinal cord as well as changes in distal peripheral nerve fibers.^{149,169} CNS manifestations with prolonged exposure include headache, dizziness, depression, memory impairment, and impaired sexual arousal⁴⁷. Exposed persons occasionally display spasticity as well as extrapyramidal signs with tremor, bradykinesia, and cogwheel rigidity.

The diagnosis of carbon disulfide neurotoxicity is suggested by a combination of both CNS and PNS dysfunction in a setting of exposure. Abnormalities on electroencephalographic and psychologic testing are common. There is no characteristic clinical profile, and routine laboratory tests, including CSF examination, are usually normal.

Morphology

Human postmortem studies have revealed small, scattered foci of necrosis in the brain. Unfortunately, there are no adequate histologic studies of postmortem peripheral nerve changes and no reports of nerve biopsies in carbon disulfide toxicity.

Rats exposed to 750 ppm of carbon disulfide develop hind limb weakness and ataxia after 6 weeks¹⁴⁸. Dogs intoxicated with carbon disulfide eventually lose tendon reflexes and become spastic in the lower extremities¹⁰. Investigations in rats and rabbits, utilizing contemporary histologic techniques, have clearly demonstrated that carbon disulfide produces primary axonal degeneration, characterized by giant fusiform axonal swellings containing accumulations of 10 nm neurofilaments^{87, 97, 149}. The spatiotemporal evolution of these changes in the distal segments of both long peripheral nerve axons and long CNS fiber tracts indicates that prolonged exposure to carbon disulfide causes a central-peripheral distal axonopathy. The distribution and nature of the axonal changes due to carbon disulfide resemble those produced by the hexacarbons⁶¹. Retinogeniculate degeneration may also occur⁴⁴.

Electrophysiology

Nerve conduction studies are useful in detecting subclinical neuropathy in workers exposed to low levels of carbon disulfide. Seppalainen and Tolonen documented slowed motor conduction in the legs of exposed subjects¹⁴⁷. Knave and associates found that age-weighted motor conduction velocities were successively decreased among heavily exposed workers with 5-30 years of exposure⁹³. Mild slowing of digital sensory nerve conduction may be the only abnormality in the early stages of neuropathy and fibrillation potentials are present in distal leg muscles¹⁷⁰. Non-specific electroencephalographic abnormalities are allegedly more common in carbon disulfide exposed workers than in the general population, as are abnormalities in standard psychologic test batteries¹⁴⁹.

Nerve conduction velocities in rats and rabbits exposed to carbon disulfide are slowed; motor conduction slowing may precede weakness and fibrillation potentials can be detected in paretic muscles¹⁴⁸. Abnormalities of visual, brain stem, auditory, and somatosensory evoked potentials are detectable in intoxicated rats¹⁷⁰.

Pathogenesis

The pathogenesis of carbon disulfide neurotoxicity may reflect the reaction with amines to form dithiocarbamates. Dithiocarbamates chelate copper and zinc, decreasing the availability of these two cofactors, resulting in enzyme inhibition. Alternatively, vitamin B6 deficiency could result from dithiocarbamates formation on pyridoxamine¹³⁷. The similarity of the axonal changes of carbon disulfide and hexacarbon neuropathy suggests a common pathogenesis, specifically the ability of both to cross link neurofilaments. Neurofilament cross-linking, with resultant neurofilament accumulations, may underlie the axonal swellings seen in carbon disulfide and hexacarbon neuropathy. In experimental animal, the initial focal axonal swellings develop just proximal to nodes of Ranvier. Myelin retraction from nodes of Ranvier is followed by segmental demyelination, and eventually distal axonal degeneration. The longest and largest axons appear the most vulnerable in both peripheral nerve and spinal cord.

The basic biochemical mechanisms underlying the neurotoxicity of carbon disulfide remain unclear^{15,38}. There are three main hypotheses: 1) a chelating effect of carbon disulfide metabolites on metals essential for enzyme function, especially copper and zinc,^{35,146} 2) direct inhibition of enzymes, such as glyceraldehydes-3-phosphate dehydrogenase, monoamine oxidase, lactic acid dehydrogenase¹⁰⁸, and dopamine dehydroxylase¹⁵, and 3) release of free radicals following cleavage of the carbon sulfur bond¹⁵.

ETHYLENE OXIDE

Ethylene oxide (EO) is a gas at room temperature; it is water soluble and widely distributed to all organs shortly following inhalation exposure. EO is a powerful alkylating agent and reacts with virtually all cellular components, including DNA, and to histidine in hemoglobin¹²⁸. Its principal industrial use is in the synthesis of ethylene glycol. EO is an effective sterilant for medical supplies and fumigant for furs and some

foods. Experimental and epidemiological studies suggest EO to be a potential carcinogen and mutagen^{138, 151}.

EO clearly causes a distal symmetric polyneuropathy in humans and in experimental animals following chronic or intermittent peak exposure at levels in excess of 250 ppm^{64, 126, 128}. Prolonged extreme low-level exposure may also be hazardous to the nervous system; one study suggests that residual EO in dialysis tubing may contribute to peripheral neuropathy in patients on long-term hemodialysis¹⁷⁷. Another report implicates potential neurotoxicity for ethylene oxide in the solvent vehicle for cyclosporine¹⁷⁸. It is also alleged that sterilizer workers may develop overt or subclinical, EO-induced CNS and PNS dysfunction.

Humans with symptomatic polyneuropathy initially experience symptoms of distal extremity numbness and weakness, accompanied by evidence of diminished sensation in the feet and hands⁶⁶. Tendon reflexes are diminished throughout and ankle jerks are absent. Motor and sensory nerve conduction velocities are mildly diminished. Encephalopathic symptoms and cognitive impairment may accompany peripheral neuropathy. Sural nerve biopsies exhibit axonal degeneration. There are no reports of postmortem findings in humans with EO intoxication. Gradual recovery from peripheral neuropathy commences following withdrawal from exposure. One report of three individuals describes normalization of motor and sensory nerve conduction, and improved neurological function at a four-year follow up examination⁶⁴.

