

Carbon Disulfide Vasculopathy: A Small Vessel Disease

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Key Words

Carbon disulfide · Vasculopathy · Encephalopathy ·
Neurotoxic disease · Risk factor

Abstract

We present the clinical manifestations of 4 male patients with acute stroke-like symptoms and polyneuropathy after long-term exposure to carbon disulfide (CS₂) in a viscose rayon plant. The ages of onset of polyneuropathy ranged from 42 to 45 years with a duration of CS₂ exposure between 6 and 21 years. The ages of onset of stroke were from 42 to 48 years. The risk factors for stroke including heart disease and diabetes were denied, except for smoking in 4, hyperlipidemia in 2 and hypertension in 1. At the initial visit in 1992, only 2 patients developed sudden onset of hemiparesis suggesting a lacunar stroke before the diagnosis of CS₂ intoxication. Brain computed tomography (CT) scans showed low-density lesions in the basal ganglia in 2 patients, cortical atrophy in 1 and normal in 1. Brain magnetic resonance image (MRI) study disclosed multiple lesions in the corona radiata and basal ganglia on T₂-weighted images in 3 patients and cortical atrophy in 1. After the diagnosis, they left their jobs for a CS₂-free environment, and improvement of the working conditions was noted. During 5 years follow-up period, another 2 patients also developed an acute episode of stroke with hemiparesis.

Brain CT and/or MRI follow-up studies in these 2 patients revealed new lesions in the basal ganglia and corona radiata. Intriguingly, a patient with previous stroke also developed new lesions in the bilateral thalami and brainstem. Carotid Doppler scan, transcranial Doppler scan and/or cerebral angiography did not show any prominent stenosis or occlusion in the major intracranial large arteries. We conclude that encephalopathy may occur in patients after long-term CS₂ exposure, probably due to impaired cerebral perfusion. The lesions tend to occur in the basal ganglia, corona radiata and even brainstem, particularly involving the small-sized vessels. In addition, the cerebral lesions may progress even after cessation of CS₂ exposure. Therefore, we suggest that CS₂ exposure may be a risk factor for stroke.

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Introduction

Chronic long-term, low-dose exposure to carbon disulfide (CS₂) may cause encephalopathy, including parkinsonian features, pyramidal tract symptoms and psychiatric symptoms in addition to polyneuropathy [1–6]. The pathogenic mechanism of the encephalopathy remains obscure. Recently, an increased incidence of mortality, hyperlipidemia, retinopathy with microaneurysm and dots hemorrhage and coronary artery disease was noted

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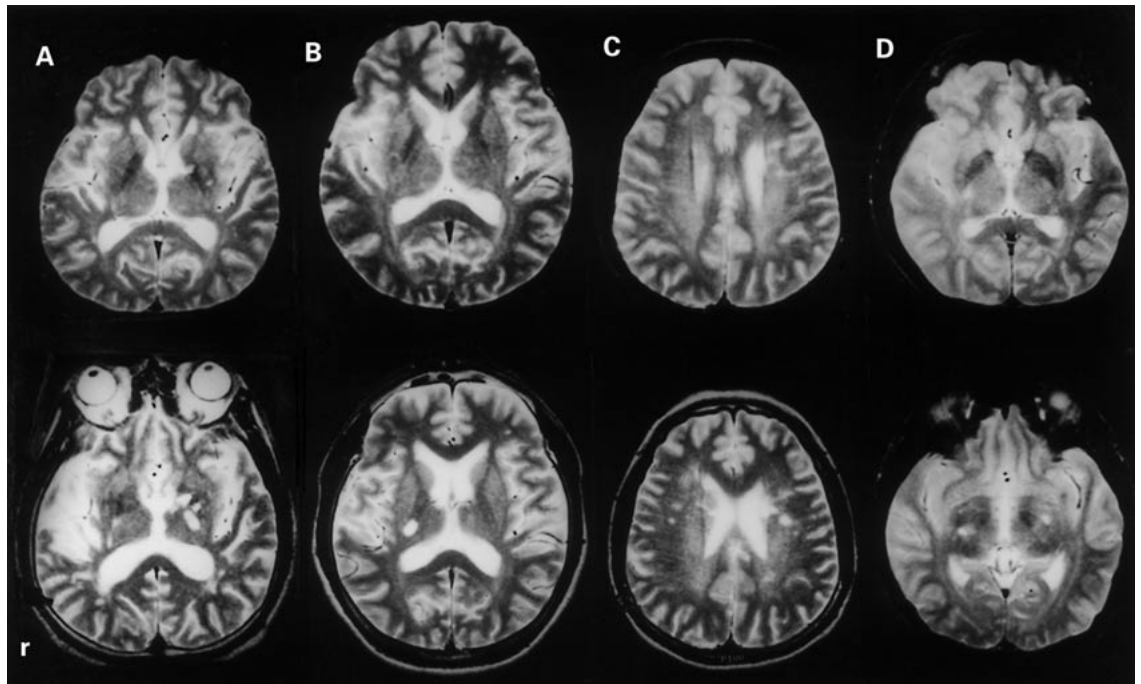


