

Chapter 167

Occupational and Environmental Neurotoxicology

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Neurotoxicology commands newspaper attention these days. Will chemical terrorism cause catastrophic numbers of deaths and innumerable neurologic sequelae in survivors? Is there a Gulf War syndrome in which exposure to anticholinesterase nerve gases caused amyotrophic lateral sclerosis (ALS)? Are the developing brains of children vulnerable to neurotoxic hazards whereby consequences of early damage may not emerge until advanced age? Are adult behavioral changes a result of subclinical occupational or environmental exposures? Can mercury intoxication result from inhalation of the element from dental amalgams and can that cause autism, Alzheimer disease, or ALS? These questions have been debated in an atmosphere of contentious uncertainty.

In this chapter we focus on the particular clinical syndromes that result from exposure to heavy metals, solvents, and natural neurotoxins (Table 167.1). Clinical diagnosis and laboratory proof of diagnosis are practical issues. Because treatment of neurotoxic damage is mainly symptomatic and supportive, recognition of disease potential and prevention are of paramount importance. We bypass detailed discussion of behavioral effects from chronic

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low-level exposures as beyond the scope of this chapter. More detailed information is provided in the General section of Suggested Readings.

TABLE 167.1 Neurotoxic Syndromes

| <i>Agent</i> | <i>Syndrome</i> | | |
|--------------|---|--------------|----------------|
| | <i>Occupational or Other Exposure</i> | <i>Acute</i> | <i>Chronic</i> |
| Metals | | | |

| | | | |
|-----------|---|------------------|--|
| Arsenic | Pesticides, pigments, paint, electroplating, seafood, smelter, semiconductors | Encephalopathy | Neuropathy |
| Lead | Solder, lead shot, illicit whiskey, insecticides, auto body shop, storage battery manufacture, smelter, paint, water pipes, gasoline sniffing | Encephalopathy | Encephalopathy, neuropathy, motor neuron disease-like syndrome |
| Manganese | Iron industry, welding, mining, smelter, fireworks, fertilizer, dry cell batteries | Encephalopathy | Parkinsonism |
| Mercury | Thermometers, other gauges; dental office (amalgams); felt hat manufacture Electroplating, photography | Headache, tremor | Neuropathy, encephalopathy with dementia, tremor |
| Tin | Canning industry, solder, electronics, plastics, fungicides | Delirium | Encephalomyelopathy |

Solvents

| | | | |
|------------------|--|----------------|--------------------------|
| Carbon disulfide | Rayon manufacture, preservatives, textiles, rubber cement, varnish, electroplating | Encephalopathy | Neuropathy, parkinsonism |
|------------------|--|----------------|--------------------------|

| | | | |
|------------------|--|----------|---------------------------------------|
| Trichlorethylene | Paints, degreasers, spot removers, decaffeination, dry cleaning, rubber solvents | Narcosis | Encephalopathy, trigeminal neuropathy |
|------------------|--|----------|---------------------------------------|

| | | | |
|--------------------------|--|----------|------------------------------------|
| Hexacarbons ^a | Paints, paint removers, varnish, degreasers, rapid-drying ink, glues, cleaning agents, glues for making shoes in poorly vented cottage industry, glue sniffing, MNBK in plastics | Narcosis | Neuropathy, encephalopathy, ataxia |
|--------------------------|--|----------|------------------------------------|

Insecticides

| | | | |
|------------------------------|--------------------------|----------------------|--------------------------------|
| Organophosphates, carbamates | Manufacture, application | Cholinergic syndrome | Ataxia, neuropathy, myelopathy |
|------------------------------|--------------------------|----------------------|--------------------------------|

| | | | |
|-----------------|---|-----------------------|---|
| Carbon monoxide | Accidental or deliberate exposure in motor vehicles, faulty gasoline-fueled heaters | Anoxic encephalopathy | Encephalopathy, delayed neuropsychiatric syndrome |
|-----------------|---|-----------------------|---|

| | | | |
|------------------|------------------------------|---|---------------------------------------|
| Methyl alcohol | Contaminated illicit whiskey | Retinal blindness | |
| Recreation abuse | | | |
| Nitrous oxide | Dental offices | Encephalopathy | B ₁₂ -deficient myelopathy |
| Seafood | | | |
| Ciguatera | | Sensory neuropathy with temperature inversion | |
| Shellfish | | Acute neuropathy | |

^aHexacarbons: n-hexane, methyl-n-butyl ketone (MNBK).

