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Follow-up studies of workers with bladder neuropathy caused by exposure to dimethylaminopropionitrile

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BAKER EL, CHRISTIANI DC, WEGMAN DH, SIROKY M, NILES CA, FELDMAN RG. Follow-up studies of workers with bladder neuropathy caused by exposure to dimethylaminopropionitrile. *Scand j work environ health* 7 (1981): suppl 4, 54—59. Following a 1978 outbreak of bladder neuropathy among workers exposed to dimethylaminopropionitrile (DMAPN), follow-up studies were performed 2 a after the original epidemic to evaluate the persistence of symptoms among a small group of initially affected workers. Although the overall prevalence of urologic and neurological symptoms fell for the 11 persons interviewed, significantly high rates of persistent symptoms were seen. Of particular concern was the increase in the prevalence of symptoms of sexual dysfunction. Physical examination identified one individual with sensorimotor neuropathy which was initially detected 2 a earlier. Three individuals who had similar neuropathic findings in 1978 were normal 2 a later. Objective neurophysiological and urologic testing revealed evidence of persistent abnormalities in several workers, but most of the objective findings had improved over the 2-a period. The follow-up of residual effects of occupational exposure to neurotoxic substances is essential to the understanding of the course of occupational illnesses.

Key terms: neurotoxin, occupational medicine, sexual dysfunction, urinary retention.

Investigations performed in 1978 (7, 8) identified a new industrial neurotoxin, dimethylaminopropionitrile (DMAPN), which caused symptoms of bladder neuropathy and other signs of neurological dysfunction among workers employed in several United States plants. Very high rates of bladder dysfunction were seen among workers in the two plants most carefully studied, attack rates varying up to 65 % of the work force employed in production activity. Follow-up evaluations performed three months after the substance was removed from the workplace revealed that approximately 85 % of those initially symptomatic workers had recovered. Conversely, persistent symptoms were seen in a small percentage of the workforce, and the current investigation focuses on the evaluation of long-term morbidity among these individuals.

The company manufactured automobile seat cushions from polyurethane foam on two parallel production lines associated with finishing, supply, storage, laboratory, and clerical areas. At the head of each production line, the ingredients of the foam were compounded. These ingredients included toluene di-isocyanate, polyols, fire retardants, and a catalyst. This mixture was poured into open, waxed molds, and a cover was placed on top of the mold as the foam expanded. The closed mold

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was then passed through an oven (temperature 107—149°C), after which the cured foam cushion was removed and conveyed to the finishing room. There the foam was trimmed, repaired, inspected, and bagged in polyethylene for shipping. The mold and its cover continued on the line, and they were stripped of excess foam, sprayed with wax, and fitted with nets and wires for structural support of the next cushion.

NiAX® catalyst ESN [which contained 95 % DMAPN and 5 % bis (2-dimethylaminoethyl ether)] was introduced on one production line in August 1977 and was used irregularly until December 1977. From December 1977 both production lines used the catalyst regularly until it was withdrawn on 29 March, 1978.

Methods

All employees who reported two or more urinary symptoms at the three-month follow-up interview (8) in July 1978 were defined as "late improvers," and they were recontacted in 1980. One individual initially classified as a late improver was found, on interview in 1980, not to meet the criteria for that classification, and therefore 13 late improvers were interviewed. All subjects complaining of persistent symptoms, and eight subjects previously tested with electrophysiological procedures in 1978 were eligible for the neurological and urologic testing.

Physicians administered a standardized questionnaire covering interim medical history (1978—1980), job history, urinary symptoms, alcohol consumption, medication, and sexual history. A complete neurological examination was performed with blood pressure measured in the supine and standing position. The urologic evaluation included cystometrography using carbon dioxide according to standard techniques (3, 9) in which bladder volume is recorded at the point of first urge to void and at the point of bladder emptying. The electrophysiological evaluations included electromyography of the anal sphincter and the measurement of sacral latency time (11). Nerve conduction studies (1, 5, 12) of the right peroneal and right sural nerves were performed using a research-grade electromyograph. Skin temperature was monitored with a telethermometer and was found to be between 25 and 31°C. For the peroneal nerve conduction, a supramaximal stimulus of 0.1-ms duration was used. Sural antidromic-evoked potentials were averaged 32 times with a digital ensemble averager. The latency of the sacral-evoked response was measured from two stimulating ring electrodes placed around the penis or on the labia majora and stimulated at a 1/s frequency and for a 0.5-ms duration; the recording was made from a 37-mm concentric needle electrode placed in the external anal sphincter.

The results of the nerve conduction testing were compared with those of age and sex-matched machinists, nonexposed to neurotoxins, who served as referents for another study of industrial neurotoxins (Baker et al, unpublished manuscript). Evaluations were performed in the same laboratory under similar conditions and, in most instances, by the same physician as in 1978.

