PAPER NO. 1

NEUROTOXICOLOGY: A NEW SCIENTIFIC CHALLENGE

Peter S. Spencer, Ph.D., M.R.C. Path.

Professor of Neuroscience
and Director, Institute of Neurotoxicology
Albert Einstein College of Medicine
Bronx, New York

INTRODUCTION

Neurotoxicology is the study of actions of agents that cause adverse effects on the nervous system and behavior of humans and animals. This definition encompasses toxic chemicals of diverse origins, includes adverse effects traceable to changes in structure or function of the nervous system, special sense organs and neuroendocrine system, and recognizes the importance of conjoint study of mechanisms and effects of neurotoxins in humans and animals, experimental or otherwise. Because of the chemical complexity, delicate internal balance and enormous biological responsibility of the nervous system, chemicals with potentially neurotoxic properties are legion. Neurotoxicity is, perhaps, one of the most common types of toxic response recognized in Man.

Factors Regulating Neurotoxic Response

The net effect produced by an individual chemical present in blood depends on many factors. Ability to enter the nervous system, specific site of attack within neural tissue, concentration of the proximate toxin at the target site, chemical reactivity of this agent, and duration of exposure to target site are some of the major considerations. All of these factors are heavily influenced by circumstances surrounding exposure, the portal of body entry, the distribution within tissues, the rate of breakdown, the toxicity of metabolic products, and the efficacy of excretion. The present state of knowledge of these critical factors is limited for all but a few neurotoxic substances, and it is often difficult to predict whether a particular chemical is likely to be neurotoxic or not. The more we know about these factors in relation to any one chemical, the more accurate the judgment of neurotoxic response and the prediction of risk.

Dose and duration of exposure are pivotal concepts in determining whether an agent will produce a neurotoxic effect. Chemical agents which at certain doses elicit a profound, long-lasting response, may be harmless at low levels, or may even be required for normal nervous system function. This is well illustrated by recent experience with human exposure to vitamin B_6, whereas

small, steady quantities are mandatory for normal functioning of the nervous system; excessive amounts cause axonal degeneration and sensory neuropathy.

Duration of exposure to a particular concentration of a chemical substance plays a major role in determining whether that substance is neurotoxic and whether the pathophysiologic change is reversible. The effect of alcohol consumption is a familiar example, whereas a single large dose induces a state of drunkenness -- a totally reversible neurotoxic state; repeated doses over prolonged periods elicit not only the acute response but also chronic degenerative brain disease.

When evaluating neurotoxic potency, differential individual susceptibility to chemical agents with potentially adverse effects must be considered. The principle of individual susceptibility is well known in clinical neurology where toxic side effects of certain therapeutic agents appear only in a sub-group of patients. Such individuals will commonly show an inherited trait that affects the rate of disappearance of the drug. Other population sub-groups that may be specially vulnerable to neurotoxic agents (although present evidence is limited) are the elderly and the young. Strong evidence of susceptibility to neurotoxic agents exists for individuals with compromised liver or kidney function. Others with special sensitivity to neurotoxic agents include those who have metabolic diseases, such as diabetes mellitus, that by themselves compromise nervous system function. Taken together, these considerations bear on the determination of acceptable levels of human exposure to chemical agents.

Types of Neurotoxic Disease

The effects of neurotoxic agents can be classified according to their apparent sites of action. This provides a rational approach to understanding the clinical consequences of exposure and a starting point to an enquiry directed at mechanism(s) of toxicity. The basic cellular components of the nervous system--neuron and axon, glial cells, and myelin--form the basis for this classification system. Those chemicals affecting neurons may (a) perturb neuroelectrical transmission by altering the function of ionic channels in excitable membranes, (b) disrupt the integrity of neurotransmitter or neurohumeral systems, or (c) cause structural breakdown of axon or neuronal perikaryon. Other targets of neurotoxic chemicals include myelin or myelin-producing cells, astrocytes, muscle, and neural vasculature. Note that an agent may have more than one site of action and that this is commonly related to dose or rate of intoxication. For example, large doses of acrylamide appear to produce encephalopathy, ataxia, depletion of Purkinje cells, and subsequently, axonal neuropathy; smaller doses spread over a longer period of time also lead to axonal neuropathy while sparing Purkinje cells.

