The Effects of Toluene on the Central Nervous System

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Abstract. In recent decades the organic solvent toluene (methylbenzene) has emerged as one of the best-studied neurotoxins. Long-term and intense exposure to toluene vapors in humans who abuse spray paint and related substances has led to the recognition that toluene has a severe impact on central nervous system myelin. Chronic toluene abuse produces a devastating neurological disorder, of which dementia is the most disabling component. The clinical syndrome, toluene leukoencephalopathy, can be detected by a combination of characteristic symptoms and signs, detailed neurobehavioral evaluation, and brain magnetic resonance imaging. In this paper, we consider the impact of toluene abuse on our society, describe the specific neurobehavioral deficits in toluene leukoencephalopathy, review the spectrum of neuroimaging findings in patients with this disorder, summarize the teratogenic effects of toluene in both humans and animal models, and offer possible explanations for the range of neuropathological damage seen in brains of individuals who chronically abuse toluene.

Key Words: Dementia; Magnetic resonance imaging; Neurotoxin; Solvent vapor abuse; Toluene, Leukoencephalopathy; White matter.

THE PUBLIC HEALTH IMPACT OF INHALANT ABUSE

The abuse of volatile substances is an important problem in the United States and many other countries around the world (1). Data on the extent of this practice are difficult to acquire, but available estimates are likely to be under-representative. In the United States, the lifetime prevalence of inhalant abuse has been estimated to be 18%, and in incarcerated individuals, a figure of 33.4% has been cited (1). Urban Hispanic youth and Native Americans who reside on reservations manifest an even higher rate of inhalant abuse than the general population (1). Inhalant abuse appears to be startlingly high among younger aged children, with up to 10% to 15% of young people in the United States having used inhalants in some surveys (2). Inhalants, along with alcohol and marijuana, may serve as the initial substances of abuse for young people (3). Data from 1994 disclosed that 19.9% of eighth graders reported that they had used inhalants, with 5.6% reporting use within the past 30 days (1). Although very young children can also abuse ethanol, marijuana, and other substances, abuse of these agents is typically initiated slightly later than inhalants (1).

Toluene and other inhalants are a particular problem with minors because these drugs are widely and easily accessible, legal, and inexpensive. Although frequently encouraged, efforts to restrict the purchase of these agents by young people have not proven effective in preventing inhalant abuse. Hardware and other retail stores have been encouraged to store these substances in locked cabinets, but this procedure has not produced a major barrier to access. Even though most abusers start using inhalants at a young age, they often continue this form of substance abuse for many years. Many of our patients have inhaled these vapors for decades, and it is not uncommon to see 50- and 60-year-old individuals still engaged in this dangerous practice.

GENERAL EFFECTS OF INHALANTS ON THE BRAIN

Inhalants produce potent psychoactive effects that have been described as causing a euphoric state similar to that seen with inebriation from ethanol (1). Exposure to inhalants occurs primarily via pulmonary absorption, and significantly less absorption takes place through the skin or gastrointestinal tract (1). No special drug paraphernalia are necessary for inhalant abuse. Many abusers attain the desired effects of inhalants by simply removing the lid of a can or tube and sniffing the fumes, or spraying the aerosolized mists into the mouth. A complicating factor is that many inhalant abusers also avail themselves of other non-inhalant substances such as ethanol, marijuana, heroin, cocaine, amphetamines, 3,4-methylenedioxyamphetamine (MDMA or Ecstasy), lysergic acid diethylamide (LSD), and psilocybin. In addition, substance abusers may have coexistent disorders such as acquired immunodeficiency syndrome, traumatic brain injury, hepatic cirrhosis, and nutritional deficiencies that impact neuropathological studies. Thus the correlation between the effects of a given inhalant such as toluene and its clinical and neuroradiological findings can be difficult in some patients. Indeed, a precise assessment of the extent of exposure to inhalants cannot usually be determined.

Although many questions about the toxic effects of inhalants in general are unresolved, the nervous system...
is clearly vulnerable to toxicity from these substances (4). Organic solvents may produce encephalopathy, cerebellar dysfunction, optic and other cranial neuropathies, parkinsonism, and peripheral neuropathy (1, 4, 5). Both acute and chronic encephalopathies are common (1). Of all the inhalants, the greatest incidence of abuse of a single substance is found with toluene, prompting many human and animals studies on the specific effects of this compound.

**TOLUENE**

Toluene (methylbenzene) is an aromatic hydrocarbon, and a ubiquitous solvent in societies around the world. A component of many paints, lacquers, glues, adhesives, inks, and cleaning fluids, toluene is also widely used as a cleaning and drying agent in the rubber and lumber industries, and in the dry cleaning, motor, aviation, and chemical industries (1). More than 3 million tons of toluene are produced each year in the United States alone (6), and this solvent is found in many occupational settings and in numerous household products. Toluene is the major solvent in spray paint (1), and the inhalation of paint fumes is one of the most popular forms of inhalant abuse. Although many inhalant abusers expose themselves to a wide variety of solvents, a subset of abusers confines themselves largely or exclusively to the inhalation of paint fumes. These individuals have been studied by investigators in several countries, and enabled the collection of a substantial amount of clinical, neuroimaging, and neuropathological information on the neurotoxic effects of toluene (1, 4, 5, 7).

