occupational and environmental lung disease

Asthma-Like Symptoms in Wood Product Plant Workers Exposed to Methylene Diphenyl Diisocyanate*

Edward L. Petsonk, MD, FCCP; Mei Lin Wang, MD; Daniel M. Lewis, PhD; Paul D. Siegel, PhD, FCCP; and Bradley J. Husberg, MSPH

Background: Diisocyanates, a group of highly reactive chemicals, have frequently been associated with occupational asthma. We evaluated respiratory health in workers at a new wood products manufacturing plant that uses methylene diphenyl diisocyanate (MDI), and was designed and operated with a goal of minimizing worker exposures.

Methods: Health surveys using standardized respiratory questionnaires were done prior to the initial use of diisocyanates in the plant, and semiannually thereafter for a period of 2 years. Other testing included occupational and work practice histories, serial peak flow measurements, spirometry, methacholine challenge, and measurement of specific IgE antibodies to MDI-albumin conjugate.

Results: Of 214 plant employees who participated in at least one health survey, a follow-up survey was also available from 178 employees (83%). New-onset asthma-like symptoms (NAS) were reported by 15 of 56 workers (27%) in areas with the highest potential for exposures to liquid MDI monomer and prepolymer, vs 0 of 43 workers in the lowest potential exposure areas (p = 0.001). In the areas with high potential exposure, NAS developed in 47% of workers who had noted MDI skin staining, vs 19% without skin stains (p = 0.07). Working around and cleaning up liquid MDI represented a significant risk for asthma-like symptoms in both current smokers and nonsmokers; work with finished wood products did not. Asthma-like symptoms were associated with variable airflow limitation (odds ratio [OR], 5.0; confidence interval [CI], 1.4 to 18.7) and specific IgE to MDI-albumin (OR, 3.2; CI, 1.1 to 9.0), but not with skin prick tests to common aeroallergens (OR, 1.1; CI, 0.5 to 2.7).

Conclusions: During the first 2 years of operation, in a plant designed and operated to control exposure to diisocyanates, the development of asthma-like symptoms was reported in a relatively high proportion of the employees who worked with liquid MDI. To prevent asthma symptoms among workers, careful control of respiratory tract exposures associated with liquid MDI is important, especially during cleanup activities. Strict limitation of skin contact with diisocyanates may also be necessary. *(CHEST 2000; 118:1183–1193)*

Key words: asthma; diisocyanates; occupational asthma; respiratory protection; skin exposure; wood products

Abbreviations: CI = confidence interval; FAS = follow-up asthma-like symptoms; HSA = human serum antigen; IAS = initial asthma-like symptoms; MDI = methylene diphenyl diisocyanate; NAS = new-onset asthma-like symptoms; NIOSH = National Institute for Occupational Safety and Health; OR = odds ratio; OSHA = Occupational Safety and Health Administration; RAST = radioallergosorbent testing

BACKGROUND

Occupational asthma has become the most commonly reported occupational respiratory disease.[1,2] Diisocyanates, a group of highly reactive chemicals, have been frequently associated with the new onset of asthma in relation to work exposures,

although for industrial settings in which exposures to these chemicals are well controlled, a low prevalence of symptoms has been reported.[3–12] Recently, an opportunity was provided to prospectively study the workforce at a newly constructed manufacturing plant in which composite wood products are made utilizing a mixture of methylene diphenyl diisocyanate (MDI) monomer and oligomers as a wood binder. The management designed the plant to minimize worker exposure, including engineering controls and a comprehensive personal protection program, as they were aware that diisocyanate-induced asthma had been reported from other wood-processing facilities.[13] Respiratory protection included positive pressure air-supplied hoods in the areas of greatest concern, and air-purifying negative pressure respirators in other areas. A medical screening program was established among plant employees in order to serially evaluate respiratory health, and assess potential risk factors as part of health surveillance. We surveyed the plant workforce shortly before the initial delivery of diisocyanates to the plant, and semiannually for a period of 2 years thereafter. This article describes the prevalence of asthma-like symptoms and their association with potential MDI exposures in specific work areas, work practices, and job activities in this plant.

Process Description

The plant produces a laminated wood product. Briefly, logs, primarily yellow poplar, are brought to the plant by individual contractors, and are stored for subsequent processing in the wood yard. The logs are debarked and placed into stranding machines. The stranding machines produce thin strands of wood about 12 inches long. The strands pass through a dryer to reduce moisture content and are then placed into a blender, where they are coated with a liquid diisocyanate resin (monomer and prepolymers) and a wax. The strands are then aligned and compacted, using heat and pressure, into a laminated wood billet. The billets are cooled, trimmed, sanded, and cut into lengths and sizes appropriate for specific products. The final product is then packaged and shipped out of the plant by truck.

Materials and Methods

The study protocol was reviewed and approved by the National Institute for Occupational Safety and Health (NIOSH) Institutional Review Board, and all participants gave written informed consent.

Questionnaires

In 1995, prior to the initiation of production in the plant, a trained NIOSH survey team traveled to the plant and performed the first health survey of all workers who had been hired at that point. The survey included administration of a respiratory health questionnaire comprised of elements from previous standard instruments (British Medical Research Council, 1976).[14,15] Initial production at the plant began several months later, and follow-up health surveys were performed every 6 months for 2 years. Workers who were newly recruited during the follow-up period were also asked to complete the initial questionnaire, at the first survey following their hiring. After production began, participating workers were asked to complete an occupational history, documenting the specific job activities performed and any occupational exposures to wood and diisocyanates, as well as other potential hazards in the plant. During the recording of occupational histories, the interviewers had noted that several employees had stains from the liquid MDI resin on their clothing and skin. To follow up on this observation, during the two health surveys performed in 1996, workers were asked to also complete a short questionnaire about certain job activities and work practices. Each worker was asked about the cleanup of accidental spills of MDI, and whether he or she had noticed MDI stains on his or her clothing and/or skin. Individuals were queried about whether they participated in cleaning of the blender, where MDI is applied to the wood strands. Finally, the use of respiratory protection was assessed. Workers were asked if they used the required respiratory protection when potentially exposed to MDI, and whether they briefly removed the respirator (*eg*, to talk or cough) at any time while in a potential exposure area.

