Isocyanate-induced pulmonary diseases: a current perspective

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Chemicals of the isocyanate family are required for the production of a variety of commercial products, including insulation materials, automobile upholstery, furniture, and surface coatings. They are highly reactive with other chemicals containing hydrogen atoms. Early reports of medical toxicity appeared 25 yr ago and have been confirmed on a worldwide basis. Adverse respiratory symptoms have been the chief concern, and a wide spectrum of work-related lung diseases has been described. Although some of these reactions were undoubtedly due to primary irritation, the majority presented with airways obstructive abnormalities clearly identified as classic asthma. The possibility of an underlying hypersensitivity mechanism was suggested by the insidious onset of symptoms, a latency period of weeks to months, peripheral and tissue eosinophilia, and the elicitation of symptoms after exposure to very small subtoxic levels of these chemicals. Some cases consistent with the unique clinical features of hypersensitivity pneumonitis have also been recognized. Early animal experimental studies had suggested that immunologic factors were important etiologic components of these syndromes. However, when several independent groups of investigators could not confirm these preliminary results, the pathogenesis of these diseases soon became a highly controversial subject. Current experimental and clinical approaches have therefore been redirected to encompass the role of nonimmunologic mechanisms in the pathogenesis of adverse isocyanate reactions. Collectively, these recent investigations suggest that both immunologic and nonimmunologic mechanisms appear to be operative as causes of isocyanate-induced asthma. There is in vitro evidence both for and against possible specific pharmacologic effects of diisocyanate compounds. Parallel bronchoprovocation studies comparing the activities of diisocyanates, methacholine, and histamine suggest that diisocyanates may act either as direct pharmacologic agonists or as inducers of nonspecific bronchial reactivity. Recent evidence of immunoreactivity to both monofunctional and bifunctional isocyanates in several animal models and sensitized workers has also mandated a reassessment of immunologic factors. Hapten-specific, IgE-mediated antibody responses have been observed in both animal and human investigations. However, only a small subset of sensitized workers developed specific IgE antibodies to p-tolyl monoisocyanate and/or hexyl monoisocyanate. Both IgE and precipitating antibodies have been reported in several cases of workers sensitized to methylene diphenyl diisocyanate. Some toluene diisocyanate–sensitive patients also exhibit other types of immunologic responses, including antigen-induced lymphocyte transformation and synthesis of a leukocyte inhibitory factor. Detailed immunologic investigations have not yet been carried out in most of the suspected cases of hypersensitivity pneumonitis. Other possible nonimmunologic sequelae of isocyanate reactions include chronic bronchitis, recurrent pneumonia, pulmonary edema, and pulmonary emphysema. However, the question of chronic pulmonary disability associated with these diseases is poorly understood and requires further long-term investigation. Despite the brisk controversy that still exists about the pathogenesis of isocyanate-induced pulmonary diseases, new data derived from animal models and clinical investigation of sensitized workers suggest that application of several innovative approaches could result in early detection and treatment of clinical reactions. These are considered in the context of pre-employment screening, serial monitoring in the workplace, and postemployment surveillance. (J ALLERGY CLIN IMMUNOL 70:24, 1982.)

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Isocyanates are highly reactive chemical compounds because they contain the NCO group(s) (Fig. 1). TDIs are the most commonly used commercial isocyanates. Two isomers are available from commercial sources: 2,4-toluene diisocyanate and 2,6-toluene diisocyanate. Other important isocyanates

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Abbreviations used

TDI:	Toluene diisocyanate
HDI:	Hexamethylene diisocyanate
MDI:	Methylene diphenyl diisocyanate
NDI:	Naphthalene diisocyanate
PAPI:	Polymethylene polyphenyl isocyanate
PTI:	Para-tolyl monoisocyanate
PBL:	Peripheral blood lymphocytes
NAD:	New antigenic determinants
LIF:	Leukocyte inhibitory factor
HSA:	Human serum albumin

