Role of the Neurologist in Hazard Identification and Risk Assessment

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This review describes strategies used by a clinical neurologist in the investigation of neurotoxic disease. It emphasizes the need for a high level of suspicion that environmental substances are capable of producing impairments in neurologic and neurobehavioral functions. Because of the difficulties in differentiating neurotoxic from nonneurotoxic disease when presented with common neurological symptoms, it is necessary to rely upon corroborative evidence from past medical records, work and environmental histories, and exposure data, as well as detailed neurological examinations, to reach a conclusion about causation. Sensitive electrophysiologic and neuropsychologic test batteries are useful in identifying subclinical impairments and in providing objective confirmation of abnormalities in the central and peripheral nervous systems. Combining scientific and epidemiologic information with experience and clinical judgment, these sources of information are used in the formulation of a clinical diagnosis. When many patients among a group of people are exposed to neurotoxicants, the effects of the exposure may vary from one to another because of differences in susceptibility, duration of exposure and dosage of neurotoxicant, and other possible risk factors. Group statistics may obscure a significant effect for the larger group, despite clinically obvious effects in an individual. The neurologist applies clinical skills and refers to the accumulated neurotoxicologic literature as a frame of reference to make a diagnosis about an individual patient or a group of patients who have been exposed to particular neurotoxicants. The Boston University Environmental Neurology Assessment (BUENA) is a scheme that attempts to combine epidemiologic methodology and clinical approaches to detect effects of neurotoxic exposure. The advantages and limitations of such a strategy are discussed. — Environ Health Perspect 104(Suppl 2):227–237 (1996)

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Background

The role of the neurologist in identifying neurotoxic hazards is to clarify the patient's complaints that suggest nervous system dysfunction and to arrive at a correct anatomical and etiological diagnosis. Many different causes of disease of the nervous system can produce similar symptoms. Essential to the process of differential diagnosis is a comprehensive past medical history and an inquiry into occupational and environmental temporal circumstances surrounding the appearance of symptoms. With knowledge of the pathophysiologic mechanisms responsible for the clinical manifestations and an awareness of the risks for causing neurotoxic effects characteristic of certain chemicals, the neurologist brings a high index of suspicion to the differentiation of neurotoxic syndromes from other neurologic disorders of nonneurotoxic origin. In addition, the neurologist can determine worker fitness and assess risks of increased susceptibility in a given individual to known neurotoxicant exposures at otherwise safe levels (*1*).

Specific clinical manifestations result from damage to selected cellular elements such as the neurons, glial cells, myelin sheaths, or blood vessels. Central nervous system structures are affected more by some chemicals, while the peripheral nervous system is the main target of others. Certain substances affect both central and peripheral nervous tissues. Neurologic impairments result from direct or indirect effects of a neurotoxicant. Neurotoxic effects occur when enzymatic protective mechanisms fail to detoxify the neurotoxicant and eliminate it as a nontoxic byproduct. Neurotoxicants alter function of the nervous system by changing the lipid content of cell membranes and damaging capillary endothelium, by affecting their ability to transport ions and nutrients, by interfering with mitochondrial oxidative processes, and by disturbing neurotransmitter activity. Depending upon the neurotoxicant, the nature and duration of exposure, and the vulnerability of the cellular targets, neurotoxic effects may be reversible or irreversible.

The patient is commonly unaware of any relationship between any symptoms and his exposure to particular chemicals. He simply knows that he feels unwell. Nonspecific systemic effects of neurotoxicants include vegetative symptoms such as nausea, dizziness, and headache. The patient may not recognize changes in his behavior before they are brought to his attention by family members or co-workers. Behavioral symptoms such as poor attention, memory troubles, and delirium are obvious when they interfere with daily tasks. Central nervous system symptoms usually precede the symptoms of peripheral neuropathy. Early recognition of one case of neurotoxic disease should raise concern about possible exposure of other persons

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Abbreviations used: BUENA, Boston University Environmental Neurology Assessment; NLM, National Library of Medicine; HSDB, Hazardous Substances Data Bank; IRIS, Integrated Risk Information System; U.S. EPA, U.S. Environmental Protection Agency; NIOSHTIC, National Institute of Occupational Safety and Health Technical Information Center; EEG, electroencephalogram; MRV, mean related value; CNS, central nervous system; OSHA, Occupational Safety and Health Administration; TOSCA, Toxic Substances Control Act; R1, direct responses; WMS, Wechsler Memory Scale.

within the same environment. Continued exposure may produce effects in the others in the group, as well as allowing for further damage to those already affected.

Clinical Approach to Diagnosis of Neurotoxic Disease

Lists of chemical substances, the industries in which they might be found, and their most common neurotoxic effects can be found in reference books (*2,3*). Environmental and occupational health information can be accessed from various electronic data systems such as EPA ON-LINE Library System; National Library of Medicine (NLM) Hazardous Substances Data Bank (HSDB) and Toxnet; Integrated Risk Information System (IRIS), EPA; Medline and Toxline (Dialog Scientific Technical Network); National Institute of Occupational Safety and Health Technical Information Center (NIOSHTIC), and CD-ROM (*4*). With this information, and by learning from the patient about his work and environmental background, the clinician can be alerted to the risks of neurotoxic exposure. More likely, the patient's complaints will trigger a search for neurotoxic effects (Table 1)(*5*).

Neurologic Examination

The neurologist follows a systematic approach to differentiate nonneurotoxic disease from neurotoxic disease. A general medical examination is followed by a detailed neurologic examination to establish the clinical–anatomical basis for any symptom described. Tests of language, memory, and cognitive performance assess the patient's mental status. Observations of gait, posture, muscle tone, fine motor control, and coordination are made; motor and sensory functions of peripheral and cranial nerves are tested. Tendon reflexes and special reflexes of upper motor neuron functions are tested. Deviations from expected performance levels, considered normal in standard references or as baselines in control groups, are recorded as abnormalities. Similar neurologic signs and symptoms arise from impairment of particular neural structures, regardless of the specific cause of the malady. Selected electrophysiologic and neuropsychologic tests as well as various blood and urine tests are needed to confirm the clinical diagnosis and to separate it from others with similar presentations. The neurologist should be able to determine whether there is any abnormality in the central or peripheral nervous system and be able to localize a probable anatomical site of dysfunction.