Fig. 1. Serial brain MRI scans revealed multiple increased signal intensities in the basal ganglia on T₂W in 1992 (**A**, upper row) and some new lesions in the left basal ganglia (**A**, lower row) in 1995 in patients 1; nearly normal in 1992 (**B**, upper row) and a new lesion over the internal capsule (**B**, lower row) in 1998 in patient 2; multiple lesions over the left corona radiata in 1992 (**C**, upper row) and a deterioration of the brain lesions in 1995 (**C**, lower row) in patient 3; low signal intensity over the right internal capsule in 1992 (**D**, upper row) and multiple lesions in bilateral basal ganglia in 1996 (**D**, lower row) in patient 4. TE = 90; TR = 3,366.

after long-term CS₂ exposure [7–13]. Some researchers have proposed vasculopathy in experimental studies [1]. However, irrefutable evidence of vascular encephalopathy has not been provided in humans. In addition, neuro-radiological studies on CS₂ encephalopathy have not been well documented [14–18]. Furthermore, a follow-up study in patients with chronic CS₂ encephalopathy has not been reported.

Recently, we encountered 10 patients who developed polyneuropathy after long-term exposure to CS₂ [19, 20]. Some also had chronic encephalopathy with abnormal computed tomography (CT) and magnetic resonance image (MRI) studies in the initial evaluation [21]. During the follow-up period, another 2 patients also developed an acute-onset stroke-like episode with hemiparesis and slurred speech. We report the clinical progression and neuroimage studies in these 4 patients after cessation of exposure to CS₂. The mechanisms of CS₂ encephalopathy are discussed.

Case Reports

Patient 1

A 42-year-old man was a spinner at a viscose rayon plant for 6 years and exposed to a higher concentration (about 50–300 ppm) of CS₂. In 1991, he developed intermittent headache, dizziness, impotency, numbness and weakness of both legs and clumsiness of both hands. History of hypertension, diabetes or alcoholism was denied except for occasional smoking. His past and family histories were unremarkable. On examination in 1992, he was mentally clear with a Mini-Mental State score of 30 (total score: 30). The blood pressure was 128/86 mm Hg and the peripheral pulse was regular with 84 per minute. Decreased muscle power, absent tendon reflexes and decreased sensory function in all distal limbs as a glove and stocking-like pattern were noted, suggesting a polyneuropathy. There were neither strokes, extrapyramidal symptoms nor cerebellar signs.

Laboratory tests revealed normal concentrations of cholesterol, triglyceride and uric acid. The NCV study showed an axonal and demyelinating polyneuropathy. The somatosensory evoked potentials (SSEP) also exhibited a peripheral conduction defect. The initial brain CT scan showed a low density lesion at the left internal capsule. Brain MRI revealed multiple lesions at the left basal ganglion and bilateral corona radiata with decreased signal intensities on T₁-weighted images (T₁W) and increased signal intensities on T₂-weighted images (T₂W) and proton-weighted images (PW; fig. 1A).

The carotid Doppler scan disclosed only a minimal plaque at the right subclavian artery. The flow velocities and volumes were normal in the extracranial carotid and vertebral arteries.

