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Occupational asthma due to isocyanates

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ABSTRACT: 162 subjects who had been exposed to isocyanates, who had developed symptoms during the exposure period, or in the evening or night and, therefore, had a history compatible with isocyanate-induced asthma, were studied with inhalation challenge testing to isocyanates (toluene diisocyanate and methylene diphenyl diisocyanate) and methacholine, because they were suspected of having occupational asthma. None of these subjects had symptomatic asthma before employment. The diagnosis of occupational asthma was delayed (duration of symptoms before diagnosis: 3.9 ± 0.4 yrs). Isocyanate-asthma documented by a positive inhalation challenge to isocyanates was present in 57.4% of the subjects. A higher degree of airway responsiveness to methacholine was present in subjects with a positive isocyanate inhalation challenge compared to subjects with a negative challenge (GMean and GESM: 0.407 (1.14) *vs* 0.942 (1.14) mg). The majority of the subjects complained of shortness of breath and cough. The low proportion of atopic subjects (21.5%) and of smokers (7.5%), and the high proportion of subjects with the late component in the asthmatic reaction (71%) appear to be common features in this disease.

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Bronchial asthma is a disorder characterized by increased airway responsiveness to a wide variety of both specific and non-specific stimuli [1]. Some of these stimuli are present in the workplace, indeed, several cases of asthma are related to occupational exposure to chemicals and materials used in industry. The widespread use of these chemicals leads to asthma with increasing frequency in subjects exposed to isocyanates who have become sensitized to them. FUCHS and VALADE were the first to report that exposure to isocyanates can cause respiratory disease [2]. Many studies on isocyanate-asthma have since been performed. An immunologic mechanism causing toluene diisocyanate (TDI)-induced asthma has been suggested by SCHEEL *et al.* [3]. More recently, KAROL and co-workers have shown the presence of specific IgE antibodies for the p-tolyl portion of the isocyanate molecule in the sera of symptomatic workers [4–5]. The prevalence of specific IgE antibodies is about 20%, suggesting that it is not the major mechanism of isocyanate-asthma [6]. DAVIES *et al.*, have suggested that isocyanates act as pharmacologic inhibitors, reducing the ability of beta-adrenergic receptors to produce cyclic adenosine monophosphate (cAMP) in sufficient amounts to maintain bronchial tone [7]. Studies regarding inhalation challenge with isocyanates have also been performed [8–13]. These studies have shown that inhalation of isocyanates in the laboratory provokes early, late or dual asthmatic reactions in subjects with a history of isocyanate-asthma. Moreover, some studies suggest that asthmatic reactions to isocyanates cannot be attributed to non-specific mechanisms alone, and that, on the other hand, non-specific airway hyperresponsiveness may play a role in isocyanate-asthma [14–16]. However, isocyanate asthma can occur in sensitized subjects, even in the absence of airway hyperresponsiveness [17–19]. The mechanism of specific sensitization to isocyanates, still remains unclear [20], even though recent studies suggest that the isocyanate effect is linked to an acute inflammatory response in the airways [21–23]. The natural history of isocyanate-asthma also remains to be defined. Studies concerning the long-term follow-up of subjects with isocyanate-asthma, report that a significant proportion of subjects, who had left the workplace, continued to have respiratory symptoms and airway hyperresponsiveness to non-specific stimuli [24–28].

Isocyanate-asthma is an important occupational respiratory disease in our country, which has a large number of small furniture factories, where isocyanates are used for varnishing. In this report, the results of a study on 162 patients with a history of isocyanate asthma, are described.

