Solvents are ubiquitous in industrial societies in a wide range of processes. An estimated 49 million metric tons of solvents are produced per year in the USA alone, and more than 9·8 million people experience daily solvent exposure. Clinicians are therefore likely, in daily practice, to see patients who are exposed to these agents either occupationally or through contaminated environments. The symptoms experienced after contact with these agents are generally related to the functioning of the central (CNS) or peripheral nervous system (PNS). In many cases, such symptoms are fleeting and resolve after cessation of exposure. However, long-term chronic exposure or high-dose acute exposures can produce longer-lasting effects characterised by cognitive and behavioural changes. In some cases, the symptoms may fully or largely resolve with time, whereas in others permanent CNS or PNS damage may occur.

**Background**

The term solvents encompasses organic chemicals that differ widely in structure. The 11 general classes of solvents, with examples of each class, are listed in panel 1. There are also other substances commonly described as solvents (such as carbon disulphide) that do not fit into these classes. In addition, many common solvents are used as mixtures. For example, Stoddard solvent and thinners (hydrocarbon mixtures) are components of many products, including paints, varnishes, adhesives, glues, coatings, degreasers and cleaning agents, dyes and printing inks, floor and shoe polishes, waxes, agricultural products, and fuels.

All types of organic solvents are volatile liquids at room temperature and are lipophilic. The main routes of exposure are through inhalation and skin contact. After absorption, solvents may be exhaled unchanged, biotransformed and then excreted, or accumulated in lipid-rich tissues such as the brain, myelin, and adipose. The toxicity of individual solvents to human beings depends on the mechanism of action (which is usually related to their structure) and the amount or dose of exposure. Exposure dosage depends on several factors, including route of exposure, air concentration of the solvent, the solubility of the solvent in blood, and the amount of physical activity by the exposed person at the time of exposure. When solvents are used as mixtures or contain impurities, the effects may be additive (ie, the combined effect of two solvents equals the sum of the effect of each solvent alone), synergistic (ie, the combined effect is much greater than the sum of the effect of each solvent alone), or potentiated (ie, one solvent does not have a toxic effect in itself, but when combined with another makes that solvent substantially more toxic). Because of the large number of solvents and their increasing use in new technologies, there are many occupations in which workers can be exposed to them. Industries in which workers are often exposed to organic solvents include automotive manufacturing and repair, paint and varnish manufacturing, the electronic industry, industrial cleaning, metal-part degreasing, and dry-cleaning. Clinically, it is especially common to see patients working in dry-cleaning, the paint industry, and in occupations involving mechanical or engineering work that requires the use of degreasers. It should be noted that patients can also experience exposure environmentally, through hobbies, and by self-administration of solvents such as ethanol, toluene, and gasoline.

### Panel 1: General classes of organic solvents

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliphatic hydrocarbons</td>
<td>(eg, n-hexane)</td>
</tr>
<tr>
<td>Halogenated hydrocarbons</td>
<td>(eg, carbon tetrachloride, trichloroethylene)</td>
</tr>
<tr>
<td>Alcohols</td>
<td>(eg, methanol)</td>
</tr>
<tr>
<td>Cyclic hydrocarbons</td>
<td>(eg, cyclohexane)</td>
</tr>
<tr>
<td>Esters</td>
<td>(eg, ethyl acetate)</td>
</tr>
<tr>
<td>Ethers</td>
<td>(eg, ethyl ether)</td>
</tr>
<tr>
<td>Nitrohydrocarbons</td>
<td>(eg, ethyl nitrate)</td>
</tr>
<tr>
<td>Ketones</td>
<td>(eg, acetone, methyltetrahydrofuran)</td>
</tr>
<tr>
<td>Glycols</td>
<td>(eg, ethylene glycol)</td>
</tr>
<tr>
<td>Aromatic hydrocarbons</td>
<td>(eg, benzene)</td>
</tr>
<tr>
<td>Aldehydes</td>
<td>(eg, acetaldehyde)</td>
</tr>
</tbody>
</table>

**Epidemiology**

167 (28%) of 588 chemicals identified by the American Conference of Governmental Industrial Hygienists were cited as having neurological or behavioural effects as the basis for recommended safe exposure limits (threshold limit values). At least 25% of these chemicals are organic solvents. Many studies in the past 25 years have demonstrated the neurotoxicity of organic solvents through the use of neuroimaging, neurophysiological, and...
Panel 2: Clinical evaluation of suspected solvent-induced toxic effects