RECOGNIZING INTOXICATION CLINICALLY

Potential neurotoxins are classified as follows: (1) therapeutic drugs; (2) biologic agents; (3) radiation and electricity; (4) heavy metals; (5) solvents and vapors; (6) insecticides, herbicides, fungicides, and rodenticides; (7) air pollution; (8) food additives; and (9) social poisons. Diagnosis of neurotoxicologic damage requires clinical thoughtfulness. The history must include the composition and toxicity rating of suspected agents; whether single or mixed substances are involved; host dose exposure; and epidemiology. Additional considerations include the following:

1. Exposure may be acute high dose or chronic low dose;
 2. short or long latency may separate exposure and symptoms;
 3. pre-existing or coincidental disease may complicate diagnosis;
 4. symptoms may be numerous and nonspecific;
 5. susceptibility varies in different people, and animal toxicity does not always correlate to that in humans;
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6. damage may be reversible or irreversible;
 7. a cascade of effects may have secondary and systemic complications as well as psychological

problems;

8. secondary gain, especially in litigious countries, complicates diagnosis;
9. neurologic signs may be absent or subtle within recognized syndromes, such as: peripheral neuropathy, myelopathy, cerebellar damage, movement disorders, or encephalopathy;
10. laboratory data, which might serve as markers of neurotoxic damage, may be normal or only mildly deranged or may be nonspecific despite clear symptoms and signs of neurologic disorder;
11. other possible causes must be excluded (Table 167.2) by considering systemic or metabolic disease and evaluating therapeutic drugs the patient may be taking.

TABLE 167.2 Clues to the Diagnosis of Intoxications

Nature of exposure

Occupation with known hazard

Recreational use of known hazard

Accidental exposure to hazard

Dialysis (aluminum)

Cluster or epidemic of syndrome (seafood, "huffing")

Dietary exposure to known hazard (seafood)

Diagnosis of exclusion

Therapeutic drugs

Alcohol abuse

Illicit drug abuse

Infection

Systemic disease: renal, pulmonary, calcium, liver, endocrine, electrolytes

| | |
|--|---|
| | Inherited metabolic diseases |
| Age of patient | Children—lead encephalopathy |
| | Adolescents, young adults—sniffing, nitrous oxide |
| Associated symptoms, signs or laboratory abnormalities | |
| Lead | Gastrointestinal symptoms: colic, constipation |
| | Anemia |
| | Basophilic stippling |
| | ↑ urinary δ -aminolevulinic acid |
| Thallium | Alopecia |
| Arsenic | Mees lines (horizontal stratifications of fingernails or leuconychia) |
| Nitrous oxide | B ₁₂ deficiency |
| Specific syndromes | |
| Optic neuropathy and retinopathy | Methyl alcohol |
| SMON | Clioquinol |
| Methyl mercury | Minamata disease |
| NMBK | Trigeminal neuropathy |

NMBK, n-methyl butyl ketone; SMON, subacute myelo-optic neuropathy.

Reliable diagnosis often depends on the recognition of exposure by occupation or recreation, recognition of a specific syndrome, and elimination of other causes. Outbreaks or clusters may be encountered with mild symptoms of glue sniffing or the devastating encephalomyelopathy of Minamata disease in Japan, which was caused by methyl mercury. The circumstances of attempted suicide or fire usually identify carbon monoxide exposure; a motor running in a parked automobile or a faulty gasoline-fueled heater are most often responsible. For the following discussions, the primary at-risk occupations are listed in Table 167.1 and are not repeated in the text. Because of No. 9, a skilled, correctly interpreted neurologic examination is essential. For example, is an examinee's mild difficulty with skilled and rapid successive movements or mild loss of check with rebound just clumsiness within the range of normal, or are they manifestations of cerebellar damage?

Laboratory Evaluation

Sampling of contaminated water, air, or soil provides exposure data. Analysis of blood, hair, and nails provides data about possible heavy metal toxicity. Diagnostic tests may include electrophysiology, neuroimaging, neuropsychology, and biochemical markers. Many become positive only after irreversible damage has occurred; that is, sensitivity is poor. Likewise, specificity may also be poor, except for MRI after carbon monoxide poisoning. EMG and nerve conduction velocity are the most reliable in sensitivity and reproducibility. However, many neurotoxins affect the CNS, not the peripheral nervous system.

Acute Encephalopathy

Syndromes of stupor and coma, confusion, hyperactivity or somnolence, memory impairment, and behavioral change arise from many different disorders, as described in Chapter 1. The acute encephalopathy of lead poisoning affects children; seizures and increased intracranial pressure without a mass lesion may be clues to diagnosis. The circumstances of intoxication may be evident as in glue sniffing or dialysis dementia. Heavy metal intoxication is not encountered frequently among the causes of delirium, but may result from attempted murder by poisoning. The effects of carbon monoxide inhalation include death, prolonged coma, and subsequent dementia, or brief loss of consciousness and prompt recovery.

Chronic Encephalopathy

Dementia, with or without tremor, can arise from occupational exposure to heavy metals. Therefore, when confronted with a patient who may have been poisoned, it may be more important to know the occupational history than to order a sweeping survey of blood and urine. Mercury intoxication may be more often associated with tremor than other exposures, but this is probably not a reliable

guide. Parkinsonism can appear in workers in manganese smelters if monitoring guidelines are not heeded. Parkinsonism may also follow chronic exposure to carbon disulfide. Chronic encephalopathy is reported in workers and others exposed to solvents, such as volatile organic compounds (VOCs).