Evidence of biologic markers and environmental exposure data to confirm the presence of suspected neurotoxicants and to place the patient in a position to be exposed must be ascertained. Along with supporting historical information and biologic and environmental exposure data, the clinical findings are placed in the context of the relative importance of each parameter of neurophysiologic and neuropsychologic function to arrive at an overall diagnosis. These functions, documented by objective laboratory tests, can be used as outcomes in formal epidemiologic studies as well as in the clinical diagnosis of an individual case of neurotoxic disease.

Electrophysiologic Tests

Electroencephalography. Bioelectric potentials are generated by the neurons of the cerebral cortex and transmitted over complex synaptic networks throughout the cerebral hemispheres. Changes in these generated electromagnetic fields are recorded from the scalp by sensitive electronic equipment, electroencephalogram (EEG), and displayed as patterns of mixed frequencies, amplitudes, and topographical distributions over the cranium. Under normal waking conditions, as well as in natural sleep states, the EEG records predictable patterns. A mixture of fast and slow frequencies appear in frontal, temporal, and occipital areas in a symmetrical fashion. When the patterns, amplitudes, and frequencies are affected, an abnormality of brain function, or encephalopathy, is suspected. A sudden paroxysmal quality in the wave forms along with sharp spiky waves indicates epileptic activity; frontal slowing of the background with disappearance of the normal resting frequencies is found in metabolic or toxic brain problems; a marked difference in symmetry of the recording suggests a lateralized pathology; and a concentration of sharp, slow, or paroxysmal waves in a focal area reflects a structural lesion such as a tumor, an infarct, or an old trauma. The EEG is normal in patients with dementia of the Alzheimer type early in its course, but as in other neurodegenerative diseases, greater amounts of slowing and disorganization appear as progression occurs. Acute EEG changes such as increased amounts of slow wave activity occur during exposure to centrally acting neurotoxicants, while behavioral effects are also observed. The EEG returns to a normal pattern after removal from exposure, although behavioral manifestations may persist clinically or be detectable on formal neuropsychological tests. Abnormalities in the EEG are indicators of the physiologic state of the brain only at the time of recording, and the patterns are not specific to any particular causal substance. As with all laboratory tests, clinical correlation is necessary before significance can be given to an EEG report (*6*).

Electromyography and Nerve Conduction Tests

Appropriate use of electrophysiologic tests not only can localize pathology to individual nerves, roots, plexus, or motor neurons, but it also can characterize the pathophysiologic basis for dysfunctions as axonal, demyelinating, or both (*7*). A nerve cell body and its axon connect with other nerve cells, or neurons, by synapses and to muscle cells by complicated neuromuscular junctions. Axons of many neurons run together as fiber bundles constituting a peripheral nerve made up of thousands of individual nerve fibers of different sizes. The diameter of the fiber depends on the amount of myelin surrounding it—the more myelin, the larger the fiber diameter. The amount of myelin surrounding each nerve axon determines the speed of conduction of that axon—the less myelin, the slower the conduction time, and the more myelin, the faster the conduction time. The fastest firing fibers deliver the impulse first, with the slower fibers conducting later arriving impulses.

Each electrophysiologic parameter reflects an aspect of functioning of the motor and sensory components of a peripheral nerve. Thus, information about the integrity of the structures can be derived from the documented responses to electrical stimulation.

The complex nerve action potential recorded from the distal portion of a stimulated nerve includes all the conducted impulses of the various fiber sizes. The largest fibers and faster firing fibers determine the fastest speed of a conducted nerve impulse, that is, the shortest latency between the stimulus and the recorded response. If the number of large fibers is reduced because of demyelination, such as by toxic neuropathy, then the latency (milliseconds) between the stimulus and the recorded response will be prolonged because it is dependent upon the remaining smaller fibers to carry the impulses. If axons are damaged, nerve impulses will be conducted only by those axons remaining

Table 1. Neurologic symptoms and associated exposures.

