

# Persistent reactive airway dysfunction syndrome after exposure to toluene diisocyanate

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## Abstract

**Two police officers developed asthma like illness after a single but prolonged exposure to toluene diisocyanate (TDI) by being in the immediate vicinity of a tank car that had overturned on a highway. One officer experienced upper and lower respiratory tract symptoms with chest tightness about 4.5 hours after initial exposure. Shortness of breath, cough, and wheezing were noted the following day. The other experienced symptoms immediately on exposure, developed shortness of breath 20 minutes later, and presented with wheezing four hours after that. Follow up examinations over seven years showed persistence of respiratory symptoms and continuation of airway hyperreactivity requiring treatment.**

Chemicals of the isocyanate group are widely used for the production of various commercial products, including insulation materials, car upholstery, furniture, and surface coatings. The most commonly used diisocyanate is toluene diisocyanate (TDI) in the form of 2,4 and 2,6 isomers. Because of its volatility, it has largely been replaced by the less volatile methylene diphenyl diisocyanate (MDI) in some production processes. Other diisocyanates, such as hexamethylene diisocyanate (HDI), which is more volatile than TDI, naphthylene diisocyanate (NDI), isophorone diisocyanate (IPDI), and hydrogenated MDI (HMDI) also have commercial uses. These chemicals are highly reactive owing to the presence of  $-N=C=O$  groups and may combine readily with biological molecules containing hydrogen atoms thereby causing adverse health effects.<sup>1</sup>

In 1970 Peters and Murphy identified four general

patterns of airway response to toluene diisocyanate (TDI) in man—namely, chemical bronchitis (after exposure to high doses), isocyanate asthma (in sensitised subjects), acute, but asymptomatic, deterioration of respiratory function during a workshift, and chronic deterioration of respiratory function associated with prolonged exposure to low doses.<sup>2</sup> Subsequently, a fifth pattern of response was reported. This was described as the persistence of asthma in sensitised subjects whose exposure to isocyanates had ceased.<sup>3,4</sup> Recently, Brooks *et al* described a syndrome of an asthma like illness after exposure to high doses of respiratory irritants that was termed reactive airways dysfunction syndrome (RADS). Subjects showed non-specifically hyperreactive airways. No pre-existing respiratory disease was identifiable and evidence of previous allergy was usually not present. Symptoms may persist for several years and chronic airways disease may ensue.<sup>5</sup>

In the present report we present two cases with TDI induced respiratory illness manifested by clinical syndromes consistent with RADS.

## Case 1

A 45 year old man was referred to our occupational medicine clinic and evaluated there (by AF) in January 1983 because of respiratory symptoms related to exposure to TDI.

He reported that he was stationed as a police officer to direct traffic near a tank car that had overturned on a highway in December 1981. The manifest in the car indicated that the tank load was TDI. It was between 36° and 37°F and there was freezing rain. The patient remained near the chemical spill from 0900 to 1630. There was a "heavy smell" in the immediate proximity of the vehicle. He had no protective respiratory or other safety equipment. At about 1330 he experienced burning eyes, throat irritation, and cough and tightness of the chest. At 1700 he sought medical attention in an emergency room at a local hospital and was treated with steroids and a bronchodilator. He was discharged and continued treatment at home. The next day he had a severe episode of shortness of breath and cough. During the next ten months he complained of shortness of breath, exertional dyspnoea, non-productive cough, and occasional wheezing.

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Review of his occupational history indicates that he had worked as a police officer between 1958 and 1960 and during 1960 he worked at a gas station. Since 1966 he had been employed as a state police officer. His medical history was essentially non-contributory. He smoked half a pack of cigarettes a day between 1957 and 1981. He stopped smoking after the accident.

Physical examination showed a well developed, well nourished man in no acute distress but with a respiratory rate of 20 per minute. There was no cyanosis but slight pretibial oedema. Examination of the lungs showed diffuse wheezes and prolonged expiration bilaterally with scattered dry rales over the left middle and posterior axillary lines.