Subjects and methods

162 subjects, who had been exposed to isocyanates, and had developed symptoms during the exposure

period, or in the evening or night, were studied. Symptoms included shortness of breath, wheezing, dry cough or chest tightness. None of the subjects had symptomatic asthma before occupational exposure to isocyanates. All subjects underwent detailed clinical and occupational history, allergy skin tests (using the intradermal method with extracts of common allergens) and pulmonary function tests. All subjects had been free from respiratory infections or exposure to isocyanates for at least two weeks. No subject took cromolyn, theophylline, sympathomimetics or antihistamines within 48 h of any study. A subject was considered to be atopic if there was a history of allergic rhinitis, eczema, or positive skin reaction to two or more common allergen extracts. A skin reaction was considered to be positive when, at the site of the injection of any allergens, a wheal developed that was greater than that of the diluent control and equal to or greater than that of the histamine control solution.

Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured using a dry bellows spirometer (Ohio Mod.840, Houston, TX). Methacholine inhalation test and isocyanate inhalation tests were carried out in all the subjects at the time of the diagnosis of occupational asthma. The method of methacholine inhalation test has been described previously [22]. Briefly, aerosols were generated by a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, PA) connected to a Rosenthal-French dosimeter (R) (John Hopkins University, Baltimore, MA), driven by compressed air. Five inhalations were taken for phosphate-buffered saline and for each increasing, doubling dose of methacholine (0.5 to 64 mg/ml) administered at 5 min intervals, until a 20% fall in FEV_1 was observed. FEV_1 was measured 3 min after the beginning of each set of inhalations of aerosolized methacholine. Airway responsiveness to methacholine was measured the day before the inhalation challenge with toluene diisocyanate (TDI). Most asthmatic patients in our laboratory respond to less than 1 mg of methacholine using the generation system described above.

The methods of toluene diisocyanate and 4,4' diphenyl methane diisocyanate inhalation have been described in detail previously [21, 29]. Briefly, subjects were exposed to toluene diisocyanate (TDI) (0.018 ± 0.005 ppm) or 4,4' diphenyl methane diisocyanate (MDI) (0.016 ± 0.001 ppm) in a nine cubic metre exposure chamber. A fan in the chamber ensured adequate mixing and circulation. The temperature in the chamber was maintained at about 24°C. The duration of exposure was 30 min, or until the appearance of symptoms of asthma in the subjects who developed an early asthmatic reaction. The concentration of isocyanates generated was measured with a MDA model 7005 isocyanate detection equipment (MDA Scientific Inc., Glenview, IL). The subject was seated close to the monitor and was observed through the windows of the chamber. FEV_1 was measured immediately before and after exposure to isocyanates, then hourly for 8 h. Inhalation challenge with MDI was carried out in eight of the 162 subjects.

Specific IgE antibodies to TDI-human serum albumin (TDI-HSA) and to MDI-HSA conjugates were measured in duplicate by radioallergosorbent test (RAST, Pharmacia Diagnostic, Uppsala, Sweden) in 61 subjects. Allergo-Discs Isocyanate allergen preparations when used in Phadebas RAST, to measure the level of circulating IgE antibodies specific to 2,4 and 2,6 toluene diisocyanate and to 4,4' diphenylmethane diisocyanate. Discs with HSA served as control, correcting for any non-specific binding of IgE to HSA on the isocyanate-albumin discs. The result was expressed as a ratio of TDI-count rate or MDI-count rate to that of HSA-count rate for each sample. A ratio of 2.0 or more was considered a positive test.

Statistical analysis

An immediate or dual asthmatic reaction to isocyanates was considered to occur when FEV_1 decreased by at least 20% from baseline within 30 min (early component of a dual reaction or early reaction alone) and one or more hours (late component of a dual reaction or late reaction alone) after exposure to isocyanates.

To assess airway responsiveness, dose-response curves to methacholine were constructed by plotting the baseline value for FEV_1 and the peak value after each methacholine dose against the cumulative dose (nebulizer output × solution concentration) of methacholine delivered, on a log scale. The cumulative dose of methacholine producing a 20% fall in FEV_1 ($PD_{20}FEV_1$) was calculated by interpolation from dose-response curves and was used as a measure of airway responsiveness. In our laboratory, the day to day variability of $PD_{20}FEV_1$ was never greater than a doubling inhalation dose [30]. Logarithmic transformation of PD_{20} was used for statistical analysis. Statistical analysis was carried out with analysis of variance, chi-square test and analysis of covariance where it was appropriate [31].