He was forced to move to a CS₂-free environment, and an improvement of the working conditions with a CS₂ concentration less than 10 ppm was noted. In July of 1995, he had a sudden onset of right limb weakness and slurred speech. On evaluation, he had dysarthria, dysphagia and right hemiplegia, hemiparesis, and central type of facial palsy. Increased tendon reflexes and presence of Babinski sign were noted on the right limbs. A follow-up CT scan revealed multiple lacunar infarcts at the bilateral basal ganglia. The follow-up brain MRI scan disclosed new lesions in the bilateral basal ganglia, particularly on the left side in addition to the previous lesions (fig. 1A). Repeated carotid Doppler scan showed only minimal atherosclerosis at bilateral common carotid arteries (CCAs) and normal flow volume and flow velocities in all major extracranial and intracranial vessels. The cerebral angiography from bilateral common carotid and left vertebral artery injection failed to show any evidence of atherosclerosis in the large intracranial vessels. The serial electrocardiograms were normal. Follow-up biochemistries showed neither hyperlipidemia nor hyperuricemia except for a mild elevation of blood sugar (183 mg%) in acute stage. The blood sugar returned to normal 1 week later, and his condition was steadily improved after a conservative treatment with aspirin 100 mg daily. However, right hemiparesis and dysarthria were still noted recently.

Patient 2

A 42-year-old man working in the same viscose rayon plant for 13 years developed distal limb numbness and weakness since 1992. Generalized absence of tendon reflexes was also noted. Clinically, polyneuropathy was noted. In addition, he also developed sleep disturbance, memory impairment and emotional lability. There were neither hypertension, diabetes nor other major diseases. The blood pressure was 135/70 mm Hg, and the electrocardiogram was normal. However, he had a history of smoking with 1/2 pack per day for 20 years. The NCV study revealed a mild axonal neuropathy over bilateral peroneal and tibial nerves. Brain MRI scan showed mild cortical atrophy. Carotid Doppler scans disclosed normal bilateral CCAs. In September 1998, sudden onset of left limb weakness and slurred speech were experienced. The blood pressure was 120/60 mm Hg, and the pulse rate was 80/min. Neurological examination revealed central-type facial palsy and hemiparesis over the left side, but no sensory impairment. Tendon reflexes were increased on the left limbs and plantar reflex was dorsiflexed. Laboratory examinations showed mild elevation of hemoglobin (Hb: 17.1 g%) and mild hyperlipidemia with cholesterol 187 mg/dl (ref: < 200 mg/dl) and triglyceride 257 mg/dl (ref: 30–150 mg/dl). A repeated brain MRI scan demonstrated some lesions with hyposignal intensity on T₁W and hyper-signal intensity on T₂W over the right internal capsule and bilateral corona radiata, in addition to prominent sulci (fig. 1B). Carotid Doppler scan revealed mild atheromatous lesions in the right subclavian artery (ScA). Recently, he still had spastic gait with left hemiparesis after a conservative treatment.

Patient 3

A 51-year-old man developed generalized weakness since June 1992 after working in a viscose rayon plant for 21 years. He had noted occasional hypertension for about 4 years, but without regular treatment. There were no heart disease, diabetes or alcoholic history except for smoking, 1 pack per day for 20 years. In June 1992, he

developed right limb weakness, dizziness and drowsiness. The symptoms persisted for 3 days and he then recovered. He also complained of distal numbness over all 4 limbs for several months. When he was admitted to our hospital, blood pressure was 150/110 mm Hg, electrocardiogram and chest X-ray were normal, and hemoglobin 17.2 g%, hematocrit 51.5%, red cell count $5.71 \times 10^6/m^3$, cholesterol 286 mg/dl and triglyceride 229 mg/dl were noted. Neurological examination showed mild right hemiparesis and increased tendon reflexes on the right limbs. Brain CT was normal, but brain MRI showed multiple lesions over the left corona radiata and bilateral internal capsules (fig. 1C). Carotid Doppler scan was normal.

He retired from the plant thereafter. A follow-up brain MRI 3 years later demonstrated multiple lesions over the pons, bilateral thalami, bilateral basal ganglia and bilateral corona radiata, indicating a progression of the brain lesions (fig. 1C). Carotid Doppler scan showed mild wall thickening over the bilateral common carotid arteries with a normal flow volume in bilateral CCAs.

