INTRODUCTION

Many potential neurotoxins exist and are classified (1-7) as: 1) pharmaceutical agents, 2) biological agents, 3) radiation and electricity, 4) heavy metals, 5) solvents and vapors, 6) insecticides, herbicides, fungicides, and rodenticides, 7) air pollution, 8) food additives, 9) social poisons. The reader is referred to sources of toxicology information available on the internet (6, 7). These include but are not limited to: U.S. National Library of Medicine http://www.nlm.nih.gov; Medscape http://www.medscape.com; National Institute of Occupational Safety and Health http://www.cdc.gov/niosh/homepage.html; Neurotoxic.com http://www.neurotoxic.com

PRINCIPLES

There are a number of principles, which govern evaluation of and diagnosis of nervous system damage by toxins in humans (7-10). A detailed and accurate history and refined physical examination are required. The following are some of the principles/concepts governing neurotoxicity effects:

1) A chemical formula does not always predict
toxicity; however, precise information about an
offending substance’s composition and history
of its prior toxicity is needed;
2) There are varying degrees of toxicity of sin-
gle and of mixed substances;
3) Exposure level results from both the concen-
tration and duration of toxin contact;
4) “Innocent bystanders” may enhance toxicity;
5) Exposure may be acute high-dose or chronic
low-dose;
6) A short or long latency may occur between
exposure and toxic effects;
7) Epidemiological data is needed, e.g., effects
upon others similarly exposed.

Additional Clinical Principles

When considering a toxically exposed indi-
vidual, additional principles exist:
1) Pre-existing or coincidental disease compli-
cates diagnosis;
2) Symptoms are frequently numerous and non-
specific. Common symptoms are: headache,
memory and behavioral disturbances, numbness,
tingling and weakness of extremities;
3) Neurological deficits (signs) may be absent
and/or subtle within the syndromes classically
noted, including peripheral neuropathy, myelopa-
thy, cerebellar damage, movement disorders, and
encephalopathy (the last of which includes per-
sontality and/or intellectual disorders). Therefore,
a skilled neurological examination is essential;
4) There is variable individual susceptibility to
toxic damage among humans. Toxicity to animals
does not always correlate to human toxicity;
5) Damage may be completely reversible, par-
tially reversible or irreversible;
6) Laboratory data may be negative or mildly
deranged, despite toxic damage, or may be non-
specific;
7) A cascade of effects may occur with the de-
velopment of secondary pathology and systemic
complications;
8) Prospects of secondary gain, e.g., in litigious
countries, complicates diagnosis.

LABORATORY DATA

Ambient air sampling, when direct sampling
of an individual’s exposure is impossible to ob-
tain, provides an indirect estimate of exposure to
volatile substances. Laboratory chemical analysis
of blood and urine samples is useful after acute
high-dose exposure and after chronic low-dose
exposure to some substances, e.g., heavy metals.
Likewise, analyses of tissue, e.g., hair and nails,
for toxic substances can be pathognomonic of
toxic disease. Environmental analysis, for exam-
ple of contaminated water, soil, or air, can pro-
vide exposure data. Calculations of chemical ex-
posure through contaminated drinking water are
based on estimated daily intake concentrations of
a chemical and sometimes provide information
on absorption of a toxin. Soil samples may also
provide toxicological data, e.g., if children ingest
contaminated soil. An analysis of toxins in contami-
nated food sources is also relevant at times.

In addition to analyses of the tissues cited
above, diagnostic methods (markers) are used.
The markers that may determine whether a poten-
tial neurotoxin has produced nervous system
(NS) damage are: the history (including epi-
demiology) and neurological examination, elec-
trophysiology, neuroimaging, neuropsychology,
chemical assays, and biochemical markers.

Many become positive only after irreversible
damage has occurred, i.e., sensitivity is poor.
Likewise, specificity may be poor. It is es-
sential to determine whether neurological dam-
age is present, e.g., neuropathy, cerebellar dys-
function, encephalopathy, etc.

Electrophysiological tests include a large
number involving the central nervous system
(CNS) autonomic nervous system (ANS), and the
peripheral nervous system (PNS) (Tables I and II)
(8,11-13). Of these, needle electromyography
(EMG) and nerve conduction studies (NCS) are
the most reliable in their sensitivity and repro-
ducibility. However, when they identify neuropa-
thy, the findings are not specific to toxic neuropa-
thy.
Neuropsychological testing can reliably document toxic encephalopathy. However, performance and interpretation of such testing is subject to bias while abnormalities seen may not be specific to toxic damage (8,11,14-18). The potential effects of neurotoxins upon children and upon the developing brain is a matter of specific concern (19-21).