Physiologic and Immunologic Assessments

Spirometric testing and 8-day serial peak flow logs were requested at each biannual survey, while methacholine inhalation and bronchodilator testing were performed only at the initial and final surveys. Skin prick testing for 18 common aeroallergens was done only on the initial survey. Serum for total and MDI-albumin-specific IgE was collected on a yearly basis. Radioallergosorbent testing (RAST) scores in the top quartile were considered positive. Cross-shift, cross-week, and overall changes in $FEV_1 > 10\%$, and peak flow variability $> 20\%$ were considered evidence of variable airflow limitation. Cross-shift change $= 100 \times$ (pre-shift FEV_1 − post-shift FEV_1)/(predicted FEV_1). Cross-week change $= 100 \times$ (beginning-of-week FEV_1 − end-of-week FEV_1)/(predicted FEV_1). Overall change (spirometry variation across all surveys, with predicted value calculated based upon age at the initial survey) $= 100 \times$ (largest FEV_1 − smallest FEV_1)/(predicted FEV_1). Peak flow variation $=$ (weekly maximum − weekly minimum)/(weekly mean). Bronchial hyperresponsiveness was determined by a $\geq 15\%$ drop from baseline FEV_1 after inhalation of ≤ 25 mg/mL methacholine aerosol, or a $> 10\%$ increase in FEV_1 after inhaled bronchodilator. (See Appendix for detailed methods.)

Exposure Classification

Based on the information reported in the occupational histories, exposure indexes were assigned to individuals and to work areas. The first index of exposure was derived from each individual's report of his involvement with either diisocyanates or diisocyanate-containing products. Workers reported their job exposures as follows: (1) never enter areas with diisocyanate or diisocyanate-containing products; (2) enter areas with diisocyanates or diisocyanate-containing products but never worked directly with them; or (3) work directly with diisocyanates or diisocyanate-containing products. The latter included the composite MDI/wood products, which after cooling were thought to release little free diisocyanate.

Since exposure to the liquid MDI resin was a particular concern, a second index of exposure was derived. Workers were asked to report any occupational contact with liquid diisocyanate, either during the manufacturing process or through cleanup activities or spills. Based on the responses from all the workers assigned to a given work area, work areas were assigned a level of potential exposure to liquid MDI resin: low, < 20% of workers report exposure; intermediate, 20 to 50% report exposure; and high, > 50% of workers report liquid MDI resin exposures. Workers in job activities that required them to travel throughout the plant (*eg*, maintenance) were assigned to the high exposure category, unless they reported never working directly with diisocyanate-containing products, in which case they were assigned to the intermediate exposure category. Finally, the prior work histories of all participants were assessed for previous jobs with exposure to diisocyanate or other potential asthma-causing substances.

Case Definitions

Cases of asthma-like symptoms were defined based on the questionnaire responses. A case was defined as the presence of the following: (1) current or previous asthma (either self-reported or doctor diagnosed); or (2) current use of an inhaled bronchodilator medication; or (3) current asthma attacks, characterized by shortness of breath and wheezing, with normal breathing between attacks. Asthma-like symptoms were classified as follows: (1) initial asthma-like symptoms (IAS), in workers who met the case definition on the initial questionnaire; (2) follow-up asthma-like symptoms (FAS), in workers who met the case definition at any follow-up examination; and new-onset asthma-like symptoms (NAS), in workers who met the case definition for FAS but not for IAS.

Analysis

The prevalence of cases was evaluated in relation to each employee's report of work with MDI or MDI-containing products, potential exposure to liquid MDI resin, and specific job activities and work practices. (see "Materials and Methods"). Results of the physiologic and immunologic tests among individuals who met the FAS case definition were compared to results among those who did not meet this definition. A logistic regression model was used to investigate the combined effects of smoking and potential exposure to liquid MDI. All statistical analyses were accomplished with personal computer software (SAS version 6.12; SAS Institute; Cary, NC) using χ^2 analysis and Student's t test.

RESULTS

Study Participants

During the entire 2-year study period, a total of 276 individuals were employed, at least briefly, in the plant. Over the study period, a total of 214 employees completed the initial questionnaire, with 108 enrolling in the study prior to the first delivery of MDI to the plant. Of the 214 participants, 178 also participated in at least one follow-up survey. Of these 178 workers, a complete occupational history was available for 144, of whom over half (77 of 144) had completed the initial health survey prior to the first delivery of MDI to the plant and also reported no previous MDI exposures. The remaining 67 of 144 workers either had entered the study some time after MDI was already in use at the current plant, or indicated a previous job with MDI exposure. For these 67 workers, there was a possibility that IAS were related to current or previous job exposures to MDI. The questionnaire on work activities and practices was completed by 108 of 144 plant workers.

Table 1 shows the demographics of the workers who participated in the health surveys. The group of workers who did not return for follow-up were not markedly different from the group that did return, in relation to age, gender, height, weight, education, and smoking patterns.

Overall, among the 178 participating workers, 32

Table 1—Demographics and Smoking Among Wood Product Plant Workers by Level of Participation*

Variables	Initial and Follow-up Questionnaire, N = 178		Only Initial Questionnaire, N = 36		Initial, Follow-up, and Occupational Questionnaire, N = 144	
	Male, n = 155	Female, n = 23	Male, n = 33	Female, n = 3	Male, n = 125	Female, n = 19
Initial age, yr	31.1 ± 8.5	31.8 ± 7.3	32.4 ± 8.7	33.1 ± 12.6	31.0 ± 8.5	32.6 ± 7.5
Height, inches	68.4 ± 12.1	64.1 ± 2.2	69.9 ± 2.8	65.0 ± 1.0	69.0 ± 10.6	64.2 ± 2.2
Weight, lb	196 ± 32.1	141 ± 31.0	194 ± 35.3	135 ± 25.3	196 ± 33.0	147 ± 30.9
Grade, yr	13.5 ± 1.8	13.8 ± 1.7	13.7 ± 2.0	12.3 ± 0.6	13.6 ± 1.8	13.7 ± 1.8
Smoking status: initial						
Current	44 (24.7)		6 (16.7)		35 (24.3)	
Ex-smoker	22 (12.4)		5 (13.9)		18 (12.5)	
Never smoker	112 (62.9)		25 (69.4)		91 (63.2)	
Pack-yrs†	12.0 ± 13.6		18.9 ± 11.4		11.3 ± 9.9	
Smoking status: last follow-up						
Current	41 (23.0)		N/A		32 (22.2)	
Pack-yrs†	15.8 ± 16.2		N/A		15.4 ± 11.3	

*Data are presented as mean ± SD or No. (%). N/A = not available.
†Current and ex-smokers only.