Patient 4

A 52-year-old man developed sudden onset of left limb weakness associated with dizziness since February 1992 after working in a viscose rayon plant for 17 years. He also had frequent headache, insomnia, general fatigue and increased tendon reflexes over the left limbs. There was neither hypertension, diabetes nor alcoholism except for occasional smoking. The electrocardiogram was normal with a regular heart rate of 82/min, and the blood pressure was 110/70 mm Hg. The laboratory tests showed that cholesterol was 196 mg/dl, triglyceride 79 mg/dl, blood sugar 89 mg/dl and uric acid 5.4 mg/dl. Brain CT scan disclosed hypodense lesions in the posterior limb of the right internal capsule. Brain MRI scan also confirmed a low signal intensity on T₁W and high signal intensity on T₂W and PW over the right internal capsule (fig. 1D). The carotid Doppler scan revealed small plaque lesions in the right CCA, especially at the bifurcation and right ScA. A follow-up study in 1995 revealed that serum cholesterol was 197 mg/dl, triglyceride 77 mg/dl, glucose 88 mg/dl, uric acid 5.9 mg/dl, and the pattern of HDL-cholesterol electrophoresis was normal. The repeated CT study was performed in 1995 and still showed a small infarction over the left internal capsule. The brain MRI scan in 1996 also confirmed multiple lesions in bilateral basal ganglia (fig. 1D). A follow-up carotid Doppler scan revealed mild atheromatous lesions in bilateral CCAs with normal flow velocity. The clinical manifestations of these 4 patients with stroke-like episodes after CS₂ exposure are summarized in table 1. Table 2 shows the findings of series brain CT, MRI and carotid Doppler scans.

Discussion

The present data indicate that 4 victims working in the same viscose rayon plant developed acute stroke-like episodes after a long-term exposure to CS₂. All the 4 patients were still relatively young while they developed a stroke. Two developed a stroke before they were diagnosed to have CS₂ polyneuropathy. The other 2 patients developed a stroke-like episode 2 years and 6 years, respectively, after diagnosis. Intriguingly, the latter 2 patients had CNS lesions confirmed by MRI scans before the stroke.

Table 1. Clinical summary of 4 patients with stroke-like episodes after CS2 exposure

Patient	1	2	3	4
Current age, years/sex	50/M	50/M	51/M	52/M
Age at onset of polyneuropathy, years	42	43	42	45
Age at onset of stroke, years	45	48	42	45
Duration of exposure, years	6	13	21	17
Heart disease	-	-	-	-
Diabetes	-	-	-	-
Hypertension	-	-	+	-
Smoking	+	+	+	+
Alcoholism	-	-	-	-
Symptoms				
Headache/dizziness	+	-	+	+
Loss of libido	+	-	-	-
Sleep disorder	-	+	+	+
Memory impairment	-	+	+	-
Fatigue	+	-	+	+
Emotional lability	-	+	+	-
Parkinsonism	-	-	-	-
Slurred speech	+	+	-	-
Hemiparesis	+ (R)	+ (L)	+ (R)	+ (L)
Hemiparesthesia	+ (R)	-	-	-
Spastic gait	+	+	-	-
Polyneuropathy	+	+	+	+

M = Male; + = present; - = absent; R = right; L = left.

Table 2. Serial laboratory findings in 4 patients with stroke-like episodes after CS2 exposure

Patient		1	2	3	4
Cholesterol	1st	180	200	286 ¹	196
	2nd	161	187	146	197
Triglyceride (ref: 30–150 mg/dl)	1st	112	148	229 ¹	79
	2nd	100	257 ¹	110	77
Blood sugar (ref: 70–110 mg/dl)	1st	NA	92	100	89
	2nd	183 ¹	78	87	88
Uric acid (ref: 2.5–8.0 mg/dl)	1st	6.0	6.0	7.6	5.4
	2nd	6.5	6.3	7.5	5.9
Brain CT scan	1st	IC (L)	NA	Normal	BG (R)
	2nd	BG (bil)	NA	NA	NA
Brain MRI scan	1st	IC (L) CR (bil)	Mild cortical atrophy, hydrocephalus	BG (bil), CR (L)	IC (R)
	2nd	BG (bil), CR (bil)	IC (R), CR (bil), cortical atrophy	Pons, thalami (bil), BG (bil), CR (bil)	BG (bil)
Carotid Doppler	1st	Small plaque in ScA (R)	Normal	Normal	Small plaques in ScA (R), CCA (R)
	2nd	Minimal atherosclerosis in CCA (bil)	Mild atheromatous lesion in ScA (R)	Mild wall thickening in CCA (bil)	Atheromatous lesions in CCA (bil)
Angiography		Normal	NA	NA	NA

L = Left; R = right; bil = bilateral; IC = internal capsule; BG = basal ganglion; CR = corona radiata; NA = not available.

¹ Abnormal.

There was no obvious risk factors for stroke, including heart diseases and diabetes, except for smoking in these 4 cases, hyperlipidemia in 2 and hypertension in 1.

