



Neurobehavioral Toxicology

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GLOSSARY

cognitive domain Various modalities of behavior as expressed by the terms attention, executive function, memory (short-term and remote), visuospatial ability, motor function, and mood and affect.

critical effect The earliest discernible or measurable effect of exposure to a toxic substance.

critical organ The initial tissue to be affected by an exposure to a toxic substance.

encephalopathy A state of impaired functioning of the brain, which may include motor, sensory, and cognitive abnormalities and changes in mood and affect, as well as disturbances in attentiveness and consciousness.

executive function The behavioral process by which a person utilizes current sensory input and previously stored information and the complementary interactions of several cognitive domains to process and carry out complex independent, purposive, and problem-solving behaviors.

The adverse effects of exposure to neurotoxic chemicals on the brain manifest themselves behaviorally as changes in mood and in cognitive function. Neuropsychological testing has emerged as a means of documenting and measuring these changes. This methodology has several advantages for use in both the clinical diagnosis of chemically induced disorders and the epidemiologic investigation of neurotoxicant exposure–outcome relationships. These advantages include the documented validity and reliability of neuropsychological tests and

their known sensitivity for detecting the effects of cerebral pathology and for localizing the probable specific anatomical sites associated with many neuro-pathological and neurodegenerative processes. In addition, methods of neuropsychological testing used to estimate premorbid intellectual abilities allow investigators to uncover acquired changes in cognitive functioning associated with brain insults, including the effects of exposure to neurotoxicants. The pathological effects following brain insults that may produce measurable deficits on formal neuropsychological testing may or may not be detectable by conventional magnetic resonance imaging (MRI), computed tomography (CT), and electroencephalography studies. Although the newer imaging technologies [i.e., positron emission tomography (PET), single photon emission computed tomography (SPECT), functional MRI (fMRI), and magnetic resonance spectroscopy (MRS)] can provide additional objective evidence of an organic basis of the neurobehavioral manifestations, formal neuropsychological assessment nevertheless remains the principal means for documenting impaired function among patients exposed to neurotoxicants. This article discusses the neurobehavioral syndromes related to neurotoxicant exposure and presents a review of the clinical diagnostic approaches most utilized in their evaluation.

I. DEFINITIONS AND ACTIONS OF NEUROTOXICANTS

A. Functional and Structural Effects

Many naturally occurring (neurotoxins) and synthetic chemicals (neurotoxicants) can cause damage to the

nervous system. Disruptions of neuronal cell homeostasis occur when natural protective mechanisms fail to detoxify and eliminate a potentially hazardous chemical substance before it causes tissue damage. A neurotoxic chemical is defined as a substance that is directly and/or indirectly capable of the following: (1) altering the integrity of nerve cell membranes, thereby affecting neuronal excitability, neurotransmitter release, and synaptic activity of neurons; (2) disturbing the flow of axoplasm, thereby interfering with the transport of neurotransmitters and nutrient substances along the axon to and from the cell body; (3) disrupting cellular respiration processes; (4) disrupting protein synthesis; (5) affecting neuronal functions indirectly by damaging Schwann cells and peripheral myelin, oligodendrocytes, and central myelin and/or disrupting the normal functioning of astrocytes and microglia; and (6) disturbing extracellular fluid volume and flow by damaging capillary endothelium, thereby resulting in disruption of the integrity of the blood-brain barrier (BBB) or blood-nerve barrier (BNB). Alterations in the normal functioning of the various affected target cellular elements, such as neurons, glial cells, myelin sheaths, or blood vessels, result in neurobehavioral manifestations.

Symptoms of exposure appear when tissue concentrations of a neurotoxic chemical reach a critical threshold level, above which intracellular processes such as oxidative respiration and axonal transport become impaired. Initially, reversible functional alterations occur; often these early effects are subclinical and may only be detectable by electroencephalography, evoked potential studies, or peripheral nerve conduction velocity testing. Irreversible damage to neural systems permanently interferes with function, resulting in impaired or disabled performance of ordinary activities of daily living.

B. Behavioral Manifestations

The severity of the behavioral manifestations associated with exposure depends on the potency and the dose of the particular neurotoxicant or neurotoxin. The total dose is dependent on the intensity and duration of the exposure. Acute exposures to higher concentrations of a neurotoxic chemical require less time than do more prolonged, lower levels of exposure to reach a threshold at which there is a clinical effect. The reversibility of a neurobehavioral change also depends upon the dose and type of

neurotoxicant or neurotoxin. Chronic exposures are often associated with more gradual development of behavioral changes, which may be reversible or permanent.

Neurotoxicants and neurotoxins affect brain structures that mediate motor, sensory, and/or cognitive functioning. Many neurotoxic chemicals affect overall neurological and cognitive performance, and behavior to some degree, irrespective of their predilection for producing focal effects. Thus, diverse patterns of symptoms, signs, and neuropsychological performance deficits are not uncommon. Patients exposed to neurotoxic chemicals often complain of symptoms of encephalopathy, including changes in mood and affect, and of attention and memory problems. Overt signs of neurotoxicant exposure-induced motor system dysfunction may include spasticity, paralysis, bradykinesia, dyskinesia, dystonia, tremor, and incoordination. Subtle dysfunction of the motor system may not produce overt signs but may, nevertheless, affect performance on tests of motor function such as the Santa Ana Formboard, Purdue Pegboard, or Wechsler Digit Symbol Test. Neurotoxic chemicals affecting structures of the extrapyramidal motor system including the basal ganglia, such as manganese, produce overt signs of parkinsonism (e.g., tremor, dystonia, dyskinesia, and bradykinesia). Damage to the basal ganglia can directly and indirectly affect performance on neuropsychological tests of motor function. Cerebellar structures are sensitive to the effects of neurotoxic chemicals. These various patterns of clinical manifestations and neuropsychological performance deficits reflect an underlying neuropathology, which is dependent on the mechanism of action of the particular neurotoxicant, the exposure dose, and the type of exposure (acute or chronic) (see Table I).

II. DIAGNOSIS OF NEUROBEHAVIORAL DISORDERS

A person exposed to neurotoxic chemicals may be completely unaware of his or her own changes in behavior. This unrecognized impairment carries a risk for work-related accidents and injuries. Co-workers and/or family members often are the first to recognize changes in the patient's attention, memory, and mood and affect. If a source of chemical exposure is not immediately suspected or if the possible neurotoxic effects of a particular chemical are not well-known, the

Table I
Categories of Toxic Encephalopathies^a

| Disorder | Symptoms | Symptom duration | Pathophysiology |
|---|--|------------------|--|
| <i>Acute Organic Mental Disorders</i> | | | |
| Acute intoxication | Depression of CNS, attention and psychomotor deficits; No permanent sequelae | Minutes to hours | Reversible disruption of neurotransmission |
| Acute toxic encephalopathy | Confusion, seizures, coma; Cognitive deficits may persist | Hours to days | Hypoxia, disruption of BBB, cerebral edema |
| <i>Chronic Organic Mental Disorders</i> | | | |
| Organic affective syndrome | Disturbances of mood and affect including depression, irritability, anxiety, and fatigue; No permanent sequelae | Days to weeks | Reversible disruption of neurotransmission |
| Mild chronic toxic encephalopathy | Disturbances of mood and affect plus cognitive deficits; Improvement with cessation of exposure but mild cognitive deficits may persist indefinitely | Weeks to years | Reversible disruption of neurotransmission Limited neuronal/glial cell loss but no frank neuropathology |
| Severe chronic toxic encephalopathy | Disturbances of mood and affect plus severe cognitive deficits (including memory impairments) that interfere with activities of daily living; Deficits persist indefinitely | Years | Cortical atrophy and/or loss of white matter in CNS; focal lesions may also be seen |

^aFrom White, R. F., *et al.* (1992).

patient's behavioral changes may be attributed to other possible neurological conditions. Risk of further exposure before removal from the source(s) of exposure is thus increased. The possibility that a neurotoxic illness may underlie the patient's presenting complaints should be fully investigated using the patient's medical history, laboratory findings, and occupational and environmental exposure histories.

