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Survey of Industrial Workers for Antibodies to Toluene Diisocyanate

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A screening program was undertaken at a research and development facility of a large toluene-diisocyanate (TDI) manufacturing corporation. The purpose was to determine the occurrence of antibodies to TDI in selected worker populations. Sera were obtained at 6-month intervals from 103 employees who were exposed from 6 to 24 months to ambient workplace concentrations of TDI (0.02 ppm or less). With the use of RAST (radioallergosorbent test) containing p-tolyl isocyanate-human serum albumin as antigen, no tolyl-reactive IgE antibodies were detected in sera when workers were exposed only to ambient TDI concentrations. During the study, 20 workers had acute exposures to TDI as a result of spills or splashes. Antibody responses developed in three of four individuals whose acute exposures were accompanied by immediate respiratory symptomatology and a decrease in FEV_1 of 20% or greater. By contrast, an antibody response developed in only one of nine workers with immediate respiratory symptoms but no spirometric changes upon acute TDI exposure. No serologic response developed in the remaining workers whose acute exposure resulted in delayed-onset respiratory symptomatology without spirometric changes, or who were asymptomatic at exposure. In persons developing antibodies, an increase in tolyl-reactive IgE was observed within two months of exposure. Routine serologic screening of workers for tolyl-reactive antibodies may be of value in confirming suspected isocyanate exposure and in providing an early warning of developing TDI hypersensitivity.

Toluene diisocyanate (TDI) is used extensively in the manufacture of polyurethane for cushions, coatings, furniture and many other consumer products. Each year more than 50,000 workers in the United States are exposed to TDI and sensitivity has been reported to develop in a percentage of exposed workers.[1,2] TDI sensitivity is manifest as bronchial asthma or dermatologic symptoms, or both.[3,4]

Although considerable controversy has existed regarding the pathogenesis of TDI hypersensitivity, several groups of investigators have recently identified specific IgE antibodies in sensitized workers.[5-9] Substantial support for an immunologic mechanism for TDI hypersensitivity has also come from animal studies. In guinea pigs, repeated inhalation of TDI vapor resulted in production of TDI-specific antibodies and in pulmonary hypersensitivity to TDI.[10] Moreover, dermal exposure of guinea pigs to TDI resulted in immunologic sensitization.[11] This sensitivity was evidenced by contact hypersensitivity, specific antibody production, and in some animals by pulmonary hypersensitivity reactions to TDI. Moreover, a concentration-response relationship has been observed between the exposure concentration of TDI and the number of animals developing sensitivity.[12] In view of the immunologic response which occurs in experimental animals following exposure to known concentrations of TDI, it was of interest to determine if similar immunologic responses occur in workers as a result of TDI exposure. The study described here reports development of IgE antibodies in some workers having acute isocyanate exposure. In contrast, persons exposed to workplace concentrations of TDI within the current 0.02 ppm TLV developed neither antibodies to TDI nor TDI pulmonary hypersensitivity.

Materials and Methods

Subjects — Ambient Isocyanate Exposures. This study group comprised 103 persons hired during 1979 and the first half of 1980 at the Pittsburgh research and development facility of Mobay Chemical Corporation. Persons were selected for study if their job responsibilities were anticipated to involve work in isocyanate environments for greater than 10% of their employment. Serum was collected from these persons at hiring and thereafter at 6-month intervals to monitor for possible antibody production as a result of isocyanate exposure. Job descriptions and expected isocyanate exposure for these individuals are listed in Table 1. The majority of the workers (57%) were hired as technicians for the research and development laboratories where they would be handling isocyanates in the manufacture of rigid or flexible poly-

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Table 1. — Job Description and Expected Isocyanate Exposure of Newly Hired Employees.

Job Description	No. Workers (% Total)	Expected Isocyanate Exposure
Technician	59 (57%)	Continued
Industrial hygienist/ maintenance worker	9 (9%)	Intermittent
Engineer	35 (34%)	Occasional
Total	103 (100%)	

urethane foams. Nine (9%) were industrial hygienists or maintenance workers who were expected to have intermittent isocyanate exposure. Thirty-five (34%) were engineers whose job descriptions varied but whose work might entail a high degree of exposure to isocyanates, e.g., when involved with production startups or trouble shooting. Of this group of 103 persons, seven experienced acute isocyanate exposure during the study and were subsequently recategorized into the second study group.

Acute Isocyanate Exposure. The second study group consisted of all personnel employed in the Pittsburgh facility of Mobay who experienced acute isocyanate exposure during the years 1978 through 1980. Employees were instructed to report all isocyanate exposures, whether symptomatic or asymptomatic, to the Medical Department. During the study, 20 workers (including seven from the first study group) reported acute isocyanate exposures; 11 of these workers were involved on more than one occasion. The medical staff assessed and treated the presenting symptomatology, estimated the degree of exposure, performed spirometric studies, and obtained blood samples for antibody determinations. Subsequent blood samples were drawn from these persons two weeks after exposure, then bimonthly thereafter, until antibody values decreased to insignificant levels.