**TOLUENE ABUSE**

Toluene abusers generally employ one of two methods to achieve a “high” with this substance: “huffing,” in which a rag is soaked with toluene and the fumes are directly inhaled, and “bagging,” in which the fumes are inhaled as they arise from the solvent placed in a plastic bag. After inhalation, toluene is rapidly absorbed through the lungs and then widely distributed throughout the body (8). Most inhaled toluene is metabolized in the liver by conversion to benzoic acid by two enzymes, alcohol dehydrogenase and aldehyde dehydrogenase (6). Benzoic acid is then conjugated with glycine to form hippuric acid (80%) or glucuronic acid to form benzoyleglucuronide (20%), both of which are water soluble and readily eliminated through the kidneys (8). Hippuric acid is the major metabolite of toluene, and up to 75% of inhaled toluene is excreted in the urine as hippuric acid within 12 hours after exposure (9). Toluene is retained somewhat longer in adipose tissue, where its half-life is 0.5 to 3 days (9). The highly lipophilic nature of toluene explains its rapid concentration in the lipid-rich central nervous system (CNS; 1).

Laboratory testing for acute toluene toxicity is hampered by the fact that blood tests for toluene and urinary tests for hippuric acid are not available in most hospitals. Tests for toluene exposure, including quantitative analyses and screening panels for a number of other inhalants, are available at a limited number of reference laboratories in the country (such as National Medical Services in Willow Grove, Pennsylvania), but may require special shipping arrangements, such as sending the specimen chilled with a cold pack due to the highly volatile nature of these substances. The reader is directed to the facility’s website at http://www.nmslab.com for specifics regarding the variety of tests available, types of tubes in which specimens should be collected, and methods of analyses.

Since results of laboratory tests are usually not rapidly available, diagnosis of acute toxicity is usually made based on the clinical history, coupled with the onset of a constellation of neurological symptoms and signs consistent with inebriation (1). Patients may report or display features including dizziness, lightheadedness, sleeplessness, drowsiness, disorientation, ataxia, nystagmus, anxiety, excitability, and irritability (1). Signs of toluene abuse and addiction include the identification of paint stains on the body or clothing, a chemical breath odor, red eyes, nearby discarded spray paint cans or cans of solvent, and a drunken or dazed appearance (1).

The primary target of toluene is thought to be the CNS (6, 8), and both acute and chronic effects are recognized. The chronic encephalopathy associated with long-term toluene abuse is particularly important because it appears to be a permanent and disabling disorder related to white matter damage in the brain. Clinical, neuropsychological, and MRI studies in toluene abusers have shown relatively specific damage to white matter and a consistent profile of neurological and neurobehavioral impairment (7, 10).

**ACUTE ENCEPHALOPATHY AFTER TOLUENE INGESTION**

Clinical features of acute intoxication with toluene were first described in 1963 (11). Acute intoxication causes a variety of neurologic effects that depend on the amount of exposure. At relatively low levels of ambient toluene, just exceeding 200 ppm, fatigue, headache, paresthesias, and slowed reflexes are seen (6). Confusion develops in those exposed to levels at or above 600 ppm, and euphoria appears as levels near 800 ppm (6). Because euphoria is the desired effect, individuals with toluene abuse deliberately expose themselves to toluene levels of at least 800 ppm, and often far higher (6). Many of the symptoms resemble...
ethanol intoxication and abusers utilize toluene to achieve a “quick drunk” effect. The acute encephalopathic effects of toluene are generally reversible and not associated with neuroimaging changes. Additional acute adverse effects on the kidney (12) and cardiac systems are also recognized (1), and cardiotoxicity with lethal arrhythmia may be the cause of sudden demise in those with acute inebriation (1). Obtundation may also lead to suffocation, hypothermia due to exposure, or fatal motor vehicle accidents. A recent Forensic Pathology Check Sample case (FP00–2), from the American Society of Clinical Pathologists, reminds coroners and forensic pathologists of the potential for sudden demise during episodes of acute toluene inhalation.

**TOLUENE LEUKOENCEPHALOPATHY DUE TO CHRONIC ABUSE**

Chronic encephalopathy from toluene, a disorder known as toluene leukoencephalopathy, is an ominous sequel of this form of substance abuse and features a prominent and characteristic neurological syndrome, the most important feature of which is dementia (1, 7). The clinical severity of toluene leukoencephalopathy parallels the degree of white matter injury in the brain as seen by neuroimaging studies, and accordingly, toluene has become a prototypical brain white matter neurotoxin (7). The damage to brain white matter appears to become irreversible at some point and no treatment is currently known other than abstinence. Exactly when in the clinical course the damage becomes irreversible, an issue of paramount importance for prognostic counseling is unknown.