Neurologic symptom	Neurotoxicant	Major uses/sources of exposure
Ataxia	Metals	
	Manganese	Iron, steel industry; welding operations; metal-finishing operations of high manganese steel; fertilizers; manufacturers of fireworks, matches; manufacturers using oxidation catalysts; manufacturers of dry cell batteries
	Mercury	Scientific instruments; electrical equipment; amalgams; electroplating industry; photography; felt making; taxidermy; textiles; pigments
	Solvents	
	Carbon disulfide	Manufacturers of viscose rayon; paints; preservatives; textiles; rubber cement; varnishes; electroplating industry
	Methyl *n*-butyl ketone	Paints; lacquers; varnishes; metal-cleaning compounds; quick-drying inks; paint removers
	n-Hexane	Lacquers; printing inks; stains; pharmaceutical industry; rubber cement; glues
	Toluene	Rubber solvents; cleaning agents; glues; manufacturers of benzene; gasoline, aviation fuels; paints, thinners; lacquers
	Monomers	
	Acrylamide	Paper, pulp industry; grouting material: basements, tunnels, dams, mine shafts; photography; dyes; water, waste treatment facilities
	Insecticides	
	Organophosphates	Agricultural industry
	Chlorinated hydrocarbons (DDT, Kepone)	
Headache	Metals	
	Arsenic	Pesticides; pigments; antifouling paint; electroplating industry; seafood; smelters; semiconductors
	Lead	Solder; lead shot; illicit whiskey; insecticides; auto body shops; storage battery manufacturing plants; foundries; smelters; lead-based paint; lead-stained glass; lead pipes
	Nickel	Electroplating industry; surgical and dental instruments; nickel-cadmium batteries; paints; inks; alloys; coinage
	Tin	Canning industry; silverware; solder; electronic components; polyvinyl plastics; fungicides; coated wire
	Tellurium	Rubber vulcanization; coloring agent in glazes, glass; electronics industry; foundries; semiconductors; thermoelectric devices
	Solvents	
	Carbon disulfide	Manufacturers of viscose rayon; preservatives; rubber cement; electroplating industry; paints; textiles; varnishes
	Methyl *n*-butyl ketone	Paints; varnishes; quick drying inks; lacquers; metal cleaning compounds; paint removers
	n-Hexane	Lacquers; printing inks; pharmaceutical industry; rubber cement; stains; glues
	Perchloroethylene	Paint removers; degreasers; extraction agent for vegetable and mineral oils; dry cleaning industry; textile industry
	Toluene	Rubber solvents; glues; paints; automobile, aviation fuels; paint thinners; cleaning agents; manufacturers of benzene; lacquers; gasoline
	Trichloroethylene	Degreasers; paints; varnishes, lacquers; extraction of caffeine; dry cleaning; rubber solvents; adhesive
	Gases	
	Carbon monoxide	Exhaust fumes of internal combustion engines; acetylene welding; enclosed areas: mines, tunnels; emissions as a result of incomplete combustion
	Waste anesthetic gases	Operating rooms; dental offices
	Insecticides	
	Organophosphates	Agricultural industry
Cognitive impairment	Metals	
	Arsenic	Pesticides; pigments; antifouling paint; electroplating industry; seafood; smelters; semiconductors
	Lead	Solder; lead shot; illicit whiskey; insecticides; auto body shops; storage battery manufacturing plants; foundries; smelters; lead-based paint; lead-stained glass; lead pipes
	Manganese	Iron, steel industry; welding operations; metal finishing; fertilizers; manufacturers of fireworks, matches, oxidation catalysts, dry cell batteries
	Mercury	Scientific instruments; electrical equipment; amalgams; electroplating industry; photography; felt making; taxidermy; textiles; pigments

(*Continued*)

Table 1. Neurologic symptoms and associated exposures—*Continued*

Neurologic symptom	Neurotoxicant	Major uses/sources of exposure
	Solvents	
	Carbon disulfide	Manufacturers of viscose rayon; preservatives; rubber cement; electroplating industry; paints; textiles; varnishes
	Perchloroethylene	Paint removers; degreasers; extraction agent for vegetable and mineral oils; dry cleaning industry; textile industry
	Toluene	Rubber solvents; glues; paints; automobile, aviation fuels; paint thinners; cleaning agents; manufacturers of benzene; lacquers; gasoline
	Trichloroethylene	Degreasers; paints; lacquers, varnishes; dry cleaning industry; rubber solvents; adhesive; extraction of caffeine
	Insecticides	
	Organophosphates	Agricultural industry
Peripheral neuropathy	Metals	
	Arsenic	Pesticides; pigments; antifouling paint; electroplating industry; seafood; smelters; semiconductors
	Lead	Solder; lead shot; illicit whiskey; insecticides; auto body shops; storage battery manufacturing plants; foundries; smelters; lead-based paint; lead-stained glass; lead pipes
	Mercury	Scientific instruments; electrical equipment; amalgams; electroplating industry; photography; felt making; taxidermy; textiles; pigments
	Thallium	Rodenticides; fungicides; mercury and silver alloys; manufacturers of special lenses; photoelectric cells; infrared optical instruments
	Solvents	
	Carbon disulfide	Manufacturers of viscose rayon; preservatives; rubber cement; electroplating industry; paints; textiles; varnishes
	Methyl *n*-butyl ketone	Paints; varnishes; quick-drying inks; lacquers; metal-cleaning compounds; paint removers
	n-Hexane	Lacquers; printing inks; pharmaceutical industry; rubber cement; stains; glues
	Perchloroethylene	Paint removers; degreasers; extraction agent for vegetable and mineral oils; dry cleaning industry; textile industry
	Trichloroethylene	Degreasers; paints; lacquers, varnishes; dry cleaning industry; rubber solvents; adhesive; extraction of caffeine
	Monomers	
	Acrylamide	Paper, pulp industry; grouting material: basements, tunnels, dams, mine shafts; photography; dyes; water, waste treatment facilities
Tremors	Metals	
	Manganese	Iron, steel industry; welding operations; metal-finishing operations of high manganese steel; fertilizers; manufacturers of fireworks, matches, oxidation catalysts, dry cell batteries
	Mercury	Scientific instruments; electrical equipment; amalgams; electroplating industry; photography; felt making; taxidermy; textiles; pigments
	Solvents	
	Carbon disulfide	Manufacturers of viscose rayon; preservatives; rubber cement; electroplating industry; paints; textiles; varnishes
	Trichloroethylene	Degreasers; paints; lacquers, varnishes; dry cleaning industry; rubber solvents; adhesive; extraction of caffeine
	Insecticides	
	Chlorinated hydrocarbons (DDT, Kepone)	Agricultural industry

Modified from Feldman and Travers (*5*).

undamaged, myelinated, or relatively unmyelinated. The resultant recording will show a reduction in the amplitude (micro volts) of the evoked nerve action potential or an absence of an evoked nerve action potential. Conduction velocity (meters per second) is the speed of travel of an evoked nerve action potential between two sites of stimulation and a common end point of recording an electrical or muscle response. The conduction velocity value is calculated by subtracting the proximal latency from the distal latency and dividing the difference into the distance between the two sites of stimulation.