Serologic Procedures. — 1. RAST. All blood samples were coded by the medical department, then brought to the University of Pittsburgh for antibody determinations. Specific IgE antibodies were measured using a RAST assay employing p-tolyl isocyanate-human serum albumin (p-TMI-HSA) as antigen. Methods for antigen preparation, characterization, and binding to paper discs have been described.[13] RAST was performed by incubating 50 μl aliquots of serum with an antigen-coated disc for 16 hours at ambient temperature. After thorough washing of discs, 50 μl I^{125} — rabbit anti-human IgE (RAST reagent, Pharmacia Diagnostics) were added and discs were incubated an additional 16 hours at room temperature. Following thorough washing, discs were counted in 10 ml scintillation fluid (ACS, Amersham) using a Packard tricarb liquid-scintillation spectrometer. The amount of IgE antibody reactive with tolyl determinants on discs was determined by comparing the radioactivity bound to p-TMI-HSA-coated discs with that bound to discs which had been coated with human serum albumin (HSA). Replicate determinations differed by 10% or less.

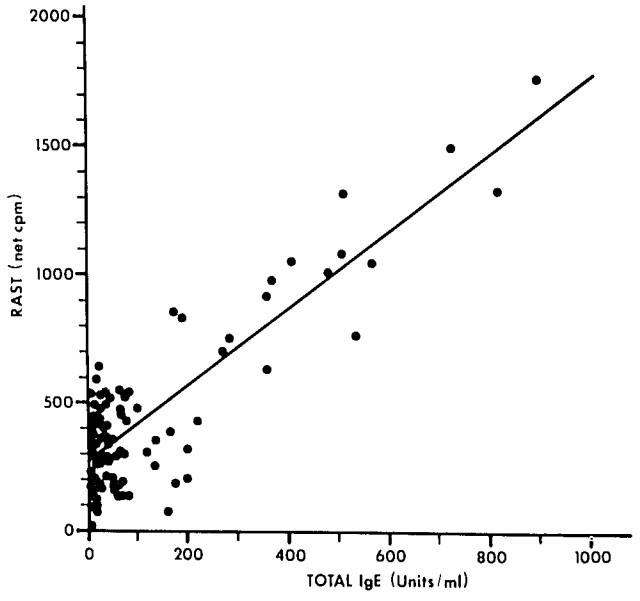

Fig 1. — Linear regression analyses of RAST and total IgE values for sera from workers prior to commencement of job duties (n = 103, y = 1.49X + 264, r = 0.8598, t = 17).

2. RAST Inhibition. The ability of p-TMI-HSA to inhibit RAST reactions was determined using a modification of a standard procedure.[14] Sera (25 μl) were incubated with 200 μg p-TMI-HSA in 25 μl buffer (PRIST diluent, Pharmacia Diagnostics). Control tubes contained serum and 25 μl buffer. After two hours at 37°C, an antigen-coated disc was added to each tube. Samples were incubated for 16 hours at ambient temperatures. Discs were thoroughly washed, then incubated with radio-labelled rabbit anti-IgE as described earlier. The percent inhibition was calculated as follows:

$$\left(\frac{\text{1-\% cpm bound above blank with inhibitor}}{\text{\% cpm bound above blank with buffer}}\right) 100$$

3. Total IgE (PRIST). Total IgE in serum samples was determined by the PRIST method using a commercial test kit (Pharmacia Diagnostics).

Pulmonary Function Measurement. — Pulmonary function was measured using Ohio Medical Product's dry rolling seal spirometer and employing the testing procedures recommended by the American Thoracic Society. All expiratory maneuver curves were back extrapolated to give the optimum FEV_1 and FEF_{25-75} values. In the event of an acute TDI spill or exposure, spirometric tests were repeated daily until values returned to pre-exposure baseline levels. Persons reporting isocyanate exposure did not return to their work area until spirometric values returned to normal. Changes in FEV_1 of 20% or greater were considered significant.

Results

Ambient Isocyanate Exposure. — Serum samples taken from 103 newly hired workers prior to commencement of job duties were evaluated for tolyl-reactive IgE antibodies (RAST) and total IgE (PRIST). Results of the assays are presented in Fig 1. Sera which yielded high RAST values contained elevated levels of total IgE. Analysis of data using simple linear regression revealed a significant correlation between the two assays (r = 0.8598, t = 17). The correlation indicated that, with these sera, RAST values could be predicted from knowledge of total IgE content. The data further implied that no serum from the 103 newly hired workers drawn at the time of hire con-

Table 2. — Acute TDI Exposures; Symptomatology, Spirometric Changes and Subsequent Antibody Responses.