Extrapyramidal and Cerebellar Syndromes

VOCs, especially toluene, may cause movement disorders. Carbon monoxide can cause both parkinsonism and cerebellar dysfunction.

Peripheral Neuropathy

Neuropathy may be caused by any heavy metal, almost always the result of occupational exposure. The symptoms are those of any sensorimotor neuropathy with acroparesthesia and distal limb weakness. Toxic optic and autonomic neuropathies seem to be rare. A hallmark of thallium neuropathy is baldness. The neuropathy of organophosphate poisoning may be accompanied by upper motor neuron signs that imply a myelopathy; sometimes the residual signs include those of the lower motor neuron, but the occupational history and sensory loss differentiate the syndrome from motor neuron disease.

Cranial Neuropathy

Trichloroethylene causes a selective sensory neuropathy of the trigeminal nerve; the syndrome is so specific that it was once seriously evaluated as a treatment for idiopathic trigeminal neuralgia. Visual loss from optic neuropathy or retinopathy is a manifestation of methanol toxicity and many therapeutic drugs.

Delayed Effects

A delayed neuropathy has been reported after organophosphate exposure and a delayed neuropsychiatric syndrome after carbon monoxide poisoning. Exposure to pesticides has been implicated in mental retardation and also in Parkinson disease.

HEAVY METAL INTOXICATION

Pathogenesis

The heavy metals have diverse toxic effects on cell nuclei, mitochondria, other organelles, cytoplasmic enzymes, and membrane lipids. Clinical syndromes may result from combinations of these effects that do not readily explain the real-life disorders or why the assault should affect the CNS in some people, peripheral nerves in others, or both.

Lead provides an example of the complexity. It interferes with the sulfhydryl enzymes of heme biosynthesis, especially δ -aminolevulinic acid dehydratase, coproporphyrin oxidase, and ferrochetalase. As a result of these partial blocks, several metabolites accumulate in blood and urine: δ -aminolevulinic acid, coprophorphyryn III, and zinc protoporphyrin. Other heme-containing enzymes are also affected, including cytochrome P450 in the liver and mitochondrial cytochrome c oxidase. Lead also interferes with calcium-activated enzymes, calcium channels, and Ca^{2+} -ATPase. Lead has similarly multiple and diverse biochemical ill effects on cell metabolism. Sorting out these interactions and their relationship to the clinical syndromes is not a simple task, and there is even less basic information about other neurotoxicants.

Nevertheless, metals and biologic toxins have been used experimentally to analyze the pathogenesis of the neuropathies according to effects on axons, myelin, or Schwann cells.

Specific Clinical Syndromes of Metal Intoxication

Lead

Acute lead encephalopathy in children, attributed to pica or ingestion of flaking lead-containing paint, was first recognized in 1904; however, lead poisoning is among the oldest of occupational diseases and remains a common metal poisoning today. Although acute toxicity is rare, chronic toxicity can cause both central and peripheral effects, the former more common in children and the latter more in adults. Adults with chronic lead exposure yielding blood lead levels of 25 to 60 µg/dL may experience irritability, headache, and depressed mood, with signs of impaired visual-motor dexterity and reaction times. Overt effects—for example, weakness and atrophy of peripheral muscles with wristdrop—occur with long-term levels of 60 or more. Because of links between lead and cognitive dysfunction, behavioral problems, as well as stunted growth in children, the U.S. Centers for Disease Control acted in 1991 to define a childhood blood concentration of 10 µg/dL as a level of concern. Periodic screening of children aged 9 to 36 months is advocated, especially because nonspecific symptoms may emerge: lethargy, anorexia, intermittent abdominal pain with vomiting, or constipation. With blood levels above 80µg/dL, children seem more susceptible than adults to overt lead encephalopathy with delirium, ataxia, seizure, stupor, or coma with associated cerebral edema. In adults, the differential diagnosis includes a flulike viral illness that, like lead poisoning, may present with headache, myalgias, anorexia, nausea, and crampy abdominal pain. However, the symptom complex may evoke a wide

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differential including: various abdominal conditions, for example, renal colic; collagen-vascular disease; acute intermittent porphria; and others. Lead-induced encephalopathy may resemble acute infectious encephalopathy.

The whole blood lead concentration is the most reliable test because urinary lead levels increase and decrease more rapidly than blood levels in response to changes in lead exposure. The mean whole blood level in adults without exposure to occupational hazards is <5 µg/dL. Standard recommendations now consider levels safe up to 30 µg/dL; some consider a higher limit of 50 µg/dL safe. Workers are monitored closely if levels exceed 40 µg/dL. The upper limit of lead in urine is 150 µg/g creatinine. Peripheral neuropathy is usually accompanied by blood lead levels greater than 70 µg/dL.