Results

The clinical features of the subjects at the time of the diagnosis of occupational asthma are shown in table 1. There were no differences in the prevalence of sex, smoking habits and atopy in the group of subjects with a positive isocyanate inhalation challenge, compared to the group with a negative test. The group of reactors had a significantly longer duration of symptoms compared to the group of non-reactors ($p < 0.01$). Fifty seven percent of the subjects with a history suggestive of isocyanate-asthma had a positive isocyanate inhalation test. A small proportion of the subjects were smokers (7.5%) and atopic (21.5%). The average duration of exposure to isocyanates ranged between nine and fourteen years and the average duration of

Table 1. - Clinical features of the 162 subjects with history of isocyanate-asthma

	Reactors	Non-reactors
n subjects	93	69
Age at diagnosis yr	34.5±1.2*	34.6±1.3
Smoking habits		
Non-smoker	67.7%	67.0%
Ex-smoker	24.7%	17.0%
Current smoker	7.5%	16.0%
Positive to one or more allergens		
Allergy skin test	21.5%	14.0%
Duration of symptoms before diagnosis yr	3.9±0.4&	2.4±0.3
Duration of exposure yr	12.8±1.0	13.1±3.1
Pulmonary function		
FEV_1 % predicted "	95.7±1.7	97.1±1.7
Type of asthmatic response		
Immediate alone	27 (29.0%)	
Late alone	32 (34.4%)	
Dual	34 (36.6%)	
Treatment during the challenge	33 (35.5%)	
Methacholine inhalation test		
$PD_{20}FEV_1$ mg before Isocyanate inhalation	0.407 (1.14)**	0.942 (1.14)ß

*: mean+SEM; **: Gmean and GSEM; &: difference between reactors and non-reactors statistically significant $p<0.01$ by analysis of variance; ß: difference between reactors and non-reactors statistically significant $p<0.01$ by analysis of covariance; predicted values from ECCS Tables [41].

symptoms between two and five years, showing that the diagnosis of occupational asthma was delayed. Ninety three subjects developed an asthmatic reaction after exposure to isocyanates in the laboratory: 27 developed an immediate reaction, 34 a dual reaction, 32 a late reaction and 33 required treatment during the challenge. Of the 93 subjects with a positive isocyanate inhalation challenge, 15 (16.1%) had FEV_1 lower than 80% predicted. All subjects had methacholine inhalation test before challenge with TDI or MDI. The geometric mean (Gmean) $PD_{20}FEV_1$ was 0.407 mg (geometric standard error of mean (GSEM) = 1.14) in the group with a positive inhalation challenge to isocyanates and 0.942 mg (GSEM = 1.14) in the subjects with a negative inhalation challenge to isocyanates. The difference was significant, after adjustment had been made for the level of FEV_1 ($p<0.01$), (fig. 1).

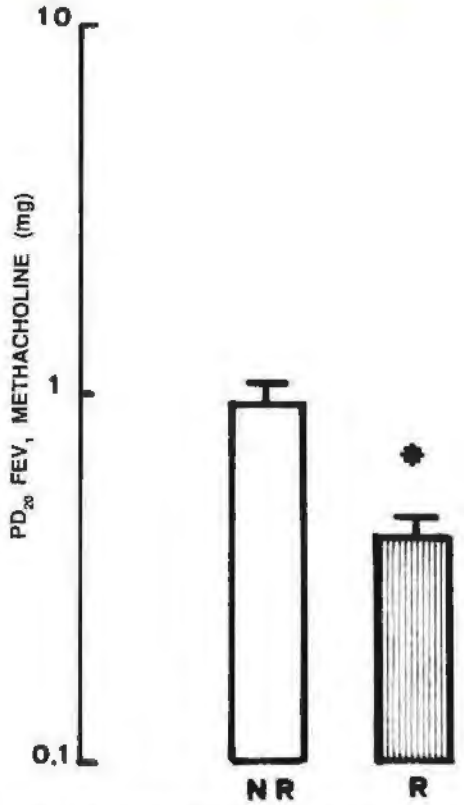

Fig. 1. Methacholine provocative doses for subjects who did not react to exposure to TDI (non-reactors = NR: open bar) and for subjects who reacted to TDI (reactors = R: stippled bar). Provocative doses were determined from the dose-response curve to methacholine aerosol, * $p<0.01$.