Worker	Date of Exposure	Spirometric Tests	Atopic Status†	IgE‡ Maximum Titer (% RAST Inhibition)
Group A: Immediate respiratory symptoms: spirometric changes				
B-09	9/78	$FEV_1 = 21\%$, $FEF_{25-75} = 49\%$	N	3595 (100%)
E-02	3/79	*$FEV_1 > 20\%$	A	1756 (41%)
B-23	8/79	$FEV_1 = 22\%$	A	2294 (50%)
B-25	7/79	$FEV_1 = 23\%$, $FEF_{25-75} = 54\%$	N	0
Group B: Immediate respiratory symptoms; no spirometric changes				
F-03	11/78	0	N	0
B-25	2/79	0	N	0
* R-07	3/79	0	N	0
B-17	6/79	0	A	1345 (40%)
P-10	10/79	0	N	0
W-09	12/79	0	N	0
S-13	3/80	0	N	0
B-19	3/80	0	N	0
B-32	11/80	0	N	0
Group C: Delayed respiratory symptoms; no spirometric changes				
B-25	11/78	0	N	0
K-11	3/78	0	N	0
K-11	5/78	0	N	0
K-11	2/79	0	N	0
K-11	2/79	0	N	0
C-22	11/79	0	N	0
W-09	8/79	0	N	0
R-07	9/80	0	N	0
Group D: No respiratory symptoms, no spirometric changes				
F-03	11/78	0	N	0
A-06	3/79	0	N	0
A-06	5/79	0	N	0
A-06	6/79	0	N	0
A-06	8/79	0	N	0
L-05	4/79	0	N	0
C-22	8/79	0	N	0
B-32	8/79	0	N	0
S-13	1/80	0 (R)	N	0
F-05	2/80	0 (R)	N	0
N-1	3/80	0 (R)	N	0
S-36	3/80	0 (R)	N	0
B-17	3/80	0 (R)	A	0
D-14	11/80	0	N	0

*Pulmonary function testing performed at a local hospital

†A, atopic person (total IgE > 200 U/ml); N, non-atopic person (total IgE < 200 U/ml)

‡Indicates absence of tolyl-reactive antibodies as determined from RAST inhibition

(R) Worker was wearing a respirator at the time of exposure

tained anti-tolyl IgE antibodies. RAST-inhibition studies supported this conclusion. Binding of sera to antigen-coated discs was not inhibited by the presence of excess p-TMI-HSA antigen in reaction tubes.

During the study, seven persons in this "newly hired" group had acute exposure to isocyanate. These cases are discussed in the following section. The remaining 96 workers in this group were exposed only to ambient TDI concentrations in the facility. These concentrations were determined to be below the threshold limit value of 0.02 ppm. Serum was obtained from the 96 workers at regular 6-month intervals for antibody analysis. A total of 316 serum samples were evaluated. With the use of RAST and RAST inhibition, no tolyl-reactive antibodies were detected in any of the samples. In addition, none of these workers gave evidence of clinical TDI sensitivity.

Acute Isocyanate Exposure — Spirometric Changes. — During the three-year study period, 1978 through 1980, 20 of the approximately 350 employees at the facility reported a total of 35 instances of acute isocyanate exposure. These episodes are listed in Table 2.

Group A comprised those persons who developed respiratory symptomatology within one hour of acute TDI exposure ("immediate" reactions) and additionally had spirometric changes immediately following exposure. Symptoms reported by persons in Group A included respiratory distress ranging from mild to moderate degrees of shortness of breath, coughing, wheezing, or tightness in the chest. The degree of exposure received by each of these individuals as the result of spills or splashes was difficult to determine. One of the workers in Group A had substantial exposure to TDI, via both inhalation and dermal contact, when he was sprayed over the upper trunk and face by a malfunctioning TDI-injection nozzle at the head of a foam machine. Another individual was exposed to TDI when a drum was accidentally hit by a forklift, blowing out a bung. Following exposure, this person put on respiratory equipment and worked for an additional five to ten minutes cleaning up the spill before he began to wheeze.

Results of serologic assays on serial blood samples from each person in Group A are presented in Figs 2

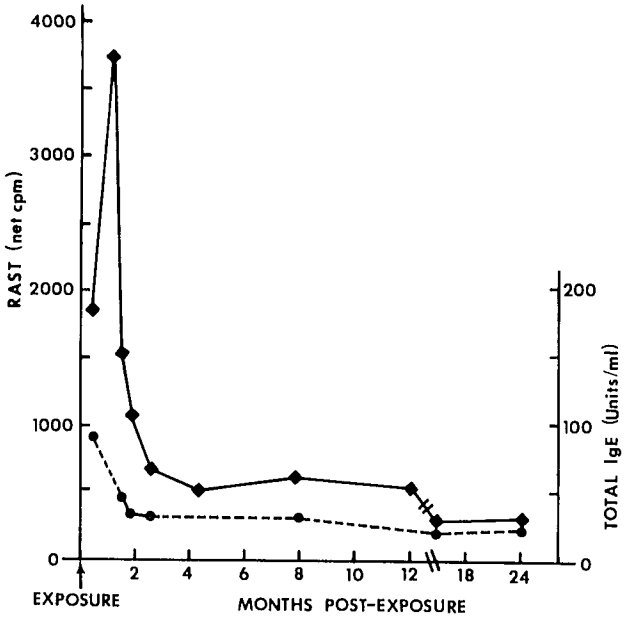

Fig 2. — RAST assay for tolyl-reactive IgE antibody and total IgE of sera following acute TDI exposure. RAST (solid line), total IgE (broken line). RAST values > 600 net cpm indicate significant antibody titer. Case B-09.