The observations made by the clinician during a neurological examination can be used to infer the probable anatomical site(s) of nervous system dysfunction and to describe the patient's functional status. Abnormal neurologic symptoms and signs are expressions of impaired function or damage to particular neural structures, regardless of the specific etiology of the lesion. Thus, neurologic findings arising from the effects of exposures to neurotoxicants may resemble those found in primary or non-neurotoxic neurologic illness. The diagnostic process integrates the clinician's observations of the patient and the results of tests on physiological, anatomical, and behavioral functions, along with his or her acumen and judgment accumulated from experience with similar cases, and reference

to a background of information contained in previously published literature.

A. Assessment of Behavior

The neurological examination begins with an assessment of the patient's ability to comprehend speech, follow simple instructions, perform complicated cognitive tasks, and perceive and identify sensory stimuli. The patient's spontaneous remarks and movements as well as those made in response to commands are evaluated for any digressions from expected norms of behavior, noting indications of the patient's orientation to person, place, time, and circumstances. Disturbances in mood and affect emerge during conversation. Engaging the patient in a conversation often reveals difficulties with attention if he or she is unable to focus well enough to follow the verbal exchange. Language comprehension is assessed by having the patient repeat simple phrases and follow simple commands. Expressive language is assessed by

listening to the patient's free speech for dysarthria, paraphasias, and neologisms. A clinical test of attention and mental control is to ask the patient to spell a word backward or to recite lists of words or numbers backward. Memory can be assessed through the details a patient is able to recall concerning medical history or through brief clinical assessment. Visuospatial and constructional ability can be assessed by having the patient draw the face of a clock with the hands set at a particular time.

Although these brief tests often reveal gross cognitive deficits associated with severe acute intoxication, acute toxic encephalopathy, and/or severe chronic toxic encephalopathy, patients with less severe or mild chronic toxic encephalopathy may present with subtle performance deficits that require formal neuropsychological assessment to detect and document. All patients exposed to neurotoxic chemicals who present with complaints of central nervous dysfunction should have formal neuropsychological testing to ascertain whether they are suffering from toxic encephalopathy.

B. Assessment of Motor and Sensory Functions

Neurological examination of motor functioning assesses the functional integrity of neurons in the cerebral cortex as well as their connections with subcortical, brain stem, cerebellar, and spinal cord pathways and the effector muscles that produce observable actions. Dysfunction in the motor cortex (upper motor neurons) results in weakness and spasticity of the limbs that are contralateral (i.e., on the opposite side of the body) to the site of the lesion. Basal ganglia dysfunction alters muscle tone and speed of response, causing bradykinesia (i.e., slowness of movement). Midbrain and brain stem structures control the coordination of cranial nerve functions such as conjugate eye movement, articulation of speech, and swallowing. Impaired cerebellar functioning results in ataxia of gait and tremulous trunk, head, and outstretched extremities. Tremors resulting from cerebellar and vestibular dysfunctions appear during actions and increase upon intention, whereas the tremor associated with Parkinson's disease appears during rest and disappears during action.

Spinal cord function is assessed by observing and recording the patient's gait, posture, muscle tone, fine motor control, and coordination. These features must be differentiated from those arising from damage to the brain. Reflexes are evaluated and muscle tone is

noted. Spinal cord lesions produce motor dysfunction on the same side (ipsilateral) as the lesion. Weakness in the arm and leg indicates disturbance in the spinal pathways on the same side if a lesion exists below the foramen magnum. In such instances, muscle atrophy occurs as well. Loss of muscle tone and total paralysis without spasticity reflects dysfunction in the lower motor neurons.

Dysfunction in the structures of the brain responsible for processing sensory information can result in syndromes of contralateral neglect, visuospatial disturbances, or cortical blindness. Sensory deficits associated with exposure to neurotoxic chemicals can be detected by studies of brain stem auditory evoked responses and visual evoked responses. (see Section III.A). Impairments in sensory function indicate the probable location of disturbed anatomy in the spinal cord, thalamus, or sensory cortex. Sensory disturbances may be ipsilateral or contralateral to the site of the spinal cord lesion, depending on the specific sensory modality affected. Clinical assessment of sensory function is readily accomplished at bedside with a wisp of cotton, a new safety pin, a tuning fork, and a reflex hammer. Fibers carrying information about light touch, vibration, and position sensation ascend without crossing in the cord (these fibers cross in the medial lemniscus); thus, sensory dysfunction is found ipsilateral to the site of the cord lesion. Conversely, fibers carrying pain and temperature sensation cross immediately after entering the cord; thus, spinal cord lesions affecting these fibers produce sensory impairments on the side of the body contralateral to the site of the lesion. The loss of sensation to pain and temperature suggests dysfunction in the ventral spinal thalamic tracts (anterolateral system) of the spinal cord, whereas position and light touch represent anatomical structures in the dorsal columns of the spinal cord.

III. DOCUMENTATION BY FORMAL DIAGNOSTIC TESTS

A. Neuropsychological Testing

1. History Taking and Clinical Interview

The questions included in the interview should address information about the patient's current symptoms as well as his or her past medical history. This process can be facilitated by having the patient complete a standardized questionnaire such as the "Boston

Occupational and Environmental Neurology Questionnaire.” Information about the patient’s performance in school and work should be obtained. It should be determined whether the patient has had any previous psychiatric, neurological, or developmental–academic problems that could affect his or her performance on neuropsychological tests. The patient should also be questioned about the history of his or her immediate family members, including details about education levels and occupations as well as medical and psychiatric histories. Past and present recreational use of drugs, alcohol, and prescribed medications that may affect performance on neuropsychological tests should be noted. The particulars of the circumstances surrounding the alleged exposure to neurotoxicants must be defined and documented. Material safety data sheets and documentation of current and past exposure levels should be obtained whenever possible.

2. Methods of Neurobehavioral Assessment

The clinical approach to the neuropsychological assessment of cognitive deficits and behavioral changes attributable to exposure to neurotoxicants is essentially the same as that applied to any neuropsychological assessment situation. The clinician must be familiar with the expected or likely behavioral effects of the various neurotoxic chemicals found in the workplace and environment to which the patient may have been exposed. An experienced neuropsychologist will be able to carry out the differential diagnostic process of determining the most likely etiology of any deficits that may be revealed by testing.

The clinical neuropsychological evaluation of patients with possible toxic encephalopathy necessitates that the clinician perform a careful and thorough examination of each patient. Many areas of cognitive function must be assessed so that exposure-related effects can be detected and other possible diagnoses comprehensively evaluated and ruled in or out. Because there is overlap between the behavioral effects of exposure to certain neurotoxic chemicals and those associated with developmental disorders (e.g., learning disabilities, attention deficit disorder), psychiatric conditions (e.g., posttraumatic stress disorder, bipolar disorder), neurological diseases (e.g., multiple sclerosis, cerebrovascular disease, primary progressive dementia, parkinsonism), and the exposure to ethanol, medications, and illegal drugs, the test battery must allow for consideration of these alternative or contributing conditions.

