

NEUROTOXICOLOGY: WHAT THE NEUROLOGIST NEEDS TO KNOW

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A search of internet sites offering detoxification programmes for the elimination of toxins from the body and the regeneration or rejuvenation of the immune system, the nervous system as well as blood, liver, and kidney, reveals three features of current popular thinking on toxins: a terrible ignorance of basic science, a poor understanding of the organisation and function of the human body, and an irrational fear of the “chemicals” that prevent us from living to our full potential. Whatever our private thoughts on the expression and exploitation of these fears, we tend to forget that the most complete text on experimental and clinical neurotoxicology lists more than 350 compounds (synthetic and naturally occurring) known to cause functional or structural damage to the nervous system.¹ We should also note that a recent survey of the body load of a number of toxic chemicals in human subjects revealed widespread accumulation of a number of known toxins of considerable clinical interest, including organochlorines, polychlorinated biphenyls (PCBs), and dichlorodiphenyl dichloroethylene (DDE),² and the continuing concern of many people over the perceived neurological damage caused, for example, by participation in military operations in the Gulf.

Many of the subjects who consider themselves neurologically damaged by exposure to “toxins”, “chemicals”, or other environmental agents will seek confirmation and reassurance that their concerns are valid, that they have a definable illness, and that their condition will be treated. Considerable numbers are referred to a neurologist or psychiatrist for help. In this article we define a neurotoxin and the science of neurotoxicology, discuss some of the factors involved in the development of the signs and symptoms of neurotoxic damage, and offer advice on the examination of the patient, the diagnosis, and the construction of a management programme (see also Blain and Harris³).

WHAT IS MEANT BY NEUROTOXICOLOGY AND NEUROTOXIN?

Neurotoxicology is defined as the science that deals with the adverse effects of naturally occurring and synthetic chemical agents on the structure or function of the nervous system. In this context a neurotoxin is a naturally occurring or synthetic chemical agent that can cause a functional or structural change in the nervous system.

IS THE NERVOUS SYSTEM PARTICULARLY SENSITIVE TO TOXIC CHEMICALS?

The answer to this question has to be a qualified yes. The nervous system is exceptionally complex and goes through a prolonged period of development characterised by cellular migration and differentiation, and synaptic pruning. The basic structures of the brain are formed in stages and the successful completion of one stage is totally dependent on the successful completion of all former stages.⁴ Thus, chemical disruption of any of the underlying processes during development can have profound structural and functional (including behavioural) consequences for the rest of the life of the animal, human or non-human. Also important are the features of mature neuronal cells and their interconnecting circuits. Neurones are post-mitotic, and so the consequences of a cell's death cannot be repaired by the proliferation of surviving cells. They are very active cells and have a high metabolic demand, servicing dendritic trees that may be very large (for example, in the Purkinje cells of the cerebellum) or axons that are very long (as in motor neurones) via highly effective systems for moving metabolites between the cell body and its dendrites and axons (retrograde and anterograde axoplasmic transport). The neurone is, therefore, exquisitely sensitive to anoxia or hypoglycaemia.

Recovery from severe neurotoxic cell death, when it does occur, usually requires a surviving neurone to expand its territory by axonal branching and the takeover of territory vacated by a dead neurone. This process is well established in the peripheral nervous system (for example, as in motor neurone disease and poliomyelitis), but is not very effective at all in the brain and spinal cord. It also has a cost because a cell with an expanded territory is unstable and likely to suffer accelerated senescence and apoptosis (fig 1). Finally, cells with long processes are vulnerable to attack at numerous sites—cell body, dendrites, axon, myelin sheath, node, terminal synaptic

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expansion, etc. Thus, the mature nervous system is remarkably vulnerable to toxin induced damage, and because any damage may disrupt the extensive communication systems that characterise the brain, neurotoxins have the capacity to affect gait and posture, the special senses, behaviour and cognition, and produce a complex pattern of clinical signs and symptoms.

