Absence of Airway Hyperreactivity to Methacholine in a Worker Sensitized to Toluene Diisocyanate (TDI)

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A worker with occupational asthma due to toluene diisocyanate (TDI) was studied. Detailed immunologic studies, including those for p-tolyl isocyanate IgE antibodies and the presence of leukocyte inhibition factor for isocyanate antigen, were negative. Clinically, the subject noted more pronounced symptoms beginning on Monday morning, following a weekend off work, and lessening of her symptoms over the working week. Methacholine challenges were negative when performed on three separate occasions, including the time when maximum symptoms were present, and again six months later, before and after bronchial challenge testing. A dose-related reponse to TDI was observed on bronchial provocation testing using nonirritating concentrations of TDI of 0.0165 and 0.030 ppm. This case provides evidence that the response of the airway to TDI may not always be accompanied by hyperreactivity to methacholine. Screening programs utilizing methacholine challenges may not always identify sensitized workers, since a negative methacholine challenge test does not exclude TDI sensitization.

Toluene diisocyanate (TDI) is a chemical used mainly in the production of polyurethane foams, but also in adhesives, insulation, lacquers, spray paints, elastomers, textile components and wire coatings. In a 1972-1974 survey, NIOSH estimated that between 50,000 and 100,000 employees in the United States were potentially exposed to isocyanates, with perhaps 5% developing adverse respiratory responses.[1]

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There have been a number of pulmonary reactions attributed to TDI, including bronchial asthma.[2-7] Both immunologic and nonimmunologic mechanisms have been ascribed to the asthma syndrome.[8-13]

Nonspecific bronchial hyperreactivity to methacholine or histamine aerosol is an important component of bronchial asthma.[14 15 16] A number of investigations have indicated that nonspecific bronchial hyperreactivity is also present among TDI reactors.[9 12 18-21] A major question is whether the nonspecific bronchial hyperreactivity found in cases of occupational asthma is a predisposing factor or a result of the asthma.[22 23 24] In cases of Western red cedar asthma, it has been suggested that bronchial hyperreactivity is the result of the asthma and may even remain years after cessation of exposure.[22] Because of the relationship between bronchial sensitivity to an occupational chemical such as TDI and evidence of bronchial hyperreactivity to methacholine or histamine, it has been suggested that methacholine challenges be used as a screening test for suspected sensitized workers.[1 24] Furthermore, it has also been proposed that this test might be useful as a screening procedure for identifying high-risk individuals during preemployment examinations, possibly determining early TDI sensitivity during periodic evaluations.

The present report describes experience with a sensitized worker who demonstrated a positive bronchial challenge to TDI but who had consistently negative methacholine challenge tests.

Case Report

The patient was a 43-year-old nonsmoking white woman with no previous or family history of atopy or of asthma. For the previous two and one-half years she had worked for a company that manufactured polyester-resin/fibrous reinforced plastic bathroom fixtures. During a part of that time she worked as a molder and was exposed to TDI from a nearby spraying operation which uti-

lized a combination vinyl-polyester-polyurethane paint mixture containing TDI. The sprayed fixtures were air-dried in close proximity to the molding operation where the patient worked. Several months prior to evaluation of the patient, large fans had been mounted outside the spray booths and directed toward the workers, with intent to provide cool air currents for the workers' comfort. The use of these fans resulted, however, in the escape of spray-booth vapors into the interior of the building and into the vicinity of the molding operation where the patient worked. A large exhaust fan located on the exterior wall near the mold operated by the patient drew vapors from the air-drying sprayed fixtures and from the spray booths themselves, across the patient's working area. The odor of organic vapors was readily apparent in the molding area.

The patient's problems first began in May 1978, approximately four months after her transfer into the molder's job. She first noticed throat irritation and a nonproductive cough which occurred primarily at work but persisted at home. By June 1978, she began experiencing episodic "smothering" sensations, with difficulty in taking a deep breath during these episodes. She noted that the symptoms were worse on Monday mornings following a weekend off work. Her symptoms usually developed approximately one hour after she began work, and reached a peak within three to four hours. On Tuesdays through Fridays, her symptoms were not as severe. The problem substantially cleared up over the weekend and on vacations, only to reoccur when she returned to work on Monday mornings. These episodes became progressively more frequent and more severe, culminating in an episode at work that required emergency treatment in January 1979. She did not return to work following that episode, and was first evaluated in mid-February 1979.