The literature on behavioral toxicology includes the results of epidemiologic studies of exposed populations as well as clinical case reports. A number of batteries have been proposed for the assessment of neurotoxic effects of industrial chemicals. It is important to note that, whereas these batteries may be well-suited to the *epidemiological* investigation of neurotoxic effects, they are too brief and lack some tests essential to the process of making a clinical differential diagnosis. In addition, some of these batteries contain tasks with no available norms upon which a clinical diagnosis could be based. The results from epidemiological studies using these test batteries are nevertheless important to the neuropsychologist performing clinical case assessments. They can provide insight into the domains of function expected to be affected and unaffected by exposure to specific neurotoxicants and aid in the selection of appropriate tests expected to be sensitive to the effects of a particular toxic chemical.

There are fundamental differences between epidemiologic and individual clinical testing endeavors. In the epidemiologic setting, tests are designed or selected to ascertain dose–response relationships between the degree of exposure and neurobehavioral outcomes among members of a group of exposed persons. In the clinical setting, one is looking for deficits relative to the expected premorbid level of performance for an individual. In the epidemiologic setting, neuropsychological test scores within the “normal” range nevertheless may support an adverse effect of exposure based on dose–response outcomes. In the clinical setting, however, scores must be at least 1–2 standard deviations below normative expectation for the subject in order to be considered indicative of a deficit. Thus, clinical examinations may require a greater degree of dysfunction in order to conclude that an exposure is having (or has had) an effect than might be seen in the research setting.

The field of neuropsychology has a number of assessment approaches, including the Halstead–Reitan method, which typically employs a set battery of tasks, and the behavioral neurology or Process Approach, which employs a flexible battery in evaluating patients with specific kinds of referral issues or who show certain types of processing deficits during the evaluation itself. We have developed a battery of tests sensitive to the effects of neurotoxic chemical (Table II).

The neuropsychologist typically employs tests with which he or she is familiar and uses frequently to examine the toxicant-exposed patient. These tests are generally classified according to the cognitive domains

Table II
Boston Extended Neurotoxicologic Battery: Clinical Version^a

| Behavioral test | Cognitive domain assessed |
|--|--|
| WAIS; WAIS-R: WAIS-III | |
| Information | Basic academic verbal skills |
| Vocabulary | Verbal concept formation |
| Comprehension | Verbal concept formation |
| Similarities | Verbal concept formation |
| Digit Spans | Attention |
| Arithmetic | Attention and calculation |
| Picture Arrangement | Sequencing and visual spatial |
| Block Design | Visual spatial |
| Object Assembly | Visual spatial |
| Digit Symbol | Psychomotor speed |
| WMS-R | |
| Information | |
| Orientation | |
| Mental control | Attention and cognitive tracking |
| Digit Spans | Attention (verbal) |
| Visual Spans | Attention (visual) |
| Logical memories | Verbal memory |
| Verbal Paired Associates | Verbal memory |
| Visual Paired Associates | Visual memory |
| Visual Reproductions | Visual memory |
| Figural Memory | Visual memory |
| Continuous Performance Test | Attention (vigilance) and reaction time |
| Trail-Making Test (A and B) | Attention, cognitive tracking and sequencing |
| Wisconsin Card Sort Test | Set formation and set shifting |
| FAS-verbal fluency | Language |
| Boston Naming Test | Language |
| Boston Diagnostic aphasia Exam - reading comprehension subtest | Language |
| Wide Range Achievement Test | Basic academic skills |
| Boston Visuospatial Quantitative Battery | Visuospatial |
| Santa Ana Form Board | Psychomotor speed |
| Milner Facial Recognition Test | Visuospatial and visual memory |
| Benton Visual Retention Test | Visual memory |
| Difficult Paired Associates | Verbal memory |
| Albert's Famous Faces Test | Retrograde memory |
| Profile of Mood States | Affect |
| Minnesota Multiphasic Personality Inventory | Personality and affect |

^aFrom White, R. F., and Proctor, S. (1995). In "Neurotoxicology: Approaches and Methods" (L. W. Chang and W. Slikker, eds.), Ch. 46, Academic Press.

they tap. Though no test is so pure that it taps only one type of cognitive processing skill or functional domain, many load heavily on one area of function or another. The most commonly assessed functional domains in neuropsychology include attention, executive function, fine manual motor skills, visuospatial abilities, language and verbal skills, anterograde (short-term) and retrograde memory, and affect and personality. Regardless of the battery of tests used, it is essential that the clinician determine an estimate of premorbid ability patterns for the patient. Any deficits uncovered on neuropsychological testing should be related to this estimate of baseline function. Neuropsychologists are typically interested in academic skills such as reading and arithmetic (which are often helpful in determining premorbid ability patterns) and in motivation to perform well on testing which can be influenced by aspects of secondary gains such as monetary compensations. The reader is referred elsewhere for descriptions of the tasks assessing these domains. The various domains mentioned earlier as well as the expected changes in performance associated with exposure to neurotoxicants are described next to provide additional insight into the neurobehavioral features of toxic encephalopathy.

a. Language-Verbal Function Language and verbal functioning are typically preserved in adults exposed to neurotoxicants. This aspect of cognitive function is relatively resistant to the effects of neurotoxic exposure-induced brain damage compared with dynamic cognitive processes, such as encoding of new memories. This is in stark contrast with the effects of stroke and other focal lesions, which may have profound impacts on language function. However, patients exposed to certain neurotoxic chemicals (e.g., carbon monoxide) may show deficits on tests requiring the application of verbal and language skills. Motor aspects of writing may be affected in those patients with movement disorders (e.g., tremor) resulting from neurotoxic exposure, whereas the grammatical aspects of writing remain intact. Exposure to neurotoxic chemicals is more likely to produce language deficits in children than in adults because disruption of encoding processes occurs during development and, thus, can lead to problems with language acquisition. The severity of the deficits seen depends upon the age of the child at the time of exposure; younger children are more vulnerable.

b. Attention and Executive Function Deficits in *attention* and *executive function* may be found on

formal testing of patients with exposures to neurotoxins. Tests of attention measure the following: (1) *simple (immediate) attention*, i.e., how much information can be grasped at once; (2) *divided attention*, which is the ability of an individual to attend to more than one task simultaneously; and (3) *vigilance or sustained attention*, which measures the ability of the subject to remain focused on a single task for long durations of time. Attention deficits impair the patient's ability to selectively focus on relevant stimuli and, therefore, may have a direct effect on concentration and an indirect effect on memory function.

Executive function is a higher order behavioral process involving the ability of the subject to appreciate and respond to complex changes in neurobehavioral task demands, including recognizing, maintaining, and shifting set as necessary to carry out such tasks. *Cognitive tracking* is an aspect of executive function often found to be impaired in those patients exposed to neurotoxic chemicals. Trail making (Trails A and B) is a cognitive tracking task that has been shown to be sensitive to problems associated with exposure to neurotoxic chemicals. *Cognitive flexibility* is another aspect of executive function that is affected in toxic encephalopathy. Difficulties in cognitive flexibility may be revealed by tasks such as the Wisconsin Card Sorting Test. Although some patients show deficits on tests of both cognitive tracking and cognitive flexibility, other patients exhibit deficits on one but not the other. It is impossible to predict which type of deficit will be seen in a patient with toxic encephalopathy, and it does not appear to be related to the type or severity of the exposure. Patients with severe deficits in executive function may have problems with their activities of daily living.

c. Memory Function Memory can be affected at several levels, including encoding of new information, retrieval of encoded information, ability to inhibit interference during learning and retrieval, and retention of encoded information. Many patients exposed to neurotoxic chemicals have relative deficits on tests of short-term or anterograde memory function compared with retrograde memory or long-term memory function. This dichotomy reflects the sensitivity to neurotoxic exposure-induced brain damage of the complex dynamic processes involved in short-term memory function, particularly encoding processes, and the relative resilience of the previously stored information tapped by tests of retrograde memory function, which is considerably more dependent upon retrieval mechanisms. Because of the divergent pat-

terns of memory impairment possible following toxic exposure, a rather extensive memory battery is used to assess these patients.