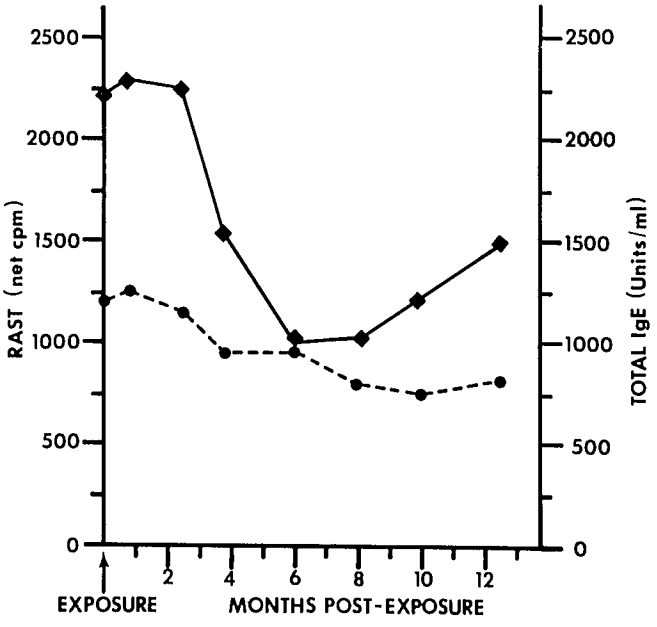

Fig 4. — RAST assay for tolyl-reactive IgE antibody and total IgE following acute TDI exposure. RAST (solid line), total IgE (broken line). For serum drawn at exposure, RAST inhibition was 30%, three weeks later RAST inhibition was 50%. Case B-23.

through 5. Tolyl-reactive IgE antibodies were detected in three of the four workers following exposure. Serologic values prior to exposure were not available in any of these cases since each worker had been employed with the corporation before inception of the study.

In the first case, B-09, a blood sample was obtained two weeks following acute exposure. The RAST titer at that time was 1,865 net cpm. The titer subsequently increased to 3595 net cpm four weeks post-exposure. Thereafter titers declined. By four months' post-exposure, values were less than 600 net cpm and no longer significant.[4] RAST-inhibition studies were performed on sera drawn 2 to 7 weeks post-exposure. RAST titers were completely (100%) inhibited by p-TMI-HSA antigen. The total IgE content of serum samples was determined and results are shown in Fig 2. Values ranged between 25 and 95 Units per ml indicating the non-atopic status of this employee ($\bar{X}$ +2D = 120 U/ml for non-atopic adults[15]).

Two other persons in Group A demonstrated elevated RAST values. Titers for these individuals are presented in Figs 3 and 4. In case E-02, the first serum sample was drawn one week following exposure. RAST at that time had a value of 1039 net cpm. The titer increased in subsequent sera and was maximal eight weeks post-exposure. RAST-inhibition assay with the latter serum indicated 41% of the titer was inhibited by p-TMI-HSA antigen. Total IgE values indicated the "atopic" status of this worker (Fig 3).

RAST titers for Case B-23 are presented in Fig 4. Serum drawn on the day of exposure had a RAST value of 2240 net cpm. Thirty percent of this binding was inhibited by p-TMI-HSA antigen. A blood sample taken three weeks later yielded the same RAST titer (2294 net cpm) but showed 50% inhibition by antigen. RAST values decreased considerably in subsequent sera. Total IgE content of sera from this worker is shown in Fig 4. On the day

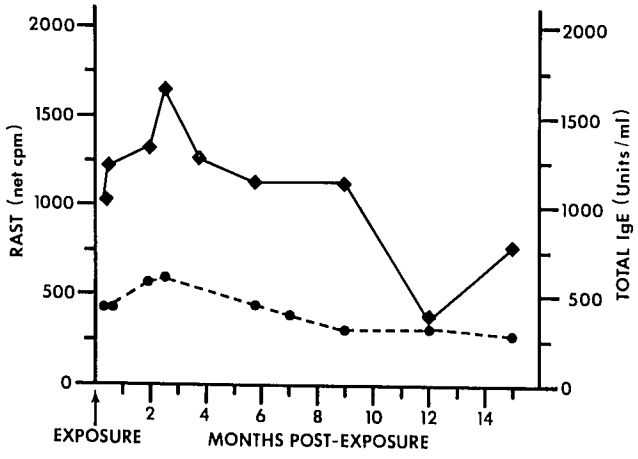

Fig 3. — RAST assay for tolyl-reactive IgE antibody and total IgE following acute TDI exposure. The first serum sample was obtained one week following exposure. RAST (solid line), total IgE (broken line). Case E-02.