Experimental animals chronically exposed to 250 ppm of EO develop widespread sensory nerve fiber degeneration in the distribution of a central-peripheral distal axonopathy^{77, 127}, as do rats chronically dosed with 1500 ppm of propylene oxide, a chemically similar substance¹²⁶. Intact animal studies demonstrate that EO exposure causes impaired fast axoplasmic transport¹²². An *in vitro* report describes degeneration in dorsal root ganglion cell neurite extensions following EO exposure¹⁷⁷. The pathogenesis and biochemical basis of EO neurotoxicity are unknown.

**HEXACARBONS: CH₃CH₂CH₂CH₂CH₂CH₃
(*n*-HEXANE), CH₃COCH₂CH₂CH₃
(METHYL *n*-BUTYL KETONE)**

Use and Sources of Exposure

Hexacarbon neuropathy was first discovered in humans through industrial exposure and subsequently encountered in individuals practicing inhalant abuse. *n*-Hexane and methyl *n*-butyl ketone (MnBK) are considered together in this chapter because each is metabolized to 2,5-hexanedione (2,5-HD), a γ -diketone, which appears to be responsible for much of the neurotoxicity of these substances. Hexacarbon toxicology and clinical neurology have been extensively reviewed⁴¹.

n-Hexane is still widely used as an inexpensive solvent and is a minor component of gasoline and its combustion products. Occupational neuropathy has usually been

associated with industries utilizing *n*-hexane in poorly ventilated quarters (shoemaking, furniture finishing) with airborne levels in excess of 60-240 ppm. MnBK is now rarely used in its pure form, but it still may be present in some ketone mixtures and also occurs as a by-product of some wood pulping operations. Methyl ethyl ketone (MEK) sometimes is present in solvent mixtures containing either *n*-hexane or MnBK. MEK does not cause neuropathy¹⁴³; it is able to speed the development of hexacarbon neuropathy in animals and potentiate *n*-hexane neurotoxicity in humans¹¹. Methyl isobutyl ketone (MIBK) is associated with memory loss, but not with peripheral neuropathy⁶⁵.

Toxicology and Metabolism

n-Hexane and MnBK are both colorless liquids and almost insoluble in water. Their common neurotoxic metabolite, 2,5-HD, is highly water soluble. For this reason, 2,5-HD is widely used as the most convenient compound for experimental studies of hexacarbon neuropathy. MnBK is readily absorbed through the skin and respiratory tract. Cutaneous absorption of *n*-hexane may be a major route of entry in humans, but appropriate experimental studies have not been performed to confirm this. *n*-Hexane is less well absorbed via the respiratory tract than MnBK.

The metabolism of *n*-hexane and MnBK has been determined in experimental animals and in humans. *n*-Hexane can undergo oxidation to form 2-hexanol, which may be metabolized either to 2,5-hexanediol or to MnBK, both of which may be converted to 5-hydroxy-2-hexanone and then to 2,5-HD. MnBK likewise may yield 2,5-HD *in vivo*. Study of the metabolism of MnBK and *n*-hexane has identified 2,5-HD as the most persistent neurotoxic metabolite of both substances⁴¹.

Clinical features

Both males and females are affected, and the age of onset ranges from adolescence to late middle age. Individuals in different countries have been exposed to a wide variety of solvent mixtures and, in many instances, the contents and methods of chemical analysis are poorly described. The quality of the documentation of neurologic, clinical, electrophysiologic, and laboratory data varies considerably, and long-term follow-up examinations are scarce. Meticulous clinical studies of glue sniffing neuropathy have been done both in Europe and in North America^{11,93}. The Ohio MnBK study is widely held as a paradigm of the correct evaluative approach to an outbreak of an industrial toxic neuropathy⁹.

The most common initial complaint, in both industrial cases and among glue sniffers, is an insidious onset of numbness of the toes and fingers. This type of distal sensory neuropathy is generally the only clinical feature in the least severe industrial cases. The pattern of sensory abnormality is characteristically symmetric and involves only the hands and feet, rarely extending as high as the knees. Moderate loss of touch, pain, vibration, and thermal sensation is usually evident and may be accompanied by loss of the Achilles tendon reflexes; the other tendon reflexes are spared. In mild cases, there is preservation of position sense and no sensory ataxia, periosteal pain, cranial nerve abnormalities, or autonomic dysfunction. In more severe industrial cases, weakness and

weight loss occur, occasionally accompanied by anorexia, abdominal pain, and cramps in the lower extremities. Reflex loss is usually less than that observed in other polyneuropathies and, even in the moderate to severe cases, may be confined to the Achilles tendon reflexes and finger jerks. Weakness most commonly involves the intrinsic muscles of the hands and long extensors or flexors of the digits. A common complaint in these individuals is difficulty with pinching movements, grasping objects, and stepping over curbs. Instances of pure motor neuropathy are unusual in industrial cases. Vibration and position sense is only mildly impaired, and pinprick and tactile sensory loss is usually confined to the hands and feet. As the neuropathy becomes more severe, weakness and atrophy dominate the clinical picture and extend to involve proximal limb muscles. Glue-sniffing patients may display a subacute, distal to proximal progression of weakness early in the course of the disease¹¹. In a few glue sniffers, blurred vision has been a symptom, but objective evidence of visual loss has not been documented. Seizures, toxic delirium, cerebellar ataxia, tremor, or cholinergic symptoms are not described. No predisposing conditions exist for hexacarbon neurotoxicity, although one report describes a high incidence of polyneuropathy in older workers and slowed motor nerve conduction in “normal” individuals in a factory with documented cases of solvent neuropathy¹⁹. This strengthens the notion that subclinical and readily reversible hexacarbon nerve damage may be an unrecognized industrial problem.

Autonomic disturbances have been reported among the glue sniffers but not in the industrial cases. Prominent among these disturbances is hyperhidrosis of the hands and feet, occasionally followed by anhidrosis. Blue discoloration of the hands and feet, reduced extremity temperature, and Mees lines are sometimes present. Impotence occasionally occurs among glue sniffers with moderate or severe neuropathy, but its relationship to nervous system dysfunction is not established¹¹.