The subjects who required therapy during the challenge with isocyanates were older (mean: 36.4 yr) with a longer duration of exposure (mean: 14.1 yr) and of symptoms (mean: 5.3 yr). However, there was no significant difference as regards age, duration of exposure, duration of symptoms and baseline lung function between the subjects who required treatment during inhalation challenge with isocyanates and those who did not. During inhalation challenge with isocyanates, eighteen subjects improved lung function after inhalation of salbutamol, two required salbutamol and methylprednisolone *i.v.*, and thirteen subjects required salbutamol, methylprednisolone and aminophylline *i.v.* Nobody required resuscitation treatment. The characteristics of the subjects who developed an asthmatic response after exposure to isocyanates and who did not require therapy during the challenge are reported in table 2. Most of the subjects complained of shortness of breath and cough and many also complained of wheezing. There were no significant differences between the three groups as regards age, duration of exposure, atopy, smoking habits, baseline lung function and baseline airway responsiveness to methacholine, after adjustment for FEV_1 had been made. The diagnosis of occupational asthma was particularly delayed in the group of subjects with a late asthmatic response; the difference, however,

Table 2. - Clinical features of the 60 subjects with a positive isocyanate inhalation test according to the type of asthmatic response

	Subjects with IAR (n=14)	Subjects with LAR (n=24)	Subjects with DAR (n=22)
Age at diagnosis yr	28.3±2.1*	34.2±1.8	35.7±2.6
Sex	6 F, 8 M	6 F, 18 M	4 F, 18 M
Height cm	170.1±2.1	171.0±1.6	173.0±1.5
Atopic status	3 (21.4%)	5 (21.0%)	4 (18.0%)
Smoking habits			
Current smoker	1 (7.1%)	1 (4.0%)	3 (14.0%)
Non-smoker	9 (64.3%)	16 (67.0%)	15 (68.0%)
Ex-smoker	4 (28.6%)	7 (29.0%)	4 (18.0%)
Symptoms			
Shortness of breath	13 (93.0%)	23 (96.0%)	22 (100.0%)
Cough	10 (71.0%)	24 (100.0%)	19 (86.0%)
Wheezing	4 (29.0%)	8 (33.0%)	9 (41.0%)
Chest tightness	3 (21.0%)	5 (21.0%)	3 (14.0%)
Duration of symptoms before diagnosis yr	2.5±0.4	3.9±0.8	2.7±0.5
Duration of exposure yr	9.0±1.3	13.2±2.4	12.9±2.4
Pulmonary function			
FEV_1 *l*	3.8±0.2	3.7±0.1	3.7±0.1
FEV_1 % predicted	98.6±5.3	94.2±5.1	93.3±3.1
% fall in FEV_1			
immediate reaction	39.4±4.4		35.1±3.2
late reaction		33.6±2.2	37.0±3.3
Methacholine inhalation test			
$PD_{20}FEV_1$ mg	0.594 (1.33)**	0.787 (1.22)	0.459 (1.31)

*: Mean±SEM; **: Gmean and GSEM; IAR: immediate asthmatic response; LAR: late asthmatic response; DAR: dual asthmatic response

failed to reach statistical significance. Airway responsiveness to methacholine was similar in subjects who developed an immediate, a dual, or a late asthmatic response after exposure to isocyanates (fig. 2). Only the subjects who required treatment during the inhalation challenge showed a higher degree of airway responsiveness to methacholine after adjustment had been made for the level of FEV_1 (Gmean = 0.200 mg; GSEM = 1.25; difference statistically significant $p < 0.01$ from the subjects with an immediate reaction, from the subjects with a late response, $p < 0.01$; from the subjects with a dual response; $p < 0.05$, by analysis of covariance). Serologic testing performed in 61 subjects, 49 reactors and 12 non-reactors, detected specific IgE only in one subject. Nine subjects (18.4%) among the reactors and four subjects (33.3%) among the non-reactors showed high levels of total IgE.

