reactivity. Preliminary studies from our laboratory indicate that, while unusual, this may occur. It appears, however, that the increased asthma symptoms reported during seasonal exposure to ragweed are not due to decreased baseline pulmonary function or increased immunologic or cholinergic sensitivity.

REFERENCES


DISCUSSION

Dr. Oren: Were there any differences in the drug regimens of the patients in or out of season?
Dr. Rosenthal: None of the patients was very sick and there were no differences in medication.
Dr. Brooks: Was there any correlation of methacholine sensitivity and disease severity?
Dr. Rosenthal: None that was apparent.

Patterns of Airway Reactivity to Asthma Produced by Exposure to Toluene Di-isocyanate*


Occupational exposure to toluene di-isocyanate (TDI), a chemical used in the manufacture of plastics, is associated with the development of various clinical manifestations. These include respiratory tract irritation at high doses causing rhinitis, pharyngitis, and chemical bronchitis. Such responses will occur in anyone exposed to high concentration. In contrast, low dose exposure has produced effects ranging from TDI asthma in TDI workers, decreases in pulmonary function during the workshift, chronic decrease in pulmonary function with prolonged exposure and most recently, the possibility of hypersensitivity pneumonitis. The clinical manifestations associated with inhalation of low concentrations of TDI, below the accepted industrial threshold limit value of 0.02 ppm, occurs in a small group of subjects. The exact mechanism in the production of occupational asthma induced by TDI remains unknown. Recent studies by Zedda et al and by Butcher, Salvaggio and their associates have demonstrated that like other asthmatic patients, workers with a history of

*From the Pulmonary Section and Department of Medicine, Veterans Administration Hospital and Case Western Reserve University, Cleveland.

Reprint requests: Dr. Chester, VA Medical Center, 10701 East Blvd, Cleveland 44106
TDI-induced asthma exhibit bronchial hyperreactivity to known bronchoconstrictors such as methacholine. However, TDI-exposed asymptomatic workers do not show such reactivity.

These observations led us to postulate a decreased threshold in the airway irritant receptors in symptomatic TDI workers. Then, exposure to low concentrations of TDI may cause reflex bronchoconstriction by a nonspecific irritant effect. The purpose of our study was to examine the irritative effects of low concentrations of TDI, in contrast to possible immune-mediated effects.

METHODS

We studied a total of 40 subjects. Twenty were symptomatic workers using TDI in the manufacture of foam who were referred to us because of symptoms temporally related to TDI exposure. The remaining 20 subjects consisted of two control populations never occupationally exposed to TDI; ten were subjects with extrinsic asthma and ten were healthy subjects with normal pulmonary function. None of the 20 control subjects smoked.

Bronchial inhalation challenge tests to TDI and methacholine were conducted on separate days when subjects were asymptomatic. The method used for the methacholine challenge is similar to the NIH protocol. The provocation dose to achieve a 50 percent increase in specific airway resistance was expressed in breath units, 1 unit being the equivalent to 1 breath of a solution containing 1 mg/ml of methacholine.

The TDI inhalation challenge tests lasted 20 minutes and used a system that has been developed in our laboratory. The tests were studied at regular intervals (0.5, 1, 2, 4, and 6 hours). Airway responses were assessed with specific airway resistance (SRaw) measured in a constant volume variable pressure plethysmograph.

Maximum expiratory flow volume curves breathing air and repeated after helium-oxygen washout were then performed three times on each gas mixture. The largest forced vital capacity on air was matched to within 5 percent of the largest FVC breathing helium-oxygen, and the two signals were superimposed at TLC and the volume of isoflow (VsoV) and other flow parameters were derived.

A positive response to a challenge with TDI was defined as an increase in the SRaw ≥ 50 percent from the baseline measurement at any time during the six hour period following the challenge. To assess a possible dose-response relationship to TDI, subjects with a positive response (PD50 SRaw), following exposure to 0.02 ppm, were rechallenged to a lower dose, and the TDI non-responders, rechallenged with higher doses on subsequent days.