Table 2—Criteria Met for Asthma-Like Symptoms by Case Definitions in Wood Product Plant Workers (N = 178)

Case Definition	No.	Criteria			
		Doctor Diagnosis, % (No.)	Self-diagnosis, % (No.)	Asthma Attacks, % (No.)	Asthma Medication, % (No.)
IAS	20	50 (10)	65 (13)	65 (13)	20 (4)
FAS	32	16 (5)	34 (11)	91 (29)	16 (5)
NAS	22	5 (1)	23 (5)	95 (21)	5 (1)

workers (20%) met the FAS case definition, while 22 workers (12%) met the NAS case definition. In the NAS group, the duration of work prior to symptom onset ranged from 3 to 22 months (mean, 11 months). Table 2 shows the distribution of specific criteria for determining the cases of asthma-like symptoms among these 178 plant workers. For most of the NAS cases (17 of 22), the presence of attacks of wheezing was the sole defining criterion. Of the 20 workers who met the criteria for IAS, 15 workers reported no work with diisocyanates prior to the

onset of respiratory symptoms, 2 workers meeting the IAS case definition had some potential work exposure to MDI prior to symptom onset, and for 3 workers, the timing of symptom onset in relation to potential exposure was indeterminate.

Exposure Classifications and Case Prevalence

The prevalence of NAS and FAS cases showed clear relationships with individual reported exposure (Fig 1, *top*, *A*). Case distribution was also assessed by
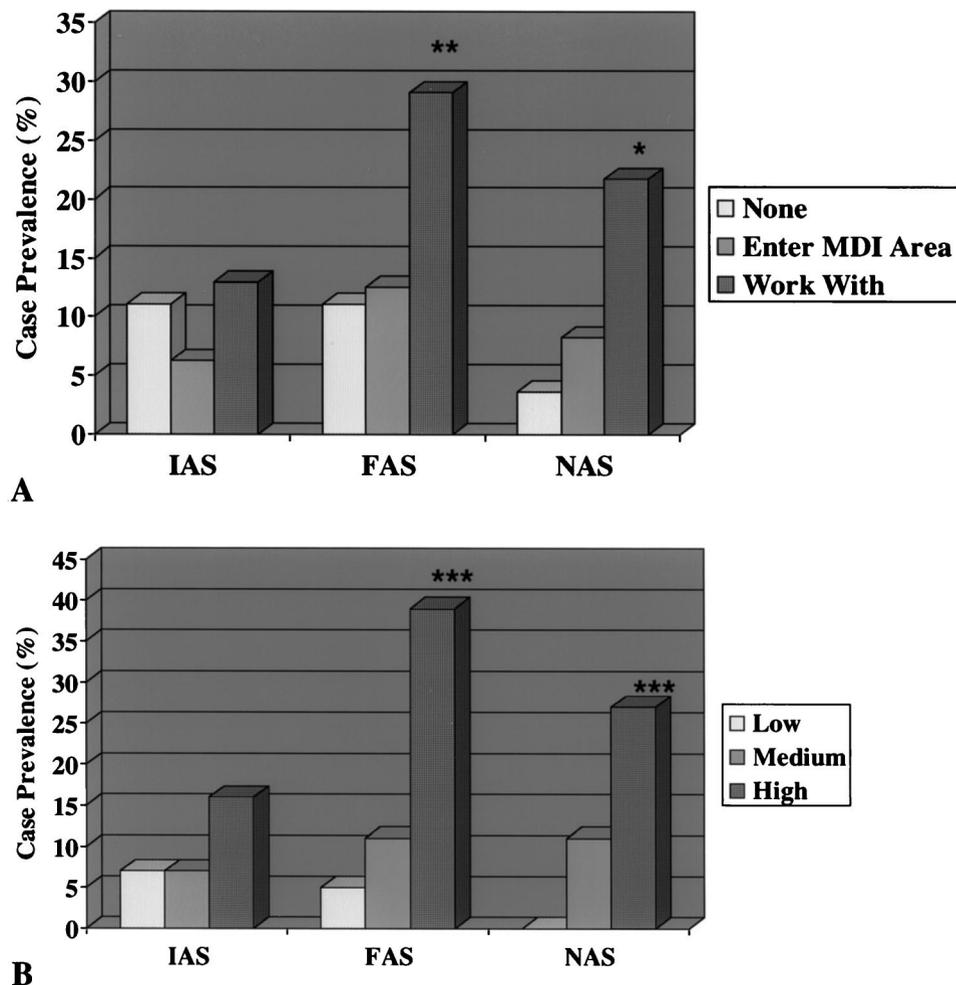

FIGURE 1. Asthma-like symptom case prevalence by individual MDI involvement (*top*, *A*) or work area potential MDI exposure (*bottom*, *B*; n = 144). * = p < 0.05; ** = p < 0.01; *** = p < 0.001.

Table 3—Case Prevalence, Self-Reported Contact With MDI, and Potential MDI Exposure, by Work Area in a Wood Product Plant (N = 144)*

Work Area	Workers, No.	Work With Liquid MDI, % (No.)	Clean Up MDI Spills, % (No.)	Exposure Potential	FAS Cases, % (No.)	NAS Cases, % (No.)
Office	24	17 (4)	13 (3)	Low	8 (2)	0
Outside	19	5 (1)	16 (3)	Low	0	0
Products	30	10 (3)	27 (8)	Int	13 (4)	13 (4)
Green wood	9	33 (3)	67 (6)	High	22 (2)	11 (1)
Dryer	21	24 (5)	52 (11)	High	38 (8)	29 (6)
Blender/press	12	92 (11)	92 (11)	High	42 (5)	33 (4)
Entire plant	29	55 (16)	55 (16)	High/int	28 (8)	17 (5)
Total	144	30 (43)	40 (58)	All	20 (29)	14 (20)

*int = intermediate.

work areas, based on the potential exposures to liquid diisocyanates in the group of workers assigned to the area (Table 3). The prevalence of both new and follow-up cases increased progressively in work areas categorized as low, intermediate, or high potential exposure to liquid diisocyanate (Fig 1, *bottom*, B). The prevalence of FAS reached 39% among workers in areas with the highest exposure potential to liquid MDI, while NAS was documented in 27% of workers from these areas, vs 0% in the lowest exposure areas (p < 0.001). The distribution of IAS showed no clear relationship to either individual or work-area exposures.

