

# An Epidemic of Urinary Retention Caused by Dimethylaminopropionitrile

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• An epidemic of urinary retention among workers in a polyurethane manufacturing plant was discovered in the spring of 1978. The most severely affected workers had neurogenic bladders confirmed by cystometrograms and mild sensory peripheral neuropathy. A survey of the plant disclosed increased incidence of urinary retention, muscle weakness, paresthesia, insomnia, and sexual dysfunction in exposed workers. A catalyst containing dimethylaminopropionitrile was identified as the probable causative agent, and after its removal no new cases occurred.

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IN THE fall of 1977, workers at a polyurethane manufacturing plant began to experience difficulty urinating. Symptoms were at first limited to men who worked the evening shift in a storage and curing area (the back room) and included hesitancy, dribbling, and decreased stream. Several workers reported they had to press firmly on their lower abdomens to maintain urination. In addition they noted they had lost any sensation of bladder distension and were voiding

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See also pp 741  
and 771.

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only once a day. Several men sought medical care but found the physicians who examined them unresponsive to their concern that the problems were job related.

In February an informal survey taken by the workers found that the problem had spread to other parts of the plant and that 22 of 40 workers on the evening shift were having similar symptoms. In early March one of the originally affected workers was hospitalized and found to have a distended bladder with a large postvoid residual. Pricking pain, temperature,

and light-touch sensations were diminished in a symmetrical distribution confined to the lower sacral dermatomes and distal portions of the legs and hands. Muscle strength was decreased distally in the intrinsic muscles of the feet and hands and the extensors and flexors of the toes.<sup>1,2</sup>

A survey of all plant employees was undertaken by the Maryland Division of Labor and Industry, which disclosed that about half of those interviewed complained of difficulty voiding. There were also frequent complaints of dizziness, weakness, temporary clouding of vision, and paresthesias.

Workers' suspicions focused on a catalyst, NIAX-catalyst ESN, which had been introduced in large quantities into production some months before the outbreak began. A list of its ingredients obtained from the manufacturer included 95% dimethylaminopropionitrile (DMAPN), 5% bis-2-dimethylaminoethylether (DMAEE), and less than 1% acrylonitrile and dimethylamine.<sup>3</sup> These suspicions were strengthened when a similar epidemic was discovered in a polyurethane plant in Massachusetts also using ESN (p 741). The use of the catalyst was halted, and a clinical investigation was begun of all workers at the affected plant, which we have designated plant A. Workers were also examined at a nearby plant (plant B) owned by the same company, which also made polyurethane but used little of the suspected catalyst in production.

## DESCRIPTION OF THE WORKPLACE

Both plants manufacture polyurethane foam products in a variety of sizes, shapes, and colors. In both plants, toluene diisocyanate (TDI) is mixed with a polyester resin, catalysts, and pigments by a nozzle suspended over the beginning of a conveyor system ("bridge"). The material foams and solidifies as it travels down the conveyors and is then cut into sections. The foam, which is warm because of the exothermic reaction of polymerization, gives off visible fumes and is left in a separate room (back room) to cure before it is processed further into blocks, rolls, or sheets. At plant A, all of the foam is produced in cylindrical lengths that are "peeled" against a razor edge to make thin sheets. This creates a tremendous increase in surface area and exposes areas close to the core, which have not cooled. At plant B, some foam is peeled, but much of it is cut into other shapes. In addition, a small cotton-batting operation, offices, and research laboratories are present. The use of the catalyst varied with the type and color of foam. Its use began in 1976 in the research laboratory at plant B. It was used only in small amounts in plant B but was used at plant A in increasing amounts during 1977.

## METHODS

The survey was conducted between April 11 and May 2, 1978. All current employees at both plants were eligible to participate. At plant A, there were 151 employees of whom 141 participated (139 men and two women). At plant B, there were 83 employees, and 75 participated (64 men and 11 women). Informed consent was obtained.

Symptoms were elicited by a questionnaire that focused on the skin, the lungs, the CNS, and the genitourinary system. Workers were specifically asked about straining, hesitancy, decreased flow, intermittent flow, distension, frequency of uri-

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nation, and the need for manual pressure to empty the bladder. They were also asked about frequency of intercourse and difficulty obtaining and maintaining erections. Findings of a complete physical examination were recorded on a standard form and included a limited neurological examination. (Cranial nerves II through XII were tested; motor strength, deep-tendon reflexes, vibratory sensation at the ankles, station, and gait were examined.) Rectal and pelvic examinations on women were not included, and some men also declined rectal examination.

