Chronic Asthma Due to Toluene Diisocyanate*

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Twelve subjects were studied with inhalation challenge testing to toluene diisocyanate (TDI) because of suspected TDI asthma based on a consistent clinical and occupational history. In seven cases, TDI asthma was documented by a positive inhalation challenge to low levels of TDI. Six of the seven TDI reactors had persistent respiratory symptoms and required daily treatment even though they had been removed from isocyanate exposure for intervals as long as 12 years (mean 4.5 years). These six TDI reactors had either dual (four cases) or late bronchospasm (two cases) to less than 20 ppb TDI, and all had a positive methacholine or cold air challenge prior to study. The one TDI reactor with a negative methacholine challenge had a positive (immediate) bronchospastic response to a TDI challenge performed one week after removal from isocyanate exposure. Five workers had a negative TDI challenge, two of whom had persistent respiratory symptoms and positive methacholine challenges at the time of TDI inhalation testing. We conclude that respiratory symptoms may persist following long-term removal from occupational exposure to TDI and are associated with nonspecific bronchial hyperreactivity. The TDI sensitivity may also persist for a long time even in the absence of any additional occupational exposure. Long-term prospective studies of symptomatic isocyanate workers are needed to fully define the extent of this problem.

Toluene diisocyanate (TDI) is an important cause of occupational respiratory disease with approximately 5 percent of exposed workers developing occupational asthma in industries using TDI. There is uncertainty regarding the long-term prognosis of workers with TDI asthma once they are removed from isocyanate exposure. Recovery of asthma after removal from isocyanate exposure has been reported; however, there are reports documenting airway flow abnormalities for days to weeks after occupational exposure or bronchial challenge to TDI in sensitized individuals. Other clinical studies suggested respiratory symptoms following isocyanate exposure persist for extended periods, but TDI sensitivity was not documented in these cases by inhalation challenge testing. Since clinical history alone may be nondiscriminatory and no in vitro test has sufficient diagnostic sensitivity or specificity, controlled bronchial challenge testing remains the only way to confirm hypersensitivity to TDI. The present report reviews our experience with 12 isocyanate workers who had been removed from their occupational exposure to TDI and who were studied with a TDI inhalation challenge test.

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METHODS AND SUBJECTS

Patients

Patients were referred to the Occupational Health Clinic for evaluation of possible TDI asthma over a five-year period from 1980 to 1985. In only 12 workers was the clinical and occupational history consistent with a diagnosis of occupational asthma due to TDI. Approximately 20 other subjects were evaluated, and the history was not consistent with a diagnosis of occupational asthma. The 12 workers reported symptoms consistent with a diagnosis of TDI asthma including cough, shortness of breath, and wheezing which occurred for the first time while working with isocyanates. These symptoms worsened with continued TDI exposure and improved when the workers were completely removed from isocyanate exposure. Three workers reported significant nocturnal asthma symptoms; chest pain was a prominent symptom in one subject (4). The ages of these 12 workers ranged from 18 to 61 years and included ten men and two women. Three workers (4, 8, and 11) were current cigarette smokers; three subjects were past cigarette smokers (1, 4, and 6). There was no personal or family history of asthma, hayfever, or other allergies prior to the onset of symptoms in ten of the 12 subjects.

Exposure to TDI was substantiated through their employer’s records. The workers held a wide variety of jobs which required different levels of skills, education, and training, but their exposure to TDI could be classified into three categories. Five individuals performed assembly line work with exposure to TDI used in a polyurethane foam injection process. Four workers were involved in spray painting polyurethane paints containing TDI, and three workers were exposed to TDI spills, often as a member of the cleanup crew.

Eight of these 12 workers reported persistent respiratory symptoms which required daily β-agonist bronchodilators and/or
aminophylline despite leaving their occupational exposure to isocyanates. In several cases, intermittent steroids were used for past management of acute asthma during the course of their respiratory disease. No subject was receiving corticosteroids at the time of evaluation nor at any time up to four weeks before admission to the hospital.

On their initial evaluation, each worker received a physical examination, pulmonary function tests, and phlebotomy for determination of serum specific IgE to various isocyanate-protein conjugates. Three persons had evidence of mild airway obstruction, and one subject had moderate airway obstruction on their initial spirometric evaluation. The remaining individuals had normal pulmonary function test results when first seen in our clinic.