Job activities and work practices were evaluated. Workers who reported cleaning the MDI blender at least once had a higher prevalence of NAS and FAS, when compared to those who never performed that activity (NAS, 28% vs 10% [p < 0.03]; FAS, 38% vs 15% [p < 0.01]). Among those employees who reported they had either worked directly with liquid MDI, or had been involved in the cleanup of this material, over one third were found to be cases on follow-up, vs only 12% of those who did not report these activities (p = 0.001). In contrast, individuals who reported sawing or otherwise working with the MDI-laminated wood product did not appear to be at an increased risk (Fig 2, *top*, A). The 32 employees who reported being current smokers at their last follow-up survey were also analyzed separately from the 112 nonsmokers. Both groups showed a significant relationship between work with potential exposure to liquid MDI and FAS, although the proportion of exposed workers with symptoms was higher among current smokers (Fig 2, *bottom*, B). To further investigate the combined effects of current smoking and potential exposure to liquid MDI, a logistic modeling procedure was used (Table 4). In this model, individual reports of work involving exposure to liquid MDI were significantly associated with FAS, while current smoking was not. A term for

the interaction between exposure and current smoking also remained in the model, suggesting an increased risk of symptoms among exposed workers who also smoked.

FAS and NAS were significantly more prevalent among workers who indicated that they had briefly removed respiratory protection, than among individuals who reported never doing this (Fig 3). Interestingly, among workers who subsequently indicated briefly removing their respirators at work, 18% had met the IAS case definition; in contrast, of the individuals who reported they never removed their respirators, none had started out with asthma symptoms (p = 0.05).

The prevalence of both NAS and FAS were also significantly greater in the group of workers who reported observing an MDI stain on their skin at least once, compared to those who had never observed such a stain. A similar although somewhat less pronounced increase in NAS and FAS was seen in association with reports of MDI clothing stains (Fig 4).

Physiologic and Immunologic Tests and Case Prevalence

Among the 178 study participants who had completed at least one follow-up questionnaire, results were available for spirometry (n = 160), peak flow (n = 130), methacholine testing (n = 103), blood tests (n = 100), and skin tests (n = 138). To assess the validity of the case definitions based on the questionnaire responses, comparisons were made to the results of physiologic and immunologic testing. The results of all tests available at each survey were evaluated in relation to case status. The available physiologic data tended to confirm the validity of the questionnaire-based case definitions used in this study. Workers with FAS showed more physiologic evidence of bronchial responsiveness, variable airflow limitation, and specific immunologic sensitiza-
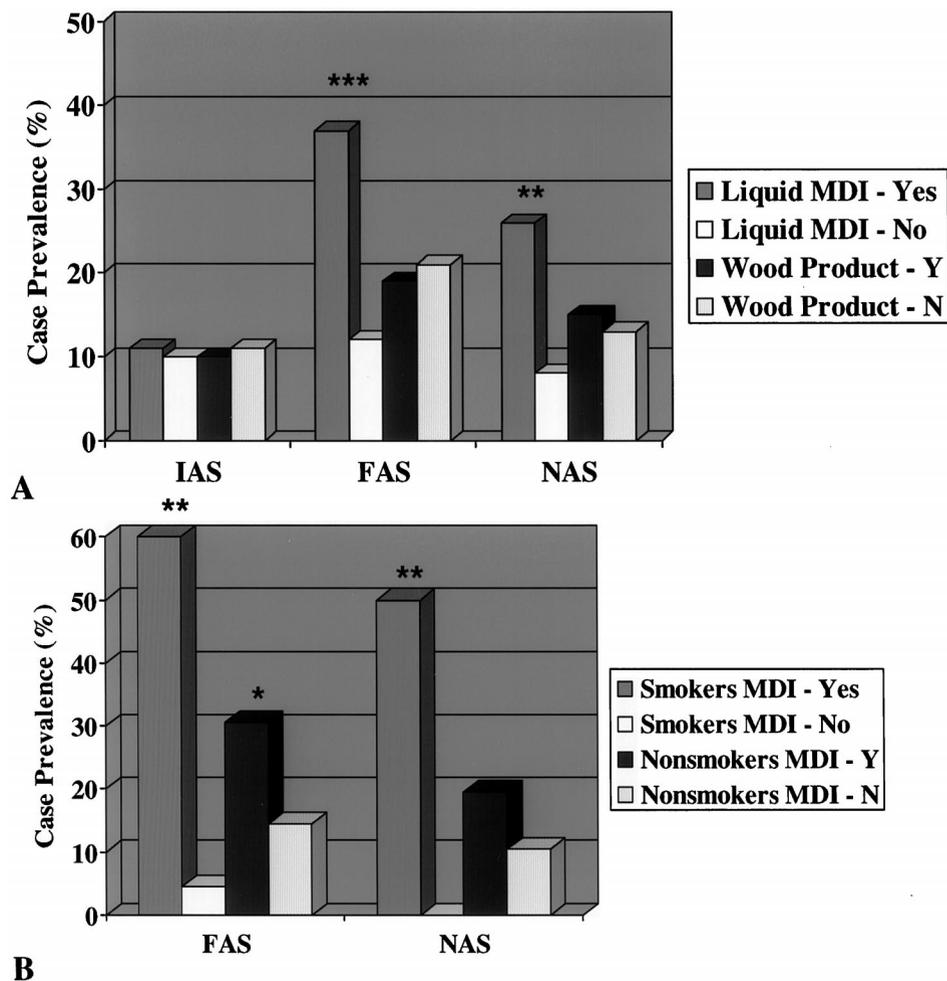
FIGURE 2. Asthma-like symptom case prevalence by work with liquid MDI or laminated wood products (*top*, *A*; n = 144), and by work with liquid MDI for nonsmokers (n = 112) and smokers (n = 32; *bottom*, *B*). * = p < 0.05; ** = p < 0.01; Y = yes; N = no.

tion than those without FAS (Table 5). Among those with initial and follow-up questionnaires and serologic results, 4 of 12 workers with NAS (33%) had MDI-albumin-specific IgE, vs 20 of 88 workers (22.7%) without NAS (p = 0.47).