Discussion

In this study we described the clinical picture of 162 patients with a history of isocyanate-asthma.

There are a large number of interesting factors in isocyanate-induced asthma. The latent period between exposure and onset of respiratory symptoms is prolonged. The proportion of atopic subjects among the 93 subjects with isocyanate-induced asthma was 21.5%; this was similar to the proportion of atopic subjects seen in other types of occupational asthma [32]. Another feature of the disease is the high

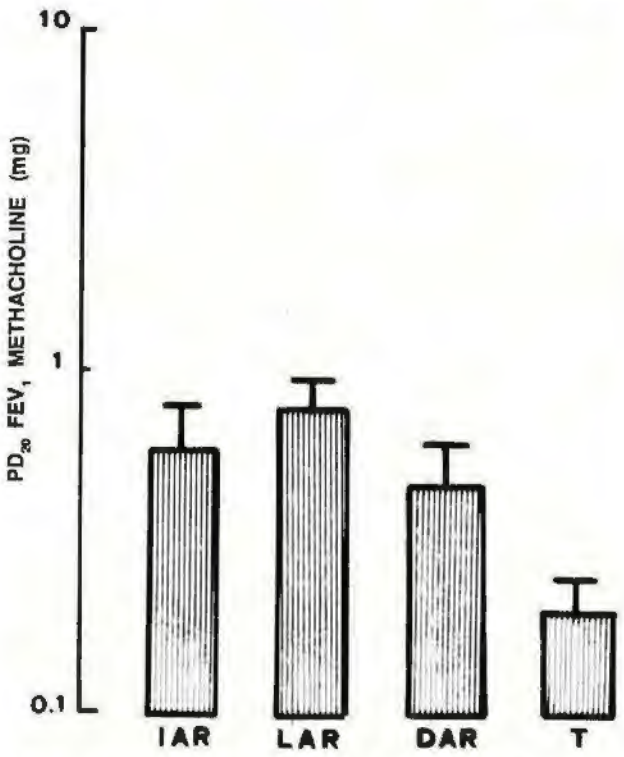

Fig. 2. Methacholine provocative doses for subjects who developed after exposure to TDI an immediate asthmatic reaction (IAR), a late asthmatic reaction (LAR), a dual asthmatic reaction (DAR) or required therapy during inhalation challenge with TDI (T).

proportion of non-smokers (67.7%). Similar findings have been reported among subjects with red cedar asthma [32]. In previous studies, an interaction between smoking and atopy in workers exposed to tetrachlorophtalic anhydride (TCPA) has been reported [33]. The high proportion of non-smokers in subjects with isocyanate-asthma suggests, as reported previously [32], that non-smokers, compared to smokers, are more susceptible to occupational asthma due to isocyanates.