In the adult, the nervous system is protected by the blood–brain and blood–axon barriers. These act effectively to retard the transfer of charged and large molecular weight compounds from circulation to nervous tissue, but do not provide protection against lipid soluble agents or against toxins that damage and render porous the blood–brain barrier. Areas not completely protected by the blood–brain or blood–nerve barriers include those regions of the brain involved in neuroendocrine activity (for example, area postrema, hypothalamus, pineal), places where the barriers are fenestrated (for example, autonomic ganglia), and motor and sensory nerve terminals. All these sites are potential points of entry for toxins.

DEVELOPMENT AND AGING

The very young are much more vulnerable to most neurotoxins than the adult. Numerous neurotoxins can gain entry to the young via placenta or breast milk, and although the efficiency of transfer may be low, exposure by these routes may extend over many weeks and months. The developing nervous system is vulnerable to much lower concentrations of most toxins than the mature, and the blood–brain barrier only slowly develops its full functional capacity. The elderly are also vulnerable, partly as a result of declining hepatic and renal function but also because the progressive age related loss of neurones as part of the aging process renders them more sensitive to the added burden of toxin induced damage. In general terms, sex differences appear to be slight in human subjects.

PREVIOUS EXPOSURE

There is a growing body of evidence suggesting that, following multiple incidents of exposure, the effects on health become progressively worse. Whether this reflects sensitisation, the cumulative effects of low level impairment of cellular function, or is caused by the accumulation of the toxic material is not always clear. However, many potentially toxic agents can persist for many years in the body, particularly those that are lipid soluble (such as PCBs), and

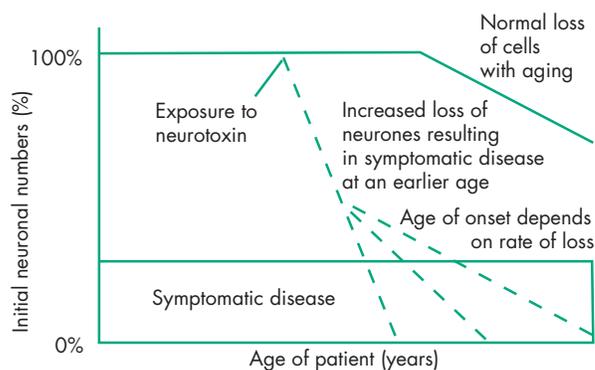


Figure 1 Increased rate of loss of neurones following exposure to a neurotoxin producing symptomatic neurological disease at an earlier stage. Reproduced from Kobayashi and Suzuki,⁵ with permission.

this phenomenon alone must be a significant contributory factor.

METABOLISM AND SEQUESTRATION

Detoxification in the liver is the primary route by which most toxic chemicals are rendered non-toxic before excretion. Sometimes a metabolic step is involved in actually enhancing toxicity—for example, n-hexane is transformed into 2,5-hexanedione and the formation of the active oxons from some organophosphates. Sequestration, particularly into plasma lipids, proteins, or body lipids, etc, may act as a “sump” from which slow release enables detoxification and excretion without the expression of clinical disease. If the rate of accumulation exceeds the rate of sequestration, metabolism and excretion, then toxic effects may be expressed. Clearly subjects with impaired hepatic or renal function are at greater risk of developing clinical signs of poisoning, even when toxin loads are relatively low.

EXPOSURE, CONCENTRATION, AND DURATION OF EXPOSURE

Potential neurotoxins can be absorbed by inhalation, contact with the skin, ingestion with food, or following parenteral injection, allowing direct contact with susceptible tissues. Obviously it would be expected that the appearance of clinical signs would be more likely after direct tissue contact than after contact with the skin, for example, but direct application to nervous tissue or injection directly into the circulation are not common events in environmental poisoning. In reality exposure mostly occurs as the result of inhalation, ingestion with food or water, or contact with the skin. Uptake into the circulation from these sources will always be highly variable, and it is impossible to calculate intuitively the toxin dose unless suitable biomarkers are available to assess the body burden of the toxin. Only in a few cases (for example, measuring red blood cell acetylcholinesterase inhibition after exposure to organophosphates) are validated biomarkers available.