The understanding of the chronic effects of toluene on the brain has evolved over the last four decades. In 1961, Grabski documented chronic cerebellar degeneration in a person who sniffed toluene for an extended period, and this individual was the first published case documenting persistent neurotoxicity from toluene (13). The first description of permanent encephalopathy from toluene dates from 1966, when the same patient reported by Grabski (13) was described as having developed emotional lability and frontal release signs after continued toluene abuse (14). A 1977 report of neurologic findings in two individuals with toluene exposure suggested that the toxic effects of the solvent were confined to the CNS (15). Neuropsychological deficits in chronic inhalant abusers were first documented in the same year (16, 17), although the possible confounding effects of multiple substance abuse (17) and the acute effects of abused inhalants were acknowledged as methodological issues (18). Nevertheless, the suggestion was made that duration of exposure was related to the degree of neuropsychological impairment (18). Further neurological studies with small numbers of patients emphasized the multifocal nature of CNS deficits, with coexistent cognitive, cerebellar, and cranial nerve dysfunction (19, 20). A variety of unusual brainstem signs were noted in some patients, including opsinclonus, ocular flutter, and ocular dysmetria (19).

**NEUROBEHAVIORAL DEFICITS IN CHRONIC TOLUENE ABUSE**

In the 1980s, more comprehensive studies of selective toluene abusers appeared. Formal evaluation of neurobehavioral function in one group of such patients documented widespread cognitive dysfunction with neuropsychological measures, including the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Memory Scale (20). Building on these observations, standardized neurobehavioral testing was undertaken in another cohort of toluene abusers and a characteristic clinical profile emerged (21). These individuals displayed a pattern of neurobehavioral deficits consisting of inattention, apathy, memory dysfunction, visuospatial impairment, and preserved language (21). On the basis of comparison with other disorders of cerebral white matter, this profile was considered to be consistent with what would be expected to result from diffuse white matter involvement (10). Moreover, further analyses showed that cognitive impairment surpassed corticospinal, cerebellar, brainstem, and cranial nerve dysfunction as the most disabling aspect of the chronic neurotoxicity syndrome (21).

In a follow-up study of 14 more toluene abusers, detailed neuropsychological testing and magnetic resonance imaging (MRI) scans showed that neuropsychological deficits in patients with toluene-induced white matter damage correlated with the patient’s neuroimaging findings (22). After blinded ratings of both neuropsychological testing and MRI scans were independently conducted, the level of cognitive impairment, often sufficient to be called dementia, was found to correlate directly with the severity of leukoencephalopathy detected on MRI (22). This study was the first to demonstrate that toluene abusers develop a dementia syndrome that directly parallels the degree of white matter damage as demonstrated by neuroimaging (22).

Subsequent studies have appeared on the cognitive effects of solvent abuse (23, 24), and toluene was judged to be the predominant solvent that was abused. A significant and selective decline of the WAIS-Revised performance intelligence quotient (IQ), and in particular the digit symbol subtest, was reported among a group of solvent abusers who had diffuse cerebral white matter changes on MRI (23). In contrast, the verbal IQ, a measure that more specifically reflects language function, was not associated with white matter changes (23). These results suggested a primary impact on sustained attention, speed of information processing and visuospatial skills, combined with relative sparing of language (23), a pattern consistent with previous neurobehavioral observations in toluene abuse (21). Rosenberg et al conducted...
the most recent study, a controlled examination of a large cohort of 55 solvent abusers and 61 users of other recreational drugs using detailed neuropsychological testing and MRI (24). Deficits in executive function and working memory were the most prominent abnormalities in the solvent abusers, and again language was spared (24), paralleling results of previous investigations (21–23). Moreover, the observed deficits demonstrated a significant degree of correlation with the degree of cerebral white matter injury (24). Taken together, these studies provide substantial evidence that a unique profile of neurobehavioral deficits in toluene abusers can be directly attributed to cerebral white matter involvement.

TOLUENE LEUKOENCEPHALOPATHY AS AN EXAMPLE OF WHITE MATTER DEMENTIA

The selective damage to white matter caused by chronic toluene abuse has offered an unprecedented opportunity for behavioral neurologists to study the specific effects of cerebral white matter disorders on behavior. In recent years it has been recognized that disorders of the cortical gray matter (e.g., Alzheimer disease), the subcortical gray matter (e.g., Parkinson disease), and the cerebral white matter each manifest a distinctive constellation of cognitive and emotional disturbances. Based largely on the initial studies of toluene leukoencephalopathy and multiple sclerosis (MS), both of which are excellent examples of white matter disorders that reliably alter neurobehavioral function, the notion of “white matter dementia” was proposed (25). Other disorders causing white matter dementia includeBinswanger’s disease, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), traumatic brain injury, the acquired immunodeficiency syndrome (AIDS) dementia complex, metachromatic leukodystrophy, cobalamin (vitamin B<sub>12</sub>) deficiency, alcoholic dementia, gliomatosis cerebri, radiation leukoencephalopathy, and normal pressure hydrocephalus (7, 10, 25, 26).