include HDI, MDI, NDI, and PAPI. The polymerization end products of chemical reactions between isocyanates and compounds containing active hydrogen atoms include such substances as rigid or flexible foams, surface (e.g., wire) coatings, adhesives, rubber, and fibers. TDI was used extensively by the German military-industrial complex during World War II. Shortly after large-scale commercial production of this compound was started by a major German chemical company in 1947, there was a rapidly expanding use of TDI-derived consumer products, including packaging, insulation materials, upholstery, paint, furniture, and plastics. For example, the demand for manufactured polyurethane foam products in the United States increased exponentially since 1955. Large-scale production of flexible foams shaped into blocks or sheets should contain no free TDI after proper curing, and the proper atmospheric control of TDI in these operations is easily achieved by modern engineering techniques. Health problems are more likely to be observed in the production of rigid polyurethane foams, which are generated with portable manufacturing equipment. Other operations that are particularly hazardous are spray blowing or frothing of the material directly on the surface of other polymerizing materials. Occupations with potential risks of isocyanate exposure[1] include the following: diisocyanate workers, polyurethane foam makers, upholstery workers, spray painters, wire coating workers, plastic foam makers, plastic molders, and rubber workers.

Early history of medical toxicity

Although human toxicity to TDI was apparently observed in Germany during World War II, the first published reports appeared in the French literature and in rapid succession from other countries in Europe.[2] The initial report of toxicity in the United States occurred in 1956.[3] Since that time, medical hazards associated with isocyanate exposure have been recognized with greater frequency, and case reports have appeared from every industrialized country in the world. Although these early publications were

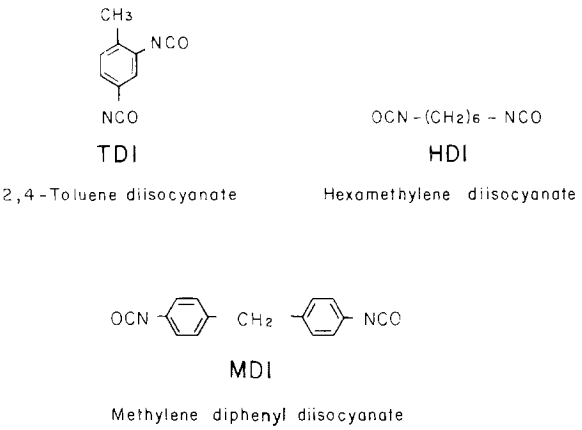

FIG. 1. Chemical structures of three major diisocyanates.

anecdotal, it is noteworthy that a wide spectrum of respiratory illnesses was described, including acute bronchitis, asthma, chronic bronchitis, bronchopneumonia, bronchiectasis, bronchiolitis obliterans, emphysema, hypersensitivity pneumonitis, and pulmonary fibrosis.

Inhaled isocyanate vapors or aerosols act as corrosive agents, with irritant manifestations at low concentrations.[4] They primarily affect the upper respiratory tract in experimental animals. Tracheitis and bronchitis with sloughing of superficial epithelium occur after exposure to 2 ppm for 4 hr. Rapid coagulation necrosis of epithelium after inhalation of 5 ppm suggests direct chemical injury. Long strips of necrotic epithelium are surrounded by inflammatory cells, which may then evoke a foreign-body inflammatory response. Apart from focal areas of peribronchial pneumonia, the parenchyma is relatively uninvolved. It is noteworthy that the morphologic appearance of lamina propria and smooth muscle appears to be normal after exposure levels of 2 ppm. The most dramatic human counterpart to animal toxicologic studies occurred in 35 firemen accidentally exposed to massive concentrations of TDI vapors while they were combating a fire in a polyurethane foam manufacturing plant.[5] The majority of these men experienced severe primary irritant effects of the upper respiratory tract. Gastrointestinal and central nervous system symptoms appeared in more than half of this group. Although objective indices of lung function were abnormal for 6 mo after the event, susceptibility to respiratory infections and cognitive changes apparently persisted for as long as 4 yr.