Slow progression is the hallmark of industrial cases. In most instances, this reflects low-level, intermittent exposure. In some glue sniffers, especially those with excessive abuse, a subacute course develops, leading, in severe cases, to quadriplegia within 2 months of the first symptoms. Acute inflammatory demyelinating polyradiculopathy (AIDP) has been a serious diagnostic consideration in some of these patients¹¹.

A universal feature of hexacarbon neurotoxicity is the continuous progression of disability (“coasting”) after removal from exposure. Coasting usually lasts for 1-4 months. The degree of recovery in most cases correlates directly with the intensity of the neurologic deficit. Individuals with a mild or moderate sensorimotor neuropathy usually recover completely within 10 months of cessation of exposure. Severely affected patients with industrial exposure also improve; some retain mild to moderate residual neuropathy on follow-up examination as long as 3 years after exposure. Such individuals, on occasion, display hyperactive knee jerks. This reflex change may reflect the degeneration in the corticospinal tracts accompanying the peripheral axonal degeneration¹⁴³.

Differential diagnosis of *n*-hexane neuropathy is based upon clinical signs that indicate distal axonopathy, an unusual degree of slowing of peripheral nerve conduction, and most importantly, a history of solvent exposure. Without a clear exposure history, peripheral

neuropathy from other metabolic or toxic causes can be difficult to exclude. Routine clinical laboratory tests, including CSF examination, usually yield normal results. Determination of blood and urinary levels of 2,5- HD are now commercially available and can confirm current exposure⁶². This test is of little use in persons with *n*-hexane neuropathy exposure which terminated months previously. A biological exposure index for occupational *n*-hexane exposure has been determined based on urinary 2,5-HD levels.

Morphology

Humans. Nerve biopsies in mild cases may be normal⁷⁵, but in individuals with overt neuropathy nerve fibers show focally swollen axons, filled with 10-nm neurofilaments and displaying myelin retraction^{9,93}. Giant axonal changes also are reported in the fasciculus gracilis in postmortem material from a glue sniffer. These changes in the PNS and CNS are indistinguishable from those in experimental hexacarbon neuropathy (see later discussion).

Experimental Animals. The neurotoxic hexacarbon have produced central-peripheral distal axonopathy in several species of experimental animal. In the PNS of rats, changes first appear in the large axons of the tibial nerve branches to the calf muscles. Subsequently, distal nerve fiber changes develop in the plantar nerves¹⁵⁸. With time, more proximal portions of the sciatic nerve become affected. The cell bodies of sensory and motor neurons remain intact. This pattern of axonal pathology has been well documented in several studies of experimental hexacarbon neuropathy following prolonged (weeks to months) low-level intoxication. The fundamental alteration is a focal condensation of neurotubules, mitochondria, and smooth endoplasmic reticulum, coupled with a massive local increase in the number of 10-nm neurofilaments. These axoplasmic changes initially develop on the proximal sides of nodes of Ranvier in distal regions of vulnerable nerve fibers; subsequently the swellings are associated with displacement of paranodal myelin¹⁵⁷.

The spatio-temporal sequence of hexacarbon distal axonopathy has been documented in *in vitro* living peripheral nerve fibers that are one component of structurally and functionally coupled cord-ganglia-muscle explants. These explants have been chronically exposed to each of the six interrelated hexacarbon metabolites¹⁷¹. Prolonged *in vitro* exposure (months) to any of these agents yields a sequence of distal change in selected large-diameter motor nerve fibers; giant axonal swellings containing excessive 10-nm neurofilaments first appear at the extreme distal tip of the broad, unbranched portion of the axon, and on the proximal side of a slightly widened tri- or multipartite node of Ranvier, which marks the origin of the terminal intramuscular branches. Subsequently, giant axonal swellings appear both proximally and distally. Prominent axonal swellings sometimes affect entire internodes and often precipitate paranodal myelin retraction. The denuded axon recovers a more normal diameter and undergoes demyelination if the toxin is removed at this stage. Continued intoxication precipitates breakdown of a distal length of nerve fiber. Cytons of motor neurons innervating affected fibers cannot be monitored in the living culture, but equivalent changes of sensory axons are not accompanied by any specific changes in their corresponding cytons.

The long ascending and descending tracts of the spinal cord are particularly vulnerable in hexacarbon neuropathy¹⁵⁸. In the rat, nerve fiber swellings first appear in the rostral part of the gracile tract and the caudal parts of ventral and ventrolateral tracts. With time, degenerative changes spread retrogradely along the affected fiber pathways. Giant axonal changes also occur in the anterior cerebellar vermis, lateral geniculate and mammillary bodies, corresponding to distal breakdown of spinocerebellar, optic, and fornical tracts, respectively¹⁴². There appears to be a species-specific selective vulnerability to degeneration in the large retinal ganglion cells of the rat; there are no similar findings in the primate visual system. One study claims that the primate optic tract is less vulnerable to 2,5-HD than to carbon disulfide or acrylamide.

Electrophysiology

Humans. In general, the degree of electrophysiologic abnormality, both electromyographic and in nerve conduction, parallels in the severity of the clinical illness.

The electromyographic abnormalities usually are symmetric and greater in distal than in proximal muscles. In patients with minimal involvement, minor denervation changes are often the only findings. Nerve conduction times and clinical examination are usually normal at this stage. In the Ohio MnBK epidemic, 37 cases were detected without clinical evidence of nervous system disease, but with the abnormal electrodiagnostic findings mentioned earlier; these cases are considered to represent subclinical MnBK neuropathy.³ The more severe cases generally display more obvious electromyographic evidence of fiber degeneration. With recovery or stabilization of the condition, the electromyographic changes disappear. Residual findings include impaired voluntary recruitment of motor units and an increase in the amplitude of motor unit action potentials.

In cases with minimal involvement, motor and sensory nerve conduction is usually normal or in the low normal range for velocity. As the clinical illness intensifies, progressive slowing of conduction ensues and, in the most extreme cases, distal peroneal nerve conduction cannot be elicited. It was noted in the Ohio outbreak that five cases displayed prolonged distal latencies in the presence of normal peroneal nerve conduction velocity. Another industrial study found both motor nerve conduction decrements in “normal workers” and a direct correlation between the duration of solvent exposure and the slowing of motor nerve conduction velocity. One study of glue sniffers describes severe slowing of motor nerve conduction, seemingly out of proportion to the degree of weakness. This report, which also incorporates a detailed study of a nerve biopsy specimen, concludes that although such profound slowing is usually associated with primarily demyelinating neuropathies, in n-hexane neuropathy it probably reflects the paranodal myelin changes caused by axonal swelling⁹³.

