Proper functioning of the nervous system is essential for a normal life. It has considerable functional and structural plasticity, and some ability to regenerate after damage, but it remains a potentially sensitive target for many harmful toxicants, acting specifically or perhaps secondarily via a metabolic process or primary target damage elsewhere.

BASIC FEATURES OF THE NERVOUS SYSTEM

Special features of the nervous system may make its toxicological responses appear different in kind from those of other tissues and organs, although they are fundamentally identical albeit modified by its complexity are:

1. Anatomy

Even at a simplistic level there are 2 distinct systems one of which is further sub-divided:

<table>
<thead>
<tr>
<th>Central</th>
<th>Peripheral</th>
<th>Autonomic</th>
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<tbody>
<tr>
<td>(CNS)</td>
<td>(PNS)</td>
<td>(ANS)</td>
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<tr>
<td>I</td>
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nervous system

In turn, each of these is subdivided into different structures, interrelated in an anatomically complex fashion based on groupings of neurons and supporting glial cells, and usually demarcating cell bodies from their interconnecting cell processes. The origins of the anatomical complexity are partly evolutionary and partly the physiological need to maintain critical homeostasis of cell bodies by protecting them with membranes of carefully controlled permeability the bloodbrain barrier (BBB) for the CNS, and the blood-nerve barrier (BNB) for the PNS and ANS. Of equal importance is the fact that the nervous system exists to sense and control distant parts of the body. Accordingly, it consists of central areas and long nerve fibres extending to and from the periphery.

It is also important that the neurons, the cells in the body for receiving, integrating and transmitting information about the external and internal worlds, are so specialised that they and their processes require metabolic assistance and anatomical support by specialised glial cells in the CNS (oligodendroglia and astrocytes) and mesodermal cells in the PNS (Schwann cells). The continued health and functioning of a nerve fibre depends on its connection with its cell body and the ability of the latter to function normally.
Development of the nervous system requires complex patterns of cell birth and death, and the growth of connections, which must be integrated in space and time, and which continue to develop throughout life, at least functionally, as the physical substrate of such long-lived changes as memory, and other alterations in use and performance.

2. Physiology

In deliberately simplistic terms, proper functioning of the nervous system depends on normal transmission of electrical impulses along nerve fibres, which requires both the integrity of the axonal extension of the neuronal cell body and its support by the appropriate glial or Schwann cells. It is also dependent on excitatory or inhibitory signal transmission between nerve fibre endings and neuronal cell bodies (at synapses) or end organs (e.g., muscle) by neuronal neurotransmitter and receptors.

The enormous general metabolic demands and importance of the CNS, for example, are shown by its requirement for 25% of the cardiac output of blood, its consumption of up to 20% of the glucose circulating in the blood stream, and its production of more than 60% of body heat output in the neonate (and about 5% in the adult).

3. Pharmacology

The reliance on chemical transmission and synaptic receptors represents a vulnerable point in toxicology, because direct agonist and antagonist analogues of neurotransmitters may affect synaptic function (e.g., such drugs as beta-blockers at sympathetic receptors, atropine blocking muscarinic cholinergic receptors, and curare blocking cholinergic receptor on muscle cells). The total reliance of nerve fibre on metabolic processes in neuronal cell bodies makes them susceptible to disorders of metabolism at the centre or transport along axons.

4. Dysfunction and Pathology

The complexity of the anatomy and physiology of the Nervous System (NS) makes it essential to dissect every form of disorder, whether due to natural disease or due to chemical toxicant, into its pattern of functional damage and pathological lesions. Once the sites affected and the physiological dysfunction and structural damage have been analysed, the pattern of the disorder will be apparent, and it is that pattern which is likely to give a clue to mechanism, may well suggest a cause, and which will certainly indicate the prognosis of disability and recovery of the affected individual.

The toxicology of the NS in principal is no different from that of any other system in the body. It may appear more complex and so be more difficult to analyse, but that only shows the greater importance of clearly delineating what has happened and where are the lesions.
DETECTION AND ANALYSIS OF TOXIC EFFECTS ON THE NERVOUS SYSTEM

The detection and assessment of the state of the nervous systems are analogous in man and laboratory animals, although the highest functions are best studied in the former and more detailed analysis is possible in the latter and in in vitro procedures.

There are different approaches to analysis, which should be synthesised in understanding a problem of toxicity. Which to employ in diagnosing or assessing a particular problem, in following a disorder, or in screening exposed subjects or animals to detect an effect, should depend on the anatomical pattern of pathological lesions and on the nature of the functional disorders produced, as well as on the most effective diagnostic and experimental techniques available.

1. Clinical Examination

In order of complexity of function, what is assessed by clinical examination is:

(A) Highest Level Function
    group and individual behaviour
    cognitive function (reasoning, intelligence)
    memory
    learning
    spontaneous complaints of illness
    All these are closely interrelated and are dependent on subtle, underlying physiological processes.

