Neurological Dysfunction of the Bladder in Workers Exposed to Dimethylaminopropionitrile

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• **Neurogenic bladder dysfunction, characterized by hesitancy, need to strain, decreased stream, and increased duration of urination, developed in 104 (63%) of 166 employees working in the manufacture of polyurethane foam. Highest rates of illness (69%) occurred in production workers, and no illness occurred in office or warehouse workers. Onset of the epidemic coincided with introduction of a catalyst, dimethylaminopropionitrile (DMAPN), and monthly case incidence rates increased as DMAPN use increased. Outbreak ceased abruptly when DMAPN use was stopped. Of eight patients who underwent neurourologic testing during recovery, seven lacked either detrusor reflex or normal sensation of bladder filling; seven had a subclinical sensory abnormality; three had prolonged sacral-evoked responses; and two of these three had limb motor neuropathies. Dimethylaminopropionitrile is unique among known neurotoxins in producing urinary symptoms more frequently than limb nerve symptoms.**

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A VARIETY of industrial chemicals are neurotoxins, including some heavy metals, organic solvents, and organo-phosphorous compounds. Recently, *n*-hexane and methyl *n*-butyl ketone have been added to the list of neurotoxins. Clinical findings in patients with occupational neuropathy are seldom specific. The diagnosis is made by exclusion of metabolic and drug-related neuropathies and, most important, by the history of exposure to a known neurotoxin. Interestingly, both *n*-hexane and methyl *n*-butyl ketone were discovered to be neurotoxic in workplace epidemics. This report describes another such epidemic that led to the recognition of an association between exposure to dimethylaminopropionitrile (DMAPN) and a bladder neuropathy in a group of industrial workers.

See also pp 746 and 771.

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On March 28, 1978, a local board of health notified the Occupational Hygiene Physician for Massachusetts that 11 employees of a polyurethane foam factory had come to a hospital emergency room complaining of urinary difficulties. The factory management had been unable to identify a chemical cause, but we found that a new catalyst, DMAPN, had been recently introduced into the manufacturing process. Coincidentally, we had learned of a similar epidemic in another foam manufacturing plant that used DMAPN. We recommended that the new catalyst be withdrawn from the manufacturing process, and this was done on March 29. Between eight and 13 days later, we investigated the extent of the epidemic, the causal agent, and the nature of the clinical complaints.

METHODS

Background.—The outbreak occurred in a plant that manufactures automobile seat cushions from polyurethane foam. The plant has two parallel production lines (9 m apart), as well as finishing, supply, storage, laboratory, and clerical areas. At the head of each production line, the ingredients of the foam are compounded: toluene diisocyanate, polyols, fire retardants, and a catalyst. This mixture is poured into open, waxed molds, and a cover is placed on top of the mold as the

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

Population Survey.—All available employees were interviewed concerning job description, use of protective equipment, personal hygiene, and genitourinary and neurological symptoms. They completed a self-administered questionnaire concerning general symptoms and medical history. Urinalyses were performed by the dipstick method and microscopic inspection of the spun sediment. Blood samples were analyzed for complete blood cell count, differential WBC count, and levels of electrolytes, glucose, BUN, creatinine, SGOT, SGPT, lactic dehydrogenase, alkaline phosphatase, bilirubin, calcium, and uric acid and for antinuclear antibody titer. Environmental sampling was conducted simultaneously and repeated five weeks later. Three months after the original survey, those who had had urinary complaints were questioned again concerning persistent symptoms.

Table 1.—Frequency of Urinary Complaints; Foam Plant in Massachusetts, 1978

Symptoms	Cases	Noncases
Increased duration	102/104	1/104
Hesitance	98/104	0/104
Need to strain	98/104	0/104
Decreased stream	94/104	4/104
Subjective retention	70/102	4/104
Dysuria	70/104	13/104
Abdominal discomfort	61/103	6/104
Urgency	47/104	3/104
Decreased frequency	47/104	1/104
Increased frequency*	44/104	23/104
Urethral discharge	19/84	2/80
Nocturia	15/104	10/104
Gross hematuria	12/104	4/104

*Includes eight reporting decreased frequency as well during a portion of their illness.