The prevalence of cases was also evaluated in

relation to the workers' skin test responses to common aeroallergens. Overall, among the 138 individuals with valid test results, 53% showed a reaction (> 5-mm mean wheal diameter) to one or more of
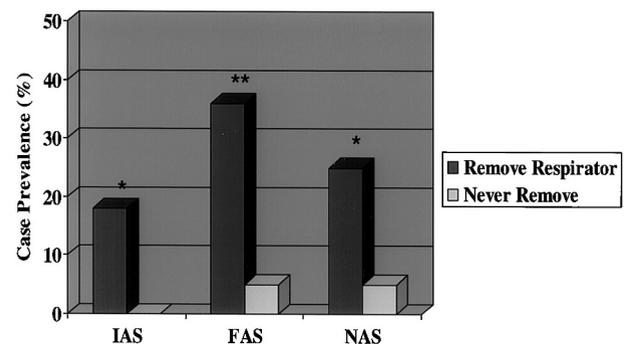
Table 4—Logistic Model of FAS in Wood Product Plant Workers

Variables	Parameter	p Value	OR	CI
Intercept	−1.7765	0.0001		
Smoking*	−1.2680	0.2378	0.28	0.03–2.3
MDI†	0.9555	0.0498	2.6	1.0–6.8
Smoking MDI‡	2.4945	0.0558	12.1	0.94–156

*Smoking = current cigarette smoker at last follow-up.
†MDI = individual report of work with liquid MDI, in process or during cleanup.
‡Smoking MDI = interaction between current smoking and liquid MDI exposure.

FIGURE 3. Asthma-like symptom case prevalence by self-reported brief removal of protective respirator (n = 108). * = p < 0.05; ** = p < 0.01; *** = p < 0.001.
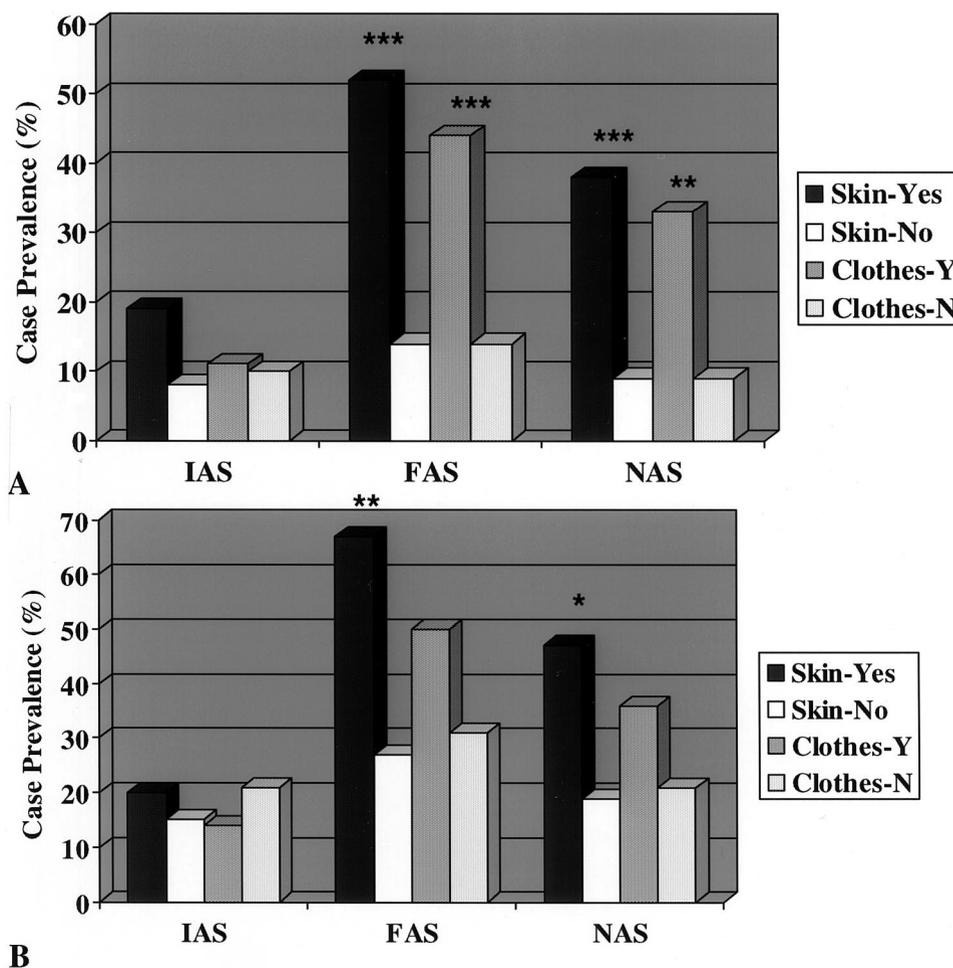
FIGURE 4. Asthma-like symptom case prevalence by skin or clothing MDI stains in all workers (*top, A*; n = 108) and high exposure group (*bottom, B*; n = 41). * = p = 0.07; ** = p < 0.01; *** = p < 0.001. See Fig 2 legend for abbreviations.

the skin test antigens, including 56% of the FAS cases and 52% of the non-FAS cases (odds ratio [OR], 1.1; confidence interval [CI], 0.5 to 2.7). When atopy was defined as showing two or more positive skin responses, 41% of both FAS cases and non-FAS cases were atopic (OR, 1.0; CI, 0.4 to 2.4). Among

workers who had both serologic results and work-practice information, the occurrence of specific IgE to MDI-human serum antigen (HSA) was also assessed in relation to the skin or clothing stains. No significant association was noted between a report of skin or clothing MDI exposure and a positive result on RAST for MDI-HSA.

Table 5—*Physiologic and Immunologic Test Results Among Wood Product Plant Workers With FAS**

Abnormality	FAS	Not FAS	p Value†
ΔFEV$_1$ > 10% (single survey)	5/30 (16.7)	5/131 (3.8)	0.009
ΔFEV$_1$ > 10% (2 yr)	10/30 (33)	26/140 (19)	0.073
Methacholine responsiveness	10/20 (50)	25/84 (30)	0.085
Serial peak flow	8/23 (35)	23/107 (21)	0.175
Specific IgE to MDI-albumin	9/21 (43)	15/79 (19)	0.023
Atopy by skin prick tests	15/27 (56)	58/111 (52)	0.926

*Data presented as No./total cases (%).
†p value by χ^2 for comparison of prevalence of abnormality among FAS vs not FAS.