Chest radiography showed right sided pleural thickening and increase in lung markings—small irregular opacities that were graded as t/t 1/0 according to the International Labour Office's International Classification of Radiographs of Pneumoconioses, 1980. Pulmonary function tests showed the following: FVC 4.34 l, 82% of predicted; FEV<sub>1</sub> 3.56 l, 90% of predicted; FEF<sub>25-75</sub> 3.59 l/sec, 92% of predicted; and TLC 5.98 l, 75% of predicted. Minimal arterial hypoxaemia with an A-a gradient of 18 at rest and exercise was noted. The PO<sub>2</sub> decreased minimally with exercise from 77 mm Hg to 72 mm Hg. Serum immunoelectrophoresis showed IgE of 55 IU/ML.

The patient has been followed up regularly by one of the authors (KN) since August 1983. The condition has improved with the lowering of the prednisone dose from 20 mg a day to 2.5 mg every three days. His exercise tolerance has improved but he still has some forced end expiratory wheezing. His pulmonary function tests in June 1985 showed: FVC 4.99 l, 96% of predicted; FEV<sub>1</sub> 3.88 l, 101% of predicted; FEF<sub>25-75</sub> 3.2 l/sec, 86% of predicted; and DLCO 29.81 ml/min/mm Hg, 101% of predicted. Another pulmonary function test in February 1987 showed: FVC 4.06 l, 81% of predicted; FEV<sub>1</sub> 3.28 l, 89% of predicted; and FEF<sub>25-75</sub> 3.09 l/sec, 85% of predicted.

### Case 2

Another police officer who was 38 was also evaluated at our occupational medicine clinic in January 1983 because of respiratory symptoms related to exposure to TDI. He was essentially well until December 1981 when he was assigned to traffic control at the same accident. He also approached the area, which had been contaminated by the chemical spill from the damaged tank car. After 30 minutes in the area, he experienced a burning throat, watery eyes, and difficulty breathing. Four hours later he went to a local hospital complaining of wheezing as well as throat and eye symptoms. He was treated with steroids and a bronchodilator.

Between that time and his clinic visit in January 1983 he had complained of intermittent shortness of breath, cough, and wheezing, and had been treated

with high doses of steroids (up to 40 mg a day) and bronchodilators. Little improvement of his condition was noted during this period.

Review of his occupational history indicated that he had never been employed in industries with potential for significant exposures to chemicals. Between 1968 and 1983 he had worked as a state police officer. Medical history included Legionnaire's disease in October 1977 for which he was admitted to hospital. Between 1965 and 1982 he smoked 1-10 cigarettes daily.

Physical examination showed diffuse inspiratory and expiratory wheezes over both lung fields. Chest radiography showed only a minimal increase in small irregular opacities, predominantly located in the left lower lung field that were classified as t/t 0/1 according to the ILO's International Classification of Radiographs of Pneumoconioses, 1980. The results of the pulmonary function tests could not be interpreted with any confidence because of poor performance.

The patient has also been followed up on a regular basis by one of the authors (KN) since 1983. He has gradually improved but at a slower pace. His required doses of prednisone fluctuated around 30 mg a day and it has been difficult to decrease the dose to below 20 mg alternating with 7.5 mg every two days. He continues to have symptoms of episodes of bronchitis with blood streaked sputum. He still complains of exertional dyspnoea and wheezing despite the medication. His pulmonary function tests in December 1985 were: FVC 4.58 l, 88% of predicted; FEV<sub>1</sub> 3.41 l, 81% of predicted; and FEF<sub>25-75</sub> 2.66 l/sec, 52% of predicted. Pulmonary function tests in September 1986 were: FVC 4.23 l, 81% of predicted; FEV<sub>1</sub> 3.31 l, 79% of predicted; and FEF<sub>25-75</sub> 3.01 l/sec, 60% of predicted.

In summary, these two patients developed a chronic bronchospastic disorder after a relatively brief episode of exposure to high doses of TDI, as suggested by the initial symptoms, when directing traffic near a vehicular accident. The symptoms have persisted for more than seven years but considerable improvement has occurred in both cases.