Questionnaire or report from patient
Occupational history
Exposure history
Symptom complaints

Neurological examination
Motor and sensory examination of CNS and PNS function
Reflex testing
Neuropsychological and imaging techniques
Nerve conduction
Electromyelogram
Evoked potentials
Single positron emission computed tomography (SPECT)
Computed tomography
Magnetic resonance imaging
Neuropsychological testing
Cognitive function
Motor function
Mood and personality assessment

Neuropsychological assessment techniques.9–12 We briefly summarise these findings here as the basis for selection of clinical assessment methods. One important result is the repeated finding that the use of these assessment techniques reveals neurotoxic effects in workers who are not obviously or clinically ill. These effects have been referred to as latent, subclinical, or preclinical.9–12

Clinical assessment

Many patients experiencing nervous-system effects of acute or chronic solvent exposure are aware that their symptoms may be related to such exposure; others are not. The doctor should be suspicious of such a connection if the patient’s occupational history or hobbies suggest that solvent exposure has occurred, and if symptoms are of the type typically described by patients experiencing intoxication. Exposure to organic solvents typically results in CNS depression and psychomotor or attentional deficits. The patient may present with complaints of fatigue, irritability, confusion, or depression, and may describe memory difficulties.13 When PNS function is affected, the patient may experience a gradual onset of symptoms, such as intermittent tingling and numbness, with progression to an inability to perceive sensation and muscle weakness.14,15

When the doctor suspects possible nervous-system disorder as a result of solvent exposure, several special clinical examinations may be useful in defining the patient’s condition (panel 2). As in any investigation of highly specific and somewhat unusual disorders, these examinations are most helpful if done by clinical specialists who have experience in examining patients with disorders related to occupational or environmental exposure to neurotoxins.

Detailed information about the patient’s symptoms and exposure history should be collected by the examining physician or a specialist in occupational and environmental medicine. Information can be collected by interview exclusively or supplemented by the use of specifically designed questionnaires.15

Neurological examinations can be used to define solvent-related neurological abnormalities of CNS or PNS function and to exclude other neurological explanations for the patient’s symptoms. The types of abnormalities seen after solvent exposure include cranial-nerve abnormalities, such as the trigeminal neuropathy that has been associated with trichloroethylene exposure,16 muscle weakness or incoordination, and PNS signs, such as insensitivity to pinprick and touch, impaired two-point discrimination, or changes in sensation to position, vibration, or temperature.17

Laboratory tests of nervous-system function can be useful in confirming clinical evidence of CNS or PNS disease. For example, nerve-conduction studies and electromyelography17 can help to confirm a suspected solvent-induced peripheral neuropathy.

Computed tomography (CT) and magnetic resonance imaging (MRI) can be used to detect the atrophic changes in the frontal lobes and cerebellum as well as white-matter lesions that have been described after exposure to certain solvents.18–20 There have been reports that evoked potentials, particularly visual evoked potentials, are also abnormal after solvent exposure.19,21 There is some evidence that SPECT may also show abnormalities.21

Neuropsychological testing can also be helpful in defining any intellectual and affective deficits that may be associated with exposure. There have been many reports on the specific neuropsychological deficits that can follow acute and chronic solvent exposure.16,24–27 including some prospective epidemiological studies of occupationally exposed groups that showed clear dose-effect relations between the degree of exposure and the magnitude of the associated behavioural deficits.12,28–29 Acute, low-dose exposures may be associated with specific changes in test performance that resolve after withdrawal from or a decrease in dose of exposure.30 However, chronic exposure can also be associated with permanent cognitive changes.19,20 Typically, these changes are dose-related, specific to particular domains, and may affect attentional capacity, executive function (the ability to deploy strategies for problem-solving and to organise responses to novel stimuli), visuospatial skills (analysis and integration of visual arrays), short-term memory, and mood/affect.29,30

Panel 3 summarises some of the issues that should be taken into account in design of a neuropsychological test battery for the clinical assessment of patients who have been exposed to neurotoxins.31 as well as a typical test battery.