Testing blood lead levels is recommended for children with presumed autism, attention deficit disorder, pervasive development disorder, mental retardation, or language problems. A diagnosis of lead intoxication is supported if blood zinc protoporphyrin exceeds 100 µg/dL or if urinary aminolevulinic acid excretion is >15 mg/L. With blood lead levels of 10 µg/dL, the activity of aminolevulinic acid dehydratase is low. At higher lead levels, the activities of coproporphyrinogen oxidase and ferrochetalase are also low. Anemia and basophilic stippling of erythrocytes are characteristic. Nerve conduction velocities are nonspecifically slow in lead and other neuropathies.

Treatment combines decontamination, supportive care, and the judicious use of chelating agents. In diseased individuals, chelation therapy commences with levels of 40 µg/dL. Supportive care may include treatment of increased intracranial pressure by standard use of intravenous mannitol and glucocorticoids, the latter because the pathophysiology of lead encephalopathy involves capillary leak. In patients with lead encephalopathy, calcium disodium edetate, or calcium ethylenediaminetetraacetic acid (EDTA), should be administered at 30mg/kg every 24 hours. Some advocate initiating chelation with a single dose of dimercaprol (British anti-Lewisite or BAL), 4 to 5 mg/kg deep intramuscularly. Alternatively meso-2, 3-dimercaptosuccinic acid (DMSA or Succimer) is advocated for treatment of moderately severe chronic lead intoxication. Childhood lead exposure carries a risk of long-lasting health impairment, especially with neurocognitive and neurobehavioral sequelae, emphasizing the need for primary prevention and for obtaining occupational and environmental information.

Mercury

The relations between elemental, inorganic, and organic forms of mercury involve transformations from one form to another. Modern epidemics include the Minamata disease from fish contaminated by methyl

mercury affecting 2,500 people in Japan; erethism in the hatting industry, which is also called the “mad hatter” syndrome from mercuric nitrate. About 10,000 tons of mercury are mined per year with 2,000 to 3,000 tons from man-made and natural sources released into the atmosphere per year. Runoff into natural bodies of water occurs as mercury exposures persist. Acute toxicity from elemental mercury may include encephalopathy and seizures, whereas its chronic toxicity includes peripheral sensorimotor neuropathy, dysarthria, and parkinsonism. Subclinical nerve conduction and neuropsychiatric abnormalities have been documented in the modern workplace.

Toxicity from organic mercury differs between short- and long-chain compounds. Organic mercury includes methyl mercury (MeHg), the cause of Minamata disease, and ethyl mercury. Minamata disease produces neuropathologic abnormalities in the cerebral cortex, cerebellum, and peripheral nerves. The short-chain compounds readily enter the CNS. Symptoms of organic mercury toxicity include the following: tremor; ataxia; dysarthria; paresthesias of the hands, feet, and mouth; visual field constriction; erethism; and spasticity. Prenatal exposure to MeHg can cause severe congenital abnormalities such as micrognathia, microcephaly, mental retardation, blindness, and motor deficits. Excessive MeHg intake has been reported in fish-eating communities in Greenland, the Faroe Islands, the Seychelles, the Madeira Basin of the Amazon River, and New Zealand. Several observations indicate that the immature brain is highly susceptible to MeHg toxicity from prenatal maternal exposure.

The 24-hour urine mercury concentration may assess both recent exposure and elimination of tissue burden. The normal blood concentration is less than 10 to 20 $\mu\text{g/L}$, and the urinary level is less than 20 $\mu\text{g/L}$. Treatment consists of decontamination and chelation, with established guidelines. If the person is symptomatic, dimercaprol is given intramuscularly 3 to 5 mg/kg every 4 hours for day 1, every 12 hours on day 2, and then once a day for the next 3 days, followed by a 2-day interruption. Other agents are 2,3-dimercaptosuccinic acid and 2,3-dimercapto-propane-1-sulfonate, a water-soluble form of BAL. All agents are somewhat effective for organic and inorganic mercury poisoning.

Prevention of mercury intoxication requires monitoring in high-risk occupations, including dental offices, and correction of inadequate ventilation, avoiding vacuuming of spilled mercury, and removal of workers whose urinary level has increased fourfold or is $>50 \mu\text{g/L}$. Control of industrial pollution may require major efforts.

Arsenic

Acute arsenic poisoning is a multisystem disaster, with vomiting, bloody diarrhea, myoglobinuria, renal failure, arrhythmias, hypotension, seizures, coma, and death. In survivors, Mees lines on the fingernails and sensorimotor

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neuropathy appear in 7 to 14 days, sensory symptoms dominate, and weakness is more profound in the legs than in the arms and hands. Slow and incomplete recovery takes years. Nerve conduction velocities are typically slow. Cognition may be impaired in some survivors, depending on the severity of the acute encephalopathy.