At the time of initial evaluation, the patient was essentially asymptomatic. Physical examination was entirely within normal limits except for the presence of uterine fibroids, which were scheduled to be removed by a hysterectomy the following week. Pulmonary function tests were within normal limits, and methacholine challenge was negative at this time. Based on her history of episodic smothering reactions related to work, it was presumed that her asthma was due to occupational exposure to TDI, present at the worksite in the spray-paint system. It was also assumed that the route of exposure was through exhaust of TDI vapors across her work area originating from the air-drying fixtures, as well as from the spray-paint booth operation. Changes in plant ventilation were recommended, which might eliminate her exposure to TDI and thus enable her to resume work.

She remained off work for six months, and resumed work in July 1979. She apparently had no significant reactions during her first week at work; however, on Monday, one week after resuming work and following her first weekend at home, she developed a smothering episode at work. During the remainder of the week she noted chest tightness and throat irritation which began approximately three hours following commencement of work, but which did not result in her having major difficulty in breathing or in the sensation of difficulty in taking a deep breath. On Monday of the second week following her return to work, she had another severe smothering episode which began approximately two and one-half hours following the beginning of work and lasted approximately five hours. The next day one of the authors (A.B.S.) went to the plant and performed pulmonary function tests before, during and after work, using a Vitalograph spirometer. She was asymptomatic throughout the workshift. Her forced vital capacity (FVC) ranged between 3.78 and 4.0 liters, and her forced expiratory volume at one second (FEV_1) ranged between 2.95 and 3.10 liters. Arrangements were then made with her private physician to perform spirometric measurements should she experience another episode. The following Monday, she again experienced the onset of an episode, approximately five and one-half hours into the workshift and two hours after the spray-paint operation was started. She was taken by the plant manager to her physician's office, where spirometry indicated an FVC of 2.90 liters and FEV_1 of 2.3 liters. Isoproterenol inhalation resulted in prompt improvement of symptoms, with an increase in FVC to 4.35 liters and FEV_1 to 3.5 liters. Given spirometric documentation of reversible airways obstruction during an episode that began at work, and which appeared to be temporally related to the beginning of the spray-paint operation, she was admitted to the General Clinical Research Center (GCRC) for inhalation challenges to TDI, the presumed offending agent for her episodic smothering attacks.

Immunological Study

Specific IgE to tolyl portion of isocyanate was measured by modification of the radioallergosorbent technique, RAST.[25,26] Methyl cellulose discs were activated by cyanogen bromide and coupled with TDI-human serum albumin (HSA), p-tolyl and o-tolyl isocyanate-HSA conjugates. The coupled discs were then used in the routine RAST procedure.[25] Results were expressed as percentage binding compared to a normal reference control with low IgE. The amount of radioactivity bound by the patient's serum was 3.2%. When the test was repeated two days later, the amount was 2.9%. This test had been performed in February 1978 (six months earlier) with a similar result (less than 3.0%). Mean percent binding of the reference control was 24.3.

RAST testing for a battery of common allergens, including ragweed, timothy grass, box elder, and cat and dog dander, showed less than 3% binding, and was considered negative. A test for lymphocyte inhibition factor (LIF) to TDI antigen was performed.[27] The size of migration was traced with projection microscopy and measured by planemetry. The migration index was calculated by comparing the average migration of antigen-containing cultures without antigen.

Pulmonary Function Studies

Baseline pulmonary function tests at the time of admission to the GCRC were normal, and were performed using a precalibrated dry-rolling CPI spirometer. FVC was 4.3 liters or 112% of predicted; FEV_1 was 3.2 liters or 109% of predicted; and FEV_1/FVC was 74%.

Methacholine Challenge

Methacholine challenges were performed, utilizing an aerosol-generating system which records both methacholine concentration and volume breathed. The test is

considered positive when there is a reduction of FEV_1 of 20%. In previous studies on 22 subjects with bronchial asthma of varying severity, the amount of inhaled methacholine (concentration multiplied by inspired volume) that produced a 20% decrease was determined; the mean methacholine concentration resulting in a positive test was 129 μg. In eight of these subjects with normal pulmonary function tests (FEV_1/FVC at least 70% or greater), the mean methacholine concentration was 220 μg. In the patient studied, methacholine challenges were performed twice prior to TDI bronchial inhalations (six months and one day before), and a third time on the following TDI bronchial challenge testing. In each case, the tests were negative even at methacholine doses of more than 2,000 μg and cumulative amounts of more than 4,000 μg.