In our epidemiologic analysis, we assumed all employees who worked in the production or finishing rooms to be at risk of exposure to DMAPN. These at-risk employees were compared with employees working in nonmanufacturing areas such as the warehouse. We defined a case of bladder dysfunction as an employee who experienced any two of the following four symptoms: hesitancy, straining to void, decreased force of stream, and increased duration of urination. We defined a late improver as a case that had persistent urinary symptoms at reinterview three months later.

Neurourologic Evaluation.—Eight symptomatic workers, five men and three women, were referred for neurourologic testing 2½ weeks after cessation of DMAPN exposure. Neurologists evaluated mental status, all cranial nerves, reflexes, coordination, sensory system, and gait. The criteria for clinical neuropathy were either upper and lower extremity distribution of one abnormality or at least two of the following: numbness, paresthesia, decreased pinprick sensation, decreased vibratory sensation, decreased tendon reflexes, and muscle weakness.

Nerve conduction studies on peroneal, sural, and pudendal nerves were performed with a research-grade electromyograph, using standard techniques.[1-5] Skin temperature of the limbs was monitored by a telethermometer as being 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. Latency of the sacral-evoked response was measured by placing two stimulating ring electrodes around the penis or on the labia majora, stimulating at a 1-per-s frequency and 0.5-ms duration, and recording from a 37-mm concentric needle electrode placed in the external anal sphincter. The normal latency was considered to be less than 42 ms in men; no data exist for the corresponding normal latency in women.

Cystometrograms were performed with a commercial gas cystometer using CO_2 infusion at 120 cc/min via a No. 16 or 18 F urethral catheter. The patients reported the first sensation of filling and the first urge to void and were then asked to void without straining. The bulbocavernosus reflex was elicited in males by squeezing the penis and in females by pulling on the urethral catheter. Four patients were tested for a supersensitive response to 5 mg of subcutaneous bethanecol in repeated cystometrogram.[6]

RESULTS

Epidemiologic Data.—Of 230 em-

Table 2.—Neurourologic Findings in Eight Cases of Bladder Dysfunct

	Neurological Examination			Peroneal Motor Nerve				Sural Sensory Nerve	
						Amplitude, mV, Normal Range, 2.2-14.8			
Age, yr/Sex	Sensory Abnormalities	Motor Abnormalities	Clinical Impression	Distal Latency, ms, Normal Range, 3-6.5	Velocity, m/s, Normal Range, 38-59	Ankle	Knee	Velocity, m/s, Normal Range, 40-54.7	Amplitude, μV, Normal Range, 6-42
26/M	Numbness; decreased vibration, both lower extremities	Hyporeflexia; absent ankle jerks	Sensorimotor neuropathy	6.8*	43.4	0.65*	0.65*	32.5*	21.0
45/M	Decreased vibration; proprioception; light touch in toes	Decreased ankle jerks	Sensorimotor neuropathy	4.3	47.3	4.0	4.0	35.0*	3.5*
23/M	Decreased vibration, left lower extremity	None	Probably normal	4.6	48.6	2.8	2.8	46.6	14.0
30/M	Decreased proprioception, lower extremities	None	Sensory abnormality	5.5	44.6, 46.0	5.6	5.0	38.8*	6.0
42/M	Numbness; decreased light-touch, pinprick, both lower extremities	None	Sensory neuropathy	4.0	49.5	3.0	3.0	43.5	. . .
29/F	Minimal decreased vibration, all limbs distally	None	Sensory neuropathy	5.0	63.0	3.5	3.5	48.8	. . .
37/F	Mild hyperesthesia, feet	None	Sensory abnormality	3.9	58.5	9.0	7.5	46.0	25
24/F	Decreased light-touch, pinprick, both lower extremities distally	None	Sensory neuropathy	4.0	54.6	7.5	7.5	56.0	33

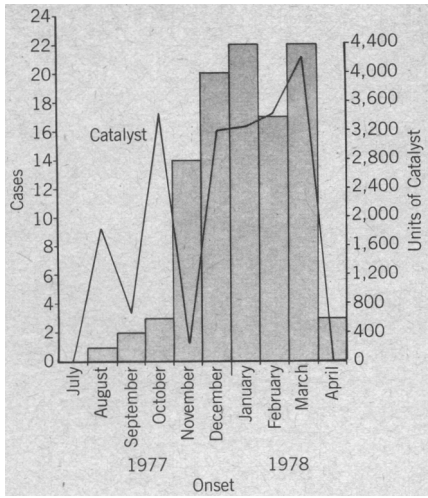

Fig 1.—Cases of bladder dysfunction in plant workers, by month of onset and amount of catalyst used; Massachusetts, July 1977 to April 1978.

