Environmental Neurotoxic Illness: Research for Prevention

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Recognition of the deleterious neurological effects of chemicals has evolved from anecdotal observation to studies of illness in persons exposed to high doses. Now, the more subtle effects of exposures to environmental neurotoxicants are being documented: reduction in intelligence, impairment in reasoning ability, shortening of attention span, and alteration of behavior. Substances to which millions of persons are exposed occupationally and in the general environment that can result in such deficits include lead, organophosphorus pesticides, certain chlorinated hydrocarbons, carbon disulfide, solvents, and mercury. The first step in the prevention of neurological impairments due to environmental exposures is to assess the toxicity of chemicals. Fewer than 10% of the 70,000 chemicals in commercial use have been evaluated for neurotoxicity. This knowledge gap needs to be narrowed by building on existing systems of toxicity testing. Concurrent with assessment of chemicals will be tiers of *in vivo* screening tests to measure functional and structural changes following exposures *in vitro*. Epidemiologic surveillance of populations at high risk will continue to inform on the ranking of suspect or known neurotoxicants. Research and researchers must become more sophisticated in the development and application of refined biologic markers so the findings can be used to detect absorption of toxicants and early neurological or neurobehavioral dysfunction before disability occurs and to protect human health and the environment. — Environ Health Perspect 102(Suppl. 2):117–120 (1994).

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**Introduction**

While the recognition of the deleterious neurological effects of exposure to chemicals such as lead has existed since ancient time, the scientific documentation of neurologic injury following exposure to certain chemicals arose from the study of acute illness in persons exposed to high doses of environmental toxicants. The scenarios leading to illnesses included: children who ate chips of lead-based paint developed encephalopathy; persons who consumed wood alcohol (methanol) became blind; exposure to organophosphorus pesticides led to coma, convulsions, and respiratory paralysis. Some epidemics of neurotoxic diseases due to environmental contamination have become too well known: blindness and ataxia due to consumption of fish laden with organic mercury in Minamata Bay, Japan, and of fungicide-treated grain in Iraq; spinal cord degeneration and peripheral neuropathy caused by tri-o-cresyl phosphate (TOCP) in cooking oil in Morocco and in patent medicine (Ginger Jake) in the United States; tremors, anxiety attacks, and loss of coordination due to the pesticide Kepone (chlordecone) in Hopewell, Virginia; and the parkinsonism caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a contaminant of synthetic heroin, in California and Hawaii (1). Some are less well known and others, such as the current outbreak in Cuba, continue to puzzle us. Past and current experiences that have affected tens of thousands of persons have clearly established that environmental chemicals can be toxic to the nervous system, leading to neurologic and psychiatric illnesses.

Injury to the nervous system due to toxic chemicals in the environment is now being acknowledged as an important public health problem, yet precisely because it remains so broadly defined, studies therefore remain fragmented. Part of this too broad definition derives from the imprecise definition of terms. In this report we too use broad terms. "Environment" encompasses the wide range of extragenetic factors that cause injury/impairment to body systems. These factors include ambient exposures (air, water, soil), diet, occupational exposures (physical and psychosocial elements), recreational exposures (alcohol, tobacco, drugs) among many.

"Neurotoxicology" is deemed to include the insult(s) to any and all structures and functions of the nervous systems in all their complexity and diversity and overlap; motor, sensory, cognition, psychological, emotional elements, separate and conjoint. A major question is whether any associations observed in epideimics (large or small) reflect isolated occurrences or are manifestations of pervasive and widespread associations between toxic environmental chemicals and neuropsychologic impairment (2). The question remains central to the issues confronting neurotoxicology today.

**Subclinical Neurotoxicity**

The newly developed measurement tools that allow detection of more subtle neurologic damage add the dimension of subclinical damage to the question of chemicals in the environment exerting dose-related adverse effects. Such subclinical neurotoxic effects can include lower intelligence, impaired reasoning ability, shorter attention span, alterations in behavior. Although subtle in appearance, the changes following exposure to lead, mercury, organophosphorus pesticides, some chlorinated hydrocarbons, and solvent mixtures, can be devastating in effect. Because the central nervous system has little capacity for repair, the damage can be irreversible. The recognition of subclinical
neurotoxicity raises the possibility that some fraction of neurologic and psychiatric illness, such as parkinsonism, motor neuron disease, demyelinating illness, and some forms of dementia can be exacerbated and possibly caused by chronic, low level exposure to environmental neurotoxicants (3).