d. Motor Skills Motor function is affected in some patients exposed to neurotoxic chemicals. Patients may show performance deficits on tests sensitive to motor deficits, including Finger Tapping and the Santa Ana Formboard. Motor function deficits can interfere with the patient's performance on many neurobehavioral tests (e.g., Digit Symbol). For example, a patient with bradykinesia may perform poorly on timed tasks measuring performance in domains other than motor function because they simply move more slowly. The neuropsychologist using the behavioral neurology or Process Approach can take into consideration the effects of motor deficits on other neurobehavioral tasks and utilize this information in his or her assessment and interpretation of the patient's performance.

e. Visuospatial Abilities Visuospatial deficits are seen following exposure to certain neurotoxins (e.g., mercury). Performance on tests such as Block Design and the Rey-Osterreith Complex Figure (copy trial) may be below expectation in a patient exposed to neurotoxins.

3. Strengths of Neuropsychological Tests

Neuropsychological test procedures have some inherent strengths and weaknesses with regard to making clinical diagnosis.

A. They are reliable because they have been standardized with regard to scoring and administration. For this reason, they can be given in the same manner by different clinicians.

B. Normative values are available for these tests so that performance can be judged with regard to level of performance. These norms allow the clinician to compare the patient's performance to that evidenced by persons of the same age and, often, of the same gender and educational achievement. For some tests, norms specific to countries outside of the United States are available, as are norms for specific groups within the U.S. population (e.g., Hispanics).

C. The tests have been well-validated, and a great deal is known about how performance on one test relates to performance on similar tests. In addition, extensive information is available concerning the brain structures that participate most directly in the completion of tasks (brain-behavior relationships revealed

by the tasks) and the patterns of performance on the tests among patients with specific developmental, neurological, motivational, and psychiatric disorders.

4. Weaknesses of Neuropsychological Tests

A. In persons with low premorbid intellectual abilities, it can be difficult to identify subtle deficits in function because they are performing at the floor of the tests already (many tasks have high floors).

B. When there is a long delay between exposure and neuropsychological testing, physiological recovery and/or use of compensatory strategies by the patient may occur, obscuring changes in function that may have been evident at the time of exposure. Among patients whom we have seen longitudinally from the time of exposure until several years after exposure ceased, it is clear that for some cases we would not have been able to diagnose the toxicant-related effects or determine the minor residuum of those effects had we not seen the patient early.

C. For some subgroups of patients within the U.S. population, particularly immigrants who do not speak English as a first language, normative values may be unavailable or available only for a limited number of tests.

D. In patients for whom sick-role playing or embellishment is an issue, inconsistencies in test performance or exaggeration of performance deficits may obscure mild or subtle brain dysfunction associated with exposure to toxic chemicals.

E. Conditions with overlapping pathologies can make differential diagnosis difficult. For example, patients with white matter lesions may have multiple sclerosis, a toxicant-induced condition, or both. Similar problems hold for parkinsonism affecting basal ganglia function, which can occur secondary to toxicant exposure, infections, infarcts, or a combination of these brain insults. Cerebrovascular disease is also a problem because it presents with a frontal-subcortical picture on neuropsychological testing similar to that of many toxic chemicals. Furthermore, exposure to certain neurotoxicants (e.g., mercury) that may be associated with hypertension can lead to brain dysfunction.

B. Neurophysiological Testing

Neurophysiological tests of central nervous system functioning, such as electroencephalography and evoked potentials, are obtained to provide additional

objective evidence of an organic basis for the clinical behavioral findings. These tests can be used to detect possible diseases other than the disorder attributable to exposure to neurotoxicants. Abnormalities are not always revealed by these tests, but, when present, they may lend further support to a diagnosis of toxic encephalopathy.

1. Electroencephalography

The electroencephalogram (EEG) seen in a healthy adult has a relatively consistent pattern under normal waking, resting, and sleeping states. Disruptions of normal brain electrical activity are associated with changes in the symmetry, amplitude, and/or frequency of the EEG patterns. For example, epileptic activity is associated with a paroxysmal quality to the waveforms and sharp, spiked discharges. A focal concentration of sharp, slow, and/or paroxysmal waves in a particular area may indicate an underlying structural lesion, such as a neoplasm, stroke, or traumatic brain injury. Marked asymmetry of the EEG pattern suggests lateralized pathology. In contrast, encephalopathy due to endogenous or exogenous toxic disturbances is associated with diffuse bilateral slowing of the background rhythm and the disappearance of normal resting frequencies. As with all laboratory tests, the significance of the EEG report depends on correlation with other clinical information. In the differential diagnosis of neurotoxic syndromes and non-neurotoxic, neurological disease, the EEG is most helpful when an abnormality is seen during or in close chronological proximity to neurotoxicant exposure because the EEG pattern normalizes in reversible acute encephalopathy when the patient is removed from the source of exposure. The EEG tracing may not return to normal after the patient is removed from exposure to certain neurotoxicants (e.g., trimethyltin) and, therefore, is useful in documenting the presence of organic changes attributable to exposure.

2. Evoked Potentials

Evoked potentials (EPs) are used to assess the integrity and function of sensory pathways and are recorded after stimulation of peripheral sensory (afferent) nerve fibers in the extremities and/or by direct recording over the dorsal columns of the spinal cord. The EPs consist of visual evoked potentials, brain stem auditory evoked potentials, and somatosensory evoked potentials.

Visual evoked potentials (VEPs) are used to assess the integrity of the pathways of the optic system, including the optic nerve and chiasm, the optic tract to the geniculate nuclei, and the calcarine cortex. Two types of VEPs, flash visual evoked potentials (FVEPs) and pattern shift visual evoked potentials (PSVEPs), have been used to study the effects of exposure to neurotoxic chemicals.

Brain stem auditory evoked potentials (BAEPs) arise following stimulation of the auditory nerve. The auditory pathway generates a complex waveform that is recorded through electrodes attached to the patient and projected on the screen of an oscilloscope. Wave I reflects activation of the auditory nerve, whereas waves II and III reflect the activation of structures in the pontomedullary region. The sources of waves IV and V are less clearly defined but appear to be related to functions of the upper pons and lower midbrain. The absolute latencies of each wave are recorded, but interpeak latencies of waves I–III, III–V, and I–V are more consistent and reproducible and, therefore, are utilized in clinical testing. Brain stem auditory evoked potentials can be used to detect insults caused by ototoxic substances.

Somatosensory evoked potentials (SEPs) are recorded from electrodes placed over the sensory cortex after activation of a peripheral sensory or mixed nerve. The stimulus is conveyed centrally in the spinal cord and is then projected to the contralateral cerebral cortex. Technique is important in obtaining reliable measures. SEPs are usually tested in both upper and lower extremities, and interpeak latencies are more consistent and can help to localize pathology along the path of the peripheral nerve through the spinal cord, brain stem, and thalamus to the cortex.

Because many neurotoxic chemicals affect peripheral nerves, it is commonly the most distal sites of sensory conduction that are slowed and affect the cortically evoked SEPs in patients exposed to neurotoxic chemicals. Therefore, it is uncertain whether SEPs offer any advantage over standard nerve conduction velocities, except for studies of conduction through the spinal cord posterior columns and in instances where proximal nerve blocks or asymmetrical problems are being considered in the differential diagnosis.