Results

History. The 11 late improvers who were surveyed were mostly male (82 %), English speaking (82 %), and relatively young (median age 36 a). They had few chronic medical problems (2 persons on medication — 1 lithium carbonate, 1 antibiotics). There were no diabetics, and only one of the eleven drank more than 20 ounces (591 ml) of ethanol per week.

Although the overall prevalence of urologic and other symptoms was less than in 1978, a considerable proportion of the group continued to report abnormal symptoms (table 1). In fact, the proportion reporting sexual difficulties (loss of libido or impaired sexual function) increased over the 2-a period (table 1). No clear associations between job category, age, or demographic characteristics and disease persistence were seen.

Physical Examination. Three of the ten individuals complaining of symptoms were noted to have neurological abnormalities in a physical examination. One, a 29-year-old white male, had a sensorimotor neuropathy characterized by decreased pinprick sensation in the lower extremities

and hyperreflexic ankle jerks. A 43-year-old male had hyperreflexic knee jerks and ankle clonus. A third individual had signs consistent with a right lower extremity radiculopathy. The remaining seven patients had normal neurological findings.

The neurological examinations of the four individuals who were examined in both years (1978 and 1980) showed that three of the four had objective abnormalities in 1978 (sensory or sensorimotor neuropathy) which were not detected in the follow-up examination in 1980. One individual showed a persistent sensorimotor neuropathy in the physical examination.

Neurological testing. Significant differences were not generally observed (table 2) when the results of the nerve conduction testing of the ten exposed workers were compared with those of the referents.

Three individuals had abnormalities affecting the lower limbs (table 3). Motor amplitude, sensory amplitude, and sensory velocity were affected more often than motor velocity.

Urologic testing. In the urologic testing, sacral latency time was normal for all ten individuals. Three workers who had prolonged sacral latencies in 1978 had normal values in 1980 (table 4). Sphincter electromyograms (EMG) were abnormal for two workers in 1978, but returned to normal in 1980. The first sensation of bladder filling occurred at abnormally large volumes in two patients in 1980 who had had normal values in 1978. The detrusor reflex, which was absent in two of these patients in 1978, was present, but it occurred at unusually large bladder volumes in 1980.

Table 1. Symptom prevalence among late improvers — 1978, 1980.

Symptom	Number with symptom (N = 11)	
	1978	1980
Urinary hesitancy	11	7
Need to strain to urinate	11	5
Incomplete bladder emptying	9	6
Sexual difficulties (loss of libido or impaired sexual function)	3	5
Parasthesia	3	6
Dry mouth	5	1
Weakness in arms/legs	5	5

Discussion

This investigation has documented the persistence of abnormal symptoms of urinary tract dysfunction along with objective evidence of neurological damage in a small group of workers exposed to the industrial catalyst DMAPN 2 a previously. Their symptoms improved considerably after removal from exposure to the substance, but continued improvement ceased

Table 2. Electrodiagnostic study results for cases and referents.

Nerve	Dimethylaminopropionitrile-exposed (N = 10)		Referents (N = 29)		t-Value
	Mean	SD	Mean	SD	
Peroneal					
Distal latency (ms)	4.73	1.60	4.17	0.86	1.06
Velocity (m/s)	49.44	4.60	48.87	4.34	0.033
Amplitude (mv)					
Knee	3.78	2.15	5.33	2.33	1.91 *
Ankle	4.04	2.03	5.69	2.39	1.81 *
Sural					
Velocity (m/s)	40.58	14.57	47.75	5.12	1.22
Amplitude (mv)	18.1	12.25	13.88	6.58	1.09

* $p < 0.05$, one-tailed t-test.

approximately 1 a prior to our investigations. As was the case in the original investigation (8), we were unable to identify any individual factor that would account for the persistence of symptoms in this group compared with the vast majority of workers at the plant who recovered without residual effects. The only distinguishing factor which separated those with persistent symptoms from those recovering completely was the severity of their initial illness. Those most severely

Table 3. Results of the neurological testing of individuals tested in 1978 and 1980.

Age (a)/sex	Electrodiagnostic neurological testing					
	Peroneal nerve				Sural nerve	
	Motor velocity (m/s)	Distal latency (m/s)	Amplitude (mv) Ankle	Amplitude (mv) Knee	Sensory velocity (m/s)	Amplitude (mv)
47/male						
1978	47.3	4.3	4.0	4.0	35 [a]	3.5 [a]
1980	46.0	8.5 [a]	4.0	3.0	Absent	Absent [a]
29/male						
1978	43.4	6.8 [a]	0.6 [a]	0.6 [a]	32.5 [a]	21.0
1980	45.0	6.4	0.4 [a]	0.4 [a]	46.0	11.0
32/male						
1978	46.0	5.5	5.6	5.0	38.8 [a]	6.0
1980	44.2	5.0	6.0	6.0	38.0 [a]	12.0
44/male						
1978	49.5	4.0	3.0	3.0	43.5	—
1980	50.8	4.2	2.0 [a]	2.0 [a]	44.8	25.0
Normal range	38—59	3—6.5	2.2—14.8		40—54.7	6—42

[a] Outside normal range.