High doses of a toxic chemical will give rise to an acute toxic response, but prolonged exposure to low concentrations of a toxin may only cause a slowly developing chronic response. The circumstances of exposure and the toxicity of the toxin will determine which of these is the more serious.

THE CLINICAL EXAMINATION

Clinical neurotoxicology is a relatively new, but under-resourced, subspeciality of clinical neurology and the appropriate examination and investigation of patients can be time consuming and frustrating. It also requires a good working relationship between neurologists, clinical neurophysiologists, occupational physicians, psychiatrists, and clinical psychologists, and possibly ear, nose, and throat specialists. So, what is important in the examination?

The most important part of the clinical neurotoxicological examination is a detailed history. What were the first identifiable clinical signs of neurotoxicity? How did the symptoms and signs develop? What was the relation between initial exposure and the onset of symptoms? Was exposure brief or continuous? What was the nature of the exposure—was it by inhalation, contact with the skin, ingestion with food, etc? Is the history suggestive of an organic disorder that is consistent with the signs and symptoms? Would an occupational physician or clinical toxicologist consider there

to be a potential causative relation between the putative neurotoxin and the clinical signs and symptoms?

The history is followed by a detailed clinical examination which must focus on a systematic examination of the central and peripheral nervous system and gross testing of cognitive function. Any clinical neurophysiological investigation will involve more than simple electroencephalogram (EEG) and electromyogram (EMG) and visual evoked potentials. Brain stem auditory evoked potentials and somatosensory potentials may also be monitored. Computed tomographic and magnetic resonance imaging scans are likely to be helpful in the identification of structural damage. The clinical signs elicited and symptoms expressed need to be interpreted with care as they may be compromised by aging or an underlying progressive organic disease. This is especially important as many cases of putative neurotoxic damage will present to the neurologist months or years after the initial exposure to the toxin. There may be a temptation to biopsy if there is evidence of toxin induced pathology, but accessible tissues are realistically limited to muscle, peripheral nerve, and the motor point. Though of potential interest, biopsies are not often definitive, rarely inform clinical management, and are difficult to justify unless the results of the clinical examination suggest strongly that there is an underlying degenerative disorder for which a biopsy will provide a definitive diagnosis (for example, prenodal swelling in hexane neuropathy). Bates⁶ has provided a very useful flow chart relevant to the examination procedure (fig 2).

If organic disease can be excluded, how can causation be established? Schaumburg⁷ has suggested five cardinal signs:

- (1) Presence of the suspected agent is confirmed by history and either environmental and clinical chemical analysis
- (2) Severity and temporal onset of the condition are commensurate with duration and level of exposure
- (3) The condition is self limiting and clinical improvement follows removal from exposure
- (4) Clinical features display a consistent pattern that correspond to previous cases
- (5) Development of a satisfactory corresponding experimental in vivo or in vitro model is absolute proof of causation.

The first criterion may be problematic because we do not have really good biomarkers of exposure for the majority of neurotoxins; the fifth criterion is out of the question for most clinicians as it requires access to well established academic toxicology facilities.

CLASSIFICATION OF NEUROTOXIC DISEASE

Although it is common practice to consider neurotoxic syndromes in terms of the toxic agents—for example, heavy metals, solvents, pesticides—the matching of chemical structure to neurotoxicity is imprecise and often unpredictable. The alternative is to consider neurotoxic syndromes in terms of their clinical presentation—for example, encephalopathy, movement disorders, or peripheral neuropathy. The problem with this approach is that many forms of neurotoxicity are expressed as a complex syndrome involving peripheral and central nervous systems with neurological as well as psychiatric signs. Nevertheless, the use of clinical data as the basis of a system of classification is probably the most useful to the clinician.