Occurrence of Neurotoxic Disease

Most human neurotoxic disease in the United States is iatrogenic in origin and results from prolonged treatment with anticonvulsants, anticholinergics, neuroleptics, antiparkinsonian and antineoplastic drugs. However, neurotoxic disease is encountered in many other settings. Substance abuse, particularly involving ethanol, narcotics, hallucinogens, central stimulants, solvents, and nitrous oxide, leads to short or more longer lasting neurological dysfunction. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), an impurity in a synthetic psychoactive drug that produces rapid-onset parkinsonism, is a recent example of the latter phenomenon. In the occupational setting, the acute cholinergic crisis associated with pesticide overexposure is commonplace among pesticide workers, and there is concern that these agents may produce long-lasting, subtle alterations of behavior and memory. Many other substances found in the workplace have been indicted in neurological illnesses ranging from polyneuropathy to organic brain syndrome. Environmental pollutants with neurotoxic potential are pervasive and include carbon monoxide, lead, and mercury. Neurotoxic agents in foodstuffs, present as intrinsic components, are responsible for large outbreaks of neurological disease in the Third World. For example, excessive consumption of cassava (Manihot esculenta) or the chickling pea (Lathyrus sativus) precipitates spastic paraparesis. Adulterants present in food also have been held responsible for neuromuscular disease, the Spanish "Toxic Oil Syndrome," a phasic multisystem disease which led to global neuromuscular atrophy in the more severely affected, being the most recent example. Mycotoxins still contaminate food for human consumption in certain parts of the world, ergot and aflatoxin are two of several associated with neurological disease. Other important biological neurotoxins are those associated with botulism, tetanus, and diphtheria. Numerous animals secrete or harbor potent toxins, including agents that disturb nerve conduction and synaptic transmission. Neurotoxic substances such as arsenic and thallium compounds occasionally are deliberately added to food for homicidal or suicidal purposes. Chemicals with experimentally proven neurotoxic potential also exist as food additives (monosodium glutamate), flavors, and fragrances (2,6-dinitro-3-methoxy-4-t-butyltoluene) and certain anti-seborrheic agents (zinc pyrithione). Substances with potential neurotoxic properties are therefore encountered in food, air, and water, in the general environment, and in domestic and occupational settings.

Conclusion

The science of neurotoxicology is in its infancy. The scale of the problem has been recognized, the scope of the discipline defined, and a preliminary classification of neurotoxic response developed. Some information is available on the relative frequency of neurotoxic disease in developed and developing countries, and in which environmental or social niches these diseases

occur. The challenge facing basic and clinical neurotoxicologists is to understand how these diseases develop and how they can be prevented. Since many neurotoxic conditions mimic naturally occurring neurological diseases, investigations designed to determine the biological actions of neurotoxic chemicals will undoubtedly illuminate other types of nervous-system compromise. Viewed from this perspective, the neurotoxic agent is not only a threat to human health, but also a powerful investigatory tool.

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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

BRUCE O. STUART, PhD
Director Toxic Hazards Division
Air Force Aerospace Medical Research Laboratory

ERRATA SHEET

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MacFarland, H. N. (1982), Chronic gasoline toxicity, The Toxicology of Petroleum Hydrocarbons, American Petroleum Institute, Publication No. 847-90000, pp. 78-86.

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Papers were presented covering molecular mechanisms of n-hexane neurotoxicity, metabolism of n-hexane and anatomical effects of neurotoxins. The pathological, metabolic, electrophysiological and biochemical characteristics of organophosphorus induced neurotoxicity were discussed in specific presentations. The male reproductive system as a target organ and specific problems associated with mixture toxicology were subjects of individual sessions. Occupational health data bases, early detection of environmental exposure and effects of exposure to Agent Orange were discussed in papers.

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