Bronchial Challenge Test to TDI

Bronchial provocation studies wei performed on the day following the second of three methacholine challenges. Tests were performed with two different concentrations of TDI, administered on separate days. A specially designed inhalation challenge system has been developed in the clinic laboratory. This system delivers a dilute mixture of TDI and air, and concentrations of TDI are measured continuously with a monitor. Compressed air is delivered through Teflon tubing which divides air into two streams. The air is passed over a stoppered Teflon beaker containing 99.6% pure 2,4-TDI maintained in an adjustable temperature water bath. The TDI airstream leaves the beaker, and is then diluted with the other airstream. By means of adjustments in the air flow and the beaker temperature, various concentrations of TDI can be generated. The air mixed with TDI then passes into a 24.9-liter mixing chamber made of Plexiglass and spray coated with Teflon. The patient breathes through a mouthpiece attached to this chamber where concentrations of TDI were continuously monitored, and were found to remain stable prior to, during and following inhalation challenges. Two concentrations of TDI were used for testing, 0.0165 ppm and 0.030 ppm.

Fig 1 shows the results of inhalation challenges for two different concentrations of TDI, performed on separate days, when the patient was asymptomatic and when baseline pulmonary function tests were normal. Following inhalation of a saline control, no fall in FEV_1 was noted, and pulmonary function tests remained stable. Following inhalation of 0.0165 ppm TDI for 20 minutes, a fall in FEV_1 was noted, reaching a maximum decrease of 12.5% by 30 minutes and returning to baseline by three hours. The patient did not complain of dyspnea or chest tightness. There were no abnormal physical findings noted on auscultation of the chest. Following inhalation of 0.030 ppm TDI for 20 minutes, and after a stable control period and negative response to the saline control, there was a more dramatic reduction in FEV_1. This reached a maximum decrease of 31.2% by 25 minutes and returned to near baseline control levels by one and one-half hours. The patient complained of chest tightness at 25 minutes after inhalation (corresponding to a 31.2% reduction in FEV_1); scattered inspiratory and expiratory wheezes were heard on auscultation of the chest. She

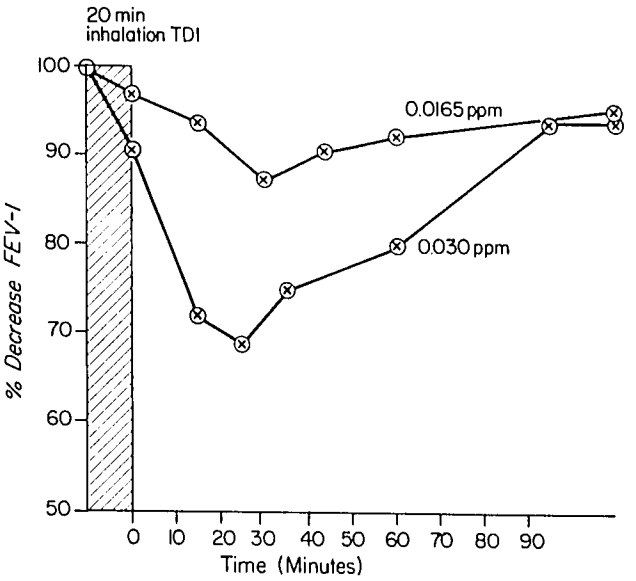

Fig 1. — Bronchial provocation testing for TDI. Following a 20-minute inhalation period, a maximum decrease in FEV_1 of 12.5% was noted at 0.0165 ppm TDI and a 31.2% decrease at 0.030 ppm.

became asymptomatic over the next half hour and pulmonary function tests returned to normal. In both inhalation challenges, pulmonary function testing was continued over a 12-hour period. No late asthmatic reaction or change in pulmonary function testing was noted.

Discussion

The patient studied in this investigation had a clinical presentation of occupational asthma and evidence of reversible airways obstructive disease. She demonstrated what appeared to be a dose-related reduction in FEV_1 following inhalation of TDI by bronchial challenges. The bronchial inhalation challenges were performed at low concentrations so that the airway responses noted were not believed to be irritative in nature.[28-31]

A most important observation was that there was absence of hyperreactivity of airways to methacholine. The test was performed at the time of maximum symptomatology, but also before and after TDI bronchial inhalation challenges. Immunologic investigations were negative, revealing the absence of specific IgE antibodies to p-tolyl isocyanate by RAST and the absence of cellular immunologic response to TDI antigen, as determined by LIF.