Acceptable normal values are usually those that fall within 1 or 2 standard deviations (SD) from laboratory or control means. We (*8*) consider values 2 SD from the mean abnormal in clinical settings for a patient; a more limited range of acceptable values is used from time to time for tests with greater degrees of variability in response, such as the direct response of the blink reflex (*9,10*). Neurophysiologic test results that fall anywhere within 2 SD are therefore considered within the normal range. However, subtle dysfunction may exist among many, but not all, of a group of nerve fibers without affecting the overall average and fastest conduction time reflecting this partial impairment enough to give a value outside 2 SD. In such instances, comparison of the actual mean related value (MRV) (*11*) for a given parameter should be made with the actual MRV of a

previous or later test in the same patient. The MRV would show changes from baseline, all within the acceptable normal range of 2 SD for each test, and a significant change in the MRV over time would reveal the relative effects.

In a group of affected individuals, subclinical toxic neuropathy may be present although no one member exhibits overt clinical neurotoxic effect. In this situation, analysis of the population requires different statistical approaches such as those for central tendencies (means, modes, and medians). The statistical power of field studies of toxic neuropathy may uncover a significant degree of neurotoxic effect below values usually accepted as clinically normal in individual patients in an office practice (*12*). Subgrouping and unit analysis have been used to define relationships between exposure and neurophysiologic impairments as measured by electrophysiologic techniques (*13,14*).

Electrophysiologic tests are not applied uniformly. Differences in techniques and instrumentation and variables among study populations often account for inconsistency among the data collected and its interpretation (*15*). The clinical neurologist must take this into account when evaluating the results obtained in individual cases and especially in groups of individuals. Published and generally accepted electrophysiologic procedures should be used to measure and report motor and sensory latencies and amplitudes of evoked nerve action potentials and to calculate conduction velocities (*9,16,17*).

Neuropsychologic Tests

Acute, mild, transient, and usually reversible effects of neurotoxicants on the central nervous system (CNS) are common experiences of most people who work with volatile and aromatic substances (e.g., glues and varnish) or with poor ventilation or who imbibe ethyl alcohol. Severe acute effects may include headache, seizures, or delirium. More chronic manifestations are less obvious.

Initial stages of neurobehavioral toxicity include altered affect, depression, sleep disturbances, apathy, fatigue, and diminished mental efficiency. Persistent mood disorders associated with impaired cognitive functioning may be symptomatic of toxicant-induced CNS dysfunction but are sometimes incorrectly attributed to primarily psychiatric causes. It is difficult to attach a neurotoxic etiology to behavioral symptoms unless there are corroborative data indicating exposure. The alleviation of symptoms upon withdrawal from the suspected source of exposure to neurotoxicants is a valuable clue to such a relationship. Serial formal neuropsychologic testing can document changes in performance in the various domains of cognitive and mental function.

The encephalopathy that occurs following occupational or environmental exposure to neurotoxicants in adults is usually characterized by deficits in one or more of the following functional areas: attention, executive function, fluency (verbal or visual), motor abilities, visuospatial skills, learning and short-term memory, and mood and adjustment (Table 2) (*18*). Neuropsychologic testing determines the character of a deficit and relates the findings to other information gathered from clinical and social evaluations. A qualified neuropsychologist, experienced in testing patients with occupational and environmental neurotoxicant exposures, will recognize the importance of designing a test battery that will control for demographic and cultural variables, premorbid cognitive status, changes in mood state and perceptual experiences, energy levels, personality, and motivational influences. In addition, the test battery must be able to recognize the effects of specific neurotoxicants to which the patient is suspected of having been exposed. These are some questions to be answered: Do the deficits in test results explain problems exhibited by the patient in his daily life? Do the findings suggest the existence of other disorders (neurologic, psychiatric, motivational, developmental, medical)? Are the test results consistent with those described in the literature or previously observed in other cases of neurotoxicant exposure? What are possible treatment approaches?

The test results are scored and interpreted by a qualified neuropsychologist. Some neurologists have sufficient experience in behavioral neurology to be able to evaluate the various descriptions of test performance and conclusions for each of the instruments of the test battery. Consideration of other neurologic findings on examination allows the neurologist as well as the neuropsychologist to reconcile discrepancies or to corroborate the findings on anatomical–clinical grounds in the interpretation of test results. The use of imaging techniques such as computerized axial tomography or magnetic resonance imaging are often necessary to exclude brain lesions such as old traumas, vascular malformations and other congenital or developmental conditions, neoplasia, or multiple sclerosis-type demyelinative diseases.

Neurotoxicants produce specific effects on the hippocampus, while others affect the white matter, basal ganglia, cerebellum, frontal lobes, or occipital cortex. Each possible site of neuropathologic impairment will be associated with different patterns of neuropsychologic deficit. The main tasks in the differential diagnosis of toxic encephalopathies by formal neuropsychologic testing include characterization of premorbid cognitive status; dissociation of the effects of coexisting psychiatric disorders; dissociation of the effects of coexisting medical and neurologic disorders; and differentiation of the specific effects of exposure to different neurotoxicants (in cases of multiple toxicant exposures, substance abuse, or prescription drug use).

Biologic Markers and Exposure Data

The temporal relationship of symptoms, circumstances of possible exposure, and course of disease helps to place the patient's risk for neurotoxic effects. From the clinical examination, the neurologist identifies the impaired functions and infers the location of probable damage within the nervous system. The patient may provide much of the needed information by interview or by completing a questionnaire. Unless the suspected neurotoxic conditions still exist when the patient is identified, it is difficult to obtain timely environmental exposure measurements. Frequently, metabolism and excretion of a possible causal neurotoxicant has occurred before blood, urine, feces, hair, or nail samples can be taken, which reduces the chances of obtaining a tissue level of a neurotoxicant or its metabolite to verify exposure. Peak levels of absorbed material may have passed by the time the possibility of neurotoxic disease is recognized. Prompt efforts must be made to substantiate exposure while residual levels may still be detected in the suspected environment as well as in the patient.