There have been few reports on nerve conduction in individuals recovering from hexacarbon neuropathy. In the Ohio MnBK cases showing clinical recovery, motor nerve conduction velocity tended to return to normal. A comprehensive study that analyzed visual, somatosensory, and brain stem auditory evoked potentials describes abnormalities in all modalities.

Experimental Animals. Various physiologic studies have been performed in experimental animals, including visual evoked responses and peripheral electrodiagnostic studies. One study has recorded visual evoked potentials from monkeys exposed to MnBK and describes increased latencies after 4 months²⁸. The authors suggest that these findings represent the electrophysiologic consequences of terminal giant axonal changes found in the optic tract of animals with hexacarbon neuropathy¹⁴².

Several studies report early (preclinical) and progressive reduction in conduction velocities of sciatic and ulnar nerves in animals receiving neurotoxic hexacarbons^{83,131}. These changes are ascribed to the focal demyelination accompanying giant axonal swelling, although one report emphasizes that nerve conduction changes precede demyelination.⁸³

Pathogenesis

The neurotoxic mechanism of action of *n*-hexane, and more specifically the γ -diketones, has been extensively studied in the 30 years since the initial human outbreaks of peripheral neuropathy. A recent review states that “although a number of hypotheses have been proposed and many important aspects of the mechanism have been clarified, the molecular determinants and pathological significance of axonal neurofilament accumulation and the ultimate mechanism of axonal degeneration remain unclear”⁴¹.

In general, most studies indicate that 2,5-HD exposure impairs axonal transport. It is widely held that the neurofilament itself is the target of γ -diketones, and alterations in filament structure and metabolism are the ultimate causes of axonal dysfunction and degeneration. This notion is supported by experiments that detect neurofilament accumulations at sites along the axon following the direct applications of 2,5-HD at those loci¹³². It has been suggested that the initial step is formation of a 2,5-dimethylpyrrole adduct from covalent binding of 2,5-HD to amine groups in neurofilaments. This is the fundamental reaction in the “pyrrole hypothesis”^{340,55,139,179}. Once formed, pyrrole adducts can undergo additional oxidative reactions to yield secondary, cross-linked derivatives. It is suggested that the cross-linking of neurofilaments results in disruption of neurofilament metabolism and their accumulation at the internodes.

Other studies have suggested targets other than the neurofilament protein since there is some evidence that distal axonal degeneration can occur in the absence of neurofilament accumulation. Covalent binding of 2,5-HD to microtubule-associated protein occurs *in vivo*, and 2,5-HD alterations of elemental composition and water content may implicate a primary attack on axonal homeostasis¹⁰¹.

Methyl Bromide (CH₃Br)

Methyl bromide is a colorless, nonflammable gas, which is odorless at low concentrations, but which has a chloroform-like odor at high concentrations. It is used as

an insecticidal fumigant, refrigerant, fire extinguisher, as a solvent for oil extraction from nuts, flowers, and seeds, and as an industrial methylating agent. Intoxication is usually through the lungs, but absorption is also possible via the gastrointestinal tract and skin. Methyl bromide is rapidly and almost completely metabolized in the liver. Maximum allowable inhalation is reported to be 5 ppm.

Acute intoxication initially results in mucosal irritation followed by malaise and gastrointestinal distress. Within hours there ensues signs and symptoms of severe central nervous system dysfunction, including headache, dizziness, dysarthria, visual impairment, delirium or psychosis, seizures, and myoclonus. Recovery is common after low dose exposure, but high dose intoxication may cause coma with eventual death.

Chronic high-level exposure may result in a syndrome characterized by dysfunction of pyramidal tracts, cerebellum, and peripheral nerves^{14,82}. Behavioral abnormalities may coexist. There are few well detailed reports of methyl bromide peripheral neuropathy. Most describe distal, symmetric sensorimotor neuropathy developing over 3-7 months of exposure⁹⁵. Neuropathy is heralded by acral paresthesias and pain, followed by distal leg weakness, hand clumsiness, and gait ataxia. Findings include a stocking distribution of pain and touch, distal leg weakness, and tender calf muscles. The Achilles tendon reflexes are lost. Mild optic neuropathy may be present, with early loss of color vision^{22,29}. The overall clinical pattern most closely suggests a distal axonopathy, but there are few confirmatory, pathologic specimens. The cerebrospinal fluid is normal. In one case, electrophysiologic studies showed a distal, predominantly motor axonopathy. Sensory conduction studies may potentially be normal²⁸. A sural nerve biopsy showed loss of predominantly large myelinated fibers²⁸. Postmortem findings in a fatal case following high dose acute exposure demonstrated neuronal loss in dorsal root ganglia and axonal degeneration in nerve roots and proximal nerve segments¹⁶⁷. Gradual improvement, with complete recovery in milder cases, occurs within a year after withdrawal from exposure.

The mechanism of methyl bromide neurotoxicity remains uncertain. Toxicity appears to be due to methyl bromide itself, rather than its metabolite, methonal, or the bromide ion^{14,124,129}. The finding of segregated microtubules in the nodes of Ranvier in one study suggests that methyl bromide may impair axonal flow, resulting in a distal axonopathy. There may also be a potential pathogenetic role for the methylglutathione metabolites methanethiol and formaldehyde. This is suggested by two individuals with comparable acute methyl bromide exposure, one of whom with normal erythrocyte glutathione transferase activity developed severe neurotoxicity, while the other, who lacked detectable enzyme activity, displayed minimal symptoms⁵⁹.