C. Neuroimaging Studies

Highly sophisticated, computerized radiological methodologies can delineate images of the cerebral hemi-

spheres and ventricular systems, as well as differentiate between cerebral cortex and white matter structures. The sensitivity of neuroimaging techniques in the detection of neurotoxic effects is limited. Nonetheless, there have been reports of clinical correlations between images obtained with magnetic resonance imaging (MRI), single photon emission computerized tomography (SPECT), and positron emission tomography (PET) in the presence of exposure to various neurotoxicants.

1. Magnetic Resonance Imaging

Magnetic resonance imaging studies are invaluable in the differential diagnosis of various encephalopathies. These studies often demonstrate structural abnormalities due to strokes and neoplasms; MRI studies of severe acute and chronic toxic encephalopathy may reveal white matter changes. However, the MRI studies of patients with less severe chronic toxic encephalopathy may appear normal, despite clinical neurological and neuropsychological evidence of behavioral abnormalities and performance deficits.

In cases of hypoxia or carbon monoxide poisoning, the MRI findings show signal intensity changes in the basal ganglia (globus pallidus) that may be bilateral or unilateral. Changes in cerebral white matter are seen upon brain MRI following chronic exposure to toluene; these findings have been correlated with changes in neuropsychological performance. MRI changes are also associated with exposure to organolead compounds and inorganic mercury.

2. Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) has emerged as a possible sensitive measure of the structural and functional abnormalities associated with central nervous system dysfunction. It is an advanced level of the technology used in conventional MRI, which can detect chemical characteristics in addition to image data. Three main peaks reflecting the concentrations of *N*-acetyl-L-aspartate (NAA), creatine-phosphocreatine (Cr), and choline-containing compounds (Cho) are recorded from selected areas of interest. NAA is present within all neurons, and its concentration is elevated in several degenerative neurological conditions including amyotrophic lateral sclerosis. The Cr peak seen on MRS reflects levels of creatine and phosphocreatine, which serve as a reserve for high-energy phosphates in the cytosol of neurons. The Cho peak represents choline-containing compounds.

Choline is a precursor for the neurotransmitter acetylcholine and for the membrane constituent phosphatidylcholine. Additional chemicals of interest detectable with MRS include lactate, glutamate, glutamine, myoinositol, and γ -aminobutyric acid (GABA). Lactate is an end product of anaerobic respiration and may be elevated following exposure to hypoxia-inducing neurotoxicants such as carbon monoxide and hydrogen sulfide.

The value of MRS in the diagnosis of exposure to neurotoxicants has not been fully elucidated, but published reports indicate that this technology holds considerable promise as a diagnostic tool. For example, MRS studies of a 10-year-old boy who had documented elevated blood lead levels of 51 $\mu\text{g}/\text{dl}$ at 3 years of age revealed spectra that deviated from the expected pattern in all metabolite ratios analyzed, with a reduction in the NAA:creatine ratio for both gray and white matter. The conventional MRI of his brain done at the same time was normal. Formal neuropsychological assessment of the child was also performed at this time and revealed deficits in attention and mental control. The child also had reading, writing, and linguistic performance deficits. In contrast, his scores on tests of general knowledge were within normal limits. These neuropsychological and MRS findings were in stark contrast with those obtained for his cousin, a 9-year-old boy who was not exposed to lead and who served as a control. The neuropsychological assessment of the cousin was within normal limits and no abnormalities were seen on his MRI or MRS studies. Furthermore, the MRS findings in the patient's unexposed cousin were entirely consistent with the spectral pattern reported in previous studies of healthy individuals.

IV. BEHAVIORAL MANIFESTATIONS FOLLOWING EXPOSURE TO SELECTED CHEMICAL NEUROTOXICANTS

A. Lead

The acute symptoms of exposure to lead include abdominal colic, constipation, anorexia, vomiting, headaches, lightheadedness, dizziness, forgetfulness, anxiety, depression, irritability, excessive sweating, and muscle and joint pain. Acute symptoms subside following cessation of exposure and the reduction of blood lead levels. Chronic lead exposure results in more persistent neurological manifestations, including

peripheral neuropathy and encephalopathy. Encephalopathy is the most serious consequence of acute and chronic lead poisoning in adults and children. Seizures and coma are seen in both children and adults with inorganic lead encephalopathy, and death occurs in the most severe cases. Early recognition of the symptoms and signs of lead poisoning can minimize the neurotoxic effects of lead exposure and prevent permanent brain damage or death.

The neuropsychological testing of lead exposed children reveals impaired performance on tests of memory, visuospatial abilities, and concept formation. Meta-analysis of the published data on the effects of lead on the brain suggests that children's IQ scores are inversely related to their lead body burden. Residual cognitive deficits and behavioral disturbances have been reported in middle-aged adult survivors of childhood lead poisoning. Language function is typically spared in lead-exposed adults but is often impaired in those individuals exposed to inorganic lead as children.

We previously reported the results of comprehensive neuropsychological assessment of 18 adults (7 male, 11 female) who had been exposed to lead as children 50 years earlier. All of the exposed subjects were under the age of 4 years at the time of exposure; the mean age of the exposed subjects at the time of neuropsychological testing was 54.4 years. Eighteen age- and sex-matched subjects with no history of lead exposure served as controls. All of the exposed subjects exhibited lead lines (metaphyseal bands) upon the X ray of at least one long bone and had presented during childhood with symptoms consistent with overt lead poisoning, indicating that blood lead levels in all cases had exceeded 60 $\mu\text{g}/100\text{ ml}$. The neuropsychological test battery used included four subtests from the *Wechsler Adult Intelligence Scale-Revised (WAIS-R)*, including Similarities, Vocabulary, Picture Completion, and Block Design, the *Wechsler Memory Scale (WMS)*, Trail Making Tests A and B (attention and visuomotor functioning); controlled word association test (verbal fluency), *Raven Progressive Matrices* (nonverbal reasoning), finger tapping (motor speed), and the *Profile of Mood States (POMS)*.

Results of neuropsychological testing revealed significant deficits on the Picture Completion and Logical Memories subtests of the *WAIS-R* and *WMS*, respectively. In addition, the lead-exposed subjects showed impaired performance on the *Raven Progressive Matrices* and Trail B. These findings are consistent with persistent impairment of function in the cognitive domains of attention, executive function, concept formation, and short-term memory. Furthermore,

these findings indicate performance deficits on complex cognitive tasks that may impede the exposed individual's ability to learn new information. Whereas such subtle cognitive deficits may not be apparent during most activities of daily living, they can interfere with the exposed individual's academic and occupational achievements and advancement. Subtle cognitive deficits such as those reported in this study are particularly significant among those individuals whose premorbid IQ was below average.

Neuropsychological testing can also be used to detect and document the subclinical and clinical central nervous system effects of inorganic lead poisoning in persons exposed to lead as adults. Neuropsychological assessment of asymptomatic workers with blood lead levels greater than 50 $\mu\text{g}/100\text{ ml}$ reveals cognitive deficits on tests of psychomotor and memory functioning. Although comparisons of responses of workers on the *Profile of Mood States (POMS)* before and after reductions in levels of lead exposure indicate that tension, anger, depression, fatigue, and confusion are decreased by reductions in exposure, neurobehavioral performance deficits may not be entirely ameliorated by a similar reduction in lead exposure levels.