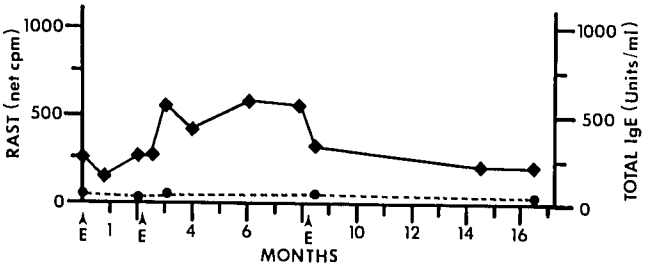

Fig 5. — RAST assay for tolyl-reactive IgE antibody and total IgE. RAST (solid line), total IgE (broken line). The employee had three acute TDI exposures (E) during the study period. No tolyl-reactive antibodies were detected. Case B-25.

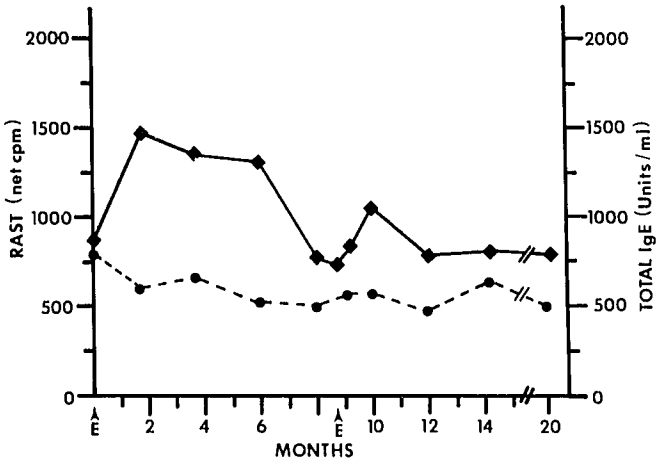

Fig 6. — RAST assay for tolyl reactive IgE antibody and total IgE. RAST (solid line), total IgE (broken line). Two acute TDI exposures occurred during the study period. RAST increased following each exposure; total IgE did not increase. Case B-17.

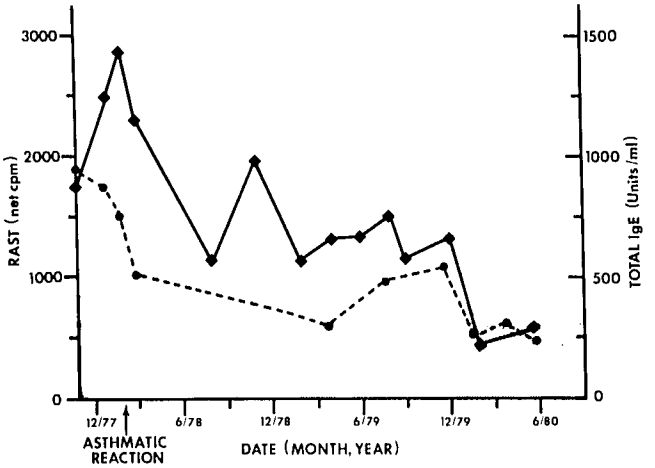

Fig 7. — RAST assay for tolyl-reactive IgE antibody and total IgE of sera drawn subsequent to a TDI pulmonary hypersensitivity reaction. RAST (solid line), total IgE (broken line). RAST antibodies were detected 18 months following the response but were no longer detected two years following response. (Shaded area indicates non-significant RAST values.)

of exposure, total IgE was 1200 U/ml. Three weeks later, the value was essentially unchanged (1250 U/ml) and subsequent sera displayed a gradual decline in total IgE content.

The fourth worker in Group A (B-25) had several acute TDI exposures. One episode in November 1978 was characterized by delayed-onset respiratory symptomatology without changes in spirometry (see Group C). Another symptomatic exposure occurred in February 1979. In July 1979, a third exposure resulted in immediate respiratory symptoms and a decrease in FEV_1 and FEF_{25-75}. The first serum sample was obtained from this person in November 1978. Use of RAST showed no detectable tolyl-reactive IgE antibodies in this sample or in any subsequent serum from this individual (Fig 5). Total IgE content of sera never exceeded 52 U/ml.

Acute Isocyanate Exposures — No Spirometric Change. — During the study, eight additional workers reported acute TDI exposure resulting in immediate respiratory symptomatology. In these cases, however, FEV_1 remained within 20% of baseline value (Table 2, Group B). Serologic evaluation indicated an antibody response in one of the eight persons. In this case, RAST titer increased two months following exposure (Fig 6). The increase was not accompanied by an elevation in total serum IgE. RAST-inhibition studies indicated 30 to 40% of the binding was attributable to specific antibodies. Total IgE content of serum samples ranged between 500 and 800 U/ml throughout the 20-month evaluation period. Serologic assays through December 1980 of the other workers in Group B revealed no production of tolyl-reactive antibodies or increase in total serum IgE.