ORGANOPHOSPHATE NEUROPATHY

Introduction

There are over 20,000 compounds classified as organophosphates. Their physicochemical properties are varied and they exist in solid, liquid, and gaseous forms. Some organophosphorus esters (OPs) cause a distal axonopathy characterized by widespread central and peripheral nervous system degeneration (organophosphate-

induced delayed peripheral neuropathy, OPIDP). This axonal effect does not involve inhibition of acetylcholinesterase (AChE), has a delayed onset following a single exposure, and has been responsible for devastating epidemics of neurotoxic injury. Neuropathy has been most widely associated with the OPs tri-*o*-cresyl phosphate (TOCP), although other OPs including leptophos, mipafox, chlorphos, and trichlorfon have also been reported to cause OPIDP. Diisopropylfluorophosphate (DFP), haloxon, and butafox may produce similar neurotoxic changes in experimental animals. Persistent health complaints in Gulf War veterans has raised the question of whether low-level, prolonged exposure to a variety of OPs could cause peripheral nerve damage¹⁰⁶. Distal axonopathy is thought to be a relatively uncommon consequence of OPs exposure, especially when compared with the well-known AChE effects. Experimental studies however indicate that OPs induced neuropathy may be more common than formerly thought, and that low-level exposure to neurotoxic OPs may produce neuropathy if combined with other less neurotoxic OPs¹⁰⁵.

Uses and Sources of Exposure

Organophosphates are most commonly used as petroleum additives, insecticides, lubricants, antioxidants, flame retardants, and plastic modifiers. Intoxication may occur due to accidental pesticide exposure from agricultural spraying. Exposure may occur in those individuals mixing or applying the pesticide or through dermal exposure from those working in the fields shortly after spraying¹¹¹. Most OPs are quickly degraded in the environment. The majority of epidemic TOCP intoxications have resulted from inadvertent adulteration of food, drink, or cooking oil. Prominent outbreaks occurred in the United States from drinking contaminated Jamaica ginger extract (jake leg paralysis), and in Morocco, from eating food cooked in contaminated oil^{90,154}. Pesticides containing organophosphate are also intentionally ingested in suicide attempts.

Toxicology

Absorption of OPs may take place through the respiratory and gastrointestinal tracts, and the skin. The rate of absorption and excretion differs among the various OPs. Once absorbed, OPs irreversibly inhibit, through phosphorylation, true AChE, located in erythrocytes and nervous tissue, and plasma pseudocholinesterase. Only depression of erythrocyte AChE is specific for OP exposure. Reduced pseudocholinesterase levels is a nonspecific finding and may be seen in many naturally occurring diseases and toxic conditions. Acetylcholinesterase inhibition causes excessive accumulation of acetylcholine (ACh) with resultant overstimulation of muscarinic and nicotinic receptors. There are acute (type I) and intermediate (type II) syndromes (see below) that reflect which receptors are preferentially affected by the excessive ACh. Cholinergic symptoms, due to muscarinic receptor overstimulation, may be apparent within hours of OPs exposure and are always evident within 1 day. Different OPs produce cholinergic signs and symptoms of varying intensity. Mild cholinergic symptoms include gastrointestinal distress such as diarrhea and vomiting, combined with lacrimation, salivation, sweating, and muscle fasciculations. Severe cases show behavioral changes, widespread weakness, and respiratory depression. Atropine may reverse the aforementioned cholinergic symptoms due to excessive muscarine receptor stimulation, but is ineffective in reversing muscle weakness due to nicotinic receptor blockade. Atropine's effect may be transient

and cholinergic symptoms may reoccur, occasionally requiring respiratory assistance. Severe exposure may cause death⁵⁰. Exposed subjects may be prone to ventricular arrhythmias when atropine is given in the presence of respiratory insufficiency and atropine should not be administered until adequate ventilation has been established⁵⁰. Pralidoxime may be of clinical benefit by accelerating the hydrolysis of inhibited AChE.

Clinical Features of Cholinergic Reactions

The nature and severity of neurologic symptoms following OPs exposure is partly dependent upon the type of OPs, the degree of exposure, and the extent of absorption. A transient, clinically heterogeneous cholinergic response usually occurs following a single OPs exposure. The type I syndrome¹⁷³ includes cholinergic symptoms due to excessive muscarinic receptor stimulation, which are evident shortly after exposure. Symptoms include gastrointestinal distress, miosis, lacrimation, salivation, diarrhea, and bradycardia. Weakness is not a component of the type I syndrome.

The type II or intermediate syndrome, so named because of its temporal appearance between the early type I syndrome and the later OPIDP, occurs 12-96 hours after exposure, is due to excessive nicotinic receptor stimulation. Despite lesser clinical renown, the type II syndrome is thought to occur more frequently than the more heralded OPIDP. The type II syndrome may result from exposure to many different OPs, including dimethoate, fenthion, methamidophos, malathion, and fenitrothion and includes fasciculations, limb and respiratory muscle weakness, tachycardia, and hypertension³⁹. Patients may be symptom free between 1 and 4 days following OPs exposure before type II symptoms occur. Respiratory distress may be the initial symptom, followed by weakness of proximal limb and neck flexor muscles. Although distal extremity strength is usually preserved, cranial nerve function may be impaired, including extraocular muscles. Sensory function is normal, but dystonic limb posturing may be present. Respiratory and cardiac failure may occur in severe cases. Occasionally, central nervous system signs appear including anxiety, confusion, blurred vision, impaired memory, tremor, convulsions, respiratory depression, and coma. Recovery usually begins about 5-15 days after exposure and proceeds in the reverse order to symptom appearance, with cranial nerve muscles recovering first, and neck flexors last. The rate of recovery depends on the type of OPs, the extent of exposure, and the manner of treatment. Occasional patients are slow to eliminate OPs, resulting in impaired AChE recovery, and persistent clinical deficits for several weeks⁵⁷. Persistent behavioral changes may be evident after acute poisoning. Atropine will modify symptoms due to excessive muscarinic receptor stimulation (type I), but not those due to nicotinic receptor overstimulation (type II). There is no correlation between the occurrence of the intermediate syndrome and the later appearance of OPIDP.