DISCUSSION

Respiratory disease among workers exposed to the group of commercially useful diisocyanate compounds has been recognized since the 1950s, and exposure limits have been established in the United States and other countries for both ceiling values and time-weighted average exposures.[16] However, recent reports continue to implicate diisocyanates, including MDI, as one of the most frequent causes of new-onset occupational asthma.[3–6] We assessed respiratory health among workers during the first 2

years of operation of a wood products plant that used MDI. The plant had been designed with special consideration to the health risks of workers. Engineering exposure controls included physical isolation and negative pressure ventilation of areas with potential MDI exposure, local exhaust ventilation of saws, and a device that allowed cooling of the billets before handling. In addition, plant management had established and supported a comprehensive personal protection program, including protective clothing and air-supplied respirators in high potential exposure areas. In spite of these efforts, NAS during the 2-year study was documented in one third of the individuals working in the MDI blending and press area, while new symptoms were also reported by 10 to 30% of those working in adjacent areas. Physiologic and immunologic testing tended to confirm the validity of the asthma-like symptoms reported on standardized questionnaires. However, case definitions based on questionnaires are generally found to have high sensitivity but low specificity. Asthma-like symptoms reported during workplace medical surveys or health screening are not synonymous with occupational asthma, and require clinical confirmation. Thus, although the true prevalence cannot be determined from the results of this study, it is very unlikely that all participants with respiratory symptoms have occupational asthma. Additionally, in the absence of the results of specific challenge tests among the symptomatic workers, the prevalence of respiratory tract sensitization to MDI in this study cannot be determined.

It is well established that inhalation of sufficient concentrations of diisocyanates can cause asthma, with the prevalence of asthma symptoms increasing with estimates of workplace exposure.[17,18] Although no environmental diisocyanate sampling is available to us from the 2-year study period, an Occupational Safety and Health Administration (OSHA) inspection was performed in November, 1997, about 7 months after the last health survey. Six personal breathing zone samplers were worn by employees in the plant, and were analyzed for MDI using the OSHA method 47. Two "bulk" samples and one wipe sample of dust from a worker's glove were also taken. None of the air samples had detectable levels of diisocyanate, but one glove wipe sample did show a measurable quantity of MDI (0.078 mg in the sample). If the available OSHA measurements were representative of plant exposures, then they do not explain the high proportion of asthma-like symptoms in these workers. However, several of the study findings may help to shed light on the risks observed. The onset of asthma has previously been associated with brief elevated exposures to diisocyanates, such as process upsets or material spills.[3] In the current

study, a number of participants reported working with or cleaning spills of liquid MDI. Consistent with the previous anecdotal reports, the development of asthma symptoms was highly associated with these activities. Additionally, due to its low vapor pressure at room temperature, exposure risk from MDI is thought to increase with application of heat. In the study plant, the development of symptoms was reported by workers in a number of plant areas, but was somewhat more common among employees who worked near the heated billet press. However, it was not possible to firmly implicate heat as a risk factor, since this was also the area of greatest potential employee exposure to MDI.

Overall, the study findings are consistent with many previous reports indicating that respiratory symptoms can result from workplace MDI exposures. However, in part, study workers with individual concerns about the potential workplace hazards might simply have been more likely to report respiratory tract symptoms. Conceivably, some of the respiratory symptoms reported by these workers could have been related to the knowledge gained during hazard training, and the subsequent increased awareness of the potential exposures. However, if this had been an important effect in this study, then the strongest associations would have been expected between symptoms and the individual worker's report of their personal MDI involvement at work. In fact, the development of symptoms was observed to be more closely associated with grouped exposure categories, work locations, and job activities, compared to individual self-reported exposures (Fig 1, 2). Thus, the pattern of the respiratory symptoms reported by workers in this study is more suggestive of an effect of actual job exposures, rather than individual worker perceptions and concerns.

The skin is recognized as an antigen-presenting organ, and previous animal studies have suggested that skin exposure to isocyanates can lead to the development of respiratory sensitization.[19] In our study, clothing and skin staining with MDI were both highly associated with asthma-like symptoms, the strength of the association being somewhat greater for skin than for clothing stains. Among the wood product workers who reported MDI skin stains, 11 of 21 workers (52%) reported asthma-like symptoms at follow-up, suggesting a possible role for skin exposures in the development of asthma symptoms. Alternatively, the symptoms associated with the skin staining could have been due to higher inhalational exposures associated with the stains. However, a strong association persisted even after stratification for potential exposure to liquid MDI. Both skin and clothing stains should indicate similar respiratory exposure. That asthma symptoms were

slightly more associated with skin stains than clothing stains suggests that the skin contact may be a potential site for sensitization.

We also observed a significant association between asthma-like symptoms and brief removal of respiratory protection. Even brief periods of respirator removal might permit a transient high exposure, sufficient to initiate sensitization and subsequent development of symptomatic asthma. An alternative explanation is suggested by the finding that many workers with asthma-like symptoms on their initial survey also subsequently reported that they briefly removed the respirator, perhaps due to the occurrence of cough or other asthma-related respiratory symptoms. Thus, although brief removal of the respirators was found to be associated with asthma-like symptoms, the results of this study cannot determine if either or both of these explanations are correct.

Of interest, work in several areas of the plant, including the handling and sawing of the composite MDI-wood products, was not associated with increased risk. The apparent absence of risk in these activities may be related to the installation of engineering controls directed at these exposures (including a billet cooler and local exhaust ventilation), as well as appreciable use of respiratory protection in this area.

The study was unique for two reasons: (1) the facility had been designed with considerable attention to worker health concerns, and should have represented a "best case" situation; and (2) many workers completed an initial health survey prior to the delivery of MDI to the plant and were followed for up to 2 years. The concurrent testing that was completed was helpful in validating the case definition with respect to evidence for variable airflow limitation, methacholine responsiveness, and immunologic sensitization to MDI-albumin conjugate.[20–23] Unfortunately, for a number of reasons, full participation in the confirmatory physiologic and immunologic testing was not obtained, and specific inhalation challenge testing was not available. An additional limitation of the study was the lack of systematic environmental measurements from the study period, so that a direct comparison of health outcomes and contemporaneous measured exposures is not possible.