In contrast to overdose reactions, the possibility of hypersensitivity as a primary etiologic factor in the pathogenesis of isocyanate-induced lung disease was suggested by the insidious onset of asthmatic symptoms in a subpopulation (about 10%) of exposed workers, gradual progression of duration and severity

of symptoms over a period of weeks to months, eosinophilia in many patients, and prompt recurrence of symptoms after exposure to subtoxic levels (<0.005 ppm) of isocyanate. Prompt recognition of this symptom complex was essential because continued exposure may have been responsible for several cases of fatal status asthmaticus.[6] Chronic symptoms of fever, malaise, nonproductive cough, and progressive dyspnea in a few patients suggested the possibility of hypersensitivity pneumonitis.[7] Alveolar infiltrates that cleared soon after removal from isocyanate exposure in the workplace were also consistent with this disease.[8]

During the period from 1960 to 1969, there was a shift of emphasis to long-term epidemiologic studies to establish safe occupational threshold limit values. In the early part of this period the threshold limit value was reduced from 0.1 to 0.02 ppm by the Occupational Safety and Health Administration.[1] Although this value may prevent toxic reactions and the development of sensitization in the vast majority of exposed workers, it has since become evident that asthma-reactive workers are still at risk under work conditions defined as safe by these limit values. One of the most interesting long-term epidemiologic studies was undertaken by Wegman et al.,[9] who investigated serial pulmonary function measurements prospectively in workers exposed to TDI levels well below the threshold limit value of 0.02 ppm. Although complete physiologic data at the conclusion of the period were available in only 57 of the original 112 members of the study group, the completed cohort included asymptomatic workers as well as those who had developed symptoms during the course of the study. The results of this investigation suggested that workers exposed to acceptable levels of TDI and who remained on the job over a period of 2 yr developed significant declines in their one second forced expiratory volumes. Several other prospective studies failed to confirm a decrease in pulmonary function in asymptomatic workers exposed to "safe" threshold limit values of TDI.[10, 11] The disparate results obtained in these three studies could be explained by different study populations (polyurethane foam product workers vs TDI workers), type of exposure (continuous vs intermittent), or the technique of measuring pulmonary function during the long-term surveillance period. A recent long-term epidemiologic study demonstrated that chronic exposure to MDI tended to cause restriction of pulmonary function, as indexed by decrease of vital capacity and a decline in the carbon monoxide gas-transfer test.[12] These physiologic parameters were significantly lower in the group with the longest exposure to this agent.

The current threshold limit value of TDI was established by early experimental animal studies, which focused primarily on establishing relatively "safe" threshold levels at which the primary irritant effects of isocyanates would not occur. Later, the immunologic aspects of TDI effects were also studied in animals in the hope of understanding the nature and/or mechanisms of the apparent sensitization process in man. Antibody responses in rabbits after parenteral immunization with TDI-protein conjugates were reported by Scheel et al.[13] It was also claimed that injection of TDI-protein conjugates could stimulate the formation of a circulating antibody directed against the TDI haptenic residue. Whether these antibodies were specifically directed against the hapten or the carrier determinant in the TDI-protein conjugates could not be ascertained by examining the raw data of these experiments. Similar results after parenteral immunization of rabbits were also obtained by Avery et al.[14] Stevens and Palmer[15] studied the effect of TDI exposure at various concentrations in small numbers of guinea pigs and monkeys and were not able to demonstrate significant immunologic responses. These conflicting experimental results in several laboratories that were probing the possible significance of immunopathogenesis raised the question of whether the variability inherent in the production of isocyanate protein conjugates could account for interlaboratory differences.[16] It could be argued that the kinetics of TDI interactions with proteins are so dependent on minor deviations of the preparatory conditions that one could not predict whether undersubstitution or oversubstitution of carrier protein with the isocyanate ligand might result or whether extensive protein cross-linking might completely bury the haptenic determinant. It was therefore self-evident that resolution of these early experimental conflicts would be a high priority for the current generation of research investigators.