In general, when a single compound is the presumed causative agent of an acute incident of neurotoxic poisoning,

a careful history and a detailed clinical examination should allow a definitive conclusion on causation. Much more problematic is our lack of knowledge and understanding of the effects of prolonged, low level exposure to known toxins, our poor understanding of the effects of exposure to a mixture of toxins, and the lack of properly controlled long term follow up studies. These problems, of course, are central to the high profile arguments about the impact on health of the presence and accumulation of low levels of multiple toxic agents in the general population. At present we lack a conceptual framework to underpin the investigation of these issues.

CLINICAL SIGNS OF NEUROTOXIC POISONING

The clinical signs and symptoms of neurotoxic poisoning may be expressed in the central, the peripheral and the autonomic nervous systems, and in skeletal muscle. They are often associated with pain, changes in the special senses of taste and smell, as well as changes in visual acuity and hearing.

Encephalopathy

Acute encephalopathies are common. Most are mild and resolve within a few days. The typical signs of headache, tiredness, confusion, loss of attention and short term memory, lack of motor coordination, and the resulting disturbance of gait, nausea, and dizziness are all common. Numerous compounds (approximately 100 ranging from Absinthe to water and including aluminium, cannabis, cocaine, domoic acid, lead, organic solvents, and trimethyltin) have been listed by Schaumburg as potential causative agents.⁷ Although acute signs are usually rapidly resolved, persistent problems may have a serious adverse effect on employment and job delivery, and there is a clear need for detailed long term follow up and psychiatric and psychological assessments (defined in detail by Blain and Harris⁸). The transition from acute (mild) to chronic (severe) encephalopathy with associated loss of cognition and psychomotor function is relatively uncommon, but has been seen following acute severe poisoning by domoic acid, aluminium, cadmium, and lead and following chronic abusive use of alcohol or organic solvents. The progression to a chronic severe encephalopathy raises an important practical consideration: if a steady deterioration occurs following isolation from exposure to the suspected agent, it is essential that everything is done to ensure that there is no underlying constitutional neurological problem.

Disorders of movement

Cerebellar dysfunction, characterised by ataxia, intention tremor, and loss of coordination is best known as a feature of chronic exposure to mercury; however, overdose with a variety of potentially toxic drugs and chemicals such as 5-fluorouracil, lithium, and acrylamide have also been implicated. The diagnosis of causation for cerebellar dysfunction is notoriously difficult.

Extrapyramidal syndromes such as parkinsonism, dystonias, dyskinesias, and tics are relatively well known toxic syndromes. The toxic mechanisms are poorly understood but usually reversible, although problems may recur many years after the original onset of the disorder. Parkinsonism is probably the best known following the outbreak of this syndrome in people exposed to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a contaminant in some drugs of abuse. Most syndromes occur as a result of overenthusiastic