We examined a 31-year-old woman who had personally undertaken the job of deleading her recently purchased home. She developed symptoms indicative of inorganic lead encephalopathy after approximately 9 months of exposure. Her blood lead level when she first presented was 146 $\mu\text{g}/100\text{ ml}$ of whole blood. Neuropsychological testing revealed poor attention and impaired memory for new material, especially visual information. Specific tests revealing impairments of central nervous system function included Digit Span, Digit Symbol, and Block Design. We reported on a similar pattern of performance in a 19-year-old man who had worked as a professional deleader for approximately 10 months. His lead levels ranged from 70 to 100 $\mu\text{g}/100\text{ ml}$ of whole blood. He sought medical attention because of problems with attention and memory. Neuropsychological testing revealed impaired performance on tests of attention, short-term memory, and visuospatial and visuomotor functioning. Specific tests revealing impaired functioning included Digit Span, Digit Symbol, Block Design, and Picture Arrangement. Performance on tests of language and vocabulary were within expectation.

The trialkyl metabolites of the organolead anti-knock agents tetramethyllead and tetraethyllead (i.e., trimethyllead and triethyllead) are potent neurotoxics. Very few studies have specifically evaluated the

persistence and/or severity of the cognitive effects associated with chronic exposure to organic lead in humans. The severity of the encephalopathy associated with organic lead poisoning has been related to the patient's body burden of inorganic lead as reflected by measurement of blood lead levels.

The findings on formal neuropsychological testing of patients with organic lead encephalopathy may be correlated with the findings on EEG studies. Both of these markers of neurotoxicant effect may show improvement after cessation of exposure, and these findings may be further improved with chelation therapy. Cognitive functioning was assessed in a 41-year-old woman who presented with symptoms of organic lead poisoning (blood lead level = 110 $\mu\text{g}/100\text{ ml}$) and an 8-month history of sniffing leaded gasoline for its euphoric effects. Neuropsychological testing revealed her to be well-oriented with intact remote memory, but her attention span and short-term memory functioning were severely impaired. The patient was unable to perform simple oral arithmetic problems, indicating deficits in attention and working memory. In addition, her performance on delayed recall tests of short-term memory indicated that she had severe deficits in this cognitive domain as well. Her attention and memory as well as other symptoms of lead poisoning were improved after chelation therapy.

Neuropsychological functioning has been assessed in a group of 39 organic lead manufacturing plant workers with a mean exposure duration of 14.7 years. The mean lifetime blood lead level among these workers was 26.1 $\mu\text{g}/100\text{ ml}$. Eighteen (46.2%) of them had neuropsychological performance deficits on tests of attention, memory, and psychomotor function. These 18 workers all underwent additional testing to rule out the existence of metabolic, infectious, or structural etiologies for their performance deficits. No alternative explanation could be found for the neuropsychological deficits seen in any of these workers.

The associations between neurobehavioral functioning and tibial bone lead and chelatable lead levels in former organic lead workers have also been investigated. Higher peak tibial lead levels were significantly associated with poorer performance on the *Wechsler Adult Intelligence Scale-Revised* vocabulary subtest, serial digit learning test, *Rey Auditory-Verbal Learning Test*, Trails B, finger tapping, Purdue pegboard, and the *Stroop Test*. Chelatable lead concentrations were significantly associated with choice reaction times. These findings suggest that past exposure to organic lead may be associated with persistent neurobehavioral performance deficits,

particularly in the domains of manual dexterity, executive function, verbal intelligence, and verbal memory, and that the severity of these deficits is related to the peak tibial lead levels that occurred during the exposure period.

B. Mercury

Symptoms of acute exposure to elemental mercury vapor include respiratory irritation, headache, fever, chills, chest pain, general malaise, nausea, and vomiting. These symptoms are often referred to as "metal fume fever syndrome." Emotional lability, depression, social withdrawal, tremors, delirium, and coma develop within 24 hr after exposure to elemental mercury. The respiratory symptoms typically resolve within days to weeks after cessation of exposure, but the CNS disturbances persist.

The tremor associated with mercury poisoning begins in the fingers and hands, then progresses to affect the eyelids and face, and eventually affects the head, neck, and torso. The tremor is rapid, may be quite severe, and is accentuated by activity and emotional excitement, increasing in amplitude of excursion upon activation. The tremor is not a resting tremor and thus its frequency is faster and differs from the characteristic resting pill-rolling tremor seen in Parkinson's disease. Continued exposure to mercury vapor results in worsening tremor, gingivitis, mood changes, withdrawal from social interactions, greater memory loss. Abnormalities also include deficits in attention, executive functioning, short-term memory, and visuospatial ability. Language, basic academic skills, and retrograde memory are usually unaffected.

Neurobehavioral effects of acute exposure to elemental mercury vapor include depression, anxiety, and social withdrawal. Assessment of cognitive and emotional functioning conducted after cessation of exposure in workers exposed elemental mercury vapor may reveal persistent cognitive deficits on tests of motor coordination, processing speed with and without a motor component, cognitive flexibility, verbal fluency, verbal memory, and visual problem-solving and conceptualization.

Adults chronically exposed to elemental mercury may demonstrate cognitive impairments, including deficits in attention, executive function, short-term memory, visuospatial ability, and motor function. Language function and long-term memory are typi-

cally spared in adults but may be impaired in persons exposed *in utero* or during childhood. A case study of a 19-year-old man with a history of chronic exposure to mercury vapors during childhood (ages 4–9 years) revealed persistent tremor and behavioral abnormalities indicative of developmental toxin-induced encephalopathy secondary to mercury exposure, including deficits on tests of language, executive function, visuospatial skills, and fine motor control. The *POMS* revealed irritability and depressive affect.

The neuropsychological effects of mercury exposure can be correlated with current and cumulative exposure doses. For example, Digit Span has been used in research settings to document a correlation between current urine mercury levels and impairments of short-term memory function among exposed persons. The Bender–Gestalt test has also revealed impairments of visuospatial skills in persons with elevated tissue mercury levels. Impaired short-term memory functioning has been correlated with the duration of exposure to mercury. The serial neuropsychological assessment of construction workers exposed to elemental mercury revealed acute and persistent CNS effects. Initial testing revealed impaired performance on tests of attention and executive functioning (Trails A and B, *Stroop Test*) and motor skills (finger tapping, grooved pegboard). Performance was correlated with cumulative excretion of mercury. Performance on Trails A and B was improved following chelation therapy. However, performance on finger tapping and the *Stroop Test* remained unchanged and performance on the grooved pegboard worsened after cessation of exposure. Thus, our experience and a review of the literature suggest that elemental mercury exposure can be expected to affect performance on tests of attention, executive functioning, and motor functioning.

Persistent impairments in short-term memory, coordination, and simple reaction time may be seen up to 10 years after removal from exposure to elemental mercury. Research studies comparing the neuropsychological functioning of former chloralkali workers with that of age-matched unexposed controls with similar educational levels reveal that performance on certain tests, including the grooved pegboard and *Benton Visual Retention Test*, is worse among those previously exposed to mercury. Formerly exposed subjects may also perform worse on other tests sensitive to attention and psychomotor function, such as Trails A and B and Digit Symbol.

The clinical picture of methylmercury encephalopathy differs somewhat from that associated with

exposure to elemental mercury. Exposure to methylmercury during critical developmental periods can lead to severe mental retardation. Neuropsychological development was reported to be so severely delayed in an individual exposed to methylmercury *in utero* during the Minimata outbreak that she never learned to speak. Adult exposure to methylmercury is associated with lesions in the occipital cortex, and performance deficits may be seen on tests of visuospatial ability. Deficits have also been reported on tests of manual dexterity in adult women exposed to methylmercury.