Pathogenesis of diisocyanate-induced asthma: current research

Since there was no early consensus about the etiologic role of hypersensitivity in experimental animals, alternative explanations were sought. The pharmacologic effects of diisocyanate compounds were explored in greater detail by several in vitro techniques. Data from one of these studies suggested that relatively high concentrations of TDI within a narrow dose range exhibited a partial beta-agonist effect on synthesis of cyclic AMP by human PBL.[17] Additional experiments revealed that TDI competed with isoproterenol-induced production of intracellular cyclic AMP of PBL. However, similar to the partial beta-agonist effect, this receptor inhibition occurred only within a restricted concentration range of TDI. More-

TABLE I. Comparison of PTI-specific IgE results in symptomatic or bronchoprovocation-positive workers studied in different occupational health surveys

Investigator	No. of symptomatic workers	No. of positive PTI RAST	% Positive	Ligand substitution (mole/mole protein)	Interpretation of test
Karol et al.[34]	Unknown	18	Unknown	10 or 15	>456 net cpm
Gallagher et al.[36]	151	4	3	13	Binding 3% or >; 2× pool of normal control sera and 2× HSA control
Butcher et al.[35]	26	4 or 5	15-19	16	Total CPM or 2× HSA control
Baur et al.[27]	55	9	16	Unknown	>0.5 Phadebas RAST U/ml
Danks et al.[37]	12	0	0	57	Total CPM of 3000-4000

CPM = counts per minute.

over, the hydrophobic nature of TDI required the use of a high concentration (10%) of dimethyl sulfoxide solvent, which could alter phospholipid mobility and render membranous receptors more vulnerable to TDI. The antagonist property of TDI differed from classic beta-adrenergic blockade because it also affected prostaglandin E_1[17] and glucagon receptors[18] and it partially attenuated antigen-induced histamine release of peripheral blood leukocytes.[18] The competitive effect of several diisocyanate compounds on isoproterenol-induced cyclic AMP was also demonstrated in the frog erythrocyte model system, but a partial beta-agonist effect for these compounds was not confirmed because their inhibition of adenylate cyclase activity was diminished by a mechanism not dependent on activation of beta-adrenergic receptors.[19] There was also an unconfirmed report that TDI reduced the activity of erythrocyte anti-cholinesterase activity.[20] Collectively, these recent experimental data suggest that isocyanates may cause nonspecific inhibition of a variety of membrane receptors and enzyme systems—effects that are consistent with the highly reactive properties of these substances.

Possible pharmacologic and/or reflex effects have also been evaluated in sensitized workers by parallel bronchoprovocation studies with diisocyanates, methacholine, and histamine. Most investigators reported that sensitized workers respond in a dose-response fashion to challenge with diisocyanate compounds.[21–27] In the case of TDI, positive reactions were obtained at challenge doses as low as 0.0001 ppm.[26] Recent viral infections may convert TDI nonresponders to responders.[24] The majority but not all workers manifesting positive responses also have nonspecific bronchial hyperreactivity after challenge with methacholine.[23, 25, 28] However, it is noteworthy that there is a small subset of sensitized workers who show no evidence of hyperreactivity to methacholine challenge.[25] It is of further interest that almost one half of TDI bronchoprovocation–positive patients failed to show manifestations of histamine hyperreactivity.[29] Therefore, under appropriate conditions that cannot be defined precisely at the present time, diisocyanate compounds may act either as direct pharmacologic agonists or as inducers of nonspecific bronchial hyperreactivity. Alternatively, it is possible that pre-existent bronchial hyperreactivity may predispose some workers to subsequent development of airway responsiveness to these compounds.[27] Although attractive from the standpoint of pre-employment selection, this theory has not been adequately tested. One of these investigations encountered a very interesting phenomenon of diisocyanate pharmacologic crossreactivity.[26] In some workers with TDI asthma, positive challenge responses were also elicited by other diisocyanate compounds to which there was no previous history of exposure.

Although most investigators now agree that nonimmunologic mechanisms are involved in the complex pathophysiologic pathways of TDI asthma, the role of immunologic factors should also be reconsidered because of more convincing experimental evidence recently obtained in independent laboratories. One group of investigators focused attention on immune responses induced by monofunctional isocyanate protein conjugates.[30] Monoisocyanates were selected for these studies because of previous inconsistent results with bifunctional reagents such as TDI. The immunogenic potential of *p*-tolyl and hexyl monoisocyanates was investigated in experimental animals[31–33] and workers sensitized to diisocyanates.[30] In the English short-hair strain of guinea pigs, hapten-specific precipitating and homocytotropic antibodies were produced by immunization with monoisocyanate-protein conjugates, but the titers of homocytotropic antibodies were low in the individual animals.[32, 33] Small amounts of IgE antibodies were also detected in about half of the immunized guinea pigs.[32]