Forced vital capacity (FVC) and forced expiratory volume in one s (FEV<sub>1</sub>) were measured on a survey spirometer. Results of the best of three trials were recorded. Blood was obtained for measurement of electrolytes, urea, calcium, uric acid, phosphorus, glucose, creatinine, protein, bilirubin, transaminases, cholesterol, triglycerides, iron, hematocrit, WBC count and differential, antistreptolysin O titer, latex fixation, and antinuclear antibody. Urinalysis was performed, including microscopic examination and testing for blood, sugar, protein, ketones, and bilirubin by dipstick.

Intravenous pyelography (IVP) with postvoid films of the bladder was made available to all workers who had persisting symptoms of urinary retention.

In tabulating results, symptoms and abnormalities of physical examination were grouped by organ systems. A worker was considered to have a positive response if he had a given symptom during the past six months or at the time of examination.

## RESULTS

The patient in the index case was still hospitalized at the time of the survey and was not included in the tabulation of results. His symptoms included urinary retention, paresthesias, weakness, impotence, and irritability.<sup>2</sup> These symptoms were common at plant A and unusual at plant B (Table 1). One worker at plant B who did have several of these symptoms had worked extensively with the catalyst in the plant laboratory during the preceding year.

Many workers reported that their symptoms had decreased or disappeared between the end of the catalyst exposure and the time of the survey. Sixty-five workers who had continuing symptoms underwent IVP. Seventeen of these had abnormal retention of contrast material in the bladder (Table 2). Three had large amounts of retained contrast, nine had moderate amounts, and five had minimal retention.

	Plant A, No. (%)	Plant B, No. (%)	P*
Total participants	141 (100)	75 (100)	...
Average age, yr	31.6	34.6	...
Symptoms			
Urinary retention	85 (60)	6 (8)	<.01
Urinary frequency	2 (1)	1 (1)	NS
Impotence or decreased libido	49 (35)	6 (8)	<.01
Constipation	13 (9)	3 (4)	NS
Insomnia	44 (31)	3 (4)	<.01
Irritability	71 (50)	16 (21)	<.01
Muscle weakness	32 (22)	4 (5)	<.01
Paresthesias	37 (26)	1 (1)	<.01
Headaches	40 (28)	14 (19)	NS

\*Determined by  $\chi^2$ .

The demonstration of postvoid residual urine on intravenous urography is not conclusive evidence of bladder dysfunction. This technique, while sensitive, may give false-positives in an unknown percentage of cases. Many patients with normal function find it difficult to void completely in the radiology department.<sup>4</sup> The technique was chosen because it provided a relatively less invasive way of determining which of the still symptomatic patients needed prompt urologic follow-up.

Cystoscopy and cystometrograms (CMGs) were performed only in those cases in whom symptoms, examination, and roentgenograms suggested intervention might be needed to prevent hydronephrosis. Only three of the survey participants had CMGs. One worker with minimal retention had normal findings from the CMG. Two workers with moderate retention had abnormal findings from CMGs, verifying persisting dysfunction.

In addition, we learned that one participant had previously had abnormal CMG findings attributed, at that time, to prostatism. He had changed his job assignment, and his symptoms had resolved spontaneously. Together with our index case, this brought the total number of exposed workers whose bladder dysfunction was confirmed by CMG to four. Only the index case required long-term intermittent catheterization.

Many of the workers with urinary retention also had sexual dysfunction. They complained of difficulty getting and maintaining erections, although complete impotence was rare. They also had decreased libido, although in some cases this may have been related to the fear several workers

Workers with symptoms of urinary retention	91
Workers who had IVPs	65
Normal IVP	48
IVP showing postvoid retention of contrast material	
Large residual	17
Moderate residual	3
Minimal residual	9
	5

\*Prevalence among workers at both plants.

expressed that their urinary problems could be contagious.

Workers who noted continuing symptoms of muscle weakness and paresthesia were referred for more thorough neurologic evaluation.

Findings from nerve-conduction studies, which were slowed in the index case, were normal. Examination disclosed a pattern of decreased sensation confined to the lower sacral dermatomes and distal portions of the legs and hands in three workers.