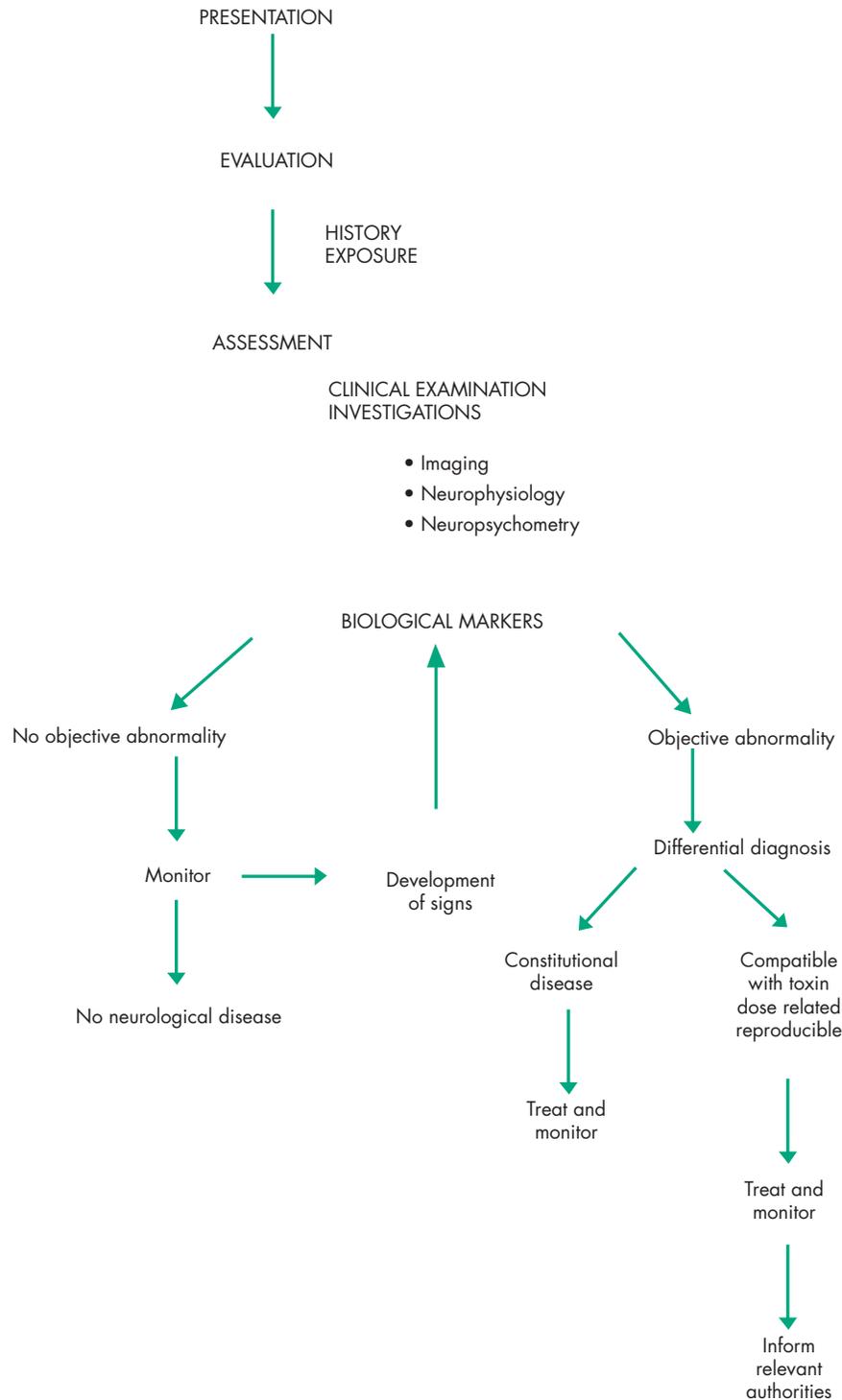


Figure 2 Management of the patient with suspected neurotoxic disease. Reproduced from Bates,⁶ with permission.

use of drugs such as the phenothiazines, rather than as a result of exposure to non-therapeutic chemicals.

Special senses

Loss of taste and smell, or changes in the perception of taste and smell, are not uncommon complaints but are difficult to test with precision, and quantitative measures are, for all practical purposes, impossible. Organic solvents are frequently implicated but there is no known pathophysiological explanation for this problem. Among the difficulties

involved in the assessment of taste is that olfaction plays a major role in the detection of “flavour” and the “perfume” of food, even though most of us would describe these as taste. A perception of change in taste is common following the use of numerous therapeutic agents, but is usually reversible.

The loss of hearing has been attributed to the abuse of organic solvents—especially toluene—but is more usually associated with the use of well known ototoxic drugs such as the aminoglycosides.

Visual system

Damage to the eye is usually caused by the direct action of a toxic or corrosive substance on the cornea and conjunctiva, or the loss of transparency of the lens associated with the formation of cataracts. Direct attack on the neural components of the visual system is less common. Mydriasis and miosis are obvious outcomes of exposure to or use of parasympathomimetic agents and anticholinesterases, and parasympatholytics such as atropine, respectively. Nystagmus may be a complication of overuse of a variety of therapeutic agents such as phenytoin and the aminoglycoside antibiotics. Direct damage to the retina, though associated with some therapeutic agents, is rarely associated with neurotoxin exposure. The optic nerve can be damaged by toluene (causing demyelination) and hexachlorophene (causing myelin deformation). Alcohol abuse (methanol or ethanol) is also associated with widespread damage to the neural components of the visual system, but it is suspected that the aetiology is confounded by the poor nutritional status of many chronic abusers of alcohol.