Intoxication by inhalation may be acute or chronic. The chronic version is “blackfoot disease” with vascular changes, gangrene, and a less severe peripheral neuropathy. The use of arsenic trioxide to treat leukemia may be followed by arsenic neuropathy.

Arsenic toxicity is a global health problem. It is estimated that tens of millions of people, for example, in Bangladesh, are at risk of excessive arsenic levels from natural geologic sources leaching into aquifers, contaminated drinking water, from mining, and from other industrial processes. Although arsenicosis with resulting cancer in various sites is a major problem, encephalopathy and peripheral neuropathy are also reported. The neuropathy is primarily axonal with secondary demyelination.

The diagnosis of arsenic intoxication is confirmed by urinary levels $>75 \mu\text{g/dL}$. Hair analysis has been used but is not reliable.

BAL therapy is also used for acute arsenic poisoning. It is most effective before symptoms of neuropathy

appear. BAL is considered more effective than penicillamine in treating the chronic neuropathy. Hemodialysis is another treatment for an acute episode.

Thallium

Despite the ban on manufacture of thallium rodenticides in the United States, accidental and suicidal exposures still occur because the poisons are available in other countries. Industrial exposure still occurs. The acute episode is dominated by gastrointestinal symptoms. Paresthesias may be noted soon afterward, but overt signs of neuropathy may take 2 weeks to appear. The encephalopathy may include cognitive impairment and choreoathetosis, myoclonus, or other involuntary movements. The unique clue to diagnosis is alopecia (loss of hair), which begins 1 to 3 weeks after exposure. Neuropathy and dermatitis may be prominent in chronic exposure.

After acute exposure, blood tests are not useful for detecting thallium because the metal is taken up by cells so rapidly that blood levels do not rise. Urinary thallium can be detected by atomic absorption spectrometry. Normal urinary values are 0.3 to 0.8 $\mu\text{g}/\text{L}$. Levels of 200 to 300 are seen in overt poisoning. A provocative test depends on potassium chloride (KCl) which is given orally in a dose of 45 mEq. Potassium displaces thallium from tissue stores, blood levels rise, and urinary content can be followed serially.

Aside from monitoring occupational exposure to thallium, an important preventive measure is protection of children against the ingestion of candylike pellets. Treatment of acute poisoning depends in part on enhancing urinary and fecal excretion of thallium by giving laxatives and using Prussian blue or activated charcoal to retard absorption. Urinary excretion is enhanced by forced diuresis and administration of KCl. Hemodialysis may be effective.

Manganese

George Cotzias, discoverer of the therapeutic value of levodopa in Parkinson disease (PD), followed an unusual path to that achievement. He was a biochemist interested in the role of metals in enzyme activity. Manganese was one such metal, and that took him to an outbreak of parkinsonism in South American miners. At about that time, Hornykewicz identified the lack of dopamine in the substantia nigra of patients with PD. Cotzias successfully pursued the treatment of PD.

Manganese intoxication, still a threat in industrial settings, reproduces the essential motor features of PD but with sufficient clinical and pathologic differences to indicate the conditions are not identical; for instance, exaggerated tendon reflexes and behavioral features occur early in manganese toxicity. The outlook is gloomy, including severe cognitive loss. Responses to levodopa and to chelation therapy are limited.

Aluminum

Dialysis dementia has been attributed to aluminum in the dialysis water and also in ingested phosphate binders used to control blood phosphorus levels. Treatment of the water and avoidance of the binders have decreased the incidence. Encephalopathy, however, has also occurred in uremic patients dialyzed with deionized water and also in some who took the binders without dialysis, implying that abnormal retention of aluminum is a characteristic of uremia.

Paresthesias and weakness were part of "potroom palsy," a complex syndrome in workers in a smelter who were exposed to pots that had not been vented properly. Other manifestations included ataxia, tremor, and memory loss.

Among discarded theories of the pathogenesis of Alzheimer disease is one that related aluminum accumulation in neurofibrillary tangles.

OTHER INTOXICATIONS

Pesticides: Organophosphates and Carbamates

Millions of agriculture workers and amateur gardeners are exposed to these substances. Also exposed are those engaged in their manufacture and those who use or store

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compounds designed for chemical warfare and/or terrorism. It is estimated that 150,000 to 300,000 people have pesticide-induced illness each year. Popular compounds include malathion, parathion, and others. Most are lipid soluble and readily absorbed after ingestion, inhalation, or application to the skin. They are powerful inhibitors of acetylcholinesterase.