Specific IgE antibodies to monofunctional isocyanates have been reported in sensitized workers.[27, 34–36] The incidence of positive reactions in symptomatic workers fluctuates considerably from laboratory to laboratory (Table I). Some of this variance may be partly due to differences of interpreting significant results by this method and in part to the obligatory requirement of continuous allergenic exposure for ongoing IgE synthesis, especially in nonatopic persons. However, as illustrated by a recent survey, complete failure to detect PTI-specific antibodies in sensitized workers could also be attributed to ligand oversubstitution or the hapten-protein conjugate used in the substrate of this test.[37] Although the initial reports of PTI-specific antibodies in sensitized workers suggested that this test could be used as a screening procedure for detection of subclinical reactivity in exposed workers, other investigators were not able to confirm the test's overall sensitivity as a predictor of asthmatic symptoms occurring after exposure to diisocyanate.[35–37]

Despite the complexity of bifunctional isocyanate-protein interactions, our laboratory elected to use such reagents in both animal and human investigations because workers are exposed to diisocyanates in the workplace. To ensure reproducibility of results, a standard preparatory technique of bifunctional isocyanate reagents was first developed.[16] This method yielded hapten-protein conjugates with stable ratios of bis-to-mono ureido derivatives (ranging from 2:1 to 3.5:1). Such conjugates were also determined to have a moderate degree of ligand substitution. Hapten-specific antibodies to these reagents were produced after immunization of susceptible strains of mice and guinea pigs.[38, 39] Diisocyanate-specific precipitating and IgE antibodies were produced in several strains of guinea pigs under the appropriate conditions of parenteral immunization. IgE antibodies to both TDI and HDI were observed in all of the immunized English short-hair strain animals. The uniform appearance of IgE reactions in these experiments was noteworthy because previous investigators had reported that only about half of these animals had synthesized antibodies of this class after immunization with monofunctional isocyanate compounds.[32] Moreover, the absolute titers of specific IgE antibodies obtained in our studies were several orders of magnitude higher than those previously reported after respiratory immunization of guinea pigs with monofunctional and/or bifunctional isocyanate compounds. Further analysis of these results indicated that the immune response mounted by guinea pigs immunized with diisocyanate haptenated protein conjugates was heterogeneous and involved multiple specificities for hapten, carrier protein, and NAD. Although apparent crossreactions between TDI and HDI were noted in these studies, the experimental evidence suggested that these were not hapten-specific and were in fact caused by crossreactivity between NAD in these hapten-protein conjugates. The guinea pig model also permitted correlation between the allergenic properties of guinea pig antisera induced by diisocyanates and in vivo respiratory responses after passive sensitization of immunologically virgin animals. These studies revealed that a minimum potency (1:160) of diisocyanate-specific guinea pig IgE antisera was required for the appearance of significant physiologic responses in passively sensitized guinea pigs.

We also re-evaluated the usefulness of bifunctional (TDI) conjugates in detecting immunoreactivity of TDI-sensitive workers. In a survey of 639 workers of a large automobile fabricating plant, there were no positive RAST results to the bifunctional conjugate, while four of 151 symptomatic workers were found to have significant titers of *p*-tolyl–specific IgE.[40] This incidence of *p*-tolyl–specific IgE was less than that reported by three other investigative teams.[27, 34, 35] However, additional studies of current symptomatic workers revealed other evidence of immunologic reactivity to TDI-protein conjugates.[36] Nine of the 15 workers demonstrated the presence of a specific LIF when their peripheral blood leukocytes were challenged with small concentrations of the TDI-protein conjugate. Some of these workers also exhibited positive LIF responses to HDI-protein conjugates even though they had never been exposed to this chemical. The most likely explanation for this unexpected reaction was the presence of NAD, which had first been noted in previous animal experimental work. Positive LIF results in this study appeared to corroborate an earlier report of antigen (TDI)-induced lymphocyte proliferation in six of seven sensitive workers.[14] Although neither of these techniques can be equated exclusively with delayed hypersensitivity, their occurrence in symptomatic workers assessed at two different medical centers suggested that greater attention should be given to the significance of sensitized lymphocytes in this disease. However, final judgment on the role of cell-mediated immunity must be open-ended because another investigator failed to confirm the presence of isocyanate-induced lymphocyte proliferation in five asthmatic workers.[22] Immediate skin reactivity in our investigation was also observed in three of four patients who consented to have these tests performed. Two other surveys of TDI-reactive airways disease revealed positive intradermal skin tests to TDI-HSA conjugates.[22, 41] In one of these reports more than half of the affected workers exhibited positive skin reactions.[41]