Records of past exposure levels and safety monitoring data maintained by the employer or health agencies are useful in estimating exposures and trying to reconstruct the circumstances of exposure. Material Safety Data Sheets from chemical manufacturers and suppliers direct the clinician to specific compounds and their peculiar characteristics and potential hazards. The assistance of a qualified industrial and environmental hygienist is required in deter-

Table 2. Neuropsychologic tests used in assessing neurotoxicity.

Domain	Description	Implications
General intellect		
Wechsler IQ tests (WAIS-R, WISC, WPPSI)	Intelligence measures	Overall level of cognitive function compared with population norms
Peabody Picture Vocabulary Test	Single word comprehension	Robust measure of verbal intelligence in adults, can be sensitive to exposure in children
Stanford-Binet	Intelligence measure	Similar to Wechsler tests
Wide Range Achievement Test	Academic skills in arithmetic, spelling, reading	Robust estimate of premorbid ability patterns in adults, can be sensitive to exposure in children
Attention, executive functioning		
Digit span (WAIS-R)	Digits forward and backward	Measures simple attention and cognitive tracking
Arithmetic (Wechsler tests)	Oral calculations	Assesses attention, tracking, and calculation
Trail-making test	Connect-a-dot task requiring sequencing and alternating sequences	Measures attention, sequencing, visual scanning, speed of processing
Continuous Performance Test	Acknowledgment of occurrence of a critical stimulus in a series of orally or visually presented stimuli	Assesses attention
Paced auditory serial addition	Serial calculation test	Sensitive measure of attention and tracking speed
Wisconsin Card Sorting Test	Requires subject to infer	Tests ability to think flexibly, decision-making rules
Verbal language		
Information (Wechsler tests)	Information usually learned in school	Robust estimate of native abilities in adults
Vocabulary (Wechsler tests)	Verbal vocabulary definitions	Fairly robust estimate of verbal intelligence, although sensitive to concreteness associated with brain damage (including toxic encephalopathy)
Comprehension (Wechsler tests)	Proverb definitions, social judgment, problem solving	Sensitive to reasoning skill, can be impaired after exposure to neurotoxicants
Similarities (Wechsler tests)	Inference of similarities between nominative words	Sensitive to reasoning skills, can be impaired after exposure to neurotoxicants
Controlled oral word association	Word list generation within alphabetical or semantic	Assesses flexibility, planning, arousal, processing speed, ability to generate strategies, somewhat sensitive to exposure
Boston Naming Test	Naming of objects depicted in line drawings	Sensitive to aphasia, also sensitive to native verbal processing deficits or those acquired through childhood exposure
Reading comprehension (Boston Diagnostic Aphasia Exam)	A direct screening test of simple reading comprehension	Sensitive to moderate-to-severe dyslexia, usually insensitive to toxic exposure in adults
Writing sample	Patient writes to dictation or describes a picture	Assesses graphomotor skills, spelling
Visuospatial, visuomotor		
Picture completion (Wechsler tests)	Identification of missing details in line drawing	Measures perceptual analysis
Digit symbol (Wechsler tests)	Coding task requiring matching symbols to digits	Complex task assessing motor speed, visual scanning, working memory
Picture arrangement (Wechsler tests)	Sequencing of cartoon frames to represent meaningful stories	Measures visual sequencing ability to infer relationships from visuospatial/social stimuli
Block design (Wechsler tests)	Assembly of 3-D blocks to replicate 2-D representations	Assesses abstract visual construction ability and planning of designs
Object assembly (Wechsler tests)	Assembly of puzzles	Measures concrete visual construction skills, Gestalt recognition
Boston Visuospatial Quantitative Battery	Drawings of common objects spontaneously and to copy	Measures constructional abilities, motor functioning
Hooper Visual Organization Test	Identification of correct outline of drawings of cut-up objects	Sensitive to Gestalt integration processing
Rey-Osterreith Complex Figure	Drawing of a complicated abstract visual design	Sensitive to deficits in visuospatial planning and construction
Santa Ana Formboard Test	Knobs in a formboard are turned 180 degrees with each hand individually and both hands together	Measures motor speed and coordination
Finger tapping	Speed of tapping with each index finger	Sensitive to lateralized manual motor speed
Memory		
Logical memories–immediate and delayed recall (IR, DR) (Wechsler Memory Scales)	Recall of paragraph information read orally on immediate and 20-min delayed recall	Sensitive to new learning and retention of newly learned information
Verbal impaired associate learning (DR) (Wechsler Memory Scales)	Two paired words are presented in a list of pairs; subject must recall second word; test is presented on immediate and delayed recall	Measures abstract verbal list IR, learning, retention
Figural memory (Wechsler Memory Scales)	Multiple choice recognition using recognition (not recall) performance measures	Assesses visual recognition and memory
Visual paired associate learning (IR, DR) (Wechsler Memory Scales)	Six visual designs are paired with six colors; recognition memory is tested immediately after the six are presented on learning trials and at delayed recall	Test of abstract visual learning using recognition (not recall) performance measures
Visual reproductions (IR, DR) (Wechsler Memory Scales)	Visual designs are drawn immediately after presentation and at delayed recall	Measures visual learning and retention

(*Continued*)

Table 2. Neuropsychologic tests used in assessing neurotoxicity—*Continued.*

Domain	Description	Implications
Delayed Recognition Span Test	Based on delayed nonmatching to sample paradigm, discs are moved about on a board to assess recognition memory for words, color, spatial locations	Assesses new learning
Peterson Task	Words or consonants presented must be recalled after a period of distraction	Measures sensitivity to interference in new learning
California Verbal Learning Test	Subject is presented with list of 16 words (which can be semantically related) over multiple learning trials and an interference list	Provides multiple measures of new learning, recall, recognition memory, use of strategies and sensitivity to interference
Rey-Osterreith (IR, DR)	Complex design is drawn from IR immediately after it has been copied and at a 20-min delayed recall	Assesses memory for visual information that is difficult to encode verbally
Personality, mood		
Profile of mood states	Sixty-five single word descriptors of affective symptoms are endorsed by degree of severity on six scales	Sensitive to clinical mood disturbance and to affective changes secondary to toxicant exposure
Minnesota Multiphasic Personality Inventory (R)	True–false responses provided on personality inventory summarized on multiple clinical dimensions	Provides description of current personality function, some scales sensitive to exposure

Modified from White et al. (*18*).

mining sufficient information to validate the patient's recall of exposure conditions. In addition, the hygienist can provide analyses of personal and environmental samplings for evidence of suspected or other pollutants.