(B) Sensory Perception - special senses - sight, learning, smell, skin sensibility, spontaneous sensibility, sensing the internal milieu, deep sensation, movement disorders.

(C) Motor Function - spontaneous movement and disorders, digit and limb movements, blood presssure.

(D) Visceromotor Function - the functions of the ANS in controlling the internal milieu, eg blood pressure, gastro-intestinal motility, etc.

In practice, many of these functions are most readily examined as integrated reactions, eg conditioned and reflexes, responses to physiological and pharmacological challenges, special procedures for higher CNS functions etc.

In these ways the central integration of sensory and motor activity can be evaluated together, as well as assessing individual components.

2. Electrophysiological Investigation

So much of the activity of the NS involves nerve impulses that study of spontaneous and induced electrical activity can reveal much about the state of the CNS and PNS, eg. the electroencephalogram (EEG) and evoked responses for the CNS, sensory and motor nerve conduction velocities, reflex actions, and the pattern of spread of nerve excitation in muscle (electromyography, EMG).
3. Pathological Investigation

It is essential in affected animals, whether in deliberate experiments or in spontaneous disease, to sample major sites in the CNS and to examine both proximal and distal parts of the PNS to detect dying back (centrifugal) neuropathies, and to distinguish demyelinating and axonal degenerations.

4. Pharmacological and Biochemical Investigations

This is the most complex area, because of the number and variety of processes that might be examined. Studies usually have to be focused on processes that the other evidence suggests may be abnormal.

Pharmacological techniques rely on additional treatment with a known agonist or antagonist to confirm a specific defect by appropriate change in the abnormality, eg atropine blockade of muscarinic features of a cholinergic crisis, or dopamine agonists relieving Parkinsonian features. Biochemical assays may range from measurement of cholinesterase to exploration of central neurotransmitters and Phase I and II metabolism. Pharmacokinetics may be especially important because of the restricted permeability and selective transport processes in the BBB and BNB.

In all these classes of investigative procedure, the essential need is to discern the pattern of the abnormality and to relate it to likely structural and biochemical disorders, which can then be explored in detail by more precise techniques.

5. Developmental Assessment

The nervous system, especially the CNS, continues major development for some time after birth, so it may be markedly affected by post-natal exposure to toxicants. Even in adult man or animal, plasticity is as vital, as in learning and memory.

This means that relating effects to developmental stage, previous experience and training, to the duration of exposure, and adjusting methods to the physiological capabilities of the organism, are more important than in toxicity affecting any other system of the body. Further, the plasticity and adaptive capacity of the CNS and PNS deteriorate with age, and that physiological decline must also be taken into account in considering exposure to a putative toxicant and its consequences.

Details of all these techniques and others can be found in appropriate monographs. It is important, however, always to consider the overall nature and pattern of the actions to be considered, and then to choose the most suitable and efficient methods for the problem to be investigated. Or, if nothing is known about the nature of the effects to be studied, the most general screening techniques should first be employed, reserving more selective methods until there is some information about the pattern of the disorder.

CHEMICAL CAUSES OF NERVOUS SYSTEM DISORDERS

The nature of the substances to be considered and the effects produced cover a very wide range of possibilities. Many neurotoxicants act both on the CNS and PNS, and probably on the
ANS, too, although that has been relatively less well studied, especially in the case of the 'dying back' neuropathies. The general toxicological impression of lesions has been affected by the greater case of detection and analysis of motor than of sensory disorders, and the simpler procedures for subjective and objective analysis of PNS damage than of CNS dysfunction. The true importance in man of developmental disorders remains to be established, because their study in experimental animals and humans is very difficult, and few rigorous attempts have been made, especially in populations as opposed to heavily exposed individuals. In the following text only selected examples are briefly quoted to illustrate points of importance as full details can be found in appropriate monographs.

1. CNS Neurotoxicants

(A) The pre-eminent examples here are the well-known problems of organic lead and organic mercury compounds, which have been associated with mass epidemics of poisoning via contamination of urban air and dust (organo-lead) and the food chain (organo-mercurials, e.g. as seed dressings, and in Minamata disease). Organomercurials have also been associated with pre- and post-natal developmental damage in man and animals.

(B) Hexachlorophene causes cerebral oedema in man and animals.

(C) Manganese mining has caused Parkinsonism in man and primates by a selective action on central dopaminergic neurons.

(D) Alcoholism and thiamine deficiency.

(E) Organophosphate pesticides and hydraulic fluid additives (triorthocresyl phosphate). These may chronically damage long tracts in the CNS as well as in the PNS, by producing 'dying back' changes (see below).

(F) Acrylamide and n-Hexane may cause a similar pattern of long tract lesions in the PNS more than in the CNS. Acute poisoning causes the cholinergic crisis.