In the past years, several studies have reported that exposure to high concentrations of CS₂ may cause headache, convulsion, delirium and even coma [1–3]. Chronic exposure to concentrations of 100 mg/m³ can cause fatigue, headache, sleep disturbance and sexual impotence [1–6]. It is believed that vascular encephalopathy may develop after a long-term exposure to low concentration of CS₂ due to arteriosclerotic changes [8]. Experimental studies also revealed cerebral arteriosclerosis after exposure to CS₂ [1]. In viscose rayon workers, chronic encephalopathy with mental retardation, pseudobulbar palsy, extrapyramidal features and long tract signs was found in some autopsy studies [2]. In recent studies, diffuse or focal brain atrophy was seen on CT scan [6, 18]. MRI abnormality was reported by Peters et al. [6] in 2 out of 4 patients. They suggested that the MRI lesions were caused by central demyelination. However, the clinical pictures, MRI and angiographic findings were not shown. In our patients, brain CT and MRI scans showed multiple lesions in the basal ganglia, corona radiata and even brainstem. Moreover, our patients developed stroke episodes clinically before or after the diagnosis of CS₂ encephalopathy, even after they had been removed from the high CS₂ environment. The data indicate that stroke episodes may occur even after cessation of CS₂ exposure, although central demyelination may also coexist.

In a Doppler ultrasound study, slight stenosis (<50%) was found in only 1 of 15 workers [16]. In our cases, carotid Doppler scan confirmed only a slight stenosis or even a patency of the carotid artery and normal hemodynamics. Furthermore, cerebral angiography revealed no significant stenosis in the extra- and intracranial major vessels in our patient. The data indicate that cerebral hypoperfusion is not due to hemodynamic changes in the large vessels. To our knowledge, cerebral angiography has not been reported previously. Our report demonstrated that CS₂ exposure may induce stroke-like episodes clinically or subclinically. From the above data, we speculate that the CT and MRI lesions may be attributed to the involvement of the intracranial small-sized vessels compatible with the previous autopsy findings [2].

The vascular toxicity of CS₂ has been studied on coronary artery disease and retinopathy. There is an increased incidence of coronary artery diseases in humans [7–13]. Although a few studies have reported that CS₂ may induce cerebral damages through vascular damages, the evidence is not sufficient. The mechanisms in the devel-

opment of vasculopathy remain unclear, although some hypotheses have been proposed including changes in lipid metabolism, changes in fibrinolytic activity, advanced lipid infiltration, acceleration of atherosclerosis and sub-clinical hypothyroidism [8]. In some recent studies, proteins of tissues, particularly long-lived proteins, such as the subunits of the neurofilament may be derivatized and cross-linked after exposure to CS₂ [22–24]. Another significant target may be low-density lipoprotein (LDL). The cross-linking of the protein moiety of low-density lipoprotein apolipoprotein B may alter the uptake of macrophages, which lead to the formation of foam cells, the initial lesion in the pathogenesis of atherosclerosis [25].

In conclusion, diffuse encephalopathy probably due to small-vessel ischemia may occur in patients after long-term exposure to CS₂. Furthermore, the CNS lesions may progress even after cessation of further CS₂ exposure. A recent brief screen for vascular events of the brain was carried out in 163 viscose rayon workers of the plant and revealed 7 workers had developed stroke-like episodes during the follow-up period. A further long-term detailed follow-up study is warranted to elucidate the problems.