Table 4. Urologic studies of dimethylaminopropionitrile-exposed workers — 1978, 1980.

Age (a)/sex	Electrodiagnostic testing		Cystometrogram	
	Sacral latency (ms)	Sphincter electromyogram	First sensation of filling (ml)	Detrusor reflex (ml)
47/male				
1978	120 [a]	Increased polyphasia	175 [a]	Absent
1980	38	Normal	Not done	Not done
29/male				
1978	43 [a]	Increased polyphasia	100	Absent
1980	33	Normal	200 [a]	700
32/male				
1978	38	Normal	50	Absent
1980	28	Normal	250 [a]	450
44/male				
1978	50 [a]	Normal	80	275
1980	35.2	Normal	100	325
Normal range	< 42		< 125 ml	

[a] Outside normal range.

affected during the initial outbreak in 1978 were those with persistent symptoms and abnormal results in the standardized testing 2 a later.

The course of the illness in the population that we studied differed somewhat from that described in a similar plant in Maryland (10), in which workers employed in a similar process experienced similar symptoms. In our experience, symptoms of sexual dysfunction became considerably more prominent in the late improver group over the 2 a following the initial illness outbreak rather than initially, as noted in Maryland (10). Since different interview techniques were used in 1978 and 1980, some of the differences in symptom prevalence noted (table 1) could be attributed to differences in the evaluation technique. However, several individuals noted that their symptoms of sexual impairment had actually become more prominent over the months following the initial episode. In both outbreaks, improvement in bladder symptomatology followed promptly after the removal of DMAPN from the workplace.

Standardized diagnostic tests were of value in this study in providing objective measures of neurological and urologic function which could be compared between 1978 and 1980. The urologic studies showed clear improvement associated with a reduction in the intensity of urologic symptoms. Some symptomatic individuals had normal urologic tests, a finding which may be attributable to the relative insensitivity of these diagnostic methods in detecting mild disease. The neurologic test results correlated weakly with the results of the urologic testing, and therefore a common pathogenesis could be responsible for the dysfunction found in these two systems.

Experimental studies of animals exposed to DMAPN and chemically related substances have attempted to elucidate the pathophysiology of this disorder. Rats and mice dosed intraperitoneally with 0.25 ml/kg experienced convulsions, tremors, and loss of the micturition response. Within a week of the discontinuance of dosing, these abnormalities disappeared. The maximum duration of exposure for these animals was two weeks (4).

The pathogenesis of DMAPN toxicity is poorly understood and can only be inferred from the limited study of a chemically similar compound [B,B' iminodipropionitrile (IDPN)] in a pathological study of one human case and from an unpublished animal study. IDPN (fig 1) has been demonstrated to have potent neurotoxic properties. Animals chronically exposed to this substance develop proximal axonal swellings associated with intraaxonal neurofilament accumulations (2). This histological abnormality has been attributed to impairment in slow axonal transport (6). In fact, this experimental neuropathy produced by IDPN is felt to represent the best experimental model of inhibition of slow axonal transport leading to peripheral neuropathy. The only neuropathological evaluation of humans exposed to DMAPN (10) showed a mild degree of axonal degeneration with axonal swellings containing disordered neurofilaments in a sural nerve biopsy specimen from a severely affected DMAPN worker. Similar histological abnormalities have been reported for other axonal neuropathies, such as those caused by acrylamide and hexane (6). An unpublished study of a subchronic administration of DMAPN to rats showed distal axonal enlargement with disordered neurofilaments (10). A syndrome of urinary retention similar to that seen in humans was not noted in this, or other, animal studies. Thus, the primary site of action for DMAPN appears to be the axon itself rather than the other portions of the neuron, and the mechanism of toxicity may relate to the inhibition of axona transport.

B,B' - iminodipropionitrile (IDPN)

dimethylaminopropionitrile (DMAPN)

Fig 1. The structure of two neurotoxic nitriles.

The syndrome associated with DMAPN exposure differs significantly from previously reported occupational neuropathies in the predominance of genitourinary dysfunction. This difference is possibly related to the metabolism of DMAPN, such that the substance is concentrated in urine, diffuses through the bladder wall, and preferentially attacks genitourinary nerve structures. Additional animal studies would be of particular value in clarifying the pathogenesis of this unique disorder.

Although the initial three-month follow-up of workers at this plant showed encouraging results in the high rate of recovery of function in these individuals, the current investigation illustrates the importance of long-term follow-up of individuals exposed to environmental neurotoxins with potentially irreversible effects. Additional follow-up studies of workers affected by other industrial neurotoxins, such as methyl-n-butyl-ketone, chlordecone, and the recently studied (13) 2-t-butylazo-2-hydroxy-5-methyl-hexane require continued follow-up to assess the course of illness in these individuals.

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