While it is reasonable to depend upon the findings and opinions of an expert consultant in area and personal sampling, the neurologist involved in evaluating the patient for neurotoxic disease must be critical when reviewing reports of environmental monitoring and exposure sampling. Important factors to consider include sensitivity and specificity of sampling and analytic methods; type of samples (area or personal sampling); timing of samples; use of personal protective equipment and safety practices; consideration of all possible routes of exposure; and exposure to combinations of neurotoxicants (*19*). As in epidemiologic research, the use of a particular biologic measurement as a marker of exposure or effect also requires validation in the clinical setting. Validity of a marker is defined in terms of its sensitivity and specificity. The predictive value of a marker to accurately identify exposure and effect is determined not only by the validity of the test itself, but also by the characteristics of the population to which the test is being applied.

Clinical relevance of markers should be interpreted cautiously. Furthermore, there are a limited number of known neurotoxicants for which exposure can be tested by biologic sampling in the clinical setting. For those biologic markers whose clinical correlations have been well studied, relevant reference values have been established and should be referred to in confirming the diagnosis of neurotoxicity in a given patient or group of patients (*20,21*).

Formulating a Diagnosis

Findings on general and neurologic examination that represent a variance from conventionally accepted clinical norms, as defined in textbooks and reference works that consider neurologic functions, are abnormalities. Sets of physiologic, anatomic, and behavioral concepts and principles accumulated from experience and derived from a database of previously published reports known to the examiner serve as a frame of reference for evaluating these abnormalities in formulating a diagnosis and in offering a causal explanation. A clinical diagnosis in a patient is arrived at by an intellectual process that integrates all available information in a systematic manner. This process should be the same whether used in the day-to-day practice of clinical medicine or in the special circumstances of evaluating self-referred individuals suspected of neurotoxic disease and involved in litigation.

Boston University Environmental Neurology Assessment (BUENA)

Diagnosing effects of neurotoxicants rests on the ability of the clinician to recognize the risk that certain environmental agents can cause adverse biologic responses in nervous tissue at critical levels of exposure and absorption. A constellation of neurologic effects ranging from subclinical or barely perceptible sensory deficits to gross behavioral abnormalities may characterize a population at risk (*22*). A high index of suspicion is needed to recognize individual cases or outbreaks of neurotoxic illness in communities, especially in the absence of a dramatic accident or an obvious hazardous waste spill. In communities where potential hazards, such as chemical waste disposal sites exist or where manufacturing processes are located near water supply sources, occurrences of exposure can be presumed (*23*).

Appropriate and sensitive procedures must be applied for detecting and characterizing disturbances in neurologic and behavioral functions, as well as documenting the nature and extent of any hazardous conditions. The U.S. Environmental Protection Agency (U.S. EPA) (*24*) uses a multi-tiered laboratory approach for testing neurotoxicity in animals, in which a variety of measurements are integrated into a health or safety index. Such multiple parameter screening procedures parallel the process of human assessment that incorporates various findings of clinical neurologic examinations, electrophysiologic measurements of peripheral and CNS functions, and observations and test scores of standardized neuropsychologic studies and leads to a clinical diagnosis.

In an effort to standardize a procedure for clinical assessment of neurotoxic disease in individuals as well as in groups, we have developed the Boston University

Environmental Neurology Assessment (BUENA) (*8*). This detailed protocol lists essential questions to be answered in order to arrive at a diagnosis of neurotoxic disease and to eliminate as many confounding variables as possible.

BUENA

a) Are the data sufficient to identify any or all complaints as being caused by a neurotoxin?
- List complaints and relate them on a time line to all possible exposures to sources of chemicals (work, home, hobby)
  - Identify symptoms and functional changes expressed, experienced, and observed by others; list evidence of mood, anxiety, sleep disturbances and effect on quality of life
  - Cite time of onset, duration, and intensity of complaints; indicate when symptoms worsen or remit in relation to exposure (e.g., work week, weekend, time of shift, on vacation)
  - Evaluate subject's family/genetic health, special sensitivities, and possible congenital factors
- List all substances and how they are used (at workplace, in home, hobbies)
  - Obtain chemical names (not trade label names), material safety data sheets, and other identifying data concerning each substance
  - Review availableworkplace information—e.g., Occupational Safety and Health Administration (OSHA)-mandated material safety data sheets and employer training program materials; employer's medical records and exposure records that, if kept by employer, must be made available under OSHA rules. Review, if available, the following: employer's Toxic Substances Control Act (TOSCA) 8c and 8e reports to U.S. EPA, employer's community right-to-know reports to local officials with regard to hazardous materials made, used, or sorted on site
- Obtain environmental and industrial hygiene air measures or drinking-water samples to prove the presence of alleged chemicals in the alleged source. Current levels are important, but levels taken in relationship to occurrence of complaints are essential
- Obtain urine and blood samples from the allegedly affected individuals and from known unexposed control subjects of similar age and occupation, especially at time of complaints, to establish body burden of chemical
- For suspect chemicals, develop information on dose–response relationships, animal studies, toxicologic and epidemiologic studies

b) Are the complaints substantiated by clinical neurologic physical examination, standardized neuropsychologic and neurophysiologic tests, and appropriate blood and urine analyses? Also, are the complaints corroborated by epidemiologic, toxicologic, or animal studies; by National Institute for Occupational Safety and Health (NIOSH), OSHA, or U.S. EPA studies of the workforce or community; by employer studies and reports to U.S. EPA or OSHA (e.g., TOSCA 8c and 8e reports)?