### Table 1 - A battery of selected electrophysiological tests useful in evaluating the central (CNS), autonomic (ANS), and peripheral (PNS) nervous systems.

<table>
<thead>
<tr>
<th>CNS</th>
<th>PNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electroencephalogram (EEG)</td>
<td>Electromyography</td>
</tr>
<tr>
<td>Computerized EEG (brain mapping)</td>
<td>Nerve conduction studies (sensory and motor)</td>
</tr>
<tr>
<td>Evoked potential studies (VER, BAER, SSEP)</td>
<td>Repetitive motor nerve stimulation</td>
</tr>
<tr>
<td>Event-related potentials (e.g., P-300)</td>
<td>Needle electromyography</td>
</tr>
<tr>
<td>Blink reflexes</td>
<td>Conventional</td>
</tr>
<tr>
<td></td>
<td>Single fiber</td>
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**ANS**

<table>
<thead>
<tr>
<th></th>
<th>Blink reflexes</th>
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<tbody>
<tr>
<td>Q-SART</td>
<td></td>
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<tr>
<td>Sympathetic skin response (SSR)</td>
<td></td>
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<tr>
<td>R-R interval</td>
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Abbreviations: VER = visual evoked response; BAER = brainstem auditory evoked response; SSEP = somatosensory evoked potential; Q-SART = quantitative sudomotor axon reflex test.

### Table 2 - Toxic neuropathy classified by electrodiagnostic findings.

<table>
<thead>
<tr>
<th>Motor or motor &gt; sensory, conduction slowing</th>
<th>Sensorimotor, no conduction slowing</th>
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<tbody>
<tr>
<td>Carbon disulfide</td>
<td>Acrylamide</td>
</tr>
<tr>
<td>Cytosine arabinoside (ara-C)</td>
<td>Arsenic (chronic)</td>
</tr>
<tr>
<td>Methyl n-butyl ketone</td>
<td>Carbon monoxide</td>
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<tr>
<td>n-Hexane</td>
<td>Colchicine (neuromyopathy)</td>
</tr>
<tr>
<td>Saxitoxin (sodium channel blocker)</td>
<td>Ethambutol</td>
</tr>
<tr>
<td>Suramin</td>
<td>Ethyl alcohol</td>
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<tr>
<td>Swine flu vaccine</td>
<td>Ethylene oxide</td>
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</table>

<table>
<thead>
<tr>
<th>Motor or motor &gt; sensory, no conduction slowing</th>
<th>Elemental mercury</th>
</tr>
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<tbody>
<tr>
<td>Cimetidine</td>
<td>Gold</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>Disulfiram (carbon disulfide?)</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Lithium</td>
</tr>
<tr>
<td>Hyperinsulin/hypoglycemia</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Nitrofuratoin</td>
</tr>
<tr>
<td>Organophosphorous esters (OPIDN)</td>
<td>Nitrous oxide (myeloneuropathy)</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Piclataxel</td>
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</table>

<table>
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<tr>
<th>Sensory only (neuropathy or neuronopathy)</th>
<th>Perhexiline</th>
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<tr>
<td>Cisplatin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Ethyl alcohol</td>
<td>Thallium</td>
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<tr>
<td>Metronidazole</td>
<td>Vincristine</td>
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<tr>
<td>Pyridoxine</td>
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<tr>
<td>Styrene</td>
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<tr>
<td>Thalidomide</td>
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<tr>
<td>Thallium (small fiber)</td>
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Neuroimaging provides an index of potential encephalopathy but, as yet, has provided sensitive and specific diagnostic data only in isolated toxic conditions, e.g., carbon monoxide. Brain CT shows nonspecific edema early in acute high-dose exposure and atrophy in the late stage. MRI shows similar effects and also provides more sensitivity, e.g., for basal ganglia and/or cerebellar damage. Although promising in their applications, MR spectroscopy, SPECT, and PET continue to be of limited usefulness in identifying metabolic and/or blood flow abnormalities after toxic exposure (21-24).