As experience with all of these disorders increased, it became apparent that a relatively specific neurobehavioral profile is associated with diffuse involvement of the brain white matter (10, 26). Patients with sufficiently severe cerebral white matter pathology can be expected to develop deficits in sustained attention, memory retrieval, visuospatial skills, frontal lobe function, and psychiatric status; in contrast, language, procedural memory, and extrapyramidal function are usually preserved (10, 26). One of the more striking aspects of this profile is the slowness of information processing that pervades the clinical presentation (10, 26). Although many patients manifest less severe impairment than do patients with disorders of cortical gray matter, a significant percentage are sufficiently affected that they fulfill clinical criteria for dementia (10, 26). While a spectrum of neurobehavioral deficits and white matter damage on MRI can be seen in patients with chronic toluene abuse, severely affected individuals with toluene leukoencephalopathy serve as an excellent example of white matter dementia (7, 10, 25, 26).

NEUROIMAGING STUDIES OF WHITE MATTER DAMAGE IN CHRONIC TOLUENE ABUSE

In the 1980s, modern neuroimaging began to be regularly applied to the study of chronic toluene abusers. A series of 20 individuals with chronic solvent vapor abuse from toluene demonstrated the use of computerized tomography (CT) to investigate brain structural abnormalities (21). In these 20 patients, CT disclosed atrophy of the cerebrum, cerebellum, and brainstem in 8 of 9 who underwent scanning (21). This study was important because it identified abnormalities in the brains of individuals who abused toluene and were not acutely intoxicated when tested, but it was apparent from the early days of CT that this technique could not provide detailed information on the brain white matter (26).

The advent of MRI offered an enormous advantage in the investigation of toluene leukoencephalopathy because of its excellent sensitivity to changes in the cerebral white matter. In a group of subjects with toluene abuse, brain MRI revealed 1) widespread atrophy (also discernible with CT), 2) loss of differentiation between the gray and white matter throughout the CNS, and 3) increased periventricular white matter signal on T2-weighted images (27). Since our initial study, other groups have regularly detected diffuse leukoencephalopathy in toluene abusers with conventional MRI techniques (28–30), which appears to begin as a periventricular pattern of involvement early in the course of the disorder (30).

As experience with toluene leukoencephalopathy and other white matter disorders grew, it was increasingly apparent that a spectrum of white matter changes could be observed by MRI (7, 10, 25, 26). Depending on the degree to which the white matter is affected by the neuropathological insult, changes may be mild, moderate, or severe (7, 10, 25, 26). Figure 1 displays MRI scans from several different chronic toluene abusers and illustrates the range of atrophy and white matter abnormalities that can be detected.

OCCUPATIONAL TOLUENE EXPOSURE

An area of uncertainty in the study of toluene leukoencephalopathy is the threshold of toluene exposure that is necessary to induce damage to the brain white matter. This issue is important not only for those individuals with inhalant abuse, but potentially for millions of other persons who are exposed to occupational levels of solvents such as toluene in their workplace or at home (7). Particularly at risk are those employed in the dry cleaning, motor, aviation, and chemical industries (1). It is important to emphasize that leukoencephalopathy from toluene
Fig. 1. The spectrum of leukoencephalopathy in toluene abuse as demonstrated by brain MRI. A: Axial T2-weighted image showing ventricular enlargement and cerebral atrophy, but only mild periventricular white matter hyperintensity. B: Sagittal T1-weighted image of the same patient shown in (A), demonstrating thinning of the corpus callosum and cerebellar atrophy. C: Axial T2-weighted image showing moderate cerebral white matter hyperintensity. D: Axial T2-weighted image demonstrating severe, diffuse cerebral white matter hyperintensity and marked ventricular enlargement. (Fig. 1C and 1D courtesy of James N. Dreisbach, MD)
or other solvents has not been proven to result from exposure to these compounds, at least at the permissible industrial levels set by the Occupational Safety and Health Administration (7). However, a single 1996 study reported subtle white matter changes on MRI scans in solvent-exposed workers (31) and raised the possibility that some workers may develop subtle, mild degrees of white matter damage (7). There is no question that the leukoencephalopathy detected by conventional MRI scanning in chronic inhalant abusers represents the severe end of the spectrum of white matter injury, and is usually detected in individuals only after many years of heavy toluene abuse. Our previous clinical and MRI studies support the idea that in the early years of even heavy toluene abuse, relatively little white matter damage can be detected by MRI scans even though it is likely that myelinotoxic injury is already occurring. In a series of toluene leukoencephalopathy patients with white matter dementia (22), the shortest duration of toluene abuse to be associated with toluene leukoencephalopathy by conventional MRI was 168 months (14 years), whereas neuropsychological evidence of impairment could appear as early as 24 months (2 years). These findings suggest that toluene leukoencephalopathy, perhaps even among those exposed to toluene in the workplace, might be detectable at earlier stages with newer advanced neuroimaging techniques that are more sensitive to microstructural leukoencephalopathy.

THE PROMISE OF ADVANCED NEUROIMAGING TECHNIQUES

Although conventional MRI allows visualization of detailed neuroanatomy, especially the cerebral white matter (7), it is not sufficiently sensitive to detect the earliest stages of white matter damage from toluene. The insensitivity of standard MRI to mild degrees of toluene leukoencephalopathy hampers early detection of individuals at risk, and it is therefore possible that a crucial opportunity for effective intervention is lost. Recent improvements in MRI technology that promise to rectify this include diffusion tensor MRI (DTI), magnetization transfer imaging (MTI), and magnetic resonance spectroscopy (MRS).