Finally, to conclude that there is a relation between solvent exposure and nervous-system dysfunction, the clinician must be convinced that an exposure has occurred. Evidence about the type and dosage of exposure can be gathered by administration of a questionnaire (self-report) to inquire about duration and types of exposure; reliance on employer records of job histories, descriptions of chemical processes, and safety or air-quality records; an industrial-hygiene evaluation of the worksite; or biological monitoring. Questionnaires and biological monitoring are generally the most feasible approaches for the clinician. In biological monitoring for specific solvents, the solvents themselves or metabolites can sometimes be measured in the patient’s blood, urine, hair, fat, or breath. This approach is the most accurate in assessment of internalised dose, but its use can be limited by the expense of sampling and measurement and concern about the accuracy of the measure.32,33

Whatever the mode of exposure assessment, there are restrictions to interpretation. First, published threshold limit values and recommended limits of exposure34 cannot be followed slavishly in assessing whether a patient
Panel 3: Clinical assessment of behavioural effects of solvent exposure

Issues to be addressed
Specificity of cognitive deficit to toxicant exposure
Estimation of native ability patterns
Differential diagnosis
Developmental specificity
Degree and types of cognitive strengths and deficits
Tests that may be sensitive to CNS effects of toxicant exposure
Wechsler adult intelligence scale-revised subtests
Wechsler memory scale, Wechsler memory scale-revised subtests
Continuous performance test
Trail-making test
Wisconsin card-sorting test
Paced auditory serial arithmetic test
Controlled work association test
Santa Ana formboard test
Finger tapping
Milner facial recognition test
Benton visual recognition test
Delayed recognition span test
Verbal-verbal paired associate learning test (selected patients)
Peterson consonant trigram task (selected patients)
California verbal learning test
Rey-Osterreith complex figure
Albert’s famous faces test (selected patients)
Profile of mood states
Minnesota multiphasic personality inventory, revised
Tests of estimated premorbid ability and motivation
Boston naming test
Writing sample
Wide range achievement test, revised
Rey 15-item test
Test of motivation and malingering

is likely to have nervous-system damage from exposure. Even if the estimated exposure is accurate, chronic long-term exposure at levels below the recommended standards has been associated with evidence of nervous-system dysfunction in some patients. The recommended exposure values are based on data from group studies and there is great individual variability in susceptibility to specific toxicants.

Diagnosis and treatment
Solvent-induced nervous-system dysfunction is diagnosed when the symptoms, signs, and evidence from laboratory studies are typical of those seen in solvent intoxication, when a solvent exposure can be confirmed, and when there is no other medical or historical explanation for the examination results. Panel 4 lists the clinical criteria to define the type and severity of solvent-induced brain dysfunction.

Differential diagnosis of CNS dysfunction secondary to solvent exposure can be tricky. Examples of neurological disorders with overlapping symptoms and laboratory findings to those seen in solvent toxicity include multiple sclerosis and cerebrovascular dementia (both of which affect the white matter and cognition). Differential diagnosis relies on history, progression, and the use of other laboratory tests and clinical findings. Some patients with solvent exposures develop psychological disorders in which cognitive changes can be seen (these include post-traumatic stress disorder, depressive disorders, and motivational disorders such as malingering or sick-role playing) or have developmental disorders in learning or attention that affect cognitive test results. In these cases, the patterns of neuropsychological test performance and history (eg, use of school records) are highly specific and informative. Many patients with histories of exposure to solvents complain of symptoms that fit diagnostic criteria for chronic fatigue syndrome or for multiple chemical sensitivity. In these disorders, cognitive test results generally differ from those found in solvent-exposed patients and the characteristic signs, symptoms, and laboratory findings of solvent intoxication are absent. Another issue important in differential diagnosis is the synergistic interaction between exposure to industrial solvents and ethanol, which can result in a more pronounced picture of nervous-system effects in an alcoholic than in a patient who abstains from alcohol use.

Treatment options in patients with toxicant-induced neurological disorders are limited. The first step is usually to remove the patient from exposure until symptoms remit, and to judge carefully whether it is advisable for the affected individual to work with solvents in the future. Such decisions may require follow-up assessments of neurological and neuropsychological status to assess recovery and residual impairments. Treatment then tends to focus on the alleviation of specific symptoms (such as headache or dizziness). In depression or amotivational states, antidepressants or stimulant treatment can be effective in improving arousal and motivation. If the patient has a post-traumatic stress disorder, psychotherapy, anxiolytic treatment, or a combination, can be beneficial. Many such patients may need support in obtaining compensation benefits expeditiously to prevent the psychological problems that can accompany prolonged...
financial losses after they are unable to continue their work. Vocational counselling may assist the patient who can no longer work with solvents in deciding on or finding a new type of work (if cognitive deficits do not preclude such options).