Biochemical markers have been excellently reviewed elsewhere in this publication (25). In summary, in progressive stages of neurotoxic disease, biochemical events usually precede structural changes and permanent NS lesions or dysfunction. The mode of action of many neurotoxic chemicals may require repeated insults at a biochemical level to produce an effect detectable in the NS or in the body as a whole. Measurement of biochemical events should give reliable indications of early-stage effects detectable in exposed persons long before the induction of overt disease. This approach is limited by the inaccessibility of the target tissue. However, some NS biochemical and molecular toxicity markers are also present in more accessible tissues, i.e., cerebrospinal fluid (CSF), blood, plasma, and peripheral blood cells. These include membrane-bound receptors; enzymes responsible for synthesis and degradation of neurotransmitters; second messengers and high-affinity uptake systems. The biomarker strategy of assessing neurotoxicity by non-invasive methods uses peripheral tissue samples as surrogate indicators. An example is the use of lymphocyte neuropathy target esterase (NTE) as a predictor of delayed polyneuropathy in subjects exposed to organophosphorous pesticides (25-27).

Figure 1 is an algorithm which provides a decision-making guide to the use of the diagnostic principles and laboratory data discussed above.

TOXIC MECHANISMS

Neurotoxins can exert their adverse effects in many ways: 1) they can alter nerve cell membranes, thereby affecting neuronal excitability, neurotransmitter release, and synaptic activity in the PNS and CNS; 2) by disturbing axoplasmic flow, thereby affecting nutrient supply, transport of neurotransmitters, proteins, and axonal structure; 3) by damaging Schwann cells and peripheral myelin and oligodendrocytes as well as central myelin and by disrupting the normal supportive functioning of astrocytes and microglia; 4) by disturbing extracellular fluid volume with resultant edema; 5) by altering systemic metabolic processes with consequent PNS and/or CNS damage; 6) by adversely affecting cerebral oxygenation, e.g., by pulmonary or cardiac damage, or by directly...
decreasing oxygenation of neuronal structures sensitive to hypoxia, e.g., mitochondria (7,28-30).

REPRESENTATIVE CASE STUDIES

Case studies can illustrate the variety of clinical effects that toxins can cause to the human NS and also provide insight into the mechanisms whereby such damage occurs. The following are a few such case studies of NS damage selected from the author’s professional experience.

1. Seven young men developed an ascending polyneuropathy more motor than sensory after inhaling a lacquer thinner recreationally. Symptoms and signs occurred within 10-20 days of inhalation and progressed to complete paralysis in 3 and death in one, the paralysis evolving over the course of 3 weeks. Incomplete recovery occurred in survivors. All had inhaled a commercially available lacquer thinner for years without adverse effects. The manufacturer changed its formula, adding 2-heptanone (15.5%), 2-nitropropane (5.8%), and n-hexane (0.5%). EMGs documented acute denervation and severely delayed nerve conduction velocities. Nerve biopsies demonstrated a predominantly axonal neuropathy with segmented demyelination. Postmortem examination of the individual who died disclosed an axonal neuropathy with severe dyning back phenomenon including necrosis of spinal cord anterior horn cells. The brain, except for agonal hypoxic changes, was normal (31).

A similar neuropathy was produced in rats that inhaled levels of toxic mixture, insufficient to produce necrosis, whereby rats exposed to the lacquer thinner mixture previously used by the victims remained normal.

These cases illustrate that volatile organic compounds (VOCs) can produce irreversible peripheral neuropathy and death. They also highlight the effects of mixed substances, which may facilitate each other’s toxic effects. A range of damage occurred, indicating variable susceptibility and/or varying dose effects. Because many others were reported to be inhaling this lacquer thinner recreationally without coming to medical attention, it is possible that mild and/or sub-clinical damage can occur to humans exposed to VOCs at lower levels, whether by voluntary or inadvertent exposure.

2. A man suffered status epilepticus, which resolved, and action (intention) myoclonus, which persisted, after accidental exposure to methyl bromide in the context of occupational house fumigation. Methyl bromide, a colorless and almost odorless gas at room temperature, is used as a refrigerant, fire extinguisher, and insecticide. Occupational exposure has resulted in damage to the kidneys, lungs, and nervous system. Nervous system manifestations include drowsiness, psychosis, seizures, dysarthria, ataxia, intention myoclonus, and peripheral neuropathy. The last occurs after chronic low doses, the others after acute high-dose exposure. An interval between exposure and onset of nervous system disease is common (32).

