

## Carbon Disulfide

The September 1998 issue of *EHP* contained two articles about the neurotoxicity of carbon disulfide. The "NIEHS News" article (1) reported on a collaborative study that involved scientists from the NIEHS (Research Triangle Park, NC), the U.S. Environmental Protection Agency (Research Triangle Park, NC), the University of North Carolina (Chapel Hill, NC), Duke University (Durham, NC), and Vanderbilt University (Nashville, TN). In this study, the neurotoxicity of carbon disulfide was detailed from the earliest molecular alterations to neurobehavioral findings to electrophysiologic and morphologic changes, and the utility of intramolecular cross-linking in hemoglobin as a biomarker was defined. I was pleased to read this report, and even more pleased to have participated in this study, but I was distressed to see the cover story in the same issue.

"Multiple System Atrophy Following Chronic Carbon Disulfide Exposure" (2), in the "Grand Rounds in Environmental Medicine," is a case report of an individual who developed a degenerative nervous system disease, olivopontocerebellar atrophy, and who had been chronically exposed to carbon disulfide while working for 34 years in a viscose rayon plant in the United States. Frumkin (2) concluded, "While this association has not previously been reported, it is clinically and pathologically consistent with a range of movement disorders seen in the setting of occupational carbon disulfide exposure."

Frumkin never saw this patient, nor was he consulted by the patient's physicians during the course of this disease; he only reviewed the medical records and diagnostic studies as an expert witness for the plaintiff in a case that failed to convince a Texas jury that a cause-and-effect relationship existed between carbon disulfide exposure and this man's disease (3). I also reviewed this material and concluded that such a relationship was not even remotely plausible; indeed, I thought that there were excellent reasons to conclude that his disease bore no relationship to the exposure. Thus, the publication of this paper raises several concerns: Why did Frumkin feel authorized to publish this report, and were the editors informed about his relationship to this case? Was the paper reviewed by experts in neurotoxicology, clinical neurology, and neuropathology? Will readers conclude that carbon disulfide causes multisystem atrophy? How many more lawsuits will be filed alleging that since B followed A, A caused B, and how many more physicians will reach this vacuous conclusion?

The individual described in this paper (2) had classical olivopontocerebellar atrophy, beginning with cerebellar ataxia and progressing over years to involve long tracks and cranial nerve nuclei in the pons. Neither the cerebellum nor the pontine nuclei are affected in carbon disulfide toxicity. However, Frumkin pointed out that olivopontocerebellar atrophy is part of a spectrum of diseases termed multisystem atrophy, which also includes striatonigral degeneration, a disease characterized by clinical parkinsonism. Although extrapyramidal involvement in carbon disulfide toxicity has been alleged in the clinical literature (4-11), the only experimental studies reporting lesions in the extrapyramidal system were published over 50 years ago and involved uncontrolled exposures to carbon disulfide that resulted in repeated apneic episodes and confounding hypoxia (12-14). Extrapyramidal lesions have never been observed in modern experimental studies, nor did the patient in Frumkin's report (2) manifest extrapyramidal signs. On the other hand, the most sensitive structure in the nervous system to carbon disulfide-induced damage is the axon, and this patient never developed evidence for an axonopathy at any time during his career or during his terminal illness. Thus Frumkin's statement that the patient's course of illness was clinically and pathologically consistent with carbon disulfide toxicity has no basis in fact.

Although it certainly was impressive to see an MRI scan on the cover of *EHP*, this paper is not based in either strong science or competent clinical medicine. We depend upon physicians who practice occupational and environmental medicine to apply the science of toxicology to the evaluation and treatment of patients who have been exposed to toxicants. When the exposure involves an agent whose toxicity has never been suspected, case reports have value in alerting physicians and the public to possible dangers. Considerable caution must be exercised, however, in assigning cause-and-effect relationships between toxicants and disease, especially when the agent in question has been in use for many decades, has been studied extensively, and has been subjected to strict regulatory standards.

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## Carbon Disulfide: Frumkin's Response

Graham offers four discrete arguments against an association between carbon disulfide and olivopontocerebellar atrophy. First, he holds that olivopontocerebellar atrophy is clinically incompatible with carbon disulfide toxicity because carbon disulfide toxicity does not affect the cerebellum or pontine nuclei. Second, he asserts that the experimental studies showing extrapyramidal involvement in carbon disulfide toxicity relied on high-dose exposures at levels sufficient to cause apnea. Third, he is concerned that this experimental literature is over 50 years old. Fourth, he argues that the axon is more sensitive to carbon disulfide toxicity than are other parts of the nervous system, suggesting that the absence of axonopathy rules out carbon disulfide toxicity. Graham presents these arguments as ex cathedra pronouncements and cites no basis for any of them. In fact, each is contradicted by available evidence.

With regard to cerebellar involvement in carbon disulfide toxicity, Graham is factually incorrect. Autopsy studies in humans with carbon disulfide toxicity are regrettably rare, but at least two have shown clear evidence of cerebellar involvement (1,2). The animal toxicology is far more extensive and has been reviewed in detail (3-5); numerous reports show cerebellar involvement in diverse species including rats (6), rabbits (7), dogs (8), and cats (9). In fact, carbon

disulfide can have quite widespread effects in the central nervous system, leading the World Health Organization (10) to conclude that

Psychic, pyramidal and extrapyramidal symptomatology, including signs from other parts of the brain (vestibular, cerebellar) give a picture compatible with diffuse effects.