Primary prevention of these disorders is essential. Prevention can be achieved through adherence to recommended standards for exposure (eg, in the USA 32,33) and by education of workers (especially among the self-employed, many of whom are responsible for their own safety measures). In addition, surveillance for early symptoms and effects of solvent exposure could prevent a great deal of morbidity. Having assessed many workers exposed to solvents and other neurotoxicants during the past 16 years, we believe that the number of patients fitting criteria for moderate solvent encephalopathy is declining. This is a hopeful sign. However, nervous-system compromise associated with solvent exposure still occurs: people who work as dry-cleaners, as self-employed artisans, and in mechanical and spray-painting shops are at risk.

Case study

Data from a patient with a clear-cut solvent-induced illness are given in the table. The patient was a self-employed glazier who had worked for longer than 32 years with a variety of solvents (benzene, toluene, zylol, methyl ethyl ketone). He had never used a respirator and had used gloves for only 2 years before he was referred to us, when he was 50 years old. He reported that he had initially sought medical attention from an occupational health specialist because of dermatitis. His physician noted symptoms of peripheral neuropathy, impotence, depression, and cognitive change, all of which were investigated in relation to his solvent exposure. The patient reported that he had felt sad for some years and remained so. He also reported that he was irritable and had memory problems, as well as headaches, dizziness, and poor balance. His neuropsychological testing indicated significant cognitive dysfunction in the domains of attention, executive functioning (inferential reasoning), fine manual motor speed, and coordination, and short-term memory. He was also found to be depressed, anxious, and irritable (though his mood findings do not explain the pattern of cognitive deficits). He was advised to stop work.

At repeat assessment 1 year later, he reported that he had experienced remarkable improvement in mood and that the outside world seemed clearer to him. However, he continued to have cognitive deficits, and to feel irritable and depressed, and he reported the additional symptom (which he had not previously noticed) that he had gradually lost his sense of smell. Neuropsychological testing showed some improvements, but he continued to show deficits in short-term memory and visuospatial function consistent with moderate residual solvent-induced encephalopathy. He agreed to a trial of antidepressant treatment and sought psychotherapeutic assistance also. Cognitive function did not improve during the next 2 years. He reported some improvement in well-being from amitriptyline and fluoxetine but expressed grief over his loss of work, although he was able to support himself on his investment income and social security disability payments.

References


We often derive from observation strong intimations of truth, without being able to specify what were the circumstances we had observed which had conveyed those intimations.1

The primary focus of literature's first decade as part of the formal curriculum of some American medical schools (1972–81) was on teaching literary students to help develop students' capacity for empathy, to enhance their skills in interpretation, and to complement the teaching of traditional medical ethics.3–4 These early concerns of literature and medicine have been discussed in the eight previous essays in this series.6–11 In the next decade (1982–91), scholars in literature and medicine, like their counterparts in many other disciplines, were increasingly drawn to the study of narrative.14–17 Defined most simply, a narrative is a story. Examples of narratives include not only well-crafted works of literature, such as short stories and novels, but also histories, professional stories such as medical case histories, and unpublished personal or family stories. The second decade of literature-and-medicine scholarship was thus marked by an interest in the centrality of narrative to the work of medicine.18–21

Scholars used tools and insights from literary theory to explore the acquisition and transmission of medical knowledge,21 to study the narrative nature of the physician-patient encounter,22–27 to analyse the conventions of various medical genres,28–28 and to consider the relationship between a physician's narrative skill and a patient's willingness to accept the diagnosis and comply with recommended treatment.19,20,26 During this second decade, scholars also began to explore more intensely the relation between narrative and medical ethics.23–27 These two directions of literature-and-medicine scholarship are now coming together: because of the inherently narrative structure of medical knowledge and practice, doctors' intellectual skills and habits better prepare them for a kind of narrative ethics than for the analytic, principle-based ethics that has dominated medical ethics for the past 25 years.

This principle-based ethics is perhaps best represented by Tom L Beauchamp and James F Childress in their textbook Principles of Biomedical Ethics, now in its fourth edition.31 In this form of analytic ethics, one begins by establishing certain principles—autonomy, beneficence/