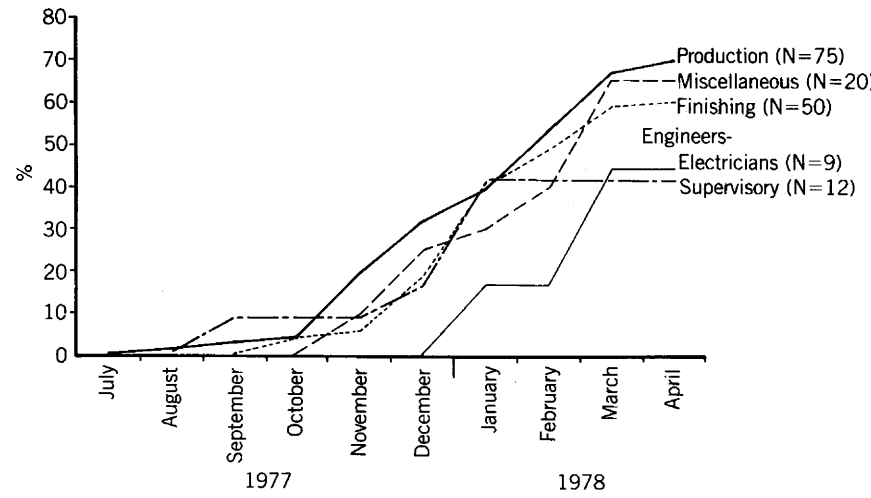

Fig 2.—Cumulative percentage of plant workers having bladder dysfunction, by month and work category; Massachusetts, July 1977 to April 1978.

ployees, 213 participated in the study. Five were excluded from subsequent analysis: an office employee in whom urinary retention developed while hospitalized for cardiac catheterization, two employees who were not interviewed, and two employees whose symptoms antedated the use of DMAPN, neither of whom were at risk of exposure. Hence, 208 employees' symptoms were analyzed, and 104 persons met the case definition. The case rate among the 166 at-risk persons was 63%. No cases occurred among the remaining 42 employees. There were 20 cases (55.6%) among 36 at-risk women and 84 cases (64.5%) among 130 at-risk men. The average age of female patients was 37.9 years; that of male patients was 31.3 years. Case incidence rates did not increase with age.

The catalyst DMAPN was introduced on one production line in August 1977 and was used irregularly until December of that year. From December 1977 through March 1978, both assembly lines used the catalyst. The amount of DMAPN used and the month of onset of new cases are shown in Fig 1. The first case occurred in August 1977, in a female mold cleaner who worked close to the area in which hot foam is removed from the mold. A few new employees showed development of urinary symptoms within the first week of employment.

The highest rate of bladder dysfunction occurred among the production line workers (Fig 2). The incidence rates in the finishing area and miscellaneous (eg, janitorial) category lagged behind the case rate among production workers. There were no striking differences in attack rates, by assembly line or by the various job descriptions, within each area. Three cases of bladder dysfunction occurred among the second-line workers in the three months before using DMAPN in that production line.

The three work shifts differed in the percentage of affected employees: of workers at risk, 78% of the second shift were classed as cases, as compared with 53% of the first shift and 58% of the third shift. However, second- and third-shift workers were affected in equal proportion when cases per person-months of exposure were calculated: .14 cases per person-month for the second shift as compared with .07 for first shift and .15 for the third shift. Since cleanup was deferred until the third shift, the second and third shifts were exposed to more scrap and waste foam on the floor than the first shift. Production was higher on second and third shifts because no production innovations were done on those shifts.

