

Occupational Asthma and IgE Sensitization in a Pharmaceutical Company Processing Psyllium^{1,2}

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Introduction

Some laxatives contain psyllium seed extracts. Psyllium, a member of the Plantago weed family, has been identified as causing occupational asthma in employees working in pharmaceutical industries preparing such laxatives (1-3). Also, cases of asthma in users exposed at home (4) and in nurses preparing psyllium at work (5-8) have been reported. To our knowledge, only 1 epidemiologic survey (3) has been carried out in a pharmaceutical company.

We surveyed a large sample of employees (130 of 140) in a pharmaceutical company where psyllium was processed. Detailed immunologic investigation for IgE sensitization was carried out, and work-related asthma was confirmed by specific inhalation tests in affected workers.

Methods

Psyllium Processing

The pharmaceutical company that was surveyed processes nearly 75 different products. The laxative containing psyllium is produced 4 to 5 times a year for periods varying from 5 to 10 days. Psyllium is obtained as a fine-grained powder and mixed with dextrose powder (50% wt/wt) in a large vessel. The mixed powder is collected in barrels, transferred to another area where it is poured into a packaging machine with a large scoop, and then bottled up.

Total and respirable dust exposures were measured during the mixing and packaging operations. Personal samples were collected on 0.8- μ pore size PVC filters using a Gilian high volume pump. A 10-mm Door Oliver cyclone was used in the sampling train for respirable dust. Sampling time varied between 2 and 4 h and covered the complete processing period.

Dust measurements were limited to the mixing and packaging areas because it was not technically possible to determine whether or not airborne dust in other areas of the plant contained any psyllium. All employees in the plant, including the office workers, were nevertheless presumed exposed to psyllium powder, because (1) mixing and packaging

SUMMARY We assessed the prevalence of occupational asthma and IgE sensitization to psyllium in a pharmaceutical company producing psyllium hydrophillic mucilloid, which is used as a laxative. Workers were intermittently exposed, approximately 5 times/yr, for periods of less than 10 days. Of the 140 employees, 130 (93%) were studied before a processing period via a questionnaire, spirometry ($n = 125$), blood sampling ($n = 118$), and skin prick tests ($n = 120$) with 7 common inhaled allergens as well as plantain and psyllium. Thirty-nine workers had a history suggestive of occupational asthma. Twenty-three of 120 (19%) showed a skin wheal diameter ≥ 3 mm to psyllium and 31 of 118 (26%) had increased specific IgE antibodies; 39 (32%) workers had at least 1 of these 2 features. Subjects with a questionnaire suggestive of asthma or occupational asthma were further investigated by serial monitoring of peak expiratory flow rates and PC_{20} methacholine before and during the psyllium processing period. All workers had spirometry repeated during the processing period. Twenty-one subjects who had a $PC_{20} < 16$ mg/ml ($n = 10$) and/or decreased their PC_{20} by a ≥ 3.2 -fold difference ($n = 4$) and/or changed their FEV₁ by $\geq 10\%$ ($n = 13$) during the processing period were referred for inhalation challenges to psyllium in the laboratory. Five of the 18 workers for whom these tests were feasible gave an immediate bronchoconstrictive reaction. All of them had positive skin tests to psyllium and were highly atopic (≥ 3 positive skin tests). It is concluded that the prevalences of occupational asthma and IgE sensitization to psyllium were at least 3.6 and 27.9%, respectively, in this pharmaceutical company. Atopy and IgE sensitization to psyllium were associated with occupational asthma.

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were not carried out in hermetically sealed areas, (2) employees involved in these operations did not change clothes before leaving the production areas, (3) the psyllium powder that was carried away from the production areas presumably entered the general ventilation system and was spread throughout the plant, and (4) 2 employees with known occupational asthma to psyllium strictly avoided the mixing and packaging areas during the production periods but were nevertheless symptomatic.

Epidemiological Survey

Initial assessment. The first part of the survey was carried out in February 1985, psyllium not having been processed for 2 months. The investigation included the following.

(1) A standardized questionnaire was administered by trained nurses to the 130 employees who had agreed to participate. Pertinent information was obtained by a questionnaire on asthma and occupational asthma recently developed by Walter W. Holland (personal communication). Asthma was diagnosed with at least 2 positive answers to the following: past medical history of asthma, cough, shortness of breath, tightness in the chest, or wheezing, the last 4 symptoms being present at work and/or off-work. Tightness in the chest and/or shortness of breath and/or cough at work associated with an im-

provement on weekends and/or holidays was suggestive of occupational asthma. Information on rhinoconjunctivitis symptoms, personal and familial atopic history (asthma, rhinitis, infantile eczema, and urticaria) and smoking habits was also obtained.

(2) Spirometry including FEV₁ and FVC was carried out in 125 subjects using an OHIO 827 spirometer (Ohio Instruments, Madison, WI) coupled with a microcomputer in conformity with the criteria of the American Thoracic Society (9). As the surveyed population included workers from several different ethnic groups, this precluded the use of uniform reference values.