Immunologic mechanisms causing TDI-induced asthma were suggested by studies of Scheel et al,[32] who demonstrated TDI-specific antibodies in rabbits exposed to 0.1 ppm TDI by inhalation for six days per week for two to four weeks. Mechanisms involving cellular immunity have also been proposed.[33] Recent reports by Karol et al[26,34] have identified specific IgE antibodies for the p-tolyl portion of the isocyanate molecule in sera of a significant number of symptomatic workers. The individual studied in the present investigation was not atopic, as confirmed by history and by the absence of specific IgE antibodies to a battery of common allergens measured by RAST testing. An immunological process operative in the patient could not be demonstrated since RAST for p-tolyl

isocyanate and LIF were negative; but this did not necessarily rule out an immunologic process. It is conceivable that IgG_4 or other antibodies were present, but these were not measured in the patient. Present findings, however, are consistent with those of other studies which also have failed to identify immunologic mechanisms in sensitized workers.[11 12 18 33 35]

An important observation is that the patient studied in the present investigation did not demonstrate hyperresponsiveness to methacholine. This test was performed on three separate occasions, including before and after provocation challenge tests to TDI. This is an interesting observation, since the question as to whether underlying airway hyperreactivity, as demonstrated by sensitivity to methacholine or histamine, predisposes an individual to TDI sensitivity and whether it is present before the development of clinically overt asthma.[1] Chester et al,[21] for example, reported that methacholine reactivity correlated with bronchial reactivity to TDI only in symptomatic workers. All workers with positive bronchial provocation tests had positive methacholine challenge studies. The methacholine responses were similar to those seen in other patients with bronchial asthma. Butcher et al[8] reported that eight of 11 sensitive workers showed positive methacholine challenge tests whereas only one of ten nonsensitized persons gave a positive response. In contrast, O'Brien et al[19] noted increased bronchial reactivity to histamine in only 17 of 31 subjects sensitive to TDI (as demonstrated by bronchial provocation testing), while 14 sensitized subjects did not react significantly to histamine.

The dose-related response to TDI that was observed in the case described here is similar to findings of others. Chester et al[21] concluded that TDI asthma was caused both by specific and nonspecific mechanisms which were partly dependent upon the dose-tested as well as upon coexistent host factors. O'Brien et al[19] reported differences in airway reactivity to varying concentrations of TDI. Butcher et al[35] showed lack of response to TDI vapors in an individual at concentrations of 0.005 ppm, but a dual response at 0.01 ppm. Porter et al[11] suggested that a dose-response relationship for sensitization was present among TDI manufacturing plant workers. Dose-related responses to TDI have also been reported by Wegman[36 37] and by Elkins et al.[29]

Thus, the data from the present, as well as from other, investigations suggest that a dose-related response to TDI may be seen in some affected workers and, in addition, that some sensitized workers may not demonstrate hyperreactivity to methacholine or histamine. The mechanism which would explain the airway response cannot be ascertained at this time. It is most likely that a number of different pulmonary reactions to TDI may occur. In high concentrations, TDI causes bronchospasm because of its patently irritating properties.[4] An immunologic mechanism is probably operative in the small percentage of sensitive workers who demonstrate p-tolyl-specific IgE antibodies in their sera.[27] These individuals are likely to be the ones who demonstrate hyperreactivity to methacholine or histamine. A late asthmatic reation which appears after one hour is also probably associated with airway hyperreactivity.

In addition to the previously mentioned pulmonary reactions, it appears that there is a group of sensitive workers who do not show evidence of an irritation or immunologic process as a cause of their asthma. The present patient, for instance, reported most pronounced symptoms on returning to work on Monday and reduction of symptoms over the working week. This is reminiscent of byssinosis.[38] TDI does not cause histamine release from basophils, while cotton extracts do.[9 13 38] Some individuals show reduced expiratory flow rates after cotton dust exposure, while others do not.[38] Perhaps host factors are important in determining responses of airways in some individuals. These responses may not necessarily require the presence of airway hyperreactivity.

A dose-related response to TDI has important environmental and regulatory implications. A safe threshold value might be identified in workers if the asthma is pharmacologic and not immunologic. Possibly, a pharmacologic mechanism may explain the acute changes and suggested chronic effects on pulmonary function testing noted in workers exposed to TDI at levels less than the current threshold limit value.[39-42] While it appears that the use of methacholine challenges as a screening test for identifying susceptible or sensitive workers may be helpful in some circumstances, it may not be completely practical since the absence of a positive test does not exclude sensitization of a worker.

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Ethical Conflict

Four states have now passed legislation that adopts a new method of capital punishment — death by drug injection. The method entails injection of a lethal dose of a drug prepared for that purpose and administered and monitored by medically trained personnel. The growing adoption of these programs raises serious ethical issues for American physicians about their continued and expanded participation in state-ordered execution of human beings for crimes.

— From "The Ethics of Medical Participation in Capital Punishment by Intravenous Drug Injection" in *The New England Journal of Medicine*, January 24, 1980.