The commonest symptoms amongst the subjects examined were shortness of breath and cough. Late asthmatic reactions occurred in 71% of the subjects, whilst immediate asthmatic reactions alone occurred in 29% of the subjects. Airway responsiveness to methacholine was similar in subjects who developed the three different patterns of asthmatic response after exposure to isocyanates, but the degree of airway responsiveness to methacholine was significantly higher in the subjects who reacted to isocyanates compared to those with a negative isocyanate inhalation challenge. There are studies suggesting that baseline airway responsiveness to methacholine is an important factor in the outcome of occupational asthma [34]; and others suggesting that subjects with an isolated late reaction have a greater degree of airway responsiveness to methacholine [35]. On the other hand, some studies suggest that a dual reaction represents a more advanced stage in the natural history of bronchial asthma [36, 37]. An IgE mediated type I mechanism has been proposed both for the immediate and for the late or dual asthmatic reaction. In red cedar asthma, IgE antibodies occurred with higher frequency in subjects with late asthmatic reactions than in those with immediate or dual reactions [14]. In this type of occupational asthma, it has been proposed that the immediate component of a dual reaction may occur as a result of heightened non-specific bronchial reactivity, suggesting that the degree of bronchial reactivity is an important factor in determining the type and severity of the asthmatic reaction. In the present study we did not find significant differences as regards duration of symptoms before diagnosis, and baseline airway responsiveness to methacholine between subjects with different patterns of asthmatic reactions. Baseline airway responsiveness to methacholine did not influence the type of asthmatic reaction but only the severity of the reaction.

In a previous study [30], we showed that airway responsiveness to methacholine increases after exposure to isocyanates only in subjects with a history of isocyanate-asthma, who develop a late or dual asthmatic reaction, and not in subjects with a history of isocyanate-asthma who develop an early reaction or in asthmatic subjects, without exposure to isocyanates and without a history of isocyanate-asthma, but with hyperreactive airways who develop no asthmatic reaction after exposure to isocyanates. These results suggest that the early asthmatic reaction is due only to smooth muscle contraction, that oedema and inflammation are not involved, and that TDI-asthma occurs only among subjects with exposure and a history of isocyanate-asthma. Isocyanates have no effect, at least at low concentrations, on hyperreactive airways, suggesting that the effect of TDI is not linked to irritation of the airways; and that therefore, baseline airway responsiveness to methacholine is not an important determinant for the type of asthmatic reaction. Moreover, in a follow-up study of patients with isocyanate-asthma, we found that baseline airway responsiveness to methacholine is also unimportant for the prognosis of the disease. Subjects with airway hyperresponsiveness to methacholine may recover, and airway responsiveness to methacholine may become normal. However, in subjects who do not recover, there are no changes in the degree of airway responsiveness to methacholine, and the subjects remain hyperreactive. In our follow-up study, we also showed that subjects with an early reaction recovered, that among subjects with dual reactions, some subjects recovered and some lost the immediate component, maintaining the late reaction; and that no subjects with a late asthmatic reaction recovered [38]. In our experience, the late reaction seems to be more important compared to the immediate alone or the dual asthmatic reaction for the persistence of respiratory symptoms. Long-term follow-up studies are necessary to better define the natural history of the disease, and to confirm these

data. Different results may also be due to different agents (TDI, western red cedar) or different populations examined. The subjects described in the present study were all working in small furniture shops, and had never been exposed to a spill of isocyanates.

Specific IgE antibodies, demonstrated by RAST, were found only in one subject, suggesting that this may not be the major mechanism of isocyanate-asthma. However, specific IgE antibodies may be present in the lung, but in unmeasurable quantities in the peripheral circulation. The presence of specific IgE may occur in exposed workers without asthma or rhinitis, indicating 'sensitization' more than disease. It is also possible, that the use of more appropriate conjugates may increase the sensitivity of the test.

The finding of a negative isocyanate challenge in subjects with a consistent history for isocyanate-asthma may be explained, at least in some subjects. For example, in some subjects, the dose of isocyanates or the length of exposure to isocyanates used in this study may be insufficient to elicit an asthmatic response. In our laboratory, in some subjects, a 30 min TDI challenge did not elicit bronchospasm, but 2 h of exposure to TDI provoked an asthmatic response (Mapp, personal observations). Alternatively, the isocyanate non-reactors may have lost their sensitivity to isocyanates after removal from exposure. These subjects may have developed symptoms due to non-specific airway hyperresponsiveness without sensitization to specific agents. Finally, these subjects may be sensitized to other agents present in the industry such as amines or catalysts used in the manufacture of isocyanates [39].