It is apparent that a global evaluation of all previous and current clinical studies does not permit a consen-

sus statement about the relative significance of immunologic factors in the final occurrence of clinical asthma. However, the majority of recent clinical surveys of TDI asthma have demonstrated some degree of immunoreactivity in subpopulations of TDI asthma. Further, our clinical studies indicated that the immunologic response occurring after exposure to isocyanates was heterogeneous. It was also suggested that this diversity could be advantageous in seeking ways of classifying various clinical subpopulations of isocyanate reactions. In this regard, four clinical subpopulations of sensitive workers were identified: (1) a small subset of workers with positive RAST results to a monoisocyanate protein adduct, (2) a greater number of reactive workers with positive LIF responses to diisocyanate protein conjugates, (3) a smaller group of workers with both positive LIF and direct skin-test responses to diisocyanate protein conjugates, and (4) another category of workers with no evidence of immunologic reactivity. It was also postulated that properly prepared and well-characterized bifunctional isocyanate conjugates could be used for future assessment of the LIF response or screening of workers by the direct skin-test technique. The value of such reagents in previous RAST surveys was negligible, but this could be subject to qualification in view of several recent reports of positive TDI-HSA–specific RAST results in sensitive workers.[27, 34]

Other nonasthmatic pulmonary reactions

Although some of the early reports of TDI sensitization described cases of pneumonia, pulmonary infiltrates, and pulmonary fibrosis, the possibility of hypersensitivity pneumonitis induced by isocyanates had not been seriously entertained until several recent case reports. In the first of these series of reports, four workers developed dyspnea associated with restrictive lung disease and reduced gas transfer.[8] One worker who had bilateral radiographic opacities was subjected to open-lung biopsy. The biopsy specimen revealed lesions ranging from an acute centrilobular inflammatory infiltrate to end-stage fibrosis. Later, a worker exposed to diisocyanates used in finishing bathtubs developed a symptom complex suggestive of hypersensitivity pneumonitis.[42] Inhalation challenge study in this subject demonstrated restrictive changes and reduced gas transfer without wheezing. This worker also experienced systemic symptoms of fever, leukocytosis, and generalized malaise after the experimental challenge. Recently, several cases of adverse reactions to MDI were also reported.[43] Significant levels of precipitating specific IgG antibody to MDI-HSA were demonstrated in these workers. Although none of these clinical reports investigated delayed hypersensitivity mechanisms, previous observations of specific lymphocyte transformation and LIF in other cases of TDI lung disease should provide impetus for future studies of cell-mediated immunity as a contributory factor in the development of hypersensitivity pneumonitis and other chronic inflammatory reactions of the lung occurring after TDI exposure.

Chronic pulmonary disability induced by diisocyanate compounds is one of the most controversial aspects in this work-related problem. Some cases in the early literature apparently experienced recurrent episodes of asthmatic bronchitis and/or bronchopneumonia. A few of these workers could not continue their work and eventually died, with final diagnoses of chronic bronchitis, emphysema, and cor pulmonale attributed to the prolonged diisocyanate exposure. As previously discussed, the possibility of long-term decrease of ventilatory capacity in most workers exposed to low levels (less than 0.02 ppm) of diisocyanates must still be considered as a potentially serious adverse effect and one that could occur insidiously without overt symptoms of respiratory difficulty.[9]

Future directions: pre-employment screening, serial monitoring, and post-employment surveillance