Graham's flat declaration that carbon disulfide spares the cerebellum contradicts decades of accumulated evidence.

With regard to the doses used in experimental studies of carbon disulfide toxicity, Graham is again factually incorrect. He first expressed his curious view in a previous publication (11), citing two studies for support. One of these studies was a primate study in which chronic exposure was punctuated by accidental high-dose exposures causing unconsciousness (but not apnea) (12). In that study, all of the affected monkeys recovered promptly from their acute intoxications and resumed a steady downhill course that continued for months. The cerebellar damage later found in all four monkeys on autopsy was therefore more likely to have resulted from chronic exposure than from acute anoxia. The second study used dogs to test the effects of chronic carbon disulfide exposures (8). Although Lewey et al. (8) did report an increase in acute symptoms such as drowsiness and gait abnormalities immediately after the dogs were removed from test chambers, they did not mention unconsciousness, apnea, or other signs of severe acute toxicity following any exposures. Severe changes in the cortex and basal ganglia, and less severe changes in the cerebellum, were observed in the dogs on autopsy (13). In many other animal studies showing cerebellar damage from carbon disulfide including, for example, the ones cited above (6,7,9), exposures were chronic and at levels too low to cause acute toxicity. Thus, Graham's belief that cerebellar damage in animals resulted from acute toxicity with anoxia is flatly contradicted by the data, including the data he cited to support his belief.

With regard to the age of the experimental literature showing extrapyramidal effects of carbon disulfide, Graham's reasoning is unsound. Unlike milk, knees, and cars, scientific observations do not go bad with time. Data of any vintage are overturned only if they are disproven by later studies using the same methods, or if the methods they used are later shown to be invalid. Neither is true of the pathologic studies discussed here.

With regard to the relative sensitivity of axons to carbon disulfide toxicity, Graham is partially correct. Peripheral nerves are certainly a primary target of car-

bon disulfide [and Graham has made important contributions to our understanding of this axonopathy (11,14)]. However, both human and animal observations demonstrate that central nervous system manifestations may occur independent of the peripheral manifestations, and may even occur in the absence of peripheral neuropathy. For example, in Lewey's large series of 120 viscose rayon workers (15), 76% of subjects had peripheral nerve dysfunction and 21% had pyramidal and extrapyramidal signs; the two findings were statistically unassociated with each other, suggesting that they occurred through distinct mechanisms. In a more recent series of 21 grain handlers with carbon disulfide exposure, 18 had cogwheel rigidity and/or akinesia, whereas only 13 had sensory loss and 7 had nerve conduction velocity and electromyography abnormalities (16). In one of the published human autopsies, there were relatively severe abnormalities in the cortex, cerebral vasculature, basal ganglia, cerebellum, thalamus, pyramidal tracts, and anterior columns, but only slight changes in the peripheral nerves (2). Thus, Graham is correct that peripheral nerve damage is common in carbon disulfide toxicity, but he seems to have gone further—insisting that axonopathy is the only lesion, and the sine qua non, of carbon disulfide toxicity. The evidence clearly shows otherwise.

Having said all this, I must admit that it is difficult to muster too much passion in defense of a case report. A case report is, after all, only a case report. The most definitive evidence of exposure–disease associations comes from well-designed epidemiologic studies supported by appropriate laboratory data. Based on his earlier comments (17), I suspect Graham and I would agree that such evidence would add much to our understanding.

Finally, with regard to medicolegal issues, Graham is partially correct. After reviewing the case, forming an impression, and writing the case report, I did testify in the trial brought by the patient and his survivors (18). The jury's conclusions have little relevance to Graham's scientific concerns or my response, but because he raised the issue, I would like to provide clarification. The jury indeed found for the defendant, not because the jury members rejected a link between carbon disulfide and disease, but because they accepted the "sophisticated employer defense." The jury held that the defendant, an outside firm that produced and supplied carbon disulfide to the patient's employer, could not be held liable for exposures that occurred on the employer's premises, when the employer should

have known enough to handle the carbon disulfide safely.

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*Editor's note: The preceding letters of Graham and Frumkin are an inevitable but not unwelcome development for "Grand Rounds in Environmental Medicine." These letters reflect the nuances surrounding issues of causation that often accompany real cases in this area. They also highlight the tension that can develop among experts when these cases enter the arena of litigation. This is not an uncommon occurrence in clinical environmental medicine. Although providing opinions and otherwise being involved in litigation may*

*provoke distaste in some medical practitioners, it nevertheless comprises an important duty; interested parties and courts need expert, well-informed opinions as a basis for settling disputes. In the second year of "Grand Rounds in Environmental Medicine," we once again express our interest in receiving submissions that are educational, well written, and capable of withstanding rigorous peer review.*

*Howard Hu  
Medical Editor*

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#### CORRECTIONS AND CLARIFICATIONS

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In "Concentration of Organochlorines in Human Brain, Liver, and Adipose Tissue Autopsy Samples from Greenland" [*EHP* 107:823–828 (1999)], the chemical name of *p,p'*-DDT is incorrect. The correct chemical name of *p,p'*-DDT is 2,2'-bis(4-chlorophenyl)-1,1,1-trichloroethane.

In the January NIEHS News article "Working for Women's Health" [*EHP* 108:A18–A19 (2000)], Roger Wiseman was incorrectly identified as a senior staff fellow. Wiseman is actually a senior investigator. *EHP* regrets the error.