c) Are the findings due to a primary neurologic disease or other medical conditions?

d) Are the findings on examination explained by any other causal factors in past medical history, previous or current unrelated exposures to substances from sources other than the one under consideration?
- Time line of past jobs, residences
- Time line of past medical history

e) Analyze individual cases for confirmatory studies and group data for cluster analysis or population statistical study

f) Identify and critically review previously published or reported cases, case–control studies, population studies, and animal studies concerning the alleged neurotoxins and relate documentation to case data

g) Estimate the damage consequences for the subject: disease, anxiety, loss of consort, functional impairments; need for special education, counseling, medical surveillance, or medical therapeutic measures; job disability, loss of earnings, etc.

h) Reevaluate after reasonable absence from all neurotoxic exposure to assess course of progression, recovery, or persistent impairment or disability.

This approach formalizes techniques as they are used in the everyday practice of medicine, where the goal is to assess impairments of an individual within his environment. In this context, differing from the traditional epidemiologic study, the clinician takes the position that even a small probability of serious illness must not be dismissed (*25*).

While the data collected by BUENA do not meet conventional criteria of an epidemiologic design, they are nevertheless reliable from scientific, clinical, and legal points of view. Rothman et al. (*26*), in arguing against the use of significance testing as the sole criterion on which to judge scientific validity in epidemiology, strongly supported the notion that reanalysis and metaanalysis of observed associations between suspected risk factors and medical conditions provides valid and useful evidence. If it were practical to design a more conventional epidemiologic study, then all the parameters, including concurrent control subjects and exposure data measures for much larger groups of subjects, would be needed for proper statistical analysis. Thus, without an elaborate epidemiologic design to which traditional statistical analyses can be applied, the results of studying small groups or well-studied exposed people can be valuable in supporting the concept that environmental factors play a role in causing neurologic disorders. By using a consistent protocol and conventional test instruments, the neurophysiologic and neuropsychologic performance of many patients, and groups of patients exposed to the same neurotoxicants, can be compared for possible generalizations.

The BUENA was used in studies of people in three separate communities suspected of having been exposed to drinking water containing trichloroethylene and other volatile organic compounds (*8*). These findings are summarized and discussed to demonstrate an effort to compare the study groups.

Group I included 28 members (9–55 years of age) of 8 families from Woburn, Massachusetts, who used well water from < 1 to 12 years. Water from the wells (*9,11*) was found to contain trichloroethylene (63–400 ppb), tetrachloroethylene (21 ppb), chloroform (12 ppb), dichloroacetylene (28 ppb), and trichlorotrifluoroethane (23 ppb). Principal complaints (years after the end of exposure) included mood changes (89%), depression (82%), fatigue (79%), impaired concentration (75%), headache (71%), and impaired memory (61%). Reflex changes (92%) and sensory impairments (14%) with clinical evidence of peripheral neuropathy (75%) were the main features on neurologic examination. Individual test parameters of neurophysiologic functions revealed reduced proximal motor nerve action potential amplitudes

and distal sensory amplitudes, distal sensory and motor latencies, and prolonged direct responses (R1) of the trigeminal–facial nerves blink reflex circuit. As a group, the R1 blink reflex differed significantly ($p < 0.0001$) from a comparison group. Subclinical neuropathy presented as was indicated by abnormalities in the neurophysiologic test responses in several patients; in those with abnormal clinical reflexes, a diagnosis of peripheral neuropathy was made in 21 (75%) members of the group. Neuropsychologic testing showed that memory was the most affected behavioral domain (89%). Significant impairments were also seen in attention/executive functions (68%), manual motor function (61%), and visuospatial skills (61%). Language/verbal functions were within expected limits. Overall, 24 (86%) of the people in this group were diagnosed as having mild to moderate encephalopathy.

Group II included 12 residents (12–68 years old) of a community located near Alpha, Ohio. Their homes were situated within 2,000 ft of a manufacturing company that used solvents in degreasing operations from 1951 through 1972. These included trichloroethylene, trichloroethane, tetrachloroethylene, sodium hydroxide, potassium permanganate, and phosphoric acid. Trichloroethane was substituted for trichloroethylene in 1972. It was established that an average of 50,000 gal per day of waste water flowed into a surface drainage ditch from 1951 through 1981. In 1986, well water serving these homes was found to be contaminated. Thirteen of 31 wells sampled were found to contain 1,1,1-trichloroethane (up to 2,569 ppb) and trichloroethylene (up to 760 ppb). Well water supplied to two of these residences also contained tetrachloroethylene (16.5 ppb), *cis*-1,2-dichloroethane (23.9 ppb), and 1,1-dichloroethane (21.7 ppb). 2-Butanone (120 ppb) was detected in one sample of water. It was suspected that the residents had been exposed to volatile organic compounds for 5 to 17 years. Two years after exposure to this water source had ended, the blood levels in these 12 individuals from these homes showed normal or mildly elevated levels of trichloroethylene and elevated levels of 1,1,1-trichloroethane, ethylbenzene, and xylene. Neurologic examination revealed no obvious abnormalities. Evidence of peripheral neuropathy included electrophysiologic abnormalities in nerve conduction parameters greater than 2 SD from the comparison group mean. Blink reflex measurements were normal. Neuropsychologic assessment showed that the most commonly affected behavioral domain was attention/executive function (83%). Memory was abnormal in 58% of the subjects.