Workers in Group C experienced acute TDI exposure (in one case on four separate occasions) and developed respiratory complaints eight to twelve hours following the exposures. These individuals were seen in the medical department the following day. At that time, they demonstrated no significant spirometric changes. In all cases, RAST assays were negative in serial serum specimens following the reported exposures.

Group D indicates 14 instances of asymptomatic exposure in which no respiratory symptoms developed and no spirometric changes were detected. In most cases, persons were not intimately involved in spills but either were in the vicinity of an acute exposure or involved in cleaning up a spill while wearing respirators (as indicated in Table 2). Using RAST, no antibodies were detected in serum samples drawn from the day of exposure through December 1980. Total IgE levels also were unchanged.

Sensitization to TDI. — Previous to this study, two persons at the facility had been identified as having respiratory hypersensitivity to TDI. During their period of sensitivity both individuals demonstrated tolyl-reactive IgE antibodies in their sera.[4] One person continued to supply serum samples for antibody evaluation two and one-half years after the last hypersensitivity reaction. Results of RAST assay for this employee are shown in Fig 7. Antibody titers were apparent in sera drawn up to 18 months following the last symptomatic exposure. Subsequent to that time, antibodies were no longer detected. This individual had shown an immediate response to bronchial provocation challenge with 0.006 ppm TDI in March 1978. Inhalation challenge with 0.02 ppm TDI in August 1979 failed to elicit a response.

Discussion

Toluene diisocyanate hypersensitivity has been recognized for many years.[18] Yet, little is known concerning exposure conditions which might contribute to induction of sensitivity.[19] Accordingly, it is uncertain whether an industrial exposure limit could be established which would protect workers from developing TDI sensitivity. The current study was undertaken to determine the incidence of TDI sensitization in workers hired into a TDI research and development facility where the ambient TDI concentration was at or below the current 0.02 ppm TLV. Workers were evaluated for clinical evidence of TDI sensitivity and for development of specific IgE antibodies. In addi-

tion, the possible contribution of excessive TDI exposure to the development of hypersensitivity was evaluated. Twenty workers involved in accidental TDI spills or splashes were examined for clinical and serologic evidence of sensitivity.

Antibodies of the IgE class have been associated frequently with immediate hypersensitivity reactions.[20] In this study, tolyl-reactive IgE and total IgE content of sera were routinely measured.

RAST was employed to evaluate serial blood samples from workers for tolyl-reactive IgE antibodies. RAST assay requires attachment of an appropriate antigen to a paper disc support. Use of TDI for antigen preparation results in self-polymerization of this hapten as well as cross-linking of carrier proteins.[21 22 23] The resulting antigen is heterogeneous with respect to composition of hapten moities as well as degree of protein polymerization.[13 21] Recently, use of p-tolyl *(mono)* isocyanate for antigen preparation proved effective in producing homogeneous monomeric hapten-protein conjugates in high yield.[5 13] The monoisocyanate antigen was also shown to be effective in detecting antibodies specific to TDI in sensitized workers[4 5 7-9] and guinea pigs.[10-13]

Through the use of RAST, no antibodies were detected in any of the 96 workers exposed only to ambient levels of TDI for periods of 6 to 24 months. Specific and total IgE values remained unchanged. Additionally, no clinical indication of TDI sensitivity was apparent in any of these workers.

In contrast to the above findings were those from employees involved in acute isocyanate exposures. Twenty employees reported a total of 35 episodes of acute TDI exposure. Pulmonary function was depressed in four instances; RAST assay was positive in three of the four cases.

Subsequent RAST assay of serial blood samples from acutely exposed workers revealed two patterns of response. The first pattern was noted in Case B-09. A sharp increase in antibody titer two months after exposure was followed by a rapid decline in antibody level. This individual was non-atopic. RAST-inhibition tests indicated that essentially all the IgE detected in RAST was specific antibody. A second pattern was apparent from Cases E-02 and B-23 in Group A. In these 2 cases, TDI exposure was associated with elevation of RAST titer. However, RAST titers were inhibited at most 50% by excess antigen. This result indicated that tolyl-reactive IgE antibodies comprised only a fraction of the total serum IgE content. RAST values in these cases did not drop as rapidly as did those in the preceding case, perhaps as a result of the influence of non-specific IgE antibodies on RAST values.

Of the nine cases of acute exposure resulting in immediate respiratory symptomatology with no change in pulmonary function, RAST titers were detected in only one instance (Table 2, Case B-17, Group B). In this case, only 40% of the antibody response was attributed to tolyl-reactive antibody. In this case, as well as in that of B-23, it is unclear whether symptomatology at exposure was a reflection of irritation caused by the high concentration of isocyanate, or whether TDI hypersensitivity contributed to pulmonary symptomatology. The presence of specific antibodies in these sera at the time of exposure may possibly be attributed to prior isocyanate exposures as both workers were established employees.