All patients were admitted to the University of Cincinnati General Clinical Research Center. Informed consent was obtained from each. The following protocol was used: day 1, history and physical exam, methacholine challenge; day 2, saline aerosol control challenge; day 3, low dose TDI challenge (10 ppb, 10 minutes); day 4, high dose TDI challenge (20 ppb, 20 minutes); and day 5, discharge. All medications not needed by the subjects were discontinued 48 hours prior to the TDI challenges. Inhaled isethionate or metaproterenol was used if needed for control of respiratory symptoms. Theophylline and corticosteroids were not used on the bronchial challenge days unless needed to treat significant bronchospasm.

Pulmonary Function Tests

Pulmonary function tests were performed according to criteria established by the American Thoracic Society using a precalibrated Ohio Medical Company dry-rolling spirometer connected to a microprocessor. Measurement of FEV₁, FVC, and flow rates were made in triplicate. The best value was chosen for analysis.

Inhalation Challenge to TDI

Inhalation challenge studies to TDI were performed using a specially designed inhalation facility for this purpose. The TDI vapors were generated by passing dry filtered air over the liquid surface of 99.6 percent 2,4-TDI. The TDI air stream leaving the generation system was diluted with another source of fresh filtered air at the chamber inlet. Different concentrations of TDI were generated by adjusting the various airflow rates. The air TDI-mixture passed into a 271 L inhalation chamber through which the patient breathed via a mouthpiece attached to the chamber. The concentration of TDI at a port next to the mouthpiece was continuously monitored by a rapid reading isocyanate recorder during and following TDI inhalation challenges. Periodic verification of TDI levels were made using the Marcali method. Serial pulmonary function tests were performed throughout day 2, 3, and 4 of the study at time 10, 20, 30, 40, 60 minutes, hourly for six hours, and at 12 and 24 hours following the inhalation challenges. A positive challenge test was defined as a 20 percent fall in FEV₁. No further testing was performed following a positive response to the low dose TDI challenge.

Bronchial Challenge to Detect Airway Hyperreactivity

In the majority of subjects, methacholine challenge tests were performed using a Collision nebulizer which delivered 11.94 μg methacholine per second (airflow rate 12.5 L/minute at 26 PSI; aerosol mass median aerodynamic diameter 1.10 μm with geometric standard deviation of 2.20 μm). The cumulative inspiratory time was measured using a Fairchild pressure sensor in combination with a Lafayette stop clock. Cumulative inspiratory dose of methacholine (in micrograms) delivered to the respiratory system was calculated from the cumulative inspiratory time and the known rate of methacholine delivery. The rate of breathing was controlled by coaching the patients to inspire for 5 to 6 seconds for each breath. The aerosol was inhaled via a disposable mouthpiece connected to a one-way Hans Rudolph valve.

Following baseline spirometry, the patient was given a 30-second isotonic saline challenge followed by repeat spirometry two minutes after challenge. Providing there is no reaction to saline, the first dose of methacholine is then given (usually 100 to 200 μg) followed by pulmonary function tests two minutes after exposure. A test is considered positive when there is a 20 percent or greater fall in FEV₁, otherwise additional methacholine is administered until a total cumulative dose of 2,000 μg is given. The provocative dose corresponding to a 20 percent fall in FEV₁ (PFEV₁) is calculated by performing a linear regression of the log transformation of dose vs percentage fall in FEV₁. Experience in our laboratory has shown that nearly all asthmatic patients respond to less than 2,000 μg methacholine using our generation system. Similar results have been reported by other investigators. In two subjects, a different method was employed. Five inhalations of increasing doses (2 mg/ml/25 mg/ml) of methacholine were used until a 20 percent fall in FEV₁ was reached.