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References

- 1 Lewey FH: Neurological, medical and biochemical signs and symptoms indicating chronic industrial carbon disulfide absorption. *Ann Intern Med* 1941;15:869–883.
- 2 Vigliani EC: Carbon disulfide poisoning in viscose rayon factories. *Br J Ind Med* 1954;11:235–244.
- 3 Hanninen H: Psychological picture of manifest and latent carbon disulfide poisoning. *Br J Ind Med* 1971;28:374–381.
- 4 Peters HA, Levine RL, Matthews CG, Sauter SL, Rankin JH: Carbon disulfide-induced neuropsychiatric changes in grain storage workers. *Am J Ind Med* 1982;3:373–391.
- 5 Peters HA, Levine RL, Matthews CG, Sauter SL, Chapman LJ: Synergistic neurotoxicity of carbon tetrachloride/carbon disulfide (80/20 fumigants) and other pesticides in grain storage workers. *Acta Pharmacol Toxicol* 1986;59(suppl 7):535–546.
- 6 Peters HA, Levine RL, Matthews CG, Chapman LJ: Extrapyramidal and other neurologic manifestations associated with carbon disulfide fumigant exposure. *Arch Neurol* 1988;45:537–540.
- 7 Hernberg S, Partanen T, Nordman CH, Sumari P: Coronary heart disease among workers exposed to carbon disulfide. *Br J Ind Med* 1970;27:313–325.
- 8 Tolonen M: Vascular effects of carbon disulfide. A review. *Scand J Work Environ Health* 1975;1:63–77.
- 9 Hernberg S, Tolonen M, Nurminen M: Eight-year follow-up of viscose rayon workers exposed to carbon disulfide. *Scand J Work Environ Health* 1976;2:27–30.
- 10 Sweetnam PM, Taylor SWC, Elwood PC: Exposure to carbon disulfide and ischemic heart disease in a viscose rayon factory. *Br J Ind Med* 1987;44:220–227.
- 11 Tiller JR, Schilling RSF, Morris JN: Occupational toxic factor in mortality from coronary heart disease. *Br Med J* 1968;4:407–411.
- 12 Oliver LC, Weber RP: Chest pain in rubber chemical workers exposed to carbon disulfide and methaemoglobin formers. *Br J Ind Med* 1984;41:296–304.
- 13 Nurminen M, Hernberg S: Effects of intervention on the cardiovascular mortality of workers exposed to carbon disulfide: 15 year follow-up. *Br J Ind Med* 1985;42:32–35.
- 14 Aaserud O, Gierstad L, Nakstad P, Nyberg-Hansen R, Hommeren OJ, Tvedt B, Russel D, Rootwelt K: Neurological examination, computerized tomography, cerebral blood flow and neuropsychological examination in workers with long-term exposure to carbon disulfide. *Toxicology* 1988;49:277–282.
- 15 Aaserud O, Hommeren OJ, Tvedt B, Nakstad P, Mowe G, Efskind J, Russel D, Jorgensen EB, Nyberg-Hansen R, Rootwelt K, Gjerstad L: Carbon disulfide exposure and neurotoxic sequelae among viscose rayon workers. *Am J Ind Med* 1990;18:25–37.
- 16 Aaserud O, Russel D, Nyberg-Hansen R, Rootwelt K, Jorgensen EB, Nakstad P, Hommeren OJ, Tvedt B, Gjerstad L: Regional cerebral blood flow after long-term exposure to carbon disulfide. *Acta Neurol Scand* 1992;85:266–271.
- 17 Kruse A, Borch-Johnsen K, Pedersen LM: Cerebral damage following a single high exposure to carbon disulfide. *J Soc Occup Med* 1982;32:44–45.
- 18 Sugimura K, Kabashima K, Tatetsu S: Computerized tomography in chronic carbon disulfide poisoning. *Brain Nerve (Tokyo)* 1979;31:1245–1253.
- 19 Chu CC, Huang CC, Chen RS, Shih TS: Carbon disulfide-induced polyneuropathy in viscose rayon workers. *Occup Environ Med* 1995;52:404–407.
- 20 Chu CC, Huang CC, Chu NS, Wu TN: Carbon disulfide induced polyneuropathy: Sural nerve pathology, electrophysiology and clinical correlation. *Acta Neurol Scand* 1996;94:258–263.
- 21 Huang CC, Chu CC, Chen RS, Lin SK, Shih TS: Chronic carbon disulfide encephalopathy. *Eur Neurol* 1996;36:364–368.
- 22 Graham DG, Amarnath V, Valentine WM, Pyle SJ, Anthony DC: Pathogenetic studies of hexane and carbon disulfide neurotoxicity. *CRC Crit Rev Toxicol* 1995;25:91–112.
- 23 Schlaepfer WW: Neurofilaments. Structure, metabolism and implications in disease. *J Neuropathol Exp Neurol* 1987;46:117–129.
- 24 Valentine WM, Amarnath V, Graham DG, Morgan DL, Sills RC: CS₂-mediated cross-linking of erythrocyte spectrin and neurofilament protein: Dose response and temporal relationship to the formation of axonal swellings. *Toxicol Appl Pharmacol* 1997;142:95–105.
- 25 Graham DG, Montine TJ, Amarnath V, et al: Cross-linking of apolipoprotein B (apo B) in the acceleration of atherosclerosis by carbon disulfide. *Toxicologist* 1995;5:126.