In this study, IgE antibodies were produced following some acute isocyanate exposures. Such antibodies are traditionally associated with immediate hypersensitivity reactions. However, definitive assessment of TDI sensitization in workers demonstrating antibodies would have required bronchial provocation challenge with TDI. This procedure was judged inappropriate for longitudinal study. On the basis of animal studies in which guinea pigs were exposed to known concentrations of TDI, evaluated for antibodies, and challenged by inhalation of TDI antigens, animals with elevated antibody titers most frequently displayed bronchial sensitivity.[10 11] TDI-exposed animals without circulating antibodies rarely displayed bronchial reactivity. Similarly, in industrial workers, an association between TDI IgE antibodies and bronchial sensitivity was recently reported. Antibodies were detected *only* in workers having bronchial sensitivity to TDI.[7 8] Finding specific antibodies to TDI in this study indicates acute exposure to TDI. It should not be assumed that all workers having circulating IgE antibodies to TDI would necessarily display asthmatic reactions upon exposure to the chemical.

In summary, workers exposed to ambient environments of 0.02 ppm TDI or lower did not develop specific IgE antibodies. In contrast, antibodies were produced in workers having acute TDI exposure accompanied by a short-term decrease in pulmonary function. In view of the serious nature of TDI sensitization, serologic screening of acutely exposed workers may offer an early indication of developing isocyanate sensitivity.

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References

1. Butcher BT, Salvaggio JE, Weill H, and Ziskind MM: Toluene diisocyanate (TDI) pulmonary disease: Immunologic and inhalation challenge studies. *J Allergy Clin Immunol* **58**:89-100, 1976.

2. Peters JM, Murphy RLH, Pagnotto LD, and Van Game WF: Acute respiratory effects in workers exposed to low levels of toulene diisocyanate. *Arch Environ Health* **16**:642-647, 1968.

3. Davies RJ and Pepys J: Occupational asthma, in Asthma. London: Chapman and Hall, 1977, pp 197-205.

4. Karol MH, Sandberg T, Riley EJ, and Alarie Y: Longitudinal study of tolyl-reactive IgE antibodies in workers hypersensitive to TDI. *J Occup Med* **21**:354-358, 1979.

5. Karol MH, Ioset HH, and Alarie YC: Tolyl-specific IgE antibodies in workers with hypersensitivity to toluene diisocyanate. *Am Ind Hyg Assoc J* **39**:454-458, 1978.

6. Karol MH and Alarie Y: Antigens which detect IgE antibodies in workers sensitive to toluene diisocyanate. *Clin Allergy* **10**:101-109, 1980.

7. Butcher BT, O'Neil CE, Reed MA, and Salvaggio JE: Radioallergosorbent testing of toluene diisocyanate-reactive individuals using p-tolyl isocyanate antigen. *J Allergy Clin Immunol* **66**:213-216, 1980.

8. Baur X, Dorsch W, Fruhmann G, et al: Klinische Symptomatik and Ergebnisse von RAST und inhalativem Provokationstest. *Zentralbl Arbeitsmed* **30**:104-109, 1980.

9. White WG, Sugden E, Morris MJ, and Zapata E: Isocyanate-induced asthma in a car factory. *Lancet* 1:756-760, 1980.

10. Karol MH, Dixon C, Brady M, and Alarie Y: Immunologic sensitization and pulmonary hypersensitivity by repeated inhalation of aromatic isocyanates. *Toxicol Appl Pharmacol* 53:260-270, 1980.

11. Karol MH, Hauth BA, Riley EJ, and Magreni CM: Dermal contact with toluene diisocyanate (TDI) produces respiratory tract hypersensitivity in guinea pigs. *Toxicol Appl Pharmacol* 58:221-230, 1981.

12. Karol MH: Immunologic responses of the respiratory system to industrial chemicals, in Symposium on Inhalation Toxicology and Technology, B. K. J. Leong (Ed.). Ann Arbor: Science Publishers (In press).

13. Karol MH: Study of guinea pig and human antibodies to toluene diisocyanate. *Am Rev Respir Dis* 122:965-970, 1980.

14. Gleich GJ, Larson JB, Jones RT, and Baer H: Measurement of the potency of allergy extracts by their inhibitory capacities in the radioallergosorbent test. *J Allergy Clin Immunol* 53:158-169, 1974.

15. Phadebas IgE PRIST® Pharmacia Diagnostics AB, Uppsala, Sweden, 1979.

16. Pepys J and Hutchcroft BJ: Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis* 112:829-859, 1975.

17. Pepys J, Pickering CAC, Breslin ABX, and Terry DJ: Asthma due to inhaled chemical agents — Tolylene di-isocyanate. *Clin Allergy* 2:225-236, 1972.

18. NIOSH: Criteria for a recommended standard. Occupational exposure to diisocyanates. U.S. Department of Health, Education and Welfare, Publication No. 78-215, 1978.

19. Ishizaka T and Ishizaka K: Biologic function of immunoglobulin E, in The Biological Role of the Immunoglobulin E System. National Institute of Child Health and Human Development, Washington, D.C., pp 34-44, 1973.