**Biologic Markers in Neurotoxicity**

Recent reports in environmental health research have defined biologic markers as indicators of events or conditions in biologic systems or samples (4,5). They are most easily classified as markers of exposure, of effect, and of susceptibility. A marker of exposure is an exogenous substance, its metabolite, or the product of its interaction with some molecule or cell as measured in an organism. A marker of effect is a measurable biochemical, physiologic or other alteration within an organism that can indicate potential or established impairment. A marker of susceptibility is that indicator of variation (inherent or acquired) in an organism’s response when challenged by exposure to a specific substance (5,6). The development and application of biologic markers of neurotoxicity are needed to augment the sensitivity and specificity of other studies. Measurements of specific lipids and proteins or of neurotransmitters or their metabolites, as well as measurement of changes in the number or affinity of specific neurotransmitter receptors, are some biochemical markers of neurologic function. Structural markers can be studied in tissues obtained at biopsy. Gaining this edge in identifying early and subclinical neurotoxic injury would allow intervention when dysfunction might still be halted, when impairment in others so exposed could be prevented. In epidemiologic and clinical studies, validated biologic markers would allow the systematic monitoring of populations at high risk and enhance the findings from other disciplines. Tests that appear to provide reliable and sensitive information on early injury are becoming more sophisticated and gaining wide application (7). The development and increased use of biologic markers of neurotoxic substances in human studies will permit precise delineation of individual exposures and the detailed assessment of dose-response relationships (8).

**Neurotoxicity Testing**

Although about 70,000 chemicals are in commercial use, very few have been evaluated. Other than pharmaceuticals, fewer than 1/10 of chemicals in commerce have been tested for neurotoxicity, and fewer yet have been thoroughly studied. Since it is unknown how many may be neurotoxicants, it is possible that large numbers of people are exposed to these potential hazards and may be suffering unrecognized injury as a result.

Closing this gap in knowledge and toxicity testing must be the essential first step in the prevention of environmental neurotoxicity. The dearth of information and resources precludes any across the board testing of all chemicals. New strategies will need to include: the identification of those chemicals most likely to be hazardous and to which large numbers of persons are exposed; the setting of priorities for testing the more ubiquitous substances; the refinement of existing neurotoxicity test systems; the development and validation of efficient, sensitive new testing systems; and the standardization of approaches to the interpretation/significance of the findings.

This strategy for neurotoxicologic assessment will extend currently available tests systems (9) based on a tiered structure. Data from the initial, screening, tier will guide decisions to test chemicals at the higher tiers, as well as decisions concerning types of testing. The screening tier will consist of a set of tests to measure chemical, structural, and functional changes in an integrated fashion, in addition to a functional observational battery. Such tests will need to be carefully validated at every stage. To address the broad functional diversity (motor, sensory, learning and memory) of the nervous system, the tests must examine multiple end points: a highly specific effect on one function of the nervous system will not necessarily entail an effect on another. The development of rapid and economical approaches will do much to overcome the drain of the current labor- and resource-intensive testing systems.

While in vitro systems are available and appear suitable for detailed studies of some neurotoxic mechanisms, they have not been used for screening. A recognized stumbling block is the establishment of a relationship between effects observed and the expression of effects at a structural or behavioral level in whole animals, particularly in humans. It is essential that such studies of the correlation between the results of in vitro systems and the findings of functional in vivo tests be conducted. In vitro assays and in whole animals should be conducted conjointly to determine the correspondence between the two types of assays. This could validate the use of in 
vitro assays as quicker, more efficient methods for screening chemicals for neurotoxicity, and allow a better understanding of the mechanisms of neurotoxic damage. Studies of neurotoxic reactions at the molecular and cellular levels might also be used to generate the more detailed mechanistic information necessary for accurate risk assessment and for development and evaluation of reliable structure-activity relationships.

In both in vivo and in vitro neurotoxicity testing, the general objective is to identify neurotoxic potential before the occurrence of human exposure. The goal is the prevention of human disease.

**Epidemiologic Studies and Neurotoxicology**

In order to provide additional information on the human neurotoxic effects of environmental chemicals and to complement screening studies in vitro and in animals, epidemiologic and clinical studies of populations exposed to potentially neurotoxic chemicals are needed. High-risk populations must be identified and monitored. Currently, public health surveillance systems for the detection of people who are potentially exposed to environmental neurotoxicants are not well developed. There is little information on the background incidence and prevalence of the major neurologic diseases in the American population (10). The evaluation of persons diagnosed with neurologic illnesses to elicit any possible environmental etiologies would be very informative.