Personal or family histories of atopic diseases do not constitute absolute contraindications to long-term, low-level exposure to diisocyanate compounds. However, previous history of personal asthma or other evidence of nonspecific bronchial reactivity such as hypersensitivity responses to methacholine, histamine, cold air, or exercise would appear to be valid reasons for denying employment. The workplace must be monitored continuously with the idea of maintaining threshold limit values well below 0.02 ppm. If the data on long-term loss of pulmonary function are eventually confirned, it is possible that the present threshold limit value of 0.02 ppm may have to be adjusted downward to 0.005 ppm. Serial lung ventilatory tests should be monitored for early evidence of obstructive changes. Some investigators have proposed that periodic methacholine testing may be a way of detecting early changes of nonspecific bronchial hyperreactivity.[28] However, it should be recognized that 20% to 30% of workers may not exhibit such hypersensitivity responsiveness and therefore methacholine testing would not be expected to detect all cases of TDI hyperresponsiveness. The RAST to either monoisocyanate or diisocyanate protein conjugates will detect only about 3% to 16% of affected workers.[27, 35, 36, 40] At present it is merely an adjunctive aid and should not be used as an all-or-none screening technique. The most reliable diagnostic test is a dose-response bronchial challenge with the suspected isocyanate. However, this must be per-

formed under controlled conditions with meticulous and continuous monitoring of TDI as it is delivered and as it exits from the challenge chamber. Therefore it is only available as a practical screening procedure in relatively few medical centers. Monitoring for possible hypersensitivity pneumonitis should include tests for lung volume and gas transfer abnormalities, periodic chest x-rays, and the presence of serum precipitins.

Several diagnostic techniques should be considered more seriously in future clinical investigations of TDI lung disease. More attention should be given to the possibility that direct skin testing could be a simpler method of detecting IgE-mediated sensitivity in affected workers. The value of in vitro lymphocyte tests as correlates of delayed hypersensitivity should be investigated more thoroughly, especially in patients who develop evidence of chronic lung changes by x-ray or pulmonary function testing. Reliable techniques for detecting isocyanate-specific IgG antibody should be assessed more thoroughly in cases of asthma and hypersensitivity pneumonitis induced by isocyanates. Specific IgG is of proven diagnostic value in hypersensitivity pneumonitis and may also be relevant in the proper interpretation of the RAST technique because it may compete and therefore interfere with specific IgE antibody binding to antigen-coupled substrate.

Lung diffusing capacity should be evaluated regularly in cases of suspected hypersensitivity pneumonitis. Other indices of bronchial reactivity such as cold air and exercise may prove to be more acceptable than methacholine in the workplace situation, and the reliability of these indices should be determined by direct comparison with methacholine testing in this disease.

Serious prospective studies should be encouraged to investigate workers who are forced to retire because of isocyanate-induced disability. If possible, serologic and lung-function testing should be continued for several years. It is known that some workers with other types of occupationally induced asthma may continue to have obstructive defects for several years after leaving their sites of employment.[44] Apart from a single report, it is not yet known whether such an analogy can be applied to TDI-induced asthma.[45]

There are many unresolved questions about pathogenesis and practical management of TDI-induced respiratory diseases. Foremost priority should be assigned to research objectives that seek to integrate the significance of immunologic and nonimmunologic factors in the pathophysiology of asthma and other chronic pulmonary lesions related to isocyanate exposure. In this regard, investigation of the effects of isocyanates on bronchial interepithelial tight junctions would appear to be a particularly promising approach to the formulation of a unitarian model of TDI asthma. There is urgent need to standardize the preparation, analysis, and storage of test antigens. A central reference bank for known positive PTI- or TDI-specific IgG and IgE human sera should be established to encourage better quality control of serologic tests performed by different laboratories. For example, it would be most helpful if RAST results could be compared with high-titered specific human sera as well as with control sera derived from cord blood. Interlaboratory controversies about specificity and sensitivity of these tests would also be resolved more objectively by comparing data with reliable reference standards. Ideally, a long-term multicenter study using the same tests reagents and monitoring techniques would tend to develop a consensus among investigators in the most cost-efficient manner. Pharmacologic and immunologic crossreactions between various isocyanates should be evaluated more extensively because many plants make use of different isocyanates in separate locations. The questions of asymptomatic decrease of lung function as a result of long-term exposure and the duration of disability after termination of exposure are amenable to scientific assessment, but such studies would be possible only through the combined resources of an industrial-medical-governmental collaborative effort.

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