DTI is a neuroimaging technique that offers a means of imaging the microstructure of brain white matter based on the diffusion of water molecules in the brain (32). In normal white matter, water diffusion is anisotropic (directional), occurring principally parallel to axons, and the degree of anisotropy detected by DTI provides information on the structural integrity of individual tracts; in contrast, isotropic diffusion indicates structural damage (32). DTI has been used to detect microstructural lesions of white matter in stroke, leukoaraiosis, traumatic brain injury, neoplasms, and MS (33, 34), even in areas that appear to be normal on conventional MRI—the so-called "normal-appearing white matter" (NAWM; 35). MTI is based on the interaction of protons in water and macromolecules in the brain using a radiofrequency saturation pulse delivered to the head. The combination of this pulse and an imaging sequence allows the derivation of a figure known as the magnetization transfer ratio (MTR), the most commonly used MTI parameter (36). In the white matter, a low MTR indicates damage to myelin and axons from a wide variety of disorders, including MS (37) and ischemia (38). As with DTI, it is anticipated that MTI will prove useful in quantitating white matter damage in areas of NAWM. MRS provides measures of brain metabolism (39), and can be used to quantitate the chemical environment of brain tissues in the brain without the need for cerebral biopsy. The cerebral white matter can be readily studied with MRS, and abnormalities of MR spectra have already been noted in many white matter disorders such as MS (39). Of all the metabolites measured by MRS, N-acetyl aspartate (NAA) is the most important because it is widely considered to be a marker of CNS axons (39). A decrease in NAA concentration, expressed as the ratio of NAA to creatine (NAA/Cr), may thus serve as an indicator of axonal damage, an important variable in considering the potential reversibility of an insult such as toluene leukoencephalopathy.

NEUROPATHOLOGY OF CHRONIC TOLUENE ABUSE

In contrast to neurotoxic agents that disrupt neurotransmitter or receptor function and elicit no structural changes, damage to brain myelin has been well documented with chronic toluene abuse, although a surprisingly small number of autopsy cases have been reported (40–43). This may in part be due to the fact that brain damage from chronic toluene abuse is probably under-recognized by pathologists. The gross pathology of toluene leukoencephalopathy is subtle and medical examiners/coroners, particularly those who cut the brain in the fresh state and do not take tissue sections for histology unless they see an obvious lesion, may miss this diagnosis. Some early reports of presumed toluene neurotoxicity are difficult to interpret because the patients were acknowledged to abuse multiple solvents and may not have represented neurotoxicity from toluene alone. An autopsied patient with chronic lacquer-thinner intoxication reported in 1976 showed peripheral neuropathy and long tract degeneration (44). Gas chromatographic and mass spectrometric analyses of the lacquer thinner showed that it contained 43.6% xylene, 15.5% 2-Heptanone, 12.7% acetone, 12.6% isobutyl acetate, 0.5% N-hexane, and 3.9% toluene (44). A second patient with a chronic encephalopathy due to gasoline sniffing reported in 1978 demonstrated cerebellar cortical atrophy (45). The findings in the first case may well be due to damage from a combination of volatile solvents in the lacquer thinner.
(44), and the second case was attributed by the authors themselves to the toxic effects of organic lead in the gasoline (45).

In 1980, Escobar et al (40) described an autopsy case of a 27-year-old man who had abused several solvents, including glue, which also may contain n-hexane or other solvents known to cause both central and distal axonal degeneration (46, 47). At autopsy the brain showed cerebr al and cerebellar atrophy and severe thinning of the corpus callosum. Microscopically, diffuse demyelination was found, but there was also significant neuronal loss in the cerebral cortex, basal ganglia, and cerebellum, intense reactive gliosis, and giant axonal degeneration in the long tracts of the spinal cord. The demyelination was interpreted by the authors as being secondary to the neuronal loss. Peripheral nerves were also affected.

Our original autopsied case was a relatively pure chronic toluene abuser who had sniffed paint on a daily basis for many years up until the time of death (41). His autopsy findings, coupled with MRI data, were the first to confirm that the brunt of the toxic damage from toluene is directed toward the CNS white matter. Grossly, there was thinning of the corpus callosum but no discernible white matter discoloration or cavitation. Microscopically, diffuse, ill-defined myelin pallor was seen in cerebral and especially cerebellar white matter (41). In the cerebral hemispheres, periventricular white matter appeared to be most affected, with better preservation of subcortical U-fibers (41). Rare perivascular, periodic acid-Schiff (PAS)-positive macrophages stuffed with dense, coarse granular debris were noted even in areas with seemingly intact myelin, but no lymphocytic inflammation was identified. Although gliosis was not evident on the Holzer and phosphotungstic-acid-hematoxylin methods for glia available to us at the time of the report, recent reexamination of this case with immunostaining for glial fibrillary acidic protein (GFAP) demonstrated reactive gliosis even in cerebral white matter areas where myelin loss was undetectable. Because cerebral and cerebellar neurons were intact and axons were preserved in areas of myelin pallor, toluene was hypothesized to be a pure myelin toxin (41). A 1992 study of toluene concentrations in various brain regions in an autopsied case of a chronic abuser offered corroborative data that the corpus callosum was preferentially targeted and the cerebral cortex was spared, although no neuropathological features of this case were provided (42).