At plant A, the highest incidence of urinary retention was found among those workers currently exposed to warm foam, although no job grouping was completely spared (Table 3). Because of mobility between jobs, current assignment did not always reflect degree of exposure during the period of use of the catalyst. Workers were divided into those who had worked in the back room where the epidemic had begun and those who had not (Table 4). The workers were then divided into those who had worked in areas with exposure to warm foam and those who had not (Table 5). There was a clear association with jobs having the highest exposure to warm foam.

To see if the removal of the catalyst

Area	Average Age, yr	N	Symptom, No. (%)				
			Urinary Retention	Muscle Weakness	Paresthesia	Insomnia	Sexual Dysfunction
"Bridge"	31.3	7	5(71)	1(14)	2(28)	2(28)	5(71)
Section cutting	31.6	7	6(85)	0(0)	3(42)	3(42)	4(57)
Hole-boring back room	33.5	13	10(76)	4(31)	4(31)	5(38)	4(31)
Material-handling back room	24.5	7	3(42)	1(14)	0(0)	1(14)	0(0)
Peeling	30.5	63	39(61)	15(23)	18(29)	17(26)	21(33)
Quality control peeling	33.4	5	4(80)	2(40)	2(40)	3(60)	3(60)
Compressing	31.4	5	1(20)	1(20)	0(0)	0(0)	1(20)
Shipping	26.4	9	5(55)	1(11)	1(11)	3(33)	3(33)
Maintenance	37.6	6	3(50)	3(50)	2(33)	3(50)	0(0)
Scrap baling	39.0	3	1(33)	0(0)	0(0)	0(0)	0(0)
Supervisory and clerical*	36.5	16	7(43)	4(25)	5(31)	7(43)	6(37)
<b>Total</b>		<b>141</b>	<b>85(60)</b>	<b>32(22)</b>	<b>37(26)</b>	<b>44(31)</b>	<b>49(35)</b>

\*Includes two women.

	In Back Room	Not in Back Room	Total
<b>Total Affected, No. (%)</b>	<b>21 (85)</b>	<b>120 (67)</b>	<b>141 (60)</b>

\*Worked in back room between February 1976 and February 1978.

	In Areas 2-6	Not in Areas 2-6	Total
<b>Total Affected, No. (%)</b>	<b>100 (73)</b>	<b>41 (29)</b>	<b>141 (60)</b>

	Plant A	Plant B	P*
Total participants	141	75	...
Average age, yr	31.6	34.6	...
Symptoms, No. (%)			
Visual disturbances	113(80)	36(48)	<.01
Dermatitis	92(65)	32(43)	<.01
Bad taste	58(41)	17(23)	<.01
Sore throat	55(39)	14(19)	<.01
Cough	42(30)	21(28)	NS
Wheezing	64(45)	21(28)	<.02
Chest tightness	79(56)	23(31)	<.01

\*Determined by  $\chi^2$ .

from production in late March had interrupted the epidemic, workers hired in January and February were compared with those hired in March. Of the eight workers hired in January and February, six had symptoms of urinary retention, and four had paresthesias. Of the ten workers hired in March, none had urinary retention, and only one worker, hired March 1, had paresthesias. None of the workers hired since March have become symptomatic, nor have any new cases occurred among other workers hired previously.

Visual disturbances, upper respiratory tract irritation, dermatitis, and pulmonary symptoms were common at both plants. There was a higher incidence of these symptoms at plant A. These were not perceived by the workers to be decreasing in frequency or severity after the removal of the catalyst (Table 6).

The most common problem was work-related visual disturbance, described as a cloudiness of vision and the appearance of rings around lights, which typically cleared from 30 minutes to several hours after work. This

effect has been described with exposure to *N*-ethylmorpholine, which causes corneal edema and which was being used at the time of the study as a catalyst.<sup>5,6</sup> Bad taste, skin problems, and upper-airway irritation were common at both plants.

Cough, wheezing, and chest tightness were also common, although only a few workers had rales or wheezing on examination.

At plant A, 35 workers (24%) and at plant B 14 workers (19%) had FVCs less than 70% predicted or FEV<sub>1</sub>-FVC less than 0.7. Seven workers at plant A and ten at plant B had wheezes or rales on examination.

Because TDI is present at both plants and cotton dust is present in one small area at plant B, these abnormalities may be work related. The incidence of abnormal pulmonary function showed no relation to the length of employment, although factors were present that could have masked such a relationship. Both TDI and cotton dust show a short-term reversible effect, and this may have influenced spirometry results, since measurements were taken throughout the workday. Also, workers known to have been sensitized to TDI had been placed in low-exposure jobs, and the jobs with heaviest exposure were usually held by workers recently hired. Finally, workers with severe problems may have left employment more frequently than those without.