CONCLUSION

Asthma-like symptoms developed in a relatively high proportion of workers during the first 2 years of production at a composite wood products manufacturing plant utilizing MDI. Certain job activities, including the cleanup of MDI spills and cleaning the MDI blender, were associated with asthma-like symptoms, highlighting the critical importance of controlling exposures during those activities. Skin staining with MDI was also associated with NAS, suggesting that the skin may be a potential site for immunologic sensitization, with subsequent risk for development of respiratory symptoms. In contrast, work with composite MDI-wood products was not associated with increased risk, at least in part due to the engineering controls directed at these exposures, as well as a comprehensive respiratory protection policy. Medical screening of exposed workers may result in early detection of asthma cases, and fewer symptoms after removal; however, primary prevention measures for diisocyanate-related asthma remain priorities.[24,25] Users of diisocyanates should consider the results of this study when designing strategies for the prevention of work-related asthma.

APPENDIX

Spirometry, Methacholine, and Bronchodilator Tests

Spirometry was performed using a dry rolling seal spirometer interfaced with a dedicated microprocessor.[26] Equipment and procedures met or exceeded those recommended by the American Thoracic Society for the performance of diagnostic spirometry.[27] A minimum of five acceptable blows were recorded at each session. Spirometry was performed on a single occasion during the initial health survey, and up to three times during subsequent surveys (preshift and postshift the first workday, and postshift the last workday of the work week). The largest values of FEV_1 and FVC at each session were selected, and compared to reference values.[28] During the first and last workplace surveys, participants with spirometry results above the lower limit of normal were requested to complete methacholine inhalation challenge testing, based on a protocol modified from Chatham et al[29] and O'Connor et al.[30] For individuals with abnormal results, spirometry was repeated at least 10 min after three inhalations of 90-μg metered doses of albuterol. Methacholine responsiveness was determined by a $> 15\%$ drop from baseline FEV_1 after inhalation of < 25 mg/mL methacholine aerosol, or a $> 10\%$ increase in FEV_1 after inhaled bronchodilator.

Serial Peak Flow Recordings

At each follow-up survey, workers were given mini-Wright peak flowmeters and log sheets. They were asked to record three peak flows every 2 h, while awake, for 8 consecutive days. Log sheets had 12 suggested recording times for each study day, starting at 2:00 AM. Many workers were required to use respiratory protection while at work, and it was thus not possible for

them to perform peak flow efforts during their work shift. All peak flow logs were screened for apparent validity, and recordings that did not appear to be valid were eliminated from the analysis. The largest of the three values at each recording time was used in all calculations. Maximum and minimum peak flows were determined for each day and for the study week. Peak flow variation was calculated as the difference between the weekly maximum and minimum readings divided by the period mean. To account for a learning effect, data from the first day were omitted from the calculation of variation. For each apparently valid 8-day peak flow recording, variable airflow limitation was considered present if the peak flow variation was > 20%.[31,32]

Skin Prick Testing

Tests were performed on the volar surface of the lower arms. The skin was cleansed with isopropyl alcohol and allowed to dry. Sites for testing were marked at least 1 inch apart. Histamine and glycerol were used for positive and negative controls, respectively, while 18 common aeroallergens (Greer Laboratories; Lenoir, NC) were used for testing. Each material to be tested was applied from a plastic well using a disposable sterile device (DermaPic System; Greer Laboratories). The device has an indentation that holds a drop of the liquid being applied, surrounded by multiple points. As the device was rotated a one-quarter turn, and light pressure applied, the skin was scratched and the liquid contacted the scratch. The site was gently blotted with gauze approximately 1 min later. After 15 min and 30 min, the greatest and the smallest diameters of each wheal were recorded. For each allergen, if the average of the two diameters was > 5 mm, the test was considered positive. An individual participant's results were excluded if (1) there was no reaction to histamine; or (2) there was a positive reaction (> 5 mm) to the negative control.

Serologic Studies

A protein-isocyanate conjugate was prepared by reacting HSA, 2 mg/mL, suspended in phosphate buffered saline solution (pH, 7.4) at 40°C with MDI aerosol for 4 h. The MDI aerosol was generated by heating 5 g of MDI to 125°C in an impinger that was flushed with dry nitrogen, and the nitrogen bubbled through the protein solution at constant flow rate of 2 L/min. The resulting conjugate was found to contain approximately 1.5 mol of isocyanate per mol protein based on the analysis of free amines before and after conjugation. Extracts were prepared from three wood samples taken from the plant. The first was made from the raw wood strands after they had been dried, the second from wood strands coated with the MDI prepolymer, and the third from the finished wood product produced by the plant. The samples were ground into fine particulates, suspended in 0.05 mol/L ammonium carbonate as a 10% (weight per volume) suspension, and gently mixed overnight at 4°C. The particulates were removed by centrifugation, and the extracts were dried by lyophilization. The resulting residue was redissolved in a carbonate buffer (pH, 9.6) and dialyzed against the same buffer. The total protein content of the dialyzed extracts was determined by the Lowry method.

The MDI-HSA conjugate and the three wood extracts were coupled to cyanogen bromide-activated Sepharose 4B beads (Pharmacia BioTech; Kalamazoo, MI) according to the recommended procedure of the manufacturer. The coupling efficiency for each protein was determined by monitoring the absorbance at 280 nm before and after reacting with the beads; between 70% and 80% of the available protein was bound by the beads. The beads were suspended in RAST buffer (0.1 mol/L phosphate buffer, pH 7.4, containing 4% fetal calf serum, 0.1% Tween 20, and 0.1% sodium azide) and stored at 4°C as a 10% (volume per volume) suspension until used in the RAST assay.

A radioallergosorbent test was developed for each antigen extract using standard procedures.[33] Briefly, allergen-coated beads were reacted with 0.05 mL serum for 3 h at room temperature on a tube rotator, washed three times with radioallergosorbent test wash solution, and reacted with iodine-125 labeled anti-human IgE (Pharmacia Diagnostics). After overnight incubation, the tubes were washed as above and counted in a gamma scintillation counter. HSA-coupled beads were included in each assay to determine nonspecific binding. RAST scores were calculated as the ratio of percent counts bound by antigen-coated beads divided by the percent counts bound by HSA-coated beads. For each antigen tested, a preliminary assay was carried out using sera from 20 to 50 exposed subjects. From that screen, two sera showing high levels of binding and two sera with low-level binding were selected and used to titrate each antigen preparation. The titration was accomplished by using different volumes of beads (25 to 300 μL) in the radioallergosorbent test assay to determine optimal antigen concentrations (ie, the bead volume that yielded maximal binding with the reactive sera, and little nonspecific binding). The optimal antigen concentration was then used to assay all sera. Both saline solution controls and sera from nonexposed individuals were used to determine the nonspecific binding values for each antigen, and these were found to be the same or less than the serum nonspecific binding values (ie, HSA-coated beads). RAST scores were calculated for each serum as the following ratio: IgE bound to allergen-coated beads/IgE bound to HSA-coated beads.