Subsequently, an eloquent neuropathological study of two paint sniffers appeared in 1994 in this journal (43). Case 1 was a 33-year-old man with a history of paint and glue sniffing since age 11, and Case 2 was a 41-year-old woman who had been addicted to paint sniffing for at least 9 years and died while inhaling paint fumes and drinking alcohol. The brain from both patients showed cerebral atrophy, with weights of 1,100 and 980 grams, respectively. Gross brain abnormalities were more readily detectable in Case 1, which showed thinning of the corpus callosum and gray, patchy discoloration and mottling of the cerebral white matter with sparing of the U-fibers. The cerebellar white matter, especially in the vermis, was more affected than cerebral white matter (43). Case 2 manifested only slight thinning of the corpus callosum on gross sections, but pale gray discoloration was found in the white matter of the posterior frontal, parietal and temporal lobes, as well as in the cerebellum. On light microscopy of Case 1, Luxol fast blue-periodic acid-Schiff (LFB-PAS) staining showed severe myelin loss especially around blood vessels. Unlike our original case in which no axonal loss could be detected (43), Bodian staining did reveal axonal reduction, albeit of a lesser degree than the myelin loss. Oligodendrocytes were reduced in number but there was only a mild gliotic reaction. PAS-positive macrophages (also immunoreactive with CD-68 and HAM-56) were most abundant in areas of greatest myelin loss, and identical to our original case (41), “even in tracts with well-preserved myelin, scattered PAS-positive macrophages were present” (43).

Case 2 differed from Case 1 in that PAS-positive macrophages were considerably fewer, the myelin loss significantly less, and the gliosis was several times more intense than in Case 1. The myelin loss was milder, more uniform, and the borders between severely depleted and moderately demyelinated areas were ill defined; features identical to those seen in our original case (41).

Electron microscopy on Cases 1 and 2 revealed that the macrophages containing coarse PAS-positive granules were packed with clusters of trilaminar inclusions, similar to those seen in adrenoleukodystrophy (ALD) (43). Biochemical analyses also showed increases in very long chain fatty acids in brain, further mimicking ALD. Despite these EM and biochemical similarities to ALD, Cases 1 and 2 showed several histological features distinctly different than ALD. Solvent vapor leukodystrophy demonstrated less lymphocytic inflammation, no lipid-laden macrophages in areas of myelin breakdown, and more patchy, incomplete, and ill-defined myelin loss than ALD (43). In addition, the ALD-like EM changes were confined to brain and no such inclusions were found in the adrenal cortical cells (Cases 1 and 2) or Leydig cells of the testis (Case 1).

In 1995, at the Diagnostic Slide Session of the American Association of Neuropathologists, Dr. William Hallday presented a dramatic case of a 24-year-old Native American woman with solvent vapor leukoencephalopathy (Case 2, 1995) that showed neuropathological features identical to Case 1 of Kornfeld et al (43). She was a known substance abuser and had been described as often being intoxicated and “smelling of glue.” Neither detailed neurological examinations nor neuroimaging were performed in life and she died by hanging. Despite
Fig. 2. Coronal brain sections from the autopsy case presented by Dr. William Halliday represent the severe end of the spectrum of white matter damage due to toluene abuse, but nevertheless show rather subtle, ill-defined, patchy discoloration of the white matter of the occipital lobe (A), with more obvious involvement of the cerebellar hemisphere (B). Low power view of
the severity of white matter damage in this case, autopsy brain sections demonstrated relatively subtle, patchy, ill-defined discoloration of cerebral white matter, especially in the occipital lobes (Fig. 2A), and the cerebellar white matter (Fig. 2B). The myelin loss was near-total in the cerebellum, except for relative sparing of the hilum and fleec of the dentate nucleus, findings identical to those described in Case 1 of Kornfeld et al (43) (Fig. 2C). In Dr. Halliday’s case, cerebellar sections showed excellent neuronal preservation in areas of severe myelin loss (Fig. 2D), numerous perivascular PAS-positive macrophages containing coarse and even linear debris (Fig. 2E), and trilaminar inclusions by EM (Fig. 2F). The severity of Halliday’s case and Case 1 of Kornfeld et al (43) contrasts sharply with the several-fold milder, ill-defined myelin pallor and significantly fewer numbers of PAS-positive, CD68-positive macrophages seen in our original case (and in Case 2 of Kornfeld et al; Fig. 2G). Our original case also manifested significant reactive astrogrocytosis, even in areas with ostensibly intact myelin (Fig. 2H). Indeed, the signature pathological feature, and perhaps the earliest morphological evidence of tolune leukoencephalopathy, seems to be the presence of astrocrosis and these perivascular PAS-positive macrophages containing coarse or laminar myelin debris, which can be found even in areas devoid of recognizable myelin damage (Fig. 2H).