An early, objective sign of OPs intoxication is electrophysiologic abnormality of neuromuscular transmission, its nature correlated with exposure severity¹⁷⁴. Single motor stimuli, applied shortly after OPs exposure, may induce spontaneous repetitive motor action potentials (SRMAPs) following the primary motor action potential¹⁶. This electrophysiologic finding is a sensitive marker of OPs exposure, but does not correlate with the severity of intoxication. The onset and progression of muscle weakness are

associated with a decremental pattern with repetitive motor nerve stimulation. The maximum decrement of motor potential amplitude occurs by the second potential, unlike myasthenia gravis where fourth potential is usually of lowest amplitude. The characteristics of repetitive stimulation abnormalities reflect the intensity of intoxication. Repetitive stimulation studies in the setting of mild weakness or improving strength are characterized by (1) a decrement in the amplitude of the second potential, evident **only** with rapid repetitive stimulation, (2) a progressive restoration of motor potential amplitude in the following motor action potentials (decrement-increment response), and (3) the presence of SRMAPs following the initial few motor potentials¹⁶. In more severe cases with greater weakness, the decremental response is evident with slower stimulation rates and SRMAPs are not observed.

Clinical Features of Organophosphate-Induced Delayed Polyneuropathy

OPIDP is much less common than the more frequently occurring cholinergic symptoms after OPs exposure, but results in considerable morbidity. The underlying pathology of OPIDP is central-peripheral axonal degeneration with clinical symptoms appearing after a latent period of 7-21 days. OPs capable of producing OPIDP almost invariably cause preceding cholinergic symptoms, although these may be subtle and unappreciated¹⁰⁶. Peripheral neuropathy is heralded by early muscle cramping and calf pain, along with tingling and burning sensations in the feet, and occasionally the hands. Weakness is an early and invariable finding and established cases may have predominant motor deficits with minimal sensory complaints. Distal muscles are the earliest and most severely affected, although proximal muscles may occasionally be involved in severe cases. The Achilles reflexes are depressed or absent, while more proximal reflexes may either be depressed, or even increased if central nervous system dysfunction is present. Cranial nerve and autonomic function are preserved. Neuropathy progression is subacute being fully expressed within a few days. Chronic progression is not seen, unlike other immune, inflammatory, or metabolic related distal axonopathies. There is one report of an acute demyelinating motor neuropathy which developed after exposure to merphos⁴⁹. Whether this neuropathy was actually acute inflammatory demyelinating neuropathy or an unusual presentation of OPs intoxication is unclear.

Symptoms and signs of central nervous system (CNS) dysfunction may be present in severe cases and represent damage to distal ends of motor and sensory tracts within the spinal cord. CNS dysfunction is usually inapparent early in the neuropathy as signs of peripheral nerve damage predominate. As time passes and peripheral nerves recover, signs of CNS dysfunction may emerge, including hyperreflexia, increased motor tone, and spastic gait. In its most severe expression, OPIDP manifests upper and lower motor neuron involvement. A common physical finding in a 30-year follow-up study of individuals with TOCP poisoning was the combination of spastic paraparesis and distal leg atrophy. Evidence of corticospinal tract dysfunction is a feature that distinguishes OPs neurotoxicity from most other distal axonopathies and may be misleading: for example, in a recent outbreak of leptophos intoxication, several cases were erroneously diagnosed as encephalomyelitis or multiple sclerosis.

The prognosis in mildly affected individuals is usually good with most making nearly a complete recovery. Others with a more severe initial deficit are left with varying degrees of morbidity, which include sequelae of both peripheral (atrophy, claw hands, footdrop) and central (spasticity, ataxia) nervous system damage. In many cases the ultimate prognosis depends more on the degree of CNS than of peripheral nerve dysfunction. There is no specific treatment once the acute cholinergic crisis has resolved¹⁴. Methylprednisolone, given to cats following exposure to the OPs diisopropylfluorophosphate, prevented the development of OPIDP⁸³. Its applicability in humans is unproven.

There has been recent concern regarding the occurrence of chronic neurologic and neurobehavioral dysfunction related to acute or prolonged, low level OP exposure. Media attention was focused on Gulf War veterans who were exposed to a variety of OPs during their military duty. The syndrome, labeled chronic OP-induced neuropsychiatric disorders (COPIND) has been linked to acute, low level exposure (phenomenon 1), as well as long-term exposures (phenomenon 2) and includes a variety of neurologic and behavioral symptoms¹⁰⁶. A critical analysis of the literature related to acute and chronic low-level OPs exposure concludes that reports have inconsistent symptoms, poor or absent correlation with OPs exposure, or significant methodologic deficiencies. To date, no consistent relationship has been found between low-level OPs exposure and peripheral neuropathy either in humans or experimental animals¹⁰⁶.

Routine clinical laboratory studies in OPIDP are usually normal¹⁷⁴. Depressed erythrocyte AChE levels suggest exposure to OPs, and early severe weakness appears to be associated with AChE levels less than 20 per cent of normal. AChE levels provide little information on the likelihood of developing OPIDP. Because erythrocyte AChE levels regenerate at the rate of about one per cent per day, patients with previous exposure may have normal levels by the time they come to medical attention. Plasma pseudocholinesterase levels have little diagnostic value. The CSF is usually acellular and the protein levels are normal or only minimally elevated. The diagnosis of OPs related neuropathy is simple if there is a clear indication of ingestion at about 2 weeks before the illness, including the presence of cholinergic symptoms. Should such evidence be lacking, this condition becomes almost impossible to establish with certainty. In the authors' experience, cases of OPs neurotoxicity have been erroneously diagnosed as multiple sclerosis. The subacute onset of a myeloneuropathy syndrome in a patient with possible OPs exposure should raise the question of OPIDP.

Pathology

Humans. Sural nerve biopsy specimens demonstrate that the longest and largest diameters axons are most vulnerable, with varying degrees of axonal degeneration and regeneration. Demyelination is not a pathologic feature of OPIDP⁸³. Postmortem studies from the 1930 Jamaica ginger TOCP outbreak revealed wallerian degeneration in peripheral nerves. Evidence of CNS dysfunction included distal degeneration in the gracile fasciculus and the corticospinal tract, indicative of central-peripheral distal axonopathy.¹³

Experimental Animals. Experimental animal studies have conclusively demonstrated that TOCP induces a distal axonopathy in several species.¹⁷ The neurotoxic effects of OPs vary according to the species of animal exposed. For example, neuropathy is clinically apparent in chickens, cats, and certain primates, but not in the rat, rabbit, and guinea pig. Histopathological studies have demonstrated distal axonal degeneration in chickens²³, cats,^{25,135} and primates⁷⁴ exposed to OPs. Such variability may be more apparent than real, however, as histopathologic studies revealed mild evidence of neuropathy in many instances where clinical signs were lacking.