20. Schick AF and Singer SG: On the formation of covalent linkages between two protein molecules. *J Biol Chem* 236:2477-2485, 1961.

21. Karol MH, Riley EJ, and Alarie Y: Presence of tolyl-specific IgE and absence of IgG antibodies in workers exposed to toluene diisocyanate. *J Environ Sci Health C13* 3:221-232, 1979.

22. Tse CST and Pesce AJ: Chemical characterization of isocyanate-protein conjugates. *Toxicol Appl Pharmacol* 51:39-46, 1979.

Erratum

The following illustrations were inadvertently omitted from the article entitled "Epidemiologic Patterns of Nasal Cancer in New York State," by George T. Ulitsky, B.S.; Stuart L. Shalat, B.S., B.A.; Karen Riccardi, B.S.; and Nicholas J. Vianna, M.D., which appeared in the September, 1981, issue of this journal, pp 632-634:

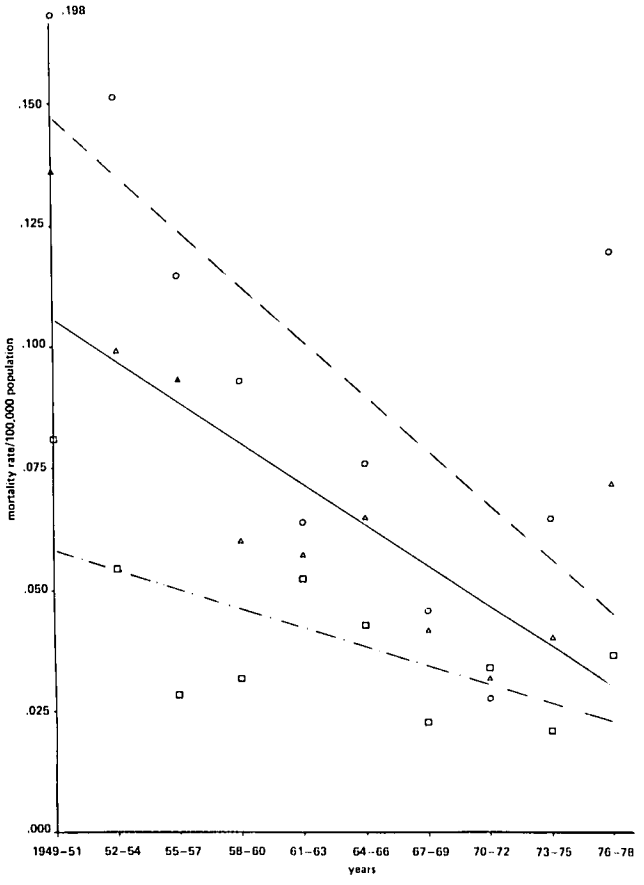

Fig 1. — Mortality trends of nasal cancer in New York State (excluding New York City) 1949 through 1978; males (——); females (_ . _); males and females combined (____); males (o) females (□); males and females combined (Δ).

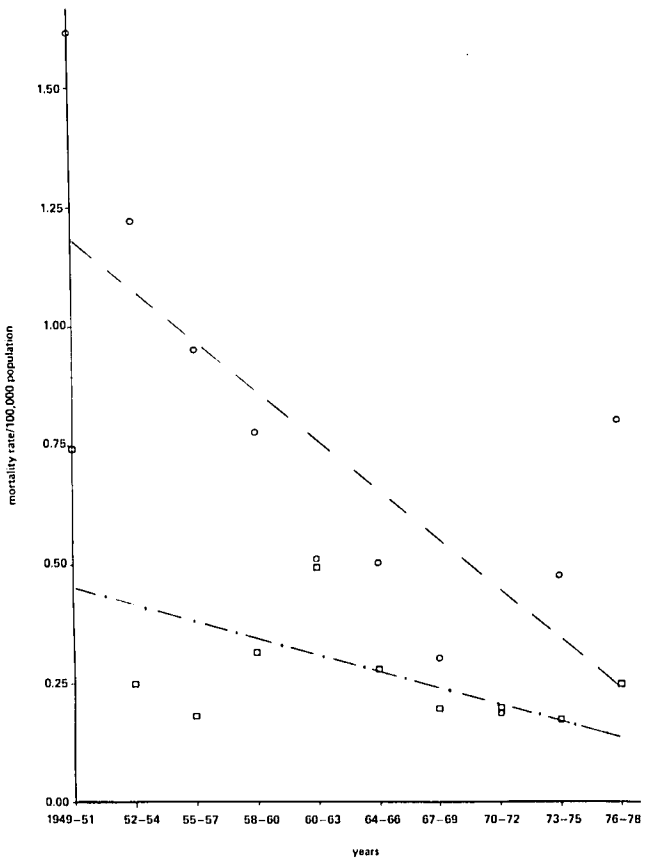

Fig 2. — Mortality trends of nasal cancer among those sixty-five years of age and older in New York State (excluding New York City) 1949 through 1978; males (——); females (_ . _); males (o); females (□).