(G) Synthetic Pyrethroids. At least in experimental animals, high 8 dose of those containing an (alpha)-cyano-group produce the Type I syndrome of flapping or paddling tremors in the rodent, possibly due to GABA antagonism. Most others cause the Type II syndrome of fine, more rapid, general tremors.

(H) MPTP. Much interest has come recently from the realisation that a simple contaminant of an illicit, addictive drug, could cause severe Parkinsonism in man and the monkey by selective damage to dopaminergic neurons.

A remote chemical resemblance to paraquat has been used as a basis for hypothetical speculations attempting to link pesticide use and Parkinsonian disease in man.

(I) Aluminium. Controversy continues about the possible role of ingested aluminium salts and senile dementia of the Alzheimer type (SDAT).
(J) Solvent Dementia. An even more strongly disputed condition is that of chronic brain damage in workers exposed to solvents in paint, eg the alkanes in white spirit, and toluene and xylene. The alleged clinical disorder is a form of mild to moderate intellectual and memory impairment, which is difficult to diagnose and the link is not generally accepted.

(K) Prenatal injury. Exposure to cytotoxic agents or irradiation may also damage the developing nervous system.

(L) Prenatal Malnutrition. Severe protein calorie shortage can certainly retard development of the nervous system, and subsequent catch-up growth may not be possible.

(M) Prenatal Vitamin Deficiencies. At least in some countries there may be a partial association between relative maternal dietary deficiency of the vitamin B complex and folic acid and the birth of the children with the Arnold-Chiari malformation of the brain. Genetic and other factors may also be involved.

(N) Brain Tumours. There are several suggestions in the literature, derived from small epidemiological studies, that human exposure to chemicals may rarely be associated with the development of glial tumours-malignant astrocytomas and neoplasms of the specialised reticuloendothelial system cells of the brain, the microglia, producing cerebral lymphomas. None is yet well established in man because of the small sizes of the groups involved, and hence the limited statistical power of the surveys, and the problems of reproductibility and such confounding factors as social class gradient, etc. The association generally has been with the 'chemical industry' or with 'monomer polymerisation to make plastics' (not particularly vinyl chloride), or, based on experimental results in animal studies, acrylonitrile has been regarded as suspect, because it is capable of producing small cell tumours in the CNS in the rat.

In man, but to be regarded as special case, profound immunosuppression, as in transplantation, does carry a significant risk of the development of cerebral lymphoma, as well as other tumours elsewhere in the body.

2. PNS Neurotoxicants

The pre-eminent examples of industrial and medical importance are organophosphate pesticides, etc., acrylamide and n-hexane and methyl butyl ketone, because they have all caused major human epidemics, due either to ignorance or incompetence.

A. Organophosphate Pesticides. Ever since 'Ginger Jake Palsy' of the early 1930's it has been known that many organophosphates (OP) developed as pesticides or used as corrosion inhibitors in industrial oils and hydraulic fluids (eg triorthocresyl phosphate, TOCP) are capable of causing a delayed peripheral neuropathy.

The disorder, which affects both motor and sensory fibres, as well as the long tracts in the spinal cord, develops more or less insidiously (depending on dose and species) some about 14 days after ingestion of the compound.

As is well known, it is due to irreversible binding of the compound to Neuronal Target
Esterase (NTE), the normal function of which is unknown. The NTE occurs widely in the brain and spinal cord and peripheral nerves, as well as in lymphocytes.

The pattern of damage follows centripetal degeneration of nerve fibres. There is no good evidence that that is due to failure of intra-axonal transport as such, but more likely it represents degeneration due to lack of some metabolically vital material, which is produced in only a limited amount and is somehow consumed along the length of the nerve fibre.

Organophosphates may also cause a second, quite distinct type of neurological disorder, due to their quite independent ability to inhibit cholinesterase, resulting in the accumulation of acetyl choline, and the diverse feature of the 'cholinergic crisis'. This is an acute and relatively short-lived disorder of CNS and PNS function, due to predictable pharmacological effects. It is reversible with time, as cholinesterase is resynthesised. And it can be treated with atropine, to block certain receptors, and oximes to regenerate cholinesterase. A similar disorder may follow exposure to other cholinesterase inhibitors, such as carbamate pesticides.

Probably all mammalian and avian species are susceptible, but such birds as the chicken are especially sensitive, hence their recommended use as test species - the 'hen neurotoxicity test'. That procedure is only appropriate for organophosphates, although frequently quite incorrectly required for other substances.

Regulation of exposure to organophosphates by control of exposure of workers in agriculture, and of the public (via ADIs for food, etc), provide a classical example of how to make a risk-benefit assessment and how to manage a public risk of great importance because of the wide use of OPs.