Three clinical stages follow in sequence. First, *acute cholinergic crisis* comprises nicotinic effects (limb weakness, fasciculation, tachycardia) and muscarinic manifestations (miosis, lacrimation, salivation). CNS signs include ataxia, seizures, altered consciousness, and sometimes coma. Second, the *intermediate syndrome* appears 2 to 4 days after exposure. Weakness may be profound, affecting the proximal limbs, cranial muscles, neck flexors, and respiration. Tendon reflexes are lost. The differential diagnosis includes the Guillain-Barré syndrome, periodic paralysis, and myasthenia gravis. Among survivors, recovery may be slow but is the rule. Third, *organophosphate-induced delayed neuropathy* appears 1 to 5 weeks after exposure. The syndrome was first described during the period of Prohibition in the United States when illicit whiskey was made in home stills; 50,000 people consumed “Jamaica ginger” or “Ginger Jake” that was later found to contain triorthocresyl phosphate. Paresthesias and distal leg weakness appeared weeks later. Triorthocresyl phosphate is not an anticholinesterase, but the syndrome was then seen after exposure to cholinergic organophosphates. The disorder has been attributed to inhibition of “neuropathy target esterase,” disruption of axonal transport, and a dying back neuropathy. Although paresthesias may be noted, the disorder is dominantly motor. Among survivors, upper motor neuron signs implicate the CNS, which, in combination with profound lower motor neuron signs, may simulate ALS except that there is no progression for years.

Exposure can be documented by levels of the drug or its metabolites in blood or urine. Measurement of red cell or plasma cholinesterase is an indirect marker. In electrodiagnostic studies, there may be a repetitive response to a single nerve stimulus.

The acute disorder is a medical emergency risking death from respiratory paralysis. If the patient has been splashed, clothing must be stripped and the skin washed thoroughly to prevent further absorption. Gastric lavage may be needed. Airway control and ventilation must be ensured and cardiac function monitored. Atropine is the best antidote. Subcutaneous doses of 0.5 to 1.0 mg are given every 15 minutes until an effect is observed in the form of dilated pupils, flushed face, dry mouth, and dry skin with cessation of sweating. To suppress airway secretions, some give intravenous doses up to 2 mg every hour. Glycopyrrolate can be added to atropine.

Oxime therapy is also recommended in seriously ill patients. These compounds reactivate acetylcholinesterase and should be given as soon as possible after exposure by continuous intravenous infusion.

Since 9/11/2001, there has been increasing concern about global terrorism, including the NBCs of nuclear (N), biologic (B), and chemical (C) agents. At least five groups of organophosphorous nerve agents are similar to, but more deadly than, agricultural organophosphate insecticides. Management of survivors of chemical terrorism will include decontamination; ventilation (high resistance airway); antidotes such as atropine or pralidoxime chloride (phosphotriesterase pralidoxime-2-chloride or 2-PAM); diazepam (for seizures); and intravenous fluids, with other supportive therapy. Subsequently, physicians will manage brain damage caused by the agents or indirectly, for example, from hypoxia and metabolic sequelae. It will be important to separate victims suffering from hysteria or panic. For example, after the 1994 terrorist subway attack in Japan involving phosphonofluoridic acid (sarin), several hundred people were chemically damaged but 5,000 worried people came to health care facilities.

Other related groups of compounds are termed insecticides, including pyrethins, pyrethroids,

organochlorines, and N,N diethyl-3-methylbenzamide (DEET). All may cause unexplained seizures.

Volatile Organic Compounds (VOC)

Neurologic syndromes to VOCs, also called *solvents*, occur after either occupational or deliberate exposure by inhalation abuse. They include aromatic and aliphatic hydrocarbons, alcohols, esters, ketones, aliphatic nitrates, anesthetic agents, halogenated solvents, and propellants. Aromatic hydrocarbons, especially toluene, produce cerebral and cerebellar damage. Aliphatic hydrocarbons caused outbreaks of peripheral neuropathy in industrial or recreational exposures to *n*-hexane or methyl-*n*-butyl ketone. Paresthesias and weakness appear distally in the legs and only later are the hands affected. Acutely, the syndrome may resemble the Guillain-Barré syndrome, including slow conduction velocity. Alternatively, progression may be slow. Optic neuropathy is rare. The characteristic pathologic change is neurofilamentous axonal swelling and distal axonal degeneration. Effective measures have reduced industrial exposure and eliminated the agents from glues formerly used for sniffing.

Other organic compounds that induce axonal neuropathy by industrial exposure are acrylamide, carbon disulfide, methyl bromide, and triorthocresyl phosphate. Halogenated hydrocarbons are toxic for the CNS by damaging nerve cell membranes and altering neurotransmission; an excitatory phase is rapidly followed by CNS depression. The compounds include chloroform, methylene chloride, and tetrachloroethane. The neurotoxic potential of one

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substance is sometimes facilitated by others in the same commercial product.