Handling of foam was not specifically associated with the bladder syndrome. There were cases in per-

)am Plant in Massachusetts, 1978

		Urologic Studies		
Sacral Latency, ms, Normal, <42	Sphincter Electromyogram	First Sensation Filling, mL, Normal, ≤125	Detrusor Reflex, mL	Comments
43*	Increased polyphasia	100	Absent	Positive bethanecol test
120*	Increased polyphasia	175*	Absent	Negative bethanecol test; impotence; testicular discomfort; 800-mL urinary retention
38	Normal	50	Absent	. . .
38	Normal	50	Absent	Negative bethanecol test
50*	Normal	80	Present at 275	Impotence; testicular discomfort
37	Normal	100	Absent	Negative bethanecol test
. . .	Normal	150*	Present at 450	. . .
35, High threshold	Normal	300*	Present at 425	. . .

sons who infrequently handled foam or chemical compounds, eg, electricians. Differences for cases were not observed in handwashing practices, exposure to chemical spills, location of eating, or showering after work; nor did these practices differ by shift. Cases were considerably more likely to have worn cotton gloves as compared with others at risk.

Some persons noted that their symptoms initially improved on weekends, with absenteeism, or during the February storm that closed the plant for a week. Once bladder dysfunction developed, 85% of the patients noted no improvement as long as DMAPN continued to be used. In contrast, between eight and 13 days after DMAPN removal, 51% of the cases showed improvement, and an additional 21% were back to normal. At the time of the resurvey three months later, 86% of the cases were asymptomatic and the remainder reported improvement. These 14 late improvers were not selectively distributed by work area or job category, exposure to chemical spills, or personal hygiene practices. They were, however, more likely to work the second shift (eight of the 14).

Clinical Aspects.—Patients complained of having to press on the lower abdomen to initiate urination; they learned to use the Valsalva maneuver to maintain the stream. Several persons volunteered that they lost the urge to urinate and voided once a day or by habit. Others described increased frequency of urination, particularly as their conditions improved. Some lost urethral sensation or, as their conditions improved, had urethral burning. The majority (Table 1) had vague abdominal discomfort that they did not associate with bladder distension.

There were no sex-specific differences in the proportions of cases experiencing specific urinary tract symptoms. Urinary tract infection was confirmed by culture in medical records for only two persons classified as cases and one patient in the noncase group, all of whom were women. Interestingly, both persons reporting incontinence were men.

Sexual difficulties occurred in 23 persons classified as cases and in six noncases. Decreased libido affected men and women in similar proportion. Ten of the 84 men suffered problems with erection and four with ejaculation; the corresponding numbers in the noncase group were one and zero of 80 male employees. With the exception of upper extremity numbness in 13 workers, no limb neurological symptoms differentiated cases from other employees.

The four women and ten men who were late improvers were an older group than other patients, with a mean age of 36.4 years; ages ranged from 21 to 54 years. They all suffered dysuria, one half had sexual dysfunction, and nearly one half complained of nausea.

Two persons underwent surgery. A 42-year-old man required suprapubic cystostomy for 2-L urinary retention; bladder emptying slowly returned to normal in the next four months away from the work environment. A 58-year-old man underwent transurethral prostatectomy for acute urinary retention; he had voiding difficulty after surgery but subsequently improved despite returning to work in exposed areas. In addition to the surgical patients, two other persons had cystoscopic examinations, and neither had evidence of structural abnormality.

There were no significant differences between cases and other employees in the proportions having abnormal urine sediments or proteinuria nor in the mean blood factors other than albumin, the mean value of which was higher in cases.

Neurourologic Data.—On neurological examination, seven of eight patients had abnormalities affecting the distal lower extremities (Table 2). Three had a distal sensory neuropathy; two, a mixed sensorimotor neuropathy; and two, a single sensory abnormality. On electrophysiological testing, one patient had a prolonged peroneal latency and reduced evoked action potentials; these findings were corroborated by considerable muscle wasting in the feet. Three patients had slowing of sural sensory nerve conduction, and one showed a reduced sural nerve amplitude as well. Three patients had prolonged sacral latency, and two of the three had evidence of partial denervation on external anal sphincter electromyographic examination.