Group III consisted of 14 people in Minnesota (8–62 years old) who were suspected of being exposed for 0.25 to 25 years to well water contaminated with volatile organic compounds. Six subjects were exposed to one well containing the following: trichloroethylene (peak level of 350 ppb), 1,1-dichloroethylene (peak level, 12 ppb), 1,2-dichloroethylene (peak level, 140 ppb), and 1,2-*trans*-dichloroethylene (peak level, 85 ppb). Eight others were served by wells with trichloroethylene levels ranging from 1,220 to 2,440 ppb. The BUENA was performed on group III members 4 to 22 years after the end of exposure to the contaminated well water. Neurologic examination showed reflex abnormalities in 79% and signs of peripheral neuropathy in 35%. Electrophysiologic tests of 20 parameters of peripheral nerve conduction function were measured in all 14 test subjects. Not all had the complete battery, but the most common abnormalities included prolonged ulnar sensory latency (71%), prolonged median sensory latency (45%), sural sensory latency (25%), and ulnar sensory amplitude (33%). Neuropsychologic tests were done on six members of one family, two parents and four young adult children. All six showed signs of impairment on memory testing and on tests of attention/executive function. All four children displayed below average performance on academic tests and on language/verbal tasks.

Metaanalysis of the Results of the Three Study Groups

The clinical, electrophysiologic, neuropsychologic, and exposure data, and other relevant demographic information obtained by the BUENA on each member of the three groups were reviewed (Table 3)(*8*). Clinical features or neurophysiologic studies appear to be less sensitive than neuropsychologic assessment as an indicator of group effects. Neurophysiologic measurements, however, were very useful in identifying evidence of subclinical or confirming clinical peripheral neuropathy in individual subjects. In all three groups, rates of diagnosis of abnormal neuropsychologic test results were higher than the expected rates of abnormal findings for the general population in the United States. The neuropsychologic parameters most frequently affected were in the domains of memory and attention/executive function. In general, patients did not show patterns of impaired test performance expectable on the basis of dysphoria alone, e.g., inconsistent responses, generalized slowing, and failures.

Explanations for differences among and between the three groups may be found in the availability and timeliness of the exposure data, the methods of analysis of the neurophysiologic test results, and in certain differences in the administration of aspects of the neuropsychologic test batteries. Exposure levels were simply those measured in the well water and not consistently determined as biologic exposure markers in the exposed people. Furthermore, the water concentrations were determined before, sometimes years before, the clinical testing was done. Cumulative exposures (cumexp) were obtained by multiplying the average exposure (ppb) by the duration of exposure (years). For purposes of analysis of current clinical and paraclinical findings, the cumexp was multiplied by the reciprocal of the interval (years) between the time when exposure stopped and the time of clinical assessment (cumexpad). A chi-square test of correlation coefficient showed no statistically significant differences among the groups in terms of the relationship between cumexp or cumexpad and symptoms, signs, or abnormal neurophysiologic parameters.

Average abnormalities in the neurophysiologic studies did not appear to be related to the cumulative exposure on a group basis. However, on an individual basis,

Table 3. Demographic information and exposure data in three communities with trichloroethylene exposure in water.

	Group I, Massachusetts	Group II, Ohio	Group III, Minnesota
Number examined	28	12	14
Age range	9–55 years	12–68 years	8–62 years
Exposure levels	63–400 ppb	3.3–330 ppb	261–2,440 ppb
Duration of exposure	<1–12 years	5–17 years	0.25–25 years
Time between exposure and exam	Approximately 5 years	1–5 years	4–22 years

Data from Feldman et al. (*8*).

there was a significant correlation (Pearson) between symptoms, signs, and abnormal electrophysiologic measures in whatever pairs. The linear regression equation also indicated a slope significantly different from zero when symptoms, signs, and abnormal electrophysiologic parameters were compared. In analyzing the neurophysiologic data, a simple application of the mean and standard deviation was considered insufficient since nerve conduction study data are thought not to follow a normal distribution (*27*).

We standardized the data on the values of the electrophysiologic test results of neurophysiologic functions in normal controls by comparing them to the Gaussian distribution, using graphical fitness, kurtosis, skewness, and equation, and transforming the values where the fitness was considered unsuitable. Transformation modes employed included natural log, log 10, cube root, square root, inverse, and negative inverse. Results were reviewed and the best transformation was chosen based on goodness of fit, skewness, kurtosis, and the need to work with the nontransformed values, if reasonable. The values for each case were converted to the working values, and the z scores, or mean related values, were calculated (*11*). Values above 2 were regarded as abnormal. The results on each patient was assessed for the absolute numbers and the proportion of abnormal electrophysiologic responses.

Differences in performance on neuropsychologic tests assessing motor speed among the three groups reflect the variations in application of some of the instruments of the battery. In group II, the Santa Ana Form Board was not given. In this group motor speed apparently was less affected than in the other two groups. Visuospatial function was affected in over half of group I members, but much less affected according to the test results in the other two groups, possibly because they were not given the Sticks test, a particularly complex task that may have been more sensitive than the other tests used. As stated above, memory test performance was often impaired in these patients. On the older Wechsler Memory Scale (WMS) given to group I, performances on visual reproduction and logical memory tasks were below expectation. However, these tasks differed from those used in the revised form of the WMS (WMS-R) that was administered to groups II and III, in which figural memory was the task that proved to be the most difficult. Performance on digit span and the Wisconsin Card Sorting Test was also impaired. The word triad task was difficult for most subjects in all three groups, as were digit span and Santa Ana.

Conclusion

The clinical neurologist is helpful in the identification of the hazards of neurotoxicants in order to distinguish symptoms that are caused by chemicals from symptoms that arise from nonneurotoxic diseases. Often, clinical manifestations of neurotoxicants are similar to those due to idiopathic neurologic disease, and exposure data and historical corroboration the only indications of probable environmental or occupation risk.

A systematic approach to the neurologic examination and the application of consistent and conventional neurophysiologic and neuropsychologic confirmatory tests are needed for identifying chemical effects. BUENA is a critical approach to putting the clinical neurologic findings in the context of exposure and possible causal relationships.

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