All of the patients who were well-studied at autopsy abused toluene, but the spectrum of severity of myelin damage between them is striking and parallels the range of white matter damage in toluene abusers seen by MRI in multiple studies (22–24, 27–30). What accounts for these differences in severity of myelin damage is unknown, but several possible explanations exist. The extent of exposure has been shown to be one important determinant, as has been documented in MRI studies that show a correlation between duration of toluene abuse and the severity of the white matter abnormalities (22, 24). Concomitant use of several different chemicals of abuse could also potentiate the myelin damage from toluene, a possibility discussed by Kornfeld et al (43). Medical personnel do not regularly see many chronic toluene abusers and most abusers are notoriously poor historians, due in part to their encephalopathy. Hence, there are major obstacles to documenting the exact duration of toluene abuse, the levels of exposure, and even the coexistent abuse of other volatile or non-volatile substances. In this regard, it is noteworthy that of these four recent well-studied patients (41, 43, Case 2 1995 Diagnostic Slide Session of AANP), the two with the most severe myelin and axonal loss were both said to have a history of “paint and glue sniffing” (Case 1 of Kornfeld and colleagues, and the case of Dr. Halliday). The patient reported by Escobar et al also showed severe myelin, axon, and neuronal loss, and was acknowledged to abuse both “thinner” and “glue;” the authors acknowledged that he was therefore exposed to both toluene and n-hexane (40). N-hexane is a known axonal toxin (46, 47), and could have accounted for the axonal loss. In contrast, Case 2 of Kornfeld et al (43) and our original case (41) were both described as “paint sniffers” only and showed significantly less myelin loss.

Finally, the possibility exists that differences in severity of myelin damage may be related to host susceptibility factors. Genetic polymorphisms in drug abusers are attracting much interest and research because they may impact drug metabolism and toxicity (48). Patients with these polymorphisms may develop toxicity with a lower dose of a drug or toxin. Recent evidence has suggested that defective metabolism of toluene may occur in some individuals because of a deficient gene coding for aldehyde dehydrogenase, one of the hepatic enzymes responsible for metabolizing toluene (6, 8, 49). This deficiency could result in higher brain exposure to toluene and a heightened risk of neurotoxicity (6, 49). In addition, the degree of myelination that exists in the individual when inhalant abuse begins may play a role in host susceptibility to tolune leukoencephalopathy. It is well known that brain myelination is an ongoing process that continues at least through the second decade (26), and because inhalant abuse typically begins in the early teen or even pre-teen years (1), most toluene abusers encounter this white matter toxin at a time when their myelin is still forming and may be most vulnerable to its toxic effects. The idea that toluene may be most damaging when myelin is being formed is corroborated by animal studies.
demonstrating that rats show a permanent reduction in forebrain myelination after prenatal toluene exposure (50).

PATHOPHYSIOLOGY OF TOLUENE BRAIN DAMAGE

The mechanism of brain white matter injury from toluene is unknown. As mentioned, this solvent, like many others, is highly lipophilic (1), and in laboratory animals toluene is preferentially distributed in lipid-rich regions of the brain (51). These observations support the notion that myelin, which contains 70% lipid, is targeted for damage. In an autopsy study of a patient who inhaled toluene prior to death, tissue concentrations were minimal in the cerebral cortex and hippocampus and were highest in the corpus callosum, the largest white matter tract in the brain (42). MRI also reveals a predilection for damage to the corpus callosum (Fig. 1B). The pathogenic action of toluene after localizing in white matter, however, is uncertain. A contribution by free radical-induced lipid peroxidation has been suggested by observations that reactive oxygen species are generated in the CNS by toluene (52) or possibly benzaldehyde, one of its metabolites (53).

Since autopsy studies show relatively specific damage to myelin with axonal sparing (41, 43), the brain damage induced by toluene may come to be understood as potentially reversible with abstinence, or even amenable to future treatments designed to restore the myelin using the existing scaffolding of preserved axons. Although no data exist on long-term outcome in toluene abusers who abstain from inhalant abuse, our experience suggests that individuals may show partial recovery once the toxic effect of toluene is no longer present (21).

EXPERIMENTAL ADULT ANIMAL MODELS OF CHRONIC TOLUENE ABUSE

Complementary to the human clinical data, several animal studies have verified that toluene targets the central, not peripheral, nervous system. Beyond this generalization, however, animal studies have not been particularly helpful in elucidating the specific mechanisms of myelin damage noted in humans. Two different studies in rats exposed to toluene by inhalation or by oral dosing showed that toluene concentrations were highest in brain-stem areas (medulla, pons) with high lipid content (42, 51), and lowest in the cerebral cortex and hippocampus, where less myelin is found (42), underscoring the lipophilic distribution of toluene (1). Other animal studies have raised the possibility that the hippocampus may be damaged by toluene, although the data are inconclusive and this area has not yet been shown to be preferentially affected in humans. Mattia et al reported that, following gavage treatment of rats with toluene, the highest level of induced reactive oxygen species was in the hippocampus; however, they confined their studies to investigating crude synaptosomal fractions from only three sites: the cerebellum, hippocampus, and striatum (52). Similarly, using rats with inhalation exposure to toluene, Korbo et al found neuronal loss in the hippocampus but only studied this single neuroanatomic site (54). More recent studies have also reported Purkinje cell loss and hippocampal neuronal loss in rats with inhalation exposure (55). In contrast, Ikehchi and Hirai investigated the effects of toluene on guinea pig hippocampal slices and found inhibition of synaptic transmission but no morphological abnormalities (56).