Five of the eight patients lacked the bladder detrusor reflex despite adequate rectal sphincter relaxation. Only one demonstrated a supersensitive response to bethanecol with a 20-cm-H_2O-increase in pressure. One patient with detrusor areflexia and two patients with normal bladder contraction had a high sensory threshold for bladder filling. Only one man had urinary retention with an 800-mL residual at catheterization.

The two patients with mixed sensorimotor neuropathy had the most striking abnormalities on electrodiagnostic studies and cystometrogram: slowed sural nerve conduction, prolonged sacral latency, absent detrusor reflex, and evidence of partial denervation on sphincter electromyogram. In addition, one had peroneal abnormalities and a bethanecol response. Each continued to have some urinary symptoms at the time of resurvey three months later. Of the six remaining patients, five had at least one abnormal urologic finding. The sixth had sacral and sensory neuropathies.

COMMENT

The identification of DMAPN as an industrial neurotoxin is corroborated by the occurrence of similar epidemics in at least five other polyurethane foam plants that had introduced the catalyst. The catalyst consists of 95% of DMAPN, 5% of bis (2-dimethylaminoethyl) ether, and less than 1% of acrylonitrile and dimethylamine from which it is formulated. Animal studies[7] show DMAPN to be the component causing urinary retention in some species. For many years dipropionitriles have been known to be axonal toxins.[8-10] A monopropionitrile, β-aminopropionitrile, is a lathyrogen and fetal toxin, but DMAPN has no such effect in experimental systems.[11-13] Although DMAPN was only recently introduced into polyurethane manufacture, it has been used for many years in the United States as a catalyst in a grouting mixture.[14] Indeed, the first North American case report[15] of acrylamide neuropathy had simultaneous exposure to DMAPN.

A rough exposure-response relationship is suggested by the amount of catalyst used in monthly production and the incidence of new cases. In addition, the differing case rates for the shifts are consistent with an

exposure-response relationship. Cases occurred in workers on the second production line before DMAPN was used on that line. This, and the finding of cases among employees with minimal, if any, skin contact with catalyst or foam product, suggest the importance of a respiratory route of exposure. Skin contact may also play a role. Unpublished animal studies (data safety sheet, "Toxicology Studies: NIAX Catalyst ESN," Union Carbide, New York) show absorption by both routes. Ten days after the catalyst was removed from production, the first environmental measurements showed that DMAPN was still present in the air of the compounding and finishing areas at 0.11 mg/cu mm. Four weeks later none was detected, but it could be extracted from the cured foam product. Since there were no environmental measurements while DMAPN was used in production, the quantitative exposures associated with this epidemic are unknown.

The DMAPN syndrome seems to be a largely reversible change in micturition compatible with a sensorimotor neuropathy. Seven of the eight patients undergoing neurourologic testing had either absent detrusor reflexes or bladder sensory abnormalities. The absence of a detrusor reflex during cystometrographic examination is common in women, but persistent perineal muscle activity is usually present when the reflex cannot be demonstrated. In these patients, however, perineal muscle relaxation was evident electromyographically.

Urinary symptoms overshadowed somatic nerve symptoms and sexual symptoms. Only 13 of 104 workers had symptoms suggesting limb neuropathy. However, seven of eight patients tested during recovery had a subclinical sensory neuropathy or abnormality. Those two patients with the most severe bladder dysfunction had motor and sacral neuropathies as well. The sacral-evoked response is a somatic reflex arc, while bladder and sexual function involve autonomic reflex arcs.

Several toxic neuropathies have autonomic effects, but these effects are minor compared with the functional disturbance of limb nerves. For example, in the case reports of acrylamide neuropathy,[15-17] only one patient had difficulty in urinating, and this was late in the course of a profound peripheral neuropathy and sweating disturbance. Rats that are poisoned subacutely with acrylamide show debilitating ataxia and weakness and, in addition, have autonomic effects of bladder distension[18] and extreme continuous penile protrusion.[19]

The catalyst DMAPN is unique among known neurotoxins in producing bladder dysfunction without producing frequent complaints of other organ or nerve dysfunction. Perhaps the bladder is affected by a urine-concentrated neurotoxin that would affect limb nerves clinically in persons having greater exposure than had the typical case in this epidemic. The mechanism by which DMAPN affects its specific target organ and nerves needs to be elucidated in animal experiments.

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