C. Manganese

Occupational exposure to manganese (Mn) occurs among miners and welders. Frequently encountered organic Mn compounds include methylcyclopentadienylmanganese tricarbonyl (MMT), which is used as an antiknock additive in gasoline. Encephalopathy and basal ganglia dysfunction with parkinsonian signs including rigidity, gait abnormalities, dysarthria, hypomimia, and bradykinesia have been reported in patients with increased brain Mn levels due to chronic liver failure. The similarities between the clinical manifestations associated with Mn intoxication and those seen in Parkinson's disease suggest that occupational and environmental exposures to this and other neurotoxic chemicals may be involved in the pathogenesis and/or alter the prognosis of certain neurodegenerative diseases. It has not been established whether exposure to Mn precipitates the occurrence of progressive idiopathic Parkinson's disease, but research suggests that the prognosis may be poorer among those persons who are predisposed to develop idiopathic Parkinson's disease who also have a history of exposure to Mn.

The initial clinical manifestations of manganese poisoning often include behavioral changes referred to collectively as "manganese psychosis." The clinical symptoms include mood changes, emotional lability, uncontrolled laughter, and hallucinations. Performance on formal neuropsychological tests may be impaired at this time. Motor disturbances, characterized by tremor, dysarthria, gait disturbance, slowness and clumsiness of movement, and postural instability, emerge with continued exposure to Mn. If exposure continues, the psychosis typically subsides, and dystonia and an awkward high-stepping gait emerge. The gait disturbance associated with Mn poisoning is easily

distinguishable from the shuffling gait of idiopathic Parkinson's disease. In some cases, the extrapyramidal symptoms of Mn poisoning may progress following cessation of exposure.

Formal neuropsychological testing can be used to document the behavioral and cognitive effects of Mn exposure in clinical and research settings. Tests of psychomotor functioning such as the Santa Ana Formboard, Digit Symbol, and finger tapping are sensitive to the neurotoxic effects of Mn. Attention and memory impairments induced by Mn exposure are revealed by tests sensitive to functioning in these two cognitive domains. Language and verbal functioning are typically spared in Mn-exposed adults, but children exposed to Mn may develop persistent impairments of language function.

Research studies investigating neuropsychological performance among Mn-exposed persons have revealed deficits at concentrations ranging from 1 to 28 mg/m³. Tests in research settings used to document deficits have included finger tapping, reaction time, and digit spans. Visual spans and tests of visual spatial ability have also been used successfully in research settings to document the effects of Mn.

The neuropsychological test performance of Mn-exposed workers with parkinsonism has been compared with those of normal controls and patients with idiopathic Parkinson's disease. Mn-exposed workers with parkinsonism perform significantly worse than do unexposed controls on the *WAIS-R*, *Milner Facial Recognition Test*, Purdue pegboard, and the Continuous Performance Test. Mn-exposed workers with parkinsonism typically perform better on the Purdue pegboard than do patients with Parkinson's disease.

Neurobehavioral testing has been performed on a group of workers from a ferromanganese alloy plant. The workers had been exposed for 1–28 years, and the mean duration of exposure was 13 years. They were divided into three groups on the basis of their Mn exposure histories. The *low-exposure* group comprised foremen, clerks, and laboratory technicians exposed to Mn concentrations of only 0.009–0.15 mg/m³ (mean blood Mn = 6.0 µg/liter, mean urine Mn = 1.7 µg/liter). The *medium-exposure* group consisted of maintenance workers with exposure levels ranging from 0.072 to 0.76 mg/m³ (mean blood Mn = 8.6 µg/liter, mean urine Mn = 2.3 µg/liter). The *high-exposure* group consisted of those workers with the highest levels of exposure of up to 2.6 mg/m³ (mean blood Mn = 11.9 µg/liter, mean urine Mn = 2.8 µg/liter). Cumulative exposure indices (CEI) were determined for each subject. Cognitive domains assessed included

attention (simple and complex reaction times), executive function (arithmetic), psychomotor function (Digit Symbol and finger tapping), short-term memory (Digit Span), and verbal understanding (vocabulary). The results of tests of psychomotor function (finger tapping and Digit Symbol) and short-term memory (Digit Span) were correlated with environmental exposure levels, as represented by individual CEI scores.

D. Trichloroethylene

Trichloroethylene (TCE) is commonly used as a degreasing solvent in industrial settings. The neurotoxic effects of TCE are associated with exposure to the parent molecule and to its environmental degradation product, dichloroacetylene (DCA). Because DCA is derived from TCE, individuals working with TCE or encountering it in nonoccupational settings are at risk for the neurotoxic effects of both chemicals.

Acute exposure to TCE induces narcosis characterized by subtle behavioral changes and subjective symptoms of drowsiness and an inability to concentrate. At higher levels of exposure, nausea, vomiting, headache, dizziness, confusion, stupor, and loss of consciousness occur. Acute exposure to very high levels of TCE has been associated with persistent neurological symptoms and death. The salient persistent effects of a severe acute exposure to TCE include facial anesthesia, reduced perception of taste, dysarthria, flattening of the nasolabial folds, ptosis, reduced pupillary response, constricted visual field, and sensorimotor neuropathy.

The 25-year serial follow-up examination of a 26-year-old man who experienced toxic encephalopathy after a single severe exposure to TCE was reported by us. Initial neuropsychological assessment of this individual revealed difficulty with sequential problem-solving and short-term memory tasks. Although daily functioning improved over the course of several years, the patient felt chronically depressed and apathetic and continued to experience problems with attention and short-term memory. These problems, which were severe enough to interfere with his ability to perform his daily activities, were documented by serial neuropsychological assessments. At a follow-up examination 16 years after the exposure incident, his performance IQ (PIQ) was 19 points lower than his verbal IQ (VIQ). Significant visuospatial deficits accounted for a large part of the discrepancy between

the patient's PIQ and VIQ. Tests of short-term memory showed deficits in both immediate and delayed recall of verbal and visual information. Tests revealing deficits included the *Benton Visual Retention Test*, Logical Memories, Paired Associates, and Visual Reproductions. In addition, the *Minnesota Multiphasic Personality Inventory (MMPI)* indicated that the patient was depressed.

Toxic encephalopathy was also seen in a 62-year-old machinist who experienced a brief acute exposure to TCE. A follow-up neuropsychological assessment of this patient performed 5.5 years after the incident revealed performance deficits on the Digit Symbol and Object Assembly sections of the *Wechsler Adult Intelligence Scale (WAIS)*. Furthermore, the patient exhibited overt impairment of executive function, lack of insight, and low motivation, all of which were associated with his past exposure to TCE.

Symptoms of chronic exposure to TCE develop insidiously whether intake occurs via a pulmonary or oral route. Memory and affect are affected by chronic exposure. For example, subjective symptoms among residents of Woburn, MA, who were exposed to TCE-contaminated well water, included headache, dizziness, fatigue, irritability, insomnia, memory and concentration impairments, and paresthesias. Effects associated with chronic occupational exposure to TCE vapors include forgetfulness, dizziness, headache, sleep disturbances, fatigue, irritability, anorexia, trigeminal nerve symptoms, sexual problems, and peripheral neuropathy. Speech and hearing disorders have been reported among children exposed to TCE through the use of contaminated drinking and bathing water. The cognitive domains most frequently affected by TCE include attention, executive functioning, short-term memory, and visuospatial ability; language and verbal skills are typically spared in adults. Children exposed to TCE may develop persistent impairments of verbal functioning, which interfere with learning later in life.