Carbon Monoxide

Carbon monoxide (CO) intoxication is a common cause of neurotoxic damage and death. Deaths averaged 5,600 per year in a recent 10-year period in the United States with 2,700 of these accidental and the rest suicidal. Statistics on nonfatal CO encephalopathy and the delayed CO-induced neuropsychiatric syndrome are imprecise. Accidents are caused predominantly by poorly ventilated gasoline-powered heaters. Toxicity results from tissue hypoxia and direct damage to cellular structures. CO competes with oxygen for binding to hemoglobin. It binds to other proteins including myoglobin and cytochrome *c* oxidase.

Symptoms may be mild, simulating viral infection, or it may occur with another emergency, smoke inhalation. Nonspecific symptoms may comprise headache, malaise, dizziness, nausea, difficulty concentrating, and dyspnea. More severe exposures can lead to coma and death. In survivors, neurologic symptoms include dementia, cerebellar dysfunction, and parkinsonism. A delayed neuropsychiatric syndrome may follow acute exposure by 3 to 240 days, with cognitive and personality changes and psychotic behavior. This syndrome occurs in 10% to 30% of CO poisonings. Although up to 10% of victims show gross neurologic or psychiatric impairment, more frequent is subtle, persistent neuropsychiatric deficit. CT, MRI, MR spectroscopy, and isotopic imaging can disclose the brain damage. Postmortem findings include multifocal necrosis; myelinopathy with discrete globus pallidus and cortical lesions, and white matter lesions.

Hematologic diagnosis is made by finding high levels of carboxyhemoglobin (COHb). Normal levels are less than 5% in nonsmokers and can be as high as 12% in two-pack-per-day smokers. Although serious toxicity is often associated with levels >25%, neurologic damage is not always directly related to the COHb level. Furthermore, serum levels may have fallen by the time the patient reaches the emergency room such that a normal COHb level does not rule out CO poisoning. Blood taken at the scene by emergency technicians can be used. Measurement of CO in expired air and in the exposure area's ambient air can also be useful. The U.S. government standard for CO prohibits exposure to more than 35 ppm, averaged over an 8-hour workday.

Initial treatment is 100% oxygen by a nonrebreather face mask, which will reduce the elimination half-life of COHb from 4 to 5 hours to 1 to 2 hours. Treatment continues until the COHb levels are below

10%. Most experts advocate hyperbaric oxygen (HBO) for treatment of symptomatic CO poisoning. It enhances elimination of COHb, with an average half-life of 20 minutes at three atmospheres. HBO therapy has been used with increasing frequency, but it is uncertain whether it hastens recovery or reduces the rate of late sequelae. Coma is a clear indication for hyperbaric therapy. Prevention is largely a matter of monitoring equipment such as gas heaters, monitoring workers, and providing public education about the hazards of running a motor vehicle in a closed space.

Nitrous Oxide Myelopathy (Layzer Syndrome)

In 1978, Layzer described 15 patients; 14 were dentists. Thirteen had abused nitrous oxide for 3 months to several years; two patients had been exposed only professionally, working in poorly ventilated offices. Symptoms included early paresthesias, Lhermitte symptoms, ataxia, leg weakness, impotence, and sphincter disturbances. Examination showed signs of sensorimotor polyneuropathy, often with signs implicating the posterior and lateral columns of the spinal cord in a pattern identical to that of subacute combined system disease owing to B₁₂ deficiency. Electrodiagnostic tests showed axonal polyneuropathy; CSF examination and other laboratory tests gave normal results. The gas interferes with the action of B₁₂.

Additional cases were reported in abusers of nitrous oxide, and improvement was seen in weeks or months after exposure ceased. Another version of the disorder was seen in people who had hematologic evidence of B₁₂ deficiency but were asymptomatic until the neurologic disorder was precipitated by nitrous oxide anesthesia for surgery. MRI shows a characteristic distribution of lesions in the spinal cord.

Scott et al. reproduced the syndrome by maintaining monkeys in an atmosphere of nitrous oxide. If the diet was supplemented with methionine, the disorder was prevented; but in controls, symptoms progressed to a moribund state; the spinal cord and peripheral nerves of the unsupplemented monkeys showed changes of combined degeneration. Inability to resynthesize methionine from homocysteine seemed responsible, and the primary neurologic lesion in human pernicious anemia may also be impaired synthesis of methionine.

Plant and Animal Poisons

Ciguatera poisoning or the *marine neurotoxic syndrome* is the most common nonbacterial form of food poisoning in the United States and Canada. It is caused by eating tropical reef fish that contain several toxins in edible parts; the toxins are thought to arise in dinoflagellates. It is endemic in subtropical regions. Food shipped to other parts of the world spreads the disease. The acute symptoms are gastrointestinal followed by sensory symptoms, paresthesias, and pruritus. *Sensory inversion* describes the peculiarity that cold feels hot and vice versa. Myalgia,

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fasciculations, areflexia, trismus, and carpedal spasm may be noted. Respiratory failure is exceptional. Other systems may be involved prominently, including pain on sexual activity.