References

1 Gannon PF, Burge PS. The SHIELD scheme in the West Midlands Region, United Kingdom: Midland Thoracic Society Research Group. Br J Ind Med 1993; 50:791–796

2 Provencher S, Labreche FP, De Guire L. Physician based surveillance system for occupational respiratory diseases: the experience of PROPULSE, Quebec, Canada. Occup Environ Med 1997; 54:272–276

3 Malo J-L, Cartier A. Occupational asthma. In: Harber P, Schenker M, Balmes J, eds. Occupational and environmental respiratory diseases. St Louis, MO: Mosby, 1995; 420–432

4 Fabri G. The prevention of occupational asthma in industries. J Investig Allergol Clin Immunol 1997; 7:377–379

5 Rosenman KD, Reilly MJ, Kalinowski DJ. A state-based surveillance system for work-related asthma. J Occup Environ Med 1997; 39:415–425

6 Tarlo SM, Liss G, Corey P, et al. A workers' compensation claim population for occupational asthma: comparison of subgroups. Chest 1995; 107:634–641

7 Burge PS. New developments in occupational asthma. Br Med Bull 1992; 48:221–230

8 Bernstein JA. Overview of diisocyanate occupational asthma. Toxicology 1996; 111:181–189

9 Deschamps F, Prevost A, Lavaud F, et al. Mechanisms of occupational asthma induced by isocyanates. Ann Occup Hyg 1998; 42:33–36

10 Raulf-Heimsoth M, Baur X. Pathomechanisms and pathophysiology of isocyanate-induced diseases: summary of present knowledge. Am J Ind Med 1998; 34:137–143

11 Musk AW, Peters JM, DiBerardinis L, et al. Absence of respiratory effects in subjects exposed to low concentrations of TDI and MDI. J Occup Med 1982; 24:746–750

12 Bernstein DI, Korbee L, Stauder T, et al. The low prevalence of occupational asthma and antibody-dependent sensitization to diphenylmethane diisocyanate in a plant engineered for

minimal exposure to diisocyanates. J Allergy Clin Immunol 1993; 92:387–396

13 Woellner RC, Hall S, Greaves I, et al. Epidemic of asthma in a wood products plant using methylene diphenyl diisocyanate. Am J Ind Med 1997; 31:56–63

14 Burney P, Chinn S. Developing a new questionnaire for measuring the prevalence and distribution of asthma. Chest 1987; 91:79S–83S

15 Ferris, BG. Epidemiology standardization project. ATS-DLD Adult Questionnaire. Am Rev Respir Dis 1978; 118:1–120

16 National Institute for Occupational Safety and Health. Criteria for a recommended standard: occupational exposure to diisocyanates. Cincinnati, OH: Department of Health Education and Welfare, 1978. Publication No. 78–215

17 Tarlo SM, Liss GM, Dias C, et al. Assessment of the relationship between isocyanate exposure levels and occupational asthma. Am J Ind Med 1997; 32:517–521

18 Vandenplas O, Cartier A, Ghezzo H, et al. Response to isocyanates: effect of concentration, duration of exposure, and dose. Am Rev Respir Dis 1993; 147:1287–1290

19 Rattray NJ, Botham PA, Hext PM, et al. Induction of respiratory hypersensitivity to diphenylmethane-4, 4[prime]-diisocyanate (MDI) in guinea pigs: influence of route of exposure. Toxicology 1994; 88:15–30

20 Baur X, Huber H, Degens PO, et al. Relation between occupational asthma case history, bronchial methacholine challenge, and specific challenge test in patients with suspected occupational asthma. Am J Ind Med 1998; 33:114–122

21 Redlich CA, Homer RJ, Smith BR, et al. Immunologic responses to isocyanates in sensitized asthmatic subjects. Chest 1996; 109:6S–8S

22 Lushniak BD, Reh CM, Bernstein DI, et al. Indirect assessment of 4,4′-diphenylmethane diisocyanate (MDI) exposure by evaluation of specific humoral immune responses to MDI conjugated to human serum albumin. Am J Ind Med 1998; 33:471–477

23 Tee RD, Cullinan P, Welch J, et al Specific IgE to isocya-nates: a useful diagnostic role in occupational asthma. J Allergy Clin Immunol 1998; 101:709–715

24 Tarlo SM, Banks D, Liss G, et al. Outcome determinants for isocyanate induced occupational asthma among compensation claimants. Occup Environ Med 1997; 54:756–761

25 National Institute for Occupational Safety and Health. Preventing asthma and death from diisocyanate exposure: NIOSH alert. Cincinnati, OH: Department of Health and Human Services, 1996. Publication No. 97–111

26 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999; 159:179–187

27 Standardization of spirometry: 1994 update; American Thoracic Society. Am J Respir Crit Care Med 1995; 152:1107–1136

28 Knudson RJ, Lebowitz MD, Holberg CJ, et al. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 1983; 127:725–734

29 Chatham M, Bleecker ER, Norman P, et al. A screening test for airways reactivity: an abbreviated methacholine inhalation challenge. Chest 1982; 82:15–18

30 O'Connor G, Sparrow D, Taylor D, et al. Analysis of dose-response curves to methacholine. Am Rev Respir Dis 1987; 136:1412–1417

31 Quackenboss JJ, Lebowitz MD, Krzyzanowski M. The normal range of diurnal changes in peak expiratory flow rates: relationship to symptoms and respiratory disease. Am Rev Respir Dis 1991; 143:323–330

32 Lebowitz MD, Krzyzanowski M, Quackenboss JJ, et al. Diurnal variation of PEF and its use in epidemiological studies. Eur Respir J 1997; 24:49S–56S

33 Hamilton RG, Adkinson NF. Measurement of total serum immunoglobulin E and allergen-specific immunoglobulin E antibody. In: Rose NR, deMacario EC, Fahey JL, et al, eds. Manual of clinical immunology. 4th ed. Washington, DC: American Society for Microbiology, 1992; 689–701