Peripheral neuropathies

These are generally thought of as being synonymous with axonopathies, but the terms are not interchangeable. A peripheral neuropathy may have its origin in the neurone, causing either cell death or dysfunction (in which case we refer to a neuronopathy). There may be degeneration of the axon (an axonopathy) or disruption of neuronal or axonal function by damaging the myelin sheath (myelinopathy or demyelinating neuropathy). The modification of ion channel function may give rise to a channelopathy, or the toxin may target nerve terminals (to cause a neuromuscular transmission syndrome). Neuronopathies can be recognised because they are more likely to be sensory and they affect those areas subserved by the affected neurones. The causative toxic mechanisms are poorly understood. Methyl mercury is the best known neurotoxin associated with this condition. Proprioception may be affected before or more severely than consequent pain, but nerve conduction velocity is maintained as is physical strength. Recovery is variable because neurones may or may not survive the toxic assault.

Demyelinating neuropathies of the peripheral nervous system result from damage to the Schwann cell or to the myelin sheath of the internode. Diphtheria toxin causes segmental demyelination by damaging the Schwann cell. Hexachlorophene and perhexilene have also been implicated in myelin disruption. Recovery depends on the replication and activation of surviving Schwann cells. Regenerated internodes are shorter than normal, nodes may be longer than normal, and myelin sheaths thinner. Conduction velocity is usually slowed in remyelinated axons. Axonopathies are the peripheral lesions that result from the destruction of the axon. The presenting features are typically gradual in onset affecting first the long axons and distal regions. Sensory signs tend to precede motor signs and there is a rapid loss of ankle reflexes. The signs then spread proximally as the axon “dies back” for as long as exposure lasts.

Recovery results from the regeneration of the damaged axons. Recovery is slow because axonal growth occurs at a rate of between 0.5–3.0 mm per day. Numerous industrial chemicals are capable of causing axon damage, including acrylamide, arsenic, carbon disulfide, n-hexane, lead, organic mercury, perhexilene, and thallium. Recovery, though slow, is usually uneventful but severe poisoning may be associated with continuing ataxia, stiffness, and hyperreflexia.

Axonal channelopathies are associated with abnormalities in axonal conduction resulting from changes in ion channel function. These typically involve natural toxins (see Harris and Goonetilleke on p iii40). The motor nerve terminal is a significant target for numerous natural neurotoxins of a diverse kind (clostridial toxins, toxins of the cone snail, snake, spider, and scorpion venoms), all of which cause the degeneration of the nerve terminal (see Goonetilleke and Harris on p iii35, and Harris and Goonetilleke on p iii40). What is not so well recognised is the importance of the nerve terminal in the expression of toxic assault by a range of toxic chemicals including organophosphates and acrylamide, both of which have been shown to cause severe damage to the motor nerve terminal.^{8,9} It is not inconceivable that most dying back axonopathies begin at the nerve terminal.

Skeletal muscle

Damage to skeletal muscle is relatively uncommon. Most toxicological problems of skeletal muscle result from actual denervation. A few myotoxic agents can cause severe muscle damage with rhabdomyolysis—clofibrate and related compounds, some of which are pesticides and organophosphates. Myotonic activity is caused by diazacholesterols and chlorophenoxyisobutyric acid based herbicides, and hypokalaemic paralysis by liquorice, diuretics, and alcohol abuse. Skeletal muscle regenerates rapidly following removal of the causative agent. The most serious acute clinical problem associated with rhabdomyolysis is the risk of acute renal failure.