The frequency of upper respiratory tract irritation and dermatitis was high at both plants. Irritant fumes were present at both, and there was no provision for protective clothing or adequate respiratory protection.

Hypertension was noted in nine workers (6%) at plant A and seven workers (10%) at plant B. One patient at plant A had hyperthyroidism noted on examination, which required hospitalization. No other serious or potentially work-related problems were found during the physical examinations.

Laboratory examinations of blood and urine were unremarkable. Twenty-one of the urinalyses showed the presence of WBCs in spun sediment. Cultures of these urines were negative, and follow-up urinalyses were all negative. The abnormalities noted initially were believed to be caused by inadequate cleansing of the meatus or

to urethritis and not to urinary tract infection.

### COMMENT

Urinary retention is not an uncommon symptom of neurologic disease, but it is distinctly unusual as the preponderant or only symptom. These workers' unique symptom complex served surprisingly to delay rather than speed the recognition of the epidemic and the identification of the agent. After reviewing medical records, it seems the first worker affected was a man in his 50s who became symptomatic nine months before the investigation and whose condition was diagnosed as prostatism. The second and most severely affected patient, whose hospitalization helped spark the investigation, had been seen by a urologist and a neurologist before his condition was correctly diagnosed by a family physician and he was referred for a thorough workup. For six months he had suggested to his physicians that the problem was work related and had been ignored.

There is now strong evidence that suspected catalyst was the causative agent. First, there was a temporal relation between the introduction of the catalyst and the onset of the epidemic. Second, the symptoms of retention, paresthesia, weakness, insomnia, and sexual dysfunction were largely confined to the plant where the catalyst was used most heavily. Finally, with cessation of exposure to the catalyst, no new cases have occurred.

Urinary retention in these patients is most likely secondary to effects on the peripheral nervous system. Bladder mucosa was normal on cystosco-

py, and some patients showed evidence of peripheral neuropathy as described previously.<sup>1,2</sup>

The catalyst is 95% DMAPN, and this rather than the minor components (DMAEE, acrylonitrile, and dimethylamine) is probably the neurotoxin responsible for this syndrome. Dimethylaminopropionitrile is structurally similar to acrylamide and iminodipropionitrile, both neurotoxic.<sup>7-11</sup> Other propionitriles have teratogenic effects<sup>12,13</sup> and have been found to produce duodenal ulcer.<sup>14</sup>

Experimental studies show that rats fed DMAPN experience distal axonal pathological conditions with abnormally enlarged motor nerve terminals. No such change was seen in rats fed DMAEE.<sup>2</sup> A similar pathological condition was seen on a muscle biopsy specimen of the most severely affected patient.<sup>1</sup>

Dimethylaminopropionitrile had been in use under another trade name for more than a decade as a catalyst in an acrylamide-polymerization waterproofing process. Protective clothing is routinely used to prevent skin or respiratory contact with acrylamide. When such precautions fail, this process has itself resulted in cases of peripheral neuropathy.<sup>8</sup> A recently described patient with peripheral neuropathy resulting from waterproofing with acrylamide and DMAPN did have symptoms of urinary retention. The overall clinical picture in this patient was typical of acrylamide neuropathy, however, and it is not clear what role DMAPN played.<sup>15</sup>

The unmasking of the toxicity of DMAPN awaited its introduction into a different industrial setting, where skin and respiratory exposure were

greater. The workers in the back room curing area had the greatest amount of direct skin contact with the foam, moving and stacking it by hand. The evening shift workers processed warm foam that had less time to give off its vapors, since day-shift workers usually used up the foam that had been allowed to cure overnight. Dimethylaminopropionitrile has been reported as well absorbed through skin,<sup>2</sup> but it is not clear whether skin or respiratory contact was the major source of absorption.

The introduction of DMAPN into the making of polyurethane resulted in two epidemics of neurotoxicity affecting the bladder primarily. The epidemics occurred simultaneously in different parts of the country, and there have been unconfirmed reports of symptomatic workers in some other plants using the same catalyst. While the majority of those symptomatic have recovered, some workers have had prolonged effects. This episode underscores the need to consider potential toxicity both of new chemicals and of previously used chemicals introduced into new industrial processes. It also highlights the need for all practitioners to pay close attention to the patient who thinks his illness may be work related. Failure to do so substantially delayed the recognition of this epidemic and caused unnecessary illness.

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