Other investigators have focused more on alterations in astrocytes than on neuronal populations (57, 58). Toluene exposure has been reported to disrupt differentiation of astrocyte precursor cells (57) and decrease astrocytic membrane-bound ATPase enzymatic activity in cultured cells in a dose-dependent fashion (58). In rat brain, toluene inhalation appears to activate astrocytes, with enhancement of GFAP immunoreactivity (59). Toluene inhalation in rats also causes the induction of basic fibroblastic growth factor, glial cell-line derived neurotrophic factor, transforming growth factor beta 1, and tumor necrosis factor-alpha (55, 59). Despite these changes in astrocytic function, little has been described in the way of white matter changes in these models, save for the study by Gotohda et al that mentions “thinning” of the cerebellar white matter in toluene-exposed rats (55). The experimental findings of astrocytic activation in animal models are, however, of great interest in light of the considerable reactive astrocytosis that has been demonstrated in several human cases of toluene abuse, even in areas with seemingly intact myelin (Fig. 2H). We would therefore concur with the comment of Gotohda et al that “astrocytes may play a role in the neurophysiological changes observed in toluene intoxication” (59).

TOLUENE AS A TERATOGEN; THE FETAL SOLVENT SYNDROME

The focus of this review has been on adolescents and adults who have practiced chronic toluene abuse, with some attention to industrial workers who experience much less occupational exposure. However, the effects of toluene on the fetuses of chronically abusing mothers also deserve mention. The first report of the fetal solvent syndrome in 1979 (60) described facial dysmorphia, growth retardation, and microcephaly similar to the fetal alcohol syndrome (60, 61). Craniofacial features of the fetal solvent syndrome include micrognathia, low set ears, flat nasal bridge, abnormal scalp hair patterning, down-turned corners of the mouth, and a large anterior fontanelle (62–65). Hearing loss and cleft palate may also be seen (66). As children grow, they may show developmental delay, hyperactivity, and cerebellar dysfunction (63, 64). A recent study showed that 16.1% of infants born to chronic
abuse mothers had major anomalies, 12.5% had fetal alcohol-like facial features, and 3.6% had cleft palate (66). Good animal models of toluene abuse embryopathy have been developed (50, 67).

SUMMARY

Toluene, a common organic solvent that for some individuals is a substance of abuse, has been recognized as a neurotoxin that damages cerebral white matter. As the primary solvent in spray paints, thinners, lacquers, and glues, toluene is inhaled for its capacity to cause euphoria. Toluene abusers with long-term, intense exposure are at risk for toluene leukoencephalopathy, a syndrome characterized by dementia, cerebellar ataxia, corticospinal tract dysfunction, brainstem signs, and cranial neuropathies. Dementia is the most disabling clinical feature, with a characteristic pattern of deficits consisting of inattention, apathy, memory dysfunction, visuospatial impairment, and preserved language, but more subtle neurobehavioral impairment often can be detected early in the disorder before dementia develops. MRI demonstrates cerebral and cerebellar atrophy, and the severity of cognitive dysfunction correlates with the degree of cerebral white matter hyperintensity on T2-weighted images. Toluene leukoencephalopathy has become a prototypical example of white matter dementia, and, more generally, underscores the importance of cerebral white matter in neurobehavioral function. Neuropathological examination shows cerebral and especially cerebellar myelin loss, perivascular macrophages stuffed with coarse or linear PAS-positive debris, and trilaminar inclusions by EM. Extent of myelin and axonal loss in patients is highly variable, possibly due to extent of exposure, age of onset of toluene abuse, coexistent abuse of other substances, or polymorphisms in the gene encoding the enzyme aldehyde dehydrogenase. Although toluene leukoencephalopathy is well documented in inhalant abusers, the potential for low-level occupational or household toluene exposure to cause brain damage is uncertain. Long term exposure to low levels of toluene has been speculated to cause neurobehavioral dysfunction, but the threshold of exposure above which leukoencephalopathy occurs is debated. Toluene abuse in pregnancy causes a constellation of teratogenic features known as fetal solvent syndrome, which is similar to the fetal alcohol syndrome. Advanced neuroimaging techniques such as diffusion tensor imaging, magnetization transfer imaging, and magnetic resonance spectroscopy promise to improve the early recognition of leukoencephalopathy in individuals exposed to toluene when the potential for reversibility is maximal. Animal studies suggest that astrocytes are activated by toluene, paralleling the reactive gliosis seen in human cases with lesser degrees of myelin damage. Despite these animal studies, however, many questions regarding the specific effects of toluene on myelin and other cellular components of the CNS remain to be answered.

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This paper is dedicated to the memory of our former colleague and friend, Neil L. Rosenberg, MD, who met an untimely death in April 2003 in Peru. Neil made major contributions to the field of neurotoxicology, particularly toluene abuse, and will be greatly missed.

REFERENCES