Psychiatric and behavioural disorders

Patients complaining of neurotoxic syndromes frequently report that they are depressed, anxious, forgetful, or simply “not right”. In most cases, the psychiatric abnormalities are relatively mild, but major problems of dementia and a parkinsonism/dementia syndrome have been associated with aluminium toxicity, a cerebellar ataxia with dementia with lithium overdose, and severe psychotic disorders with lysergic acid diethylamide (LSD). It is probable that the psychiatric/psychological problems are often ignored and even trivialised so there is little reliable information on the diagnosis, management, and prognosis of mental health problems in such groups of people. More research is needed into both the acute and chronic effects of neurotoxic exposure on mental function. Guidelines for the psychiatric and psychological assessments are available.³

FUTURE DEVELOPMENTS

The potential health risks from exposure to toxic environmental agents is now a major public health issue, and the development of expertise and facilities for the investigation of neurotoxicity in man is of growing importance. The management of patients suffering from environmental neurotoxic poisoning is professionally immature and multidisciplinary groups will need to be formed to manage the most severely affected. More effort will have to be placed on the production of diagnostic indicators of neurotoxic syndromes using fast responding biomarkers. More attention is needed in two priority areas: the effect on the developing fetus and growing infant of long term exposure to low concentrations of environmental neurotoxins; and the long term health effects of acute severe poisoning in man.

Specific research is also required to assess the continuing claims that potential neurotoxins do not have a “safe” limit because we know so little of possible toxic synergy with

exposure to multiple toxins. It is essential that neurotoxicologists take seriously the genuine anxieties of farmers, war veterans, and similar groups who have experienced ill health apparently following low level exposures to neurotoxic compounds. It is also anticipated that major advances will be made into our understanding of the interaction between environmental agents and susceptibility factors in the development of neurodegenerative disorders such as Parkinson's disease, motor neurone disease, and Alzheimer's disease.

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REFERENCES

- 1 **Spencer PS**, Schaumburg HH. *Experimental and clinical neurotoxicology*, 2nd ed. Oxford: Oxford University Press, 2000.
- ▶ **A comprehensive reference to the basic biology and medical and veterinary aspects of neurotoxicology, and an alphabetical directory of several hundred known neurotoxins.**
- 2 **World Wildlife Fund**. *Contamination. The result of WWF's biomonitoring survey*. World Wildlife Fund, 2003.
- 3 **Blain PG**, Harris JB. *Medical neurotoxicology*. London: Arnold, 1999.
- ▶ **A guide to occupational and environmental causes of neurological and psychiatric dysfunction written primarily for the clinician with no specialist knowledge of neurotoxicology.**
- 4 **Volpe JJ**. *Neurology of the newborn*, 3rd ed. Philadelphia: WB Saunders, 1995.
- 5 **Kobayashi H**, Suzuki T. Genetically determined susceptibility to environmental toxins. In: Blain PG, Harris JB, eds. *Medical neurotoxicology*. London: Arnold, 1999:141–52.
- 6 **Bates D**. Diagnosis of neurotoxic syndromes. In: Blain PG, Harris JB, eds. *Medical neurotoxicology*. London: Arnold, 1999:3–12.
- ▶ **A step by step guide to the examination of the subject thought to have been exposed to a neurotoxic agent.**
- 7 **Schaumburg HH**. Human neurotoxic disease. In: Spencer PS, Schaumburg HH, eds. *Experimental and clinical neurotoxicology*. Oxford: Oxford University Press, 2000:55–82.
- ▶ **A guide to treatment; particularly useful because of the number of case studies reported.**
- 8 **Tsujihata M**, Engel AG, Lambert EH. Motor end-plate fine structure in acrylamide dying back neuropathy: a sequential morphometric study. *Neurology* 1974;**24**:849–56.
- 9 **Kawabuchi M**, Cintra WM, Deshpande SS, *et al*. Morphological and electrophysiological study of motor nerve fiber degeneration and sprouting after irreversible cholinesterase inhibition. *Synapse* 1991;**8**:218–28.