In this report, we showed that the diagnosis of isocyanate-asthma was often delayed. Several reasons can explain the delayed diagnosis. Firstly, subjects complained of cough and shortness of breath, and these respiratory symptoms may occur only during the night. Secondly, the only symptom may be cough, and this together with the finding of normal lung volumes may lead the physician to a different diagnosis. The fact that airway responsiveness to methacholine is normal cannot exclude isocyanate-asthma. In a previous study, we have shown that isocyanate-asthma can occur even if airway responsiveness to methacholine is normal [19].

Early diagnosis and early removal from exposure to isocyanates are important and in some cases may lead to complete recovery [25]. For subjects who continue to work with isocyanates, it is imperative that they take regular medication for the treatment of asthma. Keeping in mind that the late component is a feature of the asthmatic reaction to isocyanates, and that the late reaction is associated with an increase in airway responsiveness and may explain perennial asthma, it is important to use drugs which are effective on the late reaction. The use of inhaled steroids is necessary for workers who cannot leave the workplace environment [40]. Moreover, the use of home and work peak-flow meters provides the opportunity to examine objectively the clinical course of the disease and provides the subject with confidence that therapy is effective or indicates the opportunity to find other safe alternatives to permit sufficient control to assure a normal lifestyle at home and at work.

In conclusion, isocyanate-asthma is an important cause of occupational respiratory disease. The interesting clinical features of isocyanate-asthma are the prolonged period between exposure and onset of respiratory symptoms, the low proportion of atopics and of current smokers, and the high proportion of late asthmatic reactions. Moreover, baseline airway responsiveness to methacholine is similar in subjects who developed an immediate, a dual, or a late asthmatic reaction after exposure to TDI. Only for subjects who require therapy during isocyanate inhalation challenge, is the degree of non-specific airway responsiveness higher.

Since there is no satisfactory biochemical method for diagnosis of isocyanate-asthma, there are at present two other possibilities. Firstly, to challenge the subject at his workplace by providing him with a peak flow meter and measuring peak flow rates before the onset of exposure to isocyanates and then hourly during the day and night following. Secondly, to challenge the subject in the laboratory by exposing him to low levels of isocyanates, and measuring FEV_1 before the exposure and then throughout the day and night. These two methods can provide, in a significant proportion of subjects, the diagnosis of occupational asthma. Since these two methods are time-consuming and may cause discomfort for the subject examined, it is of great importance to find accurate, but at the same time, easier methods to diagnose isocyanate-asthma.

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RÉSUMÉ: Cette étude décrit un nombre total de 162 sujets exposés aux isocyanates, ayant développé des symptômes pendant la période de contact ou le soir ou la nuit; ces sujets avaient donc des antécédents compatibles avec l'asthme induit par les isocyanates. Soupçonnés d'être atteints d'asthme professionnel, ils ont été soumis à des tests de provocation aux isocyanates (diisocyanate de toluène et diisocyanate de diphényl de méthylène) et à la méthacholine par inhalation. Aucun de ces sujets ne souffrait d'asthme symptômatique avant de commencer son travail actuel. Le diagnostic de l'asthme professionnel a été tardif (durée des symptômes avant diagnostic: $3,9 \pm 0,4$ ans). L'asthme dû aux isocyanates démontré par un test de provocation positif aux isocyanates par inhalation était présent chez 57,4% des sujets. Une faculté de réponse accrue des voies aériennes était présente chez les sujets dont le test de provocation aux isocyanates par inhalation était positif et non chez ceux dont le test de provocation était négatif (moyenne G et GESM: 0,407 (1,14) mg contre 0,942 (1,14) mg). La majorité des sujets se plaignaient de manque de souffle et d'avoir la toux. Une faible proportion de sujets atopiques (21,5%) et de fumeurs (7,5%), et une proportion élevée de sujets présentant le composant tardif de la réaction asthmatique (71%) semblent être les traits communs de cette pathologie.