Neuropsychological testing documented mild-to-moderate encephalopathy in 24 of 28 individuals who were chronically exposed to TCE-contaminated drinking and bathing water. Impaired cognitive performance was seen on the following tests: Visual Reproductions, Logical Memories, Word Triads, and the *Benton Visual Retention Test*. Significant memory impairments were seen in 24/28 cases. Attention and executive function deficits were seen in 19/28 persons, whereas visuospatial deficits and manual motor function deficits were seen in 17/28. Language and verbal functioning among the adults were almost

always within expectation. However, the neuropsychological evaluations of the children in this group indicated that the developmental stage at the time of exposure is related to the type of neurobehavioral deficits seen postexposure. Children exposed before age 18 years were shown to have deficits in a greater number of neuropsychological domains than individuals exposed as adults. In addition, these children showed a decrease in performance on the *Boston Naming Test* that was not seen in their parents. These findings suggest that children exposed to TCE suffer more diffuse damage to the brain and are more likely to develop learning disabilities.

E. Organophosphorus Compounds

Organophosphorus compounds (OPCs) are used primarily as pesticides, but many (e.g., Sarin and VX) are also used as chemical warfare agents. These compounds inhibit the activity of acetylcholinesterase, resulting in the accumulation of acetylcholine at receptors on neurons in the central and peripheral nervous systems.

Exposure to OPCs is associated with three clinically distinct syndromes: (1) acute cholinergic crisis; (2) intermediate syndrome; and (3) organophosphate-induced delayed peripheral neuropathy (OPIDN). The clinical presentation of these three syndromes reflects the different pathophysiological mechanisms that underlie each. The *acute cholinergic crisis* develops within hours of exposure to OPCs and may last as long as 96 hr. The signs and symptoms seen during the acute cholinergic crisis are due to the inhibition of acetylcholinesterase. The clinical manifestations reflect excessive stimulation of nicotinic and muscarinic receptors. Clinical manifestations include weakness, muscle fasciculations, tachycardia, miosis, lacrimation, excessive salivation, seizures, and coma.

The *intermediate syndrome* follows the acute cholinergic crisis. Symptoms begin to emerge within 24–96 hr after removal from exposure. Symptoms are due to adverse effects on muscle cells, and can persist for up to 6 weeks and include weakness of the proximal muscles of the limbs and neck. Tendon reflexes are also reduced. The cranial nerves and respiratory muscles may also be involved. Weakness of the diaphragm may necessitate intubation and respiratory support. Death may occur in the most severe cases. Prognosis is good if the patient survives, and clinical recovery is typically complete.

Organophosphate-induced delayed neuropathy (OPIDN) is characterized by clinical and electrophysiological

signs and symptoms of neuropathy that emerge 1–5 weeks after exposure. The clinical features of OPIDN include flaccid paralysis of the distal muscles of the lower and upper extremities. This clinical picture is in contrast with that of the intermediate syndrome, which involves the more proximal limb muscles. Deep tendon reflexes are reduced or absent in those patients with OPIDN. Patients report sensory symptoms of numbness and paresthesias that are aggravated by exercise. The prognosis for patients with OPIDN is variable, with clinical recovery requiring at least several months; recovery of function may be incomplete in the legs and feet of the most severe cases. Signs and symptoms indicative of CNS pathology are also noted in those patients with OPIDN. Patients with greater CNS involvement show increased tendon reflexes and the Babinski sign may be present.

Acute and chronic behavioral effects have been associated with exposure to OPCs. Changes in mood and affect including irritability, nervousness, and depression are seen during the acute cholinergic crisis. Cognitive deficits associated with the acute cholinergic crisis range from overt confusion to mild forgetfulness. These neurobehavioral manifestations may subside within days or may persist indefinitely. Formal neuropsychological testing reveals deficits in attention, executive functioning, psychomotor skills, and short-term memory. Significant neuropsychological performance deficits have been found in these patients up to several years after cessation of exposure, indicating that toxic encephalopathy can occur in some individuals exposed to OPCs.

Neuropsychological functioning has been assessed in workers with chronic exposure to OPCs who have not experienced any episodes of overt acute poisoning. The exposed workers show significantly slower reaction times when compared with unexposed controls suggesting that psychomotor processing is slowed.

Serial neuropsychological testing was completed in a 44-year-old EPA field inspector who was soaked with a large quantity of phosmet released from a crop duster airplane that was flying overhead. His acute symptoms included nausea, excessive sweating, salivation, blurred vision, and headache. He remained symptomatic over the next several days and reported experiencing anxiety, irritability, weakness, photophobia, and insomnia. He soon recovered from the acute cholinergic symptoms such as excessive sweating and salivating, but noted that he was now experiencing attention deficits and dizziness that he had never before experienced. A neurological examination and a brief neuropsychological assessment were performed 6 months

after the exposure incident. The patient's cognitive performance was within the normal ranges on Digit Span, the *Benton Visual Retention Test*, Block Designs, *Wisconsin Card Sort Test*, and the Purdue pegboard. Despite this reassurance that he was cognitively "normal," the patient continued to experience difficulty with his activities of daily living.

A more detailed neuropsychological assessment was performed approximately 2 years after the exposure incident. At testing the patient's verbal IQ was 126 and was significantly greater than his performance IQ (106). Performance deficits were noted on Trails B (attention and executive function) and Digit Symbol (psychomotor speed). Memory deficits were noted on delayed recall of both visual and verbal material; immediate recall was within expectation. His answers tended to be concrete and he missed the gestalt on tests of complex verbal reasoning. The *Profile of Mood States (POMS)* revealed depression, anger, and fatigue.

A follow-up neuropsychological assessment was performed 13 months later at 40 months after the OPC exposure incident. Overall improvement was noted on tests of executive function, visuomotor speed, and retrieval of information on delayed recall. However, the patient continued to show deficits on tests of attention and had difficulty with recall of verbal paired associates. His major problem on this testing continued to be difficulty with complex verbal reasoning tasks. The *POMS* revealed only irritability. It was concluded that the overall improvement in cognitive functioning with some residual impairments seen in this patient is consistent with recovery from an acute toxic encephalopathy that could have resulted from OP exposure. Of interest in this case is that the patient went on to complete law school, and his only residual complaints reported 10 years after the OP exposure were that he occasionally experienced unexplained symptoms of nausea, blurred vision, and anxiety. Such an instance was when he entered a local grocery store for a brief period of time and became nauseous and had blurred vision. He went home and contacted the store manager by telephone, inquiring about the possibility that he might have been exposed to a chemical used in the store. The manager informed him that the store had been sprayed with an insecticide earlier that same day. In addition, he has recognized that he feels anxious and has nonspecific discomfort at those times when he can detect aromatic substances in the air, such as perfumes, petroleum products, or auto exhaust. He has adjusted to his apparent multiple chemical sensitivity (MCS) by simply avoiding such circumstances.

The number of individuals who experience the preceding constellation of symptoms is sufficiently large that a clinician should recognize it as a behavioral syndrome. The exact pathogenesis of MCS syndrome is still unclear. Components of autonomic nervous system reactivity, olfactory triggers of emotional responses, and PTSD and features of depression make it difficult to identify a specific therapeutic intervention. Much further work is needed on this condition before it can simply be dismissed as psychogenic in origin.

V. CONCLUSION

Behavioral syndromes following exposure to neurotoxic chemicals must be differentiated from other neurological disorders. This is only accomplished with careful analysis of the time line relationship between reported exposure conditions and the emergence of symptoms. Markers of exposure such as air or water samples and biological specimens also should be obtained whenever possible to support the diagnosis. Clinical findings and/or corroborative diagnostic test data are of value when these results are interpreted in the context of developmental, academic, and social history, medical and psychiatric history, information gleaned from interviewing the patient and/or significant others, the patient's behavior in the test situation, and qualitative findings observed in the test material. Follow-up testing is useful in documenting prognosis, confirming the effect of exposure to neurotoxic chemicals, and that a neurodegenerative process is not responsible for the individual's symptoms and signs of neurologic dysfunction.

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