Degeneration of the long ascending and descending fiber tracts within the spinal cord and the ends of the dorsal spinocerebellar tracts in the medulla oblongata and cerebellum are present in pathologic specimens from OPs exposed experimental animals.²³ In the cat PNS, large diameter, heavily myelinated fibers appear most vulnerable²⁴. Axonal degeneration initially involves focal but nonterminal areas of the axon and spreads in a somatofugal direction to involve the entire distal axon.¹⁷ Ultrastructural studies of the axonal alterations describe nonspecific changes; accumulations of vesicular and membranous structures appear in the axoplasm before actual axonal degeneration.¹³⁵

Physiology

Humans. Electromyography in individuals with OPIDP usually shows evidence of acute denervation and chronic motor unit reinnervation. Neurogenic abnormalities tend to be limited to distal limb muscles in mild instances, but may be found in more proximal leg muscles in severe cases. Motor nerve conduction is either normal or only mildly slowed in the legs and normal in the arms. Sensory nerve action potentials are usually absent in the legs and of reduced amplitude in the arms. The earliest electrophysiologic changes involve diminution of sensory, rather than motor, potential amplitudes. Electrophysiologic studies appear to be a sensitive test for screening patients exposed to OPs^{95A}.

Experimental Animals. Unilateral OP neuropathy has been produced in cats by injecting DFP into the ipsilateral femoral artery.¹⁰⁷ There is a profound loss of indirectly evoked post-tetanic potentiation of indirect twitch tension in the soleus muscle, this suggests that the lesion is located in the distal axon and that OPs esters have a local toxic effect on nerve fibers.

Pathogenesis

The initial biochemical event in the development of OPIDP involves inhibition of neuropathy target esterase (NTE, formerly neurotoxic esterase) by phosphorylation⁸⁵. This enzyme is distinct from AChE. The function of NTE is unknown; it is present in brain, spinal cord, and peripheral nerve, as well as non-neural tissues such as spleen, muscle, and lymphocytes. Not all OPs that inhibit NTE are neurotoxic as some OPs that are able to inhibit NTE do not produce OPIDP. However, all neurotoxic OPs inhibit NTE, a characteristic that is used to predict whether an OP is *potentially* neurotoxic.

Phosphorylation of NTE is a rapid event, probably occurring within hours of exposure. A sufficient amount of NTE must be inhibited for OPIDP to develop (e.g., in the hen, about

70-80 per cent of brain NTE must be inhibited).⁸⁴ The amount of inhibited human NTE that is required before OPIDP occurs is not yet known, but appears to be less than required in the hen.¹⁰³ The degree of NTE inhibition varies according to the OPs and the source of NTE. For example, in the hen, brain NTE is most susceptible to inhibition by di-*i*-butyl-2,2-dichlorovinyl phosphate, followed by spinal cord NTE, and then nerve NTE.¹¹⁶ Inhibition of peripheral nerve NTE is required to develop OPIDP and no clinical deficits result if only brain NTE is inhibited. Inhibition of cord, but not nerve, NTE results in a spastic spinal syndrome, without peripheral neuropathy. The ability of neuropathic OPs to inhibit NTE from multiple sources underlies the rationale for assaying lymphocyte NTE as an industrial screening procedure to predict the likelihood for developing OPIDP in individuals exposed to neurotoxic OPs.¹⁰³ Studies in animals have documented the correlation between depressed lymphocyte NTE and, on postmortem examination, reduced nervous tissue NTE after intoxication by the combination of 2,4-dichlorophenoxyacetic acid (2,4-D), mecoprop (MCP), and chlorpyrifos.¹²⁹ Lymphocyte NTE assays are still not widely used in industry.

Although inhibited NTE is required to develop OPIDP, its presence alone is insufficient for the development of neuropathy. The development of OPIDP requires, in most cases, "aging" of the inhibited NTE enzyme, a nonenzymatic reaction involving cleavage of a lateral side chain from the phosphorylated NTE enzyme, leaving a charged monosubstituted phosphorous acid residue at the active site.^{33,34, 86,176} This critical step apparently occurs in the nerve fiber, rather than the cell body. The amount of aged inhibited NTE cannot be measured but is assumed to be proportional to the amount of inhibited NTE. The exact mechanism by which aged inhibited NTE causes OPIDP is unclear. Animal studies have correlated the presence of aged inhibited NTE with impaired retrograde transport of radioactive¹²⁵ I-labeled tetanus toxin within the sciatic nerve.¹¹⁶ Maximum reduction in axonal transport occurs 7 days after exposure, prior to morphologic evidence of axonal degeneration. Retrograde transport fails to show progressive deterioration once axonal degeneration occurs, suggesting that transport dysfunction does not result from the axonal degeneration itself¹¹⁵. Anterograde slow and rapid transport systems remain intact. Animals with insufficient NTE inhibition do not develop abnormalities of retrograde transport or clinical evidence of OPIDP. There has been some evidence suggesting that aging of NTE is not invariably necessary to develop OPIDP. Some OPs that inhibit but do not age NTE have been shown to cause neuropathy when given at extremely high doses, with almost complete inhibition of NTE. It is paradoxical that the severity of neuropathy in these cases is mild, despite the great amount of inhibited NTE. Severity of the OPIDP does not appear to correlate with the amount of aged NTE¹⁰⁴.