Biological monitoring of exposed population has been attempted by measuring nerve conduction velocity, but that has proved too variable (and too late in the disease) for field studies. The inherently simpler and more sensitive method of measuring pseudocholinesterase level in plasma (or whole blood 'cholinesterase') has proved easier and far more effective as a method for general surveillance of potentially exposed workers.

B. Acrylamide monomer is a commodity chemical polymerised on a large scale, to manufacture polyacrylamide, which is widely used in plastics coatings and adhesives.

It, too, can cause a classical, slowly progressive neuropathy in man and animals, with typical slow recovery from the ending of exposure.

The monomer is a powder, so exposure may occur by the respiratory route, as well as by ingestion. There is not normally sufficient residual monomer in the polymerised product to represent a hazard.

C. n-Hexane and Methyl Butyl Ketone are volatile solvents, at one time widely used in the manufacture of glues. They are important as a cause of a neuropathy, and because they first require metabolism to 2:5 hexanedione, which seems able to cross-link neurotubules in peripheral nerve, thereby preventing intra-axonal transport.

D. Metals. Several metals and their inorganic salts have been shown to be capable of causing peripheral neuropathy, usually on more prolonged administration of lower doses than those that affect the CNS, eg. arsenic, lead and thallium.
The commonest source of exposure has been work in factories smelting ores and refining the metals and their compounds, but other routes have occurred depending on the uses of the substances, eg arsenic and thallium-containing rodenticides contaminating food supplies, and deliberate poisoning.

Inorganic lead compounds are also an important cause of CNS damage, ranging from mild intellectual impairment to severe fits, as seen in children who have eaten lead-based paints. This is the principal source of concern about the almost universal use of tetra ethyl lead as an anti-knock agent in petrol.

E. Alcoholism. Chronic abuse of alcohol, probably in combination with thiamine (and perhaps pyridoxine) deficiency is a serious cause of peripheral neuropathy.

F. Mechanical Trauma. Although not a chemical cause, prolonged use of undamped vibrating tools causes peripheral nerve damage, especially in the hands, eg mechanical rivetting and scaling hammers, road drills, etc.

3. Recent Development and New Concerns

Three areas have become highly controversial or have become the site of major advances in the recent past.

A. MPTP and Parkinsonism. As already mentioned, a loose analogy has been drawn between the chemical structure of MPTP and the herbicidal paraquat and other bipyridyls. Attempts have also been made by epidemiological surveys of limited areas to link herbicide usage and the local incidence of Parkinsonism.

I believe so far that ideas are more attractive than realistic.

B. Aluminium and SDAT. The reasons for proposing this link are:

a. Experimentally direct injection (but not oral ingestion) of aluminium compounds into the brain, or in vitro tissue cultures, causes a neuronal degeneration with a superficial resemblance to that found in patients with senile dementia of the Alzheimer type (SDAT).

b. Patients with renal failure being treated by haemodialysis, who received an overload of aluminium salts via the dialysis solutions and via oral medication, have developed clinical dementia related to their body burden of aluminium. Clinically and pathologically it differs from SDAT.

c. There is some limited evidence that the local level of aluminium is high in certain affected cortical neurons in true spontaneous SDAT.

d. Very recently, there has been an as yet unconfirmed report associating the incidence of SDAT, with the aluminium level in the local drinking water. This is a very difficult type of survey to do, because the SDAT cannot be diagnosed with certainty except by post
mortem histopathological examination, and people move around and drink many waters from many different sources before and during the onset and progress of this slowly evolving disease. At present the case appears weak and quite uncertain.

C. Excitatory Amino Acids, Cycads and Tropical Motor Neurone Disease. The most intriguing and best founded development has been the recent work showing by dietary surveys in man and experiments in primates that feeding extracts of cycad plants over many months can cause degeneration of motor neurons - the CNS, mimicking several apparently spontaneous human diseases.

The toxic materials appear to be nitrite analogous of certain amino acids.

As cycads, which include the cassava plant and manioc, are very widely used as feeding stuffs for man and animals in the tropics, this represents a serious problem. It has long been known that such cyano-containing compounds occurred in cassava, etc., and that the plant material required holding under certain conditions to be made safe by natural degradation. There must be additional emphasis here on ensuring that appropriate preparative and cooking methods are followed.

CONCLUSIONS

Neurotoxicity may appear more complex than other types of toxicity, but provided that the pattern of functional and structural disorders is analysed, it will be seen to follow the conventional rules of toxicology. Any neurotoxic effect is serious, because of its slow progression and the possibility of late detection, and real harm to the affected individual, and indolent and possibly incomplete recovery. Monitoring workers and other exposed subjects poses problems, because of the need for repeated, difficult clinical and other investigative procedures, so biochemical markers of exposure may be preferable. As with any type of toxicity, prevention remains by far the best goal, which requires safe working practices and careful imitations of the risk of exposure.