Table 1—Clinical Summary of Seven Workers with Suspected TDI Asthma and Positive TDI Bronchoprovocaton Test

<table>
<thead>
<tr>
<th>Worker No.</th>
<th>Age</th>
<th>Job</th>
<th>Form of TDI Exposure</th>
<th>Past TDI Spill</th>
<th>Atopic Status</th>
<th>Pulmonary Function Tests</th>
<th>Methacholine Challenge</th>
<th>Type of Response to TDI Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>Structural engineer</td>
<td>Spraying polyurethane paint containing TDI</td>
<td>Yes</td>
<td>No</td>
<td>FEV₁-73% predicted FEV₁/FVC 63%</td>
<td>Positive</td>
<td>Late</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>Assembly line worker</td>
<td>Polyurethane foam seats, dashboards, steering wheels</td>
<td>No</td>
<td>No</td>
<td>Normal</td>
<td>Positive</td>
<td>Immediate and late</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>Refrigerator assembler</td>
<td>Polyurethane foam injection process</td>
<td>No</td>
<td>No</td>
<td>Normal</td>
<td>Positive*</td>
<td>Immediate and late</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>Millwright</td>
<td>TDI spills, clean up</td>
<td>Yes</td>
<td>Possible</td>
<td>FEV₁, 69% Normal</td>
<td>Positive</td>
<td>Immediate and late</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>Refrigerator</td>
<td>Polyurethane foam injection process</td>
<td>TDI spill</td>
<td>Yes</td>
<td>Normal</td>
<td>Positive</td>
<td>Late</td>
</tr>
<tr>
<td>6</td>
<td>58</td>
<td>Airconditioner worker</td>
<td>Polyurethane paint containing TDI</td>
<td>No</td>
<td>No</td>
<td>Normal</td>
<td>Positive</td>
<td>Immediate and late</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>Molder</td>
<td>Polyurethane paint containing TDI</td>
<td>No</td>
<td>No</td>
<td>Normal</td>
<td>Negative</td>
<td>Immediate</td>
</tr>
</tbody>
</table>

*Methacholine challenge was not performed in one patient. Cold air challenge was positive showing a greater than 9 percent fall.
A cold air challenge to assess the degree of nonspecific airway reactivity was performed in one subject according to a reported protocol. Briefly, a patient undergoes eucapnic hyperventilation with cold air (−40°C) for six minutes. A positive cold air challenge is defined as a 9 percent decrease in FEV1 when measured five and ten minutes postchallenge compared to a prechallenge FEV1 measurement.

Radioallergosorbent Assay

A RAST procedure using methylcellulose discs coupled with TDI-HSA, PTI-HSA, MDI-HSA, and HDI-HSA was performed as previously described. A positive result was defined as percentage of binding two times that of laboratory workers with no known exposure to isocyanates.

RESULTS

In seven cases, TDI asthma was documented by a positive inhalation challenge to TDI (Table 1). Results of baseline pulmonary function tests were generally normal (FEV1 and FVC 80 percent predicted and FEV1/FVC 70 percent) or perhaps mildly decreased in the study population as follows: spirometric findings were normal in five of seven reactors and four of five nonreactors. One reactor had a FEV1 of 73 percent predicted (and FEV1/FVC of 33 percent); the second reactor had FEV1 of 69 percent and FVC of 74 percent predicted. One nonreactor had FEV1/FVC of 67 percent. Four of the seven workers demonstrated a dual asthmatic response, two had isolated late bronchospastic responses, and another had an immediate bronchospastic response to TDI (Fig 1). The six patients with dual or late bronchospasm on TDI challenge testing had nonspecific bronchial hyperreactivity as shown by a positive methacholine challenge (five cases) or a positive cold air challenge (one case). The worker with an immediate asthmatic response to TDI had a negative methacholine challenge on three occasions before and after a positive TDI inhalation test.

The seven TDI reactors reported being exposed to TDI for one day to ten years (mean, 1.9 years) prior to the onset of their asthma symptoms. Four were exposed to TDI for less than four months before developing asthma. The subject with only one day of known TDI exposure was exposed to very high concentrations during a spill when a hose coupling became loose and drenched him with TDI. Three additional TDI reactors gave a history of past exposure to TDI spills.