RESULTS

The results of the methacholine inhalation challenges are shown in Figure 1. The data points represent the number of breath units necessary to produce a 50 percent increase in the SRaw (PD50 SRaw) for each individual subject, and the horizontal lines represent the means of each group. Mean values of the TDI responders (1.3) and the asthmatic subjects (2.2) are almost identical, both requiring small doses of methacholine to produce a 50 percent change in SRaw. Normal subjects require very large doses (12.1) and TDI non-responders (6) require an intermediate dose to produce an equivalent change. Using a Wilcoxon ranked-sum test, the difference between normal subjects and the other groups was significant (P < 0.01). Only 7 of the 11 TDI non-reactors gave a history of asthmatic symptoms temporally related to TDI exposure. The four nonreactors who were least reactive to methacholine did not give a history of asthmatic symptoms with TDI exposure.

Three patterns of bronchial response to inhalation of 0.02 ppm of TDI were observed: early, late, and dual. Nine of the 20 symptomatic workers challenged with 0.02 ppm TDI demonstrated an increase of SRaw ≥ 50 percent of the baseline resistance. Of the nine reactors, one showed an immediate response, five a dual, and three a late reaction. We view this as strong evidence that TDI may be an occupational allergen.

Comparison between workers who had a bronchial reaction to TDI and those who did not showed there were no obvious differences regarding age, sex, smoking history, atopy, duration of employment, duration of symptoms, or pulmonary function tests. None of the extrinsic asthmatics or normal subjects responded to 0.02 ppm TDI by increasing their SRaw greater than 50 percent.

Repeat testing of eight nonresponders showed a reaction in two nonresponder workers at 0.02 ppm. They both had upper respiratory viral infections a week or two before the rechallenge. During this period of increased reactivity to TDI, a repeat methacholine challenge showed increased reactivity to methacholine. Hence, TDI reactivity and increased methacholine reactivity coincided, subsequent to a viral URI. Two months later, TDI sensitivity and increased methacholine reactivity persisted in one of the two subjects while the other reverted to the previous nonreactor status.

![Figure 1. Methacholine dose-response in TDI workers, extrinsic asthmatic subjects and normal subjects. Methacholine breath units are a log scale where 1 breath unit = 1 breath of solution containing 1 mg/ml of methacholine.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21020/ 06/26/2017)
Parameters of small airway function were assessed in the non-reactor workers using maximum expiratory flow volume curves (MEVF) breathing air and repeated when breathing helium-oxygen. TDI decreased the helium response in the MEVF curve, so that the ΔFEF50 decreased and the volume of isovolume (VisoV) increased. Table 1 compares the results in asthmatic controls and TDI "non-responders" before and after challenge with 0.02 ppm TDI. All the normal subjects had a low volume of isovolume which remained low after exposure to TDI. One of the seven asthmatic patients tested increased markedly after TDI, but four of the seven TDI "non-responders" increased the volume of isovolume (VisoV) markedly after TDI. Using the criteria of a 40 percent increase in VisoV and a 40 percent decrease in ΔFEF50, five of the seven TDI "non-responders" showed evidence of small airway changes subsequent to TDI exposure. None of the asthmatics met these criteria for change (Table 1). The difference between TDI "non-responders" and asthmatic subjects was significant (P < 0.05).

We concluded that airway responses to TDI in symptomatic TDI workers can occur in either large or small airways. Therefore, sensitive tests of both large and small airways function are necessary to document the presence of TDI reactivity. Recent viral respiratory infections can increase airway reactivity to TDI. Methacholine reactivity correlates with bronchial reactivity to TDI only in symptomatic workers. However, TDI does not appear to cause asthma in symptomatic workers simply by a nonspecific irritant effect. The presence of immediate, dual and late bronchial reactions to TDI in symptomatic workers suggests the presence of specific sensitivity to TDI in these subjects. Similar doses of TDI in extrinsic asthmatic control subjects did not produce evidence of an irritative, bronchospastic effect in hyperreactive airways. It appears that TDI may cause asthma by both specific and nonspecific mechanisms partly dependent upon doses tested and coexistent host factors.

### References


### Discussion

Dr. Lakshminarayan: Does the duration of employment affect the reaction to TDI?

Dr. Chester: It does not seem to matter. In our subjects, the duration of employment to the time of initial symptoms ranged from six months to 20 years.

Dr. Lyons: Have you tried to block the reaction with atropine?

Dr. Chester: We have not tried that. There are reports that cromolyn has blocked the immediate response; I don't know if cromolyn blocks dual or late responses.

Dr. King: Have you tried exposing different parts of the airway to TDI, for instance nasal or pharyngeal mucosa, looking for geographic differences in responsiveness?

Dr. Chester: All of our subjects breathed the TDI by mask, thus exposing all of these zones. No attempts to localize irritant receptors have been undertaken.