The development of OPIDP is, in most instances, associated with those OPs that inhibit and age NTE. Failure to age is probably related to the stability of phosphorus-carbon bonds of some OPs. Pretreatment with an OPs capable of inhibiting NTE by aging protects against the subsequent development of OPIDP when exposed to other neurotoxic OPs. Infusion of such a prophylactic OPs into a single limb of an animal, before administration of a neurotoxic OPs, protects that appendage from neuropathy, while other extremities develop OPIDP.²¹ Animals pretreated with a prophylactic OPs fail to

demonstrate abnormalities of retrograde transport when exposed to neurotoxic OPs, supporting a link between aged inhibited NTE, impaired retrograde transport, and subsequent axonal degeneration.¹¹⁶ Impairment of retrograde transport may account for the accumulation of large vesicular and membranous structures seen in the nerve axoplasm before to actual axonal degeneration.¹³⁵ Many OPs that appear protective when given prior to the administration of a neurotoxic OPs, can potentiate neuropathy (promotion) if given shortly after exposure to a neurotoxic OPs. The phenomenon by which the same OPs can either protect or promote neuropathy is possible because each condition is due to effects on different targets. Protection appears to involve submaximal inhibition of NTE, while promotion requires interaction with an as yet unknown target, but probably not NTE.¹¹⁷

POLYCHLORINATED BIPHENYLS

Polychlorinated biphenyls (PCB's) have been extensively used as plasticizers and in electrical insulation. There has been considerable environmental pollution of waterways and marine life with PCBs. It is alleged, but still unproven, that developmental neurotoxicity has appeared in such populations following low-level, long-term environmental exposure^{145,91}. Outbreaks of mildly symptomatic sensory neuropathy occurred in 1968 in Japan¹²⁰, in 1978 in Taiwan^{30,31} when cooking oil became contaminated with PCBs, and in Finland¹⁵⁰ among workers exposed following an explosion of capacitors. Reports of the Taiwanese and Finnish episodes are featured by meticulous longitudinal peripheral neurophysiological evaluations. Affected individuals in Taiwan and Japan were repeatedly exposed from PCB-contaminated cooking oil; they developed acne, brown-pigmented nails, and a discharge from the meibomian glands. In the Taiwanese cases, blood levels of PCB and derivatives, polychlorinated quaterphenyls and polychlorinated dibenzofurans, were elevated at the initial evaluation, two years following exposure; they declined moderately after four years. A few persons experienced distal numbness and displayed absent tendon reflexes and slightly diminished pain and tactile sensation in the feet. Sensory nerve conduction was mildly slowed at the two year follow up, and improved to near normal values at the four year assessment. The Finnish exposure, a monophasic event, was unaccompanied by skin changes, and only vague complaints of odd "pin and prick sensations, itching or odd temperature feelings in arms and legs"¹⁵⁰. There was significant slowing of sensory nerve conduction values when measured two months after exposure, but sural nerve action potential amplitudes were unaffected. The nerve conduction abnormalities returned to near normal levels six months later. A report of sensorimotor neuropathy in three transformer maintenance workers is unconvincing because of inadequate neurophysiological documentation¹².

Rats intoxicated with tetrachlorobiphenyl develop slowed motor conduction¹²⁵. The pathogenesis of PCB neuropathy is unknown.

Biphenyl itself has also been reported to induce manifestations of sensorimotor neuropathy (thought to be demyelinating in type) and psychologic changes in individuals using this compound as a fungistatic agent to preserve citrus fruits⁶⁷.

PYRIMINIL (VICOR)

Pyriminil (vacor), a structural analogue of nicotinamide, is most commonly used as a rodenticide. Ingestion of vacor results in a rapidly progressive, severe, distal axonopathy with accompanying diabetes mellitus, autonomic dysfunction, and encephalopathy^{95B}. Diabetes is due to necrosis of pancreatic beta cells. Within hours of high dose suicidal ingestion, there ensue distal limb weakness, sensory loss with impaired postural reflexes, and cranial nerve dysfunction. Accompanying autonomic disturbances include hypotension, hypothermia, gastric hypomotility, and urinary retention. Occasionally, there may be signs of central nervous system dysfunction including visual impairment, myoclonic jerks, nystagmus, cerebellar dysfunction, and encephalopathy.¹³⁰ Early administration of nicotinamide and gastric lavage may be helpful. Gradual recovery from the neuropathy occurs, but many remain severely diabetic with residual autonomic impairment.

Animals given high dose vacor demonstrate early degeneration of distal peripheral nerve axons, possibly related to impaired fast antegrade axonal transport in distal nerve segments¹⁷⁵. The impairment of fast axonal transport in somatic and autonomic nerves may account for the rapid appearance of neuropathy after Vacor ingestion. The underlying pathogenetic mechanism remains unclear. Since early administration of nicotinamide can prevent severe dysfunction, it is postulated that vacor inhibits a NAD-dependent enzyme essential to energy metabolism.

TRICHLORETHYLENE & DICHLOROACETYLENE

Trichlorethylene (TCE) is used in dry cleaning and rubber production and as a degreasing agent. It was formerly widely employed as a general anesthetic. It is unclear whether chemically pure TCE is neurotoxic. It is suggested that cranial neuropathy stems from a decomposition product, dichloroacetylene (DCA), resulting from interaction of TCE with alkaline materials.

Acute industrial exposure or anesthetic exposure to TCE/DCA has been associated with a unique neurotoxic syndrome, namely prompt dysfunction of the trigeminal and, to a lesser extent, the facial, oculomotor, and optic nerves⁴⁵. Peripheral limb nerves have never been definitively implicated. The effect of TCE/DCA on the trigeminal nerve is so predictable that, for a time, victims of tic douloureux were intentionally exposed to it. Cranial nerves are affected after a period of exposure to high concentrations. Trigeminal neuropathy usually includes loss of sensory modalities in the entire distribution of the nerve, accompanied by weakness of muscles of mastication. Recovery occurs over a period of months, but patches of malar hypalgesia and absent corneal reflexes may be detected 12 years later⁴⁶. One postmortem report describes extensive axonal and myelin degeneration in the trigeminal nerve and its spinal and main sensory nuclei; lesser degrees of neuronal degeneration were present in facial, abducens, and vestibular nuclei and in the nucleus of the tractus solitarius²⁰.

Although most instances of trigeminal neuropathy have occurred following exposure to a mixture of trichloroethylene and its degradation product, several case reports strongly suggest that either agent alone may cause cranial neuropathy. Two reports describe vertigo and delayed onset of cranial neuropathy following inhalation of pure trichloroethylene at room temperature in the absence of alkali^{94,124}. Exposure to dichloroacetylene alone has also caused facial sensory loss^{73,140}.

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