This case illustrates that a VOC used commercially can cause central nervous system damage including transient seizure and permanent dysfunction, i.e., action myoclonus.

3. Four people developed mild ciguatera poisoning after barracuda ingestion. Acutely they suffered vomiting and diarrhea followed by weakness, myalgias, generalized pruritus, perional and distal extremities paresthesias and reversed thermal sensations, i.e., cold objects being felt as hot or burning whereas warm ones were perceived to be cool. Although these symptoms and signs of decreased discrimination of light touch in the distal extremities subsided, abnormal electrophysiological studies (EMGs) documenting normocalcemic latent tetany persisted for months. The EMG findings were consistent with ciguatoxin’s mechanism of toxicity which involves inactivation of voltage gated Na+ channels and eventual increase of nerve membrane excitability (33).

These cases illustrate that neurotoxins can exert their damage by discrete and specific electrophysiological and biochemical mechanisms.

4. A 21-year-old man began continual abuse of nitrous oxide (N2O) inhalation for the eupho-
ria and hallucinations it produced. Two years later, moderately severe peripheral neuropathy and encephalopathy ensued. These deficits progressed to profound states during four subsequent years of virtually continuous inhalation from cartridges designed to create whipped cream. The clinically apparent peripheral neuropathy was documented by EMG and nerve biopsy; clinically evident encephalopathy with dementia by neuropsychological tests. N₂O inactivates cobalamin, a necessary cofactor for enzymes involved in myelin production. Some neurotoxins cause either peripheral nervous system (PNS) or central nervous system (CNS) damage (34). This case illustrates that some cause damage to both because they interfere with metabolic processes required for the integrity of cells within both PNS and CNS.

5. Nine people were exposed to carbon monoxide (CO) because of a faulty domestic gas heater. Four, presenting with transient loss of consciousness after chronic moderate CO level exposure, suffered intellectual impairment without MRI abnormalities. The MRI spectroscopy of one demonstrated decreased n-acetyl aspartate (NAA) in the basal ganglia, bilaterally. Of 5 exposed to high levels for about 12 hours, one died prior to clinical and/or MRI evaluation. One who suffered from coma recovered but was lost to evaluation. Three, who were unconscious for a period of time ranging from hours to days, exhibited T2 MRI white matter signal abnormalities. MR spectroscopy showed decreased basal ganglia NAA in two. One of these was affected by a Parkinsonian syndrome. All four were intellectually impaired. NAA is a neuronal marker with low levels indicating neuronal loss and/or dysfunction (35).

These cases illustrate several points: 1) neurotoxins such as carbon monoxide may cause variable damage depending upon exposure levels and perhaps individual susceptibility; 2) diagnostic modalities such as brain MRI do not always show clear signs of damage that is clinically evident, e.g., intellectual impairment. Several victims who suffered intellectual impairment had normal MRI scans. The abnormal scan of one did not fully reflect his damage, which included a Parkinsonian syndrome; and 3) MR spectroscopy changes may not always parallel the degree of damage but may provide insights into the biochemical mechanisms of such damage.

CONCLUDING REMARKS

Many environmental substances have the potential for causing damage to the human NS, i.e., are potential neurotoxins. PNS damage occurs mainly in the form of a peripheral neuropathy. Damage to the cerebrum of the CNS causes mainly intellectual impairment, seizures, and movement disorders. Damage to the cerebellum of the CNS causes incoordination and ataxia. Potential damage varies according to the substance(s) involved, the duration and degree of exposure, and individual susceptibility. A detailed history of exposure and a careful neurological examination may lead to the diagnosis of neurotoxicity. A variety of laboratory tests assist in diagnosis. Once damage has occurred, specific therapy is rarely available.

REFERENCES

2. Klasser C ed Casarett & Doull’s Toxicology. New York; McGraw-Hill 1996
5. Feldman RE. Occupational and Environ-


3. American Conference of Government Industrial Hygienists (ACGIH). Documentation of the Threshold Limit Values and Biological Indices. Cincinnati, Ohio; ACGIH, 1988


7. Anger WK. Worksite behavioral research; results, sensitive methods, test batteries and the transition from laboratory data to human health. Neurotoxicology 1990;11:629-720


22. Gandini C, Prockop LD, Butera R, Locatelli

Environmental neurotoxicity in humans