The TDI reactors with bronchial hyperreactivity had been removed from isocyanate exposure for inter-

![Figure 1](http://journal.publications.chestnet.org/pdffile.cfm?url=/data/journals/chest/21542/)

**Figure 1.** Percentage of change in pulmonary function among eight subjects following inhalation challenge testing to TDI. Figure shows (top to bottom) positive reactors who experienced dual (workers 4, 2, 3, and 6), late (workers 5 and 1) or immediate (worker 7) bronchospasm with a 20 percent or greater fall in FEV1 following TDI challenge. A representative negative challenge to TDI (worker 8) is also shown.
vals as long as 12 years (mean 4.5 years, Table 2). The six TDI reactors with bronchial hyperreactivity related persistent respiratory symptoms and required bronchodilator therapy during the interval of absent occupational exposure to TDI. These six individuals had been exposed to TDI for periods ranging from six weeks to two years before symptom severity or management recognition resulted in a change of job with removal from exposure. The TDI reactor with an isolated immediate bronchospastic response to TDI was removed from the workplace one week prior to inhalation testing.

Five workers showed no significant bronchospasm to TDI inhalation challenges at either the low or high dose (Table 3). These nonreactors had been exposed to TDI for intervals ranging from one month to 16 years (mean five years). The time from TDI exposure until bronchial inhalation challenge testing was 1.2 years (range one week to three years). One of them gave a history of past exposure to TDI spills. Methacholine challenges were positive in three of these five workers. Two of these TDI nonreactors with bronchial hyperreactivity had respiratory symptoms at the time of TDI challenge testing. One of them reported experiencing protracted coughing when exposed to multiple irritants. This worker had prominent coughing but no demonstrable bronchospasm in response to his TDI inhalation challenge test. Three of the five patients were asymptomatic and were not receiving any medication at the time of their negative result on TDI challenge test.

Eight of the 12 workers had serologic measurements of specific IgE to TDI-HSA, MDI-HSA, or HDI-HSA performed by RAST testing. No significant levels of specific IgE to isocyanate-protein conjugate were demonstrated in any of these workers.

**Discussion**

In the present study, 12 workers with suspected TDI asthma were evaluated by bronchial challenge to TDI. Seven persons demonstrated sensitivity to low levels of TDI (reactors), confirming isocyanate sensitization. Six of these TDI reactors were challenged months to years after removal from their workplace exposure, demonstrating that isocyanate sensitization may persist for years in the absence of further occupational exposure. These six persons had chronic asthma symptoms and pulmonary disability despite long-term removal from exposure. Four workers had had persistent asthma for one to three years, and two workers had had asthma for nine and 12 years, respectively, after removal from the workplace.

The persistent asthma caused by TDI seems related to the presence of nonspecific bronchial hyperreactivity. Five of the TDI reactors had a positive methacholine challenge, one case showed a positive cold air

<p>| Table 2—Clinical Course of Workers with TDI Asthma Documented by a Positive Inhalation Challenge Test to TDI |
|--------------------------------------------------------|----------------------------------|-------------------|---------------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>Worker</th>
<th>Interval of TDI Exposure Until Symptom Onset</th>
<th>Interval of TDI Exposure While Symptomatic</th>
<th>Persistent Asthma Symptoms after Removal from TDI Exposure</th>
<th>Daily Medications</th>
<th>Interval from Termination of TDI Exposure until TDI Challenge Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 mo</td>
<td>6 wk</td>
<td>Yes</td>
<td>T* + β†</td>
<td>2.5 yr</td>
</tr>
<tr>
<td>2</td>
<td>2 wk</td>
<td>3 mo</td>
<td>Yes</td>
<td>T + β</td>
<td>2.5 yr</td>
</tr>
<tr>
<td>3</td>
<td>1 yr</td>
<td>1 yr</td>
<td>Yes</td>
<td>β</td>
<td>8 yr</td>
</tr>
<tr>
<td>4</td>
<td>10 yr</td>
<td>2 yr</td>
<td>Yes</td>
<td>T + β</td>
<td>3 mo</td>
</tr>
<tr>
<td>5</td>
<td>2 yr</td>
<td>6 mo</td>
<td>Yes</td>
<td>T + β</td>
<td>2 yr</td>
</tr>
<tr>
<td>6</td>
<td>1 day</td>
<td>1 day</td>
<td>Yes</td>
<td>β</td>
<td>12 yr</td>
</tr>
<tr>
<td>7</td>
<td>4 mo</td>
<td>8 mo</td>
<td>No</td>
<td>No</td>
<td>1 wk</td>
</tr>
</tbody>
</table>

*T means theophylline.
†β means β agonist bronchodilator.
challenge, and all of them required medication for daily control of respiratory symptoms. All six symptomatic TDI reactors with bronchial hyperreactivity showed late occurring responses to TDI challenge testing. It has been reported that antigen-induced late occurring asthmatic responses are associated with induction of nonspecific bronchial hyperreactivity. The present cases suggest that occupational exposure to TDI may result in a prolonged state of hyperreactive airways.

