Editorial

Solvent neurotoxicity

Our present understanding of the way certain aliphatic hydrocarbons adversely affect the nervous system has been one of the outstanding achievements in the field of neurotoxicology in recent years. The initial description of the neuropathy in workers exposed to fumes of n-hexane by Japanese observers was followed by other case reports both in America and in Europe. A similar syndrome was described in workers in a factory employing methyl n-butyl ketone, and experimental studies on rats and in cats showed that the essential pathological change was gross focal swellings of the axon from accumulations of apparently normal 10 nm intermediate filaments (neurofilaments). "Giant axonal neuropathy," as it came to be termed, was also noted in subjects addicted to the inhalation of solvents used for domestic glues and other preparations. These cases showed the same slowly developing motor and sensory neuropathy with reduced conduction velocity and very slow rate of recovery once exposure had ceased. The signs and symptoms were always distal in distribution, and ataxia and involvement of cranial nerves were not part of the syndrome.

From the metabolic studies of DiVincenzo et al and of Couri et al and their colleagues it became plain that an essential element in the story was the step-wise transformation in the tissues of n-hexane and of methyl n-butyl ketone to 2,5-hexanediol. Analogues, such as methyl ethyl ketone, that did not proceed to this product were non-toxic, although they might have the capacity to enhance the conversion of the toxic compounds by stimulating the metabolic processes involved in the transformations. The essential feature to the transformation is the production of the \( \gamma \)-diketone, a necessary structural component for the toxic effect since synthesised 2,5-heptanediol and 3,6-octanediol are also toxic, and so is 5-nonanone when given in large enough doses. O'Donohue and Krasavage have suggested from this that a better and more precise term would be "\( \gamma \)-diketone intoxication."

We owe it to Graham and his associates for taking the next step in the solution of this problem. From their reflections on the remarkable yellow staining of the fur of the groins and around the mouth of animals dosed with hexacarbons or their metabolites, they showed that the \( \gamma \)-diketone derivative had the capacity to combine with the lysyl residues in proteins and, after a final oxidation step, to produce a stable pyrrol ring configuration that was not only responsible for the chromogenic change but also for cross linked proteins. The evidence is now fairly strong that 2,5-hexanediol or its precursors are either capable of entering axons or of being metabolised in the cells to produce the toxic product and thus directly cross link the neurofilaments. A major outcome of this is that the normal structural role of the neurofilaments in the cytoskeleton of the nerve fibre is interfered with and the capacity of the long protein filaments to slip smoothly down the axon at the rate of 1 mm a day is impaired. Masses of filaments become held up at the constriction of the axons at nodes of Ranvier, the nodes become disorganised and the myelin sheath overlying the axonal swellings becomes greatly attenuated, with consequent impairment of the axon's conducting capacity. Wallerian degeneration follows as the filamentous masses block the normal supply of materials to the axon downstream.

This is certainly an intriguing story, but how far can we generalise to other solvent intoxications? Has this tale any meaning for \( \text{C}_2\text{H}_5\text{OH} \), trichlorethylene, or toluene intoxication? The answer is "yes" so far as \( \text{C}_2\text{H}_5\text{OH} \) is concerned but distinctly "no" with regard to the others. In \( \text{C}_2\text{H}_5\text{OH} \), throughout the nervous system, filament masses occur within axons in exactly the same way as in \( \gamma \)-diketone intoxication, despite the fact that this compound clearly cannot form the same chemical configuration, although the same cross linking process must occur. This probably takes place through the active sulphur released during the metabolism of \( \text{C}_2\text{H}_5\text{OH} \) to COS and then to CO\(_2\). The transformation of \( \text{C}_2\text{H}_5\text{OH} \) to diethyldithiocarbamate (DDC), which also occurs, probably has no relevance to the development of the filament accumulations. The question of the chemical mechanism of neurofilament change that goes on to the neurological damage is thus still quite open.

The other solvents are other kettles of fish. There are strong suggestions that two solvents—namely, trichlorethylene and toluene—can cause damage to the nervous system, but the others, such as white spirit and perhaps styrene, are still in the realms of clinical appraisal.

Trichlorethylene is both puzzling as to its toxic process and unique in its presentation. After inhalation the minimal signs are of sensory disturbances and anaesthesia in the trigeminal (Vth cranial nerve) area. These may become permanent and indeed it was once recommended as a treatment for the debilitating condition trigeminal neuralgia. In more severe cases of exposure the change may spread to other cranial nerves, both motor and sensory, and
again these may be permanent. The distinct impression is gained that there is local spread of some destructive process within the brain stem, a process that is difficult to conceive of as being the direct effect of a toxic chemical. Since herpes simplex vesicles (cold sores) frequently occur after exposure to trichlorethylene, it would seem not unlikely that the brain stem changes may result from an activation of a commonly present, but dormant, virus. The lack of inflammatory signs in the only necropsy case reported\textsuperscript{12} does not exclude a viral cause for the changes since in some types of virus infections of the brain inflammation may be minimal or absent. The earlier suggestion that the conversion of trichlorethylene to dichloroacetylene may be responsible for the lesions\textsuperscript{13} has not yielded any further information despite repeated animal studies.

Finally, what about toluene? Since toluene has become the principal solvent in many glues, varnishes, and paints and has become the target for solvent abusers as well as an industrial hazard, it has been the subject of several clinical reports of a unique neurological syndrome.\textsuperscript{14} The principal features of the condition are cerebellar ataxia with evidence from computed tomography scans and radiological studies of cerebellar as well as some degree of cerebral atrophy. The ataxia and the other signs of cerebellar damage are striking, and they persist in most of the reported cases. Until an animal model is developed, and there is a strong need for support for research into this question, or biopsy or necropsy material becomes available, then all we can do is to guess at the nature of the cellular changes.

It is of some interest that in the Scandinavian countries painters and others exposed for long periods to "white spirit" have been diagnosed as showing evidence of dementia, but not ataxia by contrast with toluene.\textsuperscript{15} Although computed tomography scans have once more suggested cerebellar atrophy and the EEG has suggested abnormalities in such cases, a considerable question mark hangs over the heads of these subjects and will continue to do so until more unequivocal evidence can be obtained. This will certainly need some long term funding, probably using species with brains rather more developed than that of the rat, and it seems probable at the moment that the answer may not turn out to be a lemon.

\textbf{Institute of Neurology, Queen Square, London WC1N 3BG.}

\textbf{References}

\begin{enumerate}
\item Spencer PS, Schaumburg HH. Feline nervous system responses to chronic intoxication with commercial grades of methyl n-butyl ketone and methyl ethyl ketone. \textit{Toxicol Appl Pharmacol} 1976;37:301-11.
\item Court D, Abdel-Rahman MS, Hetland LB. Biotransformations of n-hexane and methyl n-butyl ketone in guinea pigs and mice. \textit{Am Ind Hyg Assoc J} 1978;39:285-9.
\item Buxton PH, Haywood M. Polyneuritis cranialis associated with industrial trichlorethylene poisoning. \textit{J Neurol Neurosurg Psychiatry} 1967;30:511-8.
\end{enumerate}