Ascertaining of the neurotoxic effects of exposure to environmental chemicals through epidemiologic and clinical studies continues to be complicated by the very complexity, variety and subtlety of the possible reactions of the nervous system. Reactions to toxic insult can be as varied as peripheral neuropathy, alterations in the sense of taste or smell, or impaired mathematical ability. Months and years can pass between exposure and the appearance of dysfunction and disease. The subclinical changes are often subtle, unappreciated by either the subject or coworkers/family. Therefore, populations known to have been exposed to potential neurotoxicants should be followed for long periods in prospective studies; in retrospective studies of persons with neurologic illness, the possibility that exposures may have occurred many years earlier must be kept in mind. Increasingly, epidemiologic studies will need to utilize biologic markers of exposure, of toxic effects, and of susceptibility.
Risk Assessment and Neurotoxicology

Estimating the risks to humans associated with exposure to toxic chemicals in the environment most often involves extrapolation from high experimental doses used in animal tests to lower environmental doses. Gaps in available scientific data are bridged with numerous assumptions. Such risk assessment techniques have usually been applied to cancer as an end point, and techniques for assessing other types of risk are just now beginning to be developed (11). The current approach in estimating non-cancer end points, simply dividing the dose below which effects were not seen by uncertainly factors to generate a presumably safe exposure level, must be considered inadequate. Virtually all neurotoxicologic risk assessment today is limited to qualitative hazard identification and to the early stages of hazard characterization. Sufficient data or adequate paradigms are not yet available to permit quantitative evaluation of most neurotoxic risks.

Risk-assessment techniques that incorporate more quantitative information about dose-time-response relationships and mechanisms of toxicity are being developed. They will assist in assessing the benefits to human populations gained from reducing exposures to neurotoxic agents. The construction of new models for neurotoxicologic risk assessment upon the diverse susceptibilities of various individuals and populations will be facilitated by the acquisition of knowledge of the fundamental mechanisms of action of chemical toxicants on the human nervous system. How environmental chemicals cause injury will need to be delineated at the molecular and subcellular level (12). Such information will then allow much improved prediction and quantitation of the risks whose effects become evident only many years later.

Conclusions

Exposure to chemical agents in the environment can lead to neurotoxic impairment and illness. This has been demonstrated following exposure to many different agents and in individuals and in epidemics. Neurotoxicity caused by environmental toxicants ranges from neurologic to psychiatric disorders, from devastating illnesses, such as Parkinsonism and dementia, to subtle changes in behavior and limitations on memory and cognition. The complexity of the disorders reflects the enormous diversity of the nervous system's functions and the large number of cellular and subcellular targets. Greatest concern surrounds the fact that some damage in the brain can be irreversible and permanent, and that in addition to immediate effects, many neurotoxic effects become evident only after long latent periods. Chemicals can permanently alter brain development, can cause subclinical dysfunction, or reduce reserve capacity of the nervous system. On the basis of available evidence, it is not unreasonable to hypothesize that a definitive, but as yet unspecified, fraction of human neurologic and psychiatric disease is attributable to chemical agents in the environment.

The lack of quantitative or qualitative information on possible adverse effects of most chemicals in commercial use is a major obstacle to assessing the contribution of environmental chemicals to the causation of nervous system disease and dysfunction. While some chemicals are known to have neurotoxic potential, there is a particular lack of data on chronic and long-latency neurotoxic effects. Though widely used as an approach in assessment of toxicity, structure-activity relationships are less than optimal for predicting neurotoxic potential; greater fundamental understanding of mechanisms should lead to more useful applications of SARs.

The development and application of biologic markers are needed for the assessment of subclinical neurotoxic effects. Such markers can be developed through in vitro analyses, through animal studies, or during observational studies in human populations. While associations between biologic markers and disease are usually established in cross-sectional studies, a particular need to validate putative biologic markers in prospective studies exists. Only in longitudinal prospective studies of populations exposed to suspect or known neurotoxicants can the reliability of the biologic markers be accurately assessed and their predictive significance evaluated.

Current testing systems can be expanded using a tiered approach. The first tier, or screen, is intended for hazard identification. These findings and the patterns of exposure of the chemical would determine further characterization of dose-response (second tier) and mechanism (third tier). Since there is no existing validated system that satisfies all the necessary requirements for a screening program, the range of any newly developed program should extend to the detection of neurodevelopmental effects, of effects on cognitive function, and of neuroendocrine effects. Work has yet to be done to determine the predictive ability of individual screening tests; the relationship between test results and data from long-term studies in animals or epidemiologic and clinical studies will need to be validated.

There have been only limited attempts to quantify the exposure of populations to neurotoxic chemicals. Clinical evaluations in populations at risk for neurotoxicity have been inadequate and fragmented. The possibility that developmental delays in the young and some forms of dementia and Parkinsonism in the elderly might have an environmental etiology is only now becoming to be appreciated.

Delay in recognition of the possible environmental origin of neurologic and psychiatric disease derives from inadequate incorporation of the elements of environmental and occupational medicine into the training of most physicians, toxicologists, epidemiologists, risk assessors and other health providers. Greater uniformity and precision in disease definition would improve the identification of diseases of neurologic interest.

The commonly used paradigms for risk assessment are inadequate to model the risks associated with exposure to neurotoxicants. The neurotoxicologic risk assessments, that have been largely limited to the application of no-observed-effect levels and uncertainty factors, cannot accurately encompass the diversity of neurologic responses to injury; they cannot (as yet) generate risks estimates that are applicable to the multitudes and magnitudes of exposures.

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