Five persons with consistent histories for TDI asthma had negative TDI challenge studies. Three demonstrated bronchial hyperreactivity by methacholine challenge and may represent sensitized individuals tested with an insufficient TDI challenge dose. For example, worker 9 experienced prominent cough symptoms after his TDI challenge unaccompanied by significant airway obstruction. A longer TDI challenge exposure might have elicited bronchospasm, though this remains unconfirmed since further testing was not performed. The recent demonstration that a greater percentage of the 2,6 TDI isomer is released into the ambient air than the corresponding 2,4 TDI isomer in a polyurethane foam industry (though the original composition contained a minority of 2,6 TDI) raises the possibility that isomers of TDI may have different potentials for respiratory sensitization. Future inhalation challenge testing to TDI in the clinical laboratory may need to include a mixture of isomers to improve test sensitivity. Alternatively, the TDI nonreactors may have lost their sensitivity to TDI after removal from the workplace. If bronchial hyperreactivity persists after loss of TDI sensitivity, the worker may develop respiratory symptoms due to the presence of nonspecific airway hyperreactivity unrelated to isocyanate exposure. Some TDI nonreactors may not have been originally sensitized to TDI though their medical histories strongly suggested this diagnosis. These individuals may have been sensitized to other agents in the workplace such as amines added to isocyanate mixtures as catalysts in polyurethane foam manufacturing, or to other non-cross-reactive isocyanates. Of course, individuals with pre-existing hyperreactive airways may respond to a variety of nonspecific irritants in the workplace environment without sensitization to specific workplace agents.

The persistence of pulmonary complaints eventually led the worker to recognize an association between symptoms and job exposure. Despite the association between the workplace environment, all but one worker continued their employment before increasing symptom severity, or employer recognition resulted in a change of job. Continued TDI exposure after symptom onset could be important in the persistence of bronchial sensitization in the TDI reactors, but further longitudinal studies will be needed to demonstrate this in isocyanate workers. In another occupational disease, studies of Western Red Cedar workers have shown that persons with a delayed identification of cedar asthma, and hence, continued occupational exposure, were more likely to have persistent disease following their removal from the workplace.

The form of TDI exposure may be an important factor in the sensitization process and in the general prognosis. Our previous studies have indicated that workers with asthma or bronchitis symptoms were more likely to have past exposure to multiple isocyanate spills. In the current study, four workers with positive bronchial challenges to TDI reported exposure to TDI spills. Worker 6 was drenched with TDI following an industrial accident. This one and only exposure was followed by at least 12 years of respiratory symptoms. Three TDI reactors worked with polyurethane foam injection processes using TDI or other isocyanates. The development of their pulmonary disease may have occurred after unknowingly high exposure to TDI.

Workers in the present study were forced to leave their jobs because of progressive respiratory symptoms. This finding supports reports which indicate industries using isocyanates have a high turnover rate of employees. A survey of a plant using TDI in a polyurethane foam process found over 16 percent of workers reporting previous job transfers out of an isocyanate work area because of respiratory problems believed to be due to the job. Future epidemiologic studies which do not have identification and follow-up of persons leaving or transferring out of the isocyanate work area may miss affected individuals.

In summary, six reported cases of TDI asthma documented by TDI bronchial challenge testing represent a subset of isocyanate workers who experienced persistent disease associated with nonspecific bronchial hyperreactivity and isocyanate sensitization despite removal from occupational exposure. This suggests the prognosis in TDI asthma remains guarded in some workers. Long-term prospective studies of symptomatic isocyanate workers are needed in order to fully define the extent of this problem.

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