None of the physical findings is diagnostic, and there are no formal criteria for diagnosis. Most associated toxins open sodium channels, but at least one affects calcium channels. Peripheral nerve conduction velocities are often slow. Bioassays for the ciguatoxins or immunochemical methods are being developed, but none has yet achieved approval by consensus. Treatment is symptomatic.

Shellfish poisoning can result from contamination of mollusks by saxitoxin, which blocks sodium channels. The symptoms are similar to ciguatera but more severe, and respiratory depression is a threat. In the series of De Carvalho et al., cerebellar ataxia was the dominant finding and peripheral nerve conduction was normal. Recovery was rapid in those patients, but among those described by Gessner et al., 3 of 11 patients were treated with mechanical ventilation and one died. Hypertension was also prominent. Binding assays and liquid chromatography identified the toxin in serum and urine. In Japan, the agent of puffer fish poisoning is tetrodotoxin. Treatment of these conditions is symptomatic.

In 1987, an outbreak of severe encephalopathy was traced to ingestion of mussels, and the offending

toxin was identified as domoic acid, a glutamate receptor agonist. Other epidemics led to the term *amnesic shellfish poison*.

Many plants contain pharmacologically active substances that cross the blood-brain barrier with resulting delirium, hallucinations, seizures, and sedation. Cicutoxin, a stimulant, from water hemlock may be ingested after mistakenly identifying it as wild carrot or sweet potato. Sedation may follow stimulation. Others, such as andromedotoxin from rhododendron, are depressants. In 1998, 122,578 plant exposures were reported to the American Association of Poison Control Toxic Exposure Surveillance System.

Neurolethyrism is a neurotoxic disease that has caused spastic paraparesis in impoverished countries; it is linked to heavy continuous consumption of *Lathyrus* during times of drought or flood. It contains the excitatory amino acid glutamate analog β -oxalylamino-L-alanine (BOAA) which is the major candidate toxin. A similar neurologic picture is attributed to prolonged consumption of the bitter cassava, *Manihot esculenta*. A disease called konzo became prevalent in sub-Saharan Africa when the cassava root was used in times of drought where local prevalence as high as 30 per 1,000 was reported in 1990. Cassava contains a cyanoglucoside linamarin, which is enzymatically converted to cyanide, which then damages neural cells. The clinical picture is a sudden, symmetric, and permanent spastic paraplegia. As in lathyrism, males are predominately affected. Hearing loss, visual impairment, and dysarthria sometimes occur in cassavaism but are not seen in neurolethyrism. Based on epidemiologic criteria, the ALS-parkinsonism-dementia complex in the Western Pacific is an example of environmentally induced neurodegeneration. Some studies linked the use of the neurotoxic seed or seed kernel of *Cycas* spp. and the appearance of the ALS/PD/dementia complex.

Methanol (Methyl Alcohol)

Methanol intoxication is seen in drinkers who take it as a substitute for ethanol. Acute poisoning was dominated by gastrointestinal symptoms, drunkenness, and coma. Severe acidosis results from the conversion of methanol to formaldehyde and formic acid. Viscera and brain show petechial hemorrhages and edema. In the series of Liu et al., the mortality rate was 36%. Coma, seizures, and high methanol concentrations were predictors of poor prognosis. Exposure to large amounts is fatal within 72 hours. Brain CT and MRI may demonstrate signs of diffuse and multifocal damage. Visual loss is attributed to retinal metabolism of methanol (rather than an action of circulating formic acid) because the local oxidation of methanol to formic acid parallels the depletion of retinal adenosine 5'-triphosphate (ATP). Retinal glial cells may be the first target. It has therefore been suggested that inhibitors of aldehyde dehydrogenase could be therapeutic; here it would mean the administration of ethanol to block the first step of the toxic metabolic pathway. For similar reasons, administration of ethanol blocks the metabolism of methanol in the liver, and unchanged toxin is excreted in the urine. 4-Methylpyrazole (fomepizole) has also been used for this purpose. Correction of acidosis and hemodialysis may be used.

Obsolete Epidemics

Many syndromes described here could be eliminated if care were taken to protect the environment. In fact, some epidemics pointed the way to correction. For instance, the outbreak of *subacute myelo-optic neuropathy* was attributed to an oral antiparasitic agent, clioquinol. The resulting peripheral neuropathy and blindness affected an estimated 10,000 people in Japan. The practice has ceased, and there have been no new cases; investigations indicate that the drug is converted to a potent mitochondrial toxin. Another transient outbreak was the *eosinophilia-myalgia syndrome*, which involved skin, muscle, lungs, and blood vessels and axonal neuropathy. The disorder was attributed to a toxic contaminant in the preparation of tryptophan, which was taken as a health supplement. That syndrome has also largely disappeared, but it seems likely that new epidemics will appear as new industries and new health fads arise.

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