### Discussion

These patients had similar clinical presentations, developing an asthma like illness after a brief exposure to what was perceived as a high level of TDI. When the subjects were evaluated 13 months after the accident, a bronchospastic abnormality persisted according to the symptomatology and clinical findings. Their asthma like symptoms have persisted over seven years.

The clinical course of both patients is mostly consistent with RADS according to the clinical criteria reported by Brooks: (1) a documented absence of preceding respiratory complaints; (2) the onset of symptoms occurred after a single specific exposure incident or accident; (3) the exposure was to

a gas, smoke, fume, or vapour that was present in high concentrations and had irritant qualities to its nature; (4) the onset of symptoms occurring within 24 hours of exposure and persisting for at least three months; (5) symptoms simulated asthma with cough, wheezing, and dyspnoea predominating; (6) pulmonary function tests may show airway obstruction; (7) methacholine challenge testing was positive; and (8) other types of pulmonary diseases were ruled out.<sup>5</sup> Except for a history of Legionnaire's disease in one patient, the findings were consistent with RADS.

Axford *et al* reported that most individuals developed respiratory symptoms within 24 hours of a single severe exposure to TDI.<sup>6</sup> Almost four years later, 20 men described persistent respiratory symptoms. Another report by Mastromatteo described 24 individuals exposed to a single spill of TDI with six requiring admittance to hospital.<sup>7</sup> Convalescence among these patients was extremely slow with at least one individual developing asthma like symptoms for several months.

Proposed mechanisms capable of inducing airway hyperresponsiveness include altered neural tone and vagal reflexes, modified beta-adrenergic sympathetic tone, influences of various mediators including both lipo-oxygenase and cyclo-oxygenase products of arachidonate metabolism, and increase in mucosal permeability and release of mediators from airway inflammation.<sup>8-10</sup>

Pulmonary inflammation has been reported by some as pathological change in RADS with speculation that the bronchial inflammatory reaction was caused by the inhaled toxic agent.<sup>5</sup> Early studies have documented the inflammatory nature of irritant exposure to compounds such as phosgene and chlorine, which may persist for months.<sup>11,12</sup> Several other investigations have suggested that the pulmonary inflammation is responsible for a change in histamine responses, perhaps by augmenting bronchial smooth muscle response to histamine.<sup>13,14</sup> Because subepithelial irritant receptors are superficial in location, they could be affected by an extensive bronchial inflammatory response that might occur after heavy irritant exposure. Subsequent reepithelialisation and probable reinnervation of bronchial mucosa might drastically alter the threshold of the receptors and cause airways hyperreactivity.<sup>5</sup>

Another hypothesis is that epithelial damage can cause subtle disturbance of subcellular components such as the tight junctions. Vagal sensory nerve endings are located beneath the tight junctions of the airway epithelium; damage to the tight junctions could "sensitise" these receptors and result in exaggerated reflex response.<sup>8</sup> Some authors also propose that bronchial epithelial damage leads to increased epithelial permeability, thereby allowing higher concentrations of inhaled materials to reach "target" cells—for instance, sensory nerves or smooth muscle—and cause airway hyperreactivity on this basis.<sup>5,8</sup>

Immunological and pharmacological mechanisms responsible for isocyanate induced asthma have also been proposed. The classic symptoms of the immediate onset of pulmonary response has prompted the proposal of an immunological mechanism. The detection of IgE antibody in sensitised individuals, however, has not been uniformly reported.<sup>15,16</sup> Isocyanate induced asthma may occur through an autonomic imbalance between cholinergic and beta-adrenergic neural control. The inhalation of TDI stimulates the release of tachykinins, low molecular weight peptides, from tachykinin containing nerves in the airways, and can induce airway hyperreactivity.<sup>18</sup>

Airway inflammation induced by isocyanates may also cause airway hyperresponses and late asthmatic reaction.<sup>19</sup> The demonstration of late asthmatic reaction at the time of diagnosis of isocyanate induced asthma may be followed by persistence of sensitisation to isocyanates after removal from the exposure. The persistence of asthma caused by TDI has also been reported to be related to the severity of the late reaction.<sup>4</sup>

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