(3) Skin test results by the prick method (10) with a battery of 7 common inhaled allergens: tree, grass, and ragweed pollens, *D. farinae*, house dust, and dog and cat danders (Hollister-Stier, Mississauga, Ont) as well as

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plantain and psyllium (Omega, Montreal, Que) were interpretable in 120 of the subjects because 10 refused the skin tests ($n = 8$) or had dermatographia (≥ 3 mm wheal, $n = 2$). The psyllium extract was 2.5% wt/vol, and was dissolved in 50% glycerol. Positive reactions were set at a wheal ≥ 3 mm as compared with a negative control reaction to the diluent 10 min after the introduction of the allergen.

(4) Blood was drawn in order to determine the eosinophil counts. Serum was kept at -20°C for specific IgE measurements, which were carried in 118 subjects. The IgE antibodies were measured with a psyllium RAST. The solid phase was prepared by overnight incubation of 250 mg cyanogen-bromide-activated discs in a psyllium solution consisting of 250 mg psyllium powder to which 25 ml 0.1 M NaHCO_3 had been added. Serum samples from 6 nonexposed control subjects were also tested. Two standard deviations above the mean values for these 6 control subjects represented 515 cpm. Any value above 515 cpm was thus considered high.

(5) Subjects with a history suggestive of asthma and/or occupational asthma underwent a methacholine inhalation test before the production period. Methacholine inhalation test was administered with the Wright's nebulizer (output = 0.14 ml/min) at tidal volume breathing for 2 min according to the method of Cockcroft and coworkers (11) except that acetyl-beta-methylcholine (methacholine) was used instead of histamine phosphate. After nebulization of normal sa-

line, concentrations of methacholine from 0.03 to a maximum of 128 mg/ml were used. The test was stopped when a fall of 20% in FEV_1 had been reached or when the highest methacholine concentration had been used. Dose-response curves were drawn on a non-cumulative semilogarithmic scale, and the concentration of methacholine causing a fall of 20% in FEV_1 (PC_{20}) was interpolated from the dose-response curve.

Second Assessment

The second part of the survey was carried out in May 1985 during a psyllium processing period. The handling of psyllium had begun 1.5 days before the onset of the investigation. The processing operation was similar to those of the previous psyllium processing periods. At that time, 108 of the 130 workers (83%) included in the first survey were exposed. Each of them was administered a short questionnaire inquiring about any cough, shortness of breath, tightness in the chest, wheezing, and rhinoconjunctivitis symptoms during the processing. Spirometry was repeated, and blood was drawn for total white cell and eosinophil counts. In addition, every exposed subject whose first questionnaire gave a history of asthma or occupational asthma ($n = 48$) and who agreed to participate underwent the following investigation.

(1) Serial monitoring of peak expiratory flow rates (PEFR) was performed with the Wright minipeak flow meter (Clement Clarke Int., London, UK). Subjects were asked to record their PEFR 4 times a day (on awaken-

ing, at lunch, at end of workshift, at bedtime) and whenever they had chest symptoms. The higher of the 2 reproducible (± 20 L/min) values at each time was kept for analysis; PEFR was monitored during the week preceding the exposure to psyllium, then during the production period including the weekend. Daily changes were measured as [(highest value - lowest value)/highest value] $\times 100$. Any daily change $> 20\%$ on one or more days during the production period and not present before the exposure to psyllium was considered to be suggestive of occupational asthma. Daily amplitudes $> 20\%$ in PEFR have been found in asthmatic subjects (12).

(2) The methacholine inhalation test (11) was done at least 1.5 days after the exposure onset. Any fall in $\text{PC}_{20} \geq 3.2$ -fold during the production period was considered to be a significant change in nonallergic bronchial responsiveness, as this corresponds to the upper limit of the 95% confidence interval on the basis of a single determination for the between-day variation of the test in asthmatic subjects in our laboratory (13).

Specific Inhalation Challenges

After the second part of the survey, every participant ($n = 21$) with one or more of the following criteria was referred for specific inhalation challenges with psyllium: (1) fall of 10% or more in FEV_1 at the time of the production period; (2) positive immediate skin reaction to psyllium and $\text{PC}_{20} < 16$ mg/ml at 1 of the 2 previous assessments; (3) significant changes in PEFR and/or PC_{20} during the

TABLE 1
CHARACTERISTICS OF INVESTIGATED EMPLOYEES

Characteristics	Initial Assessment ($n = 130$)	Second Assessment ($n = 108$)	Specific Inhalation Challenges ($n = 18$)	
			Positive ($n = 5$)	Negative ($n = 13$)
Sex, M/F	63/67	57/51	2/3	6/7
Age, yr*	36.9 ± 10.5	37.4 ± 11.1	34.2 ± 7.8	41.7 ± 11.4
Department				
Production	37 (28.5%)	29 (26.9%)	3 (60%)	3 (23.1%)
Office	39 (30.0%)	31 (28.7%)	0 (0%)	3 (23.1%)
Others	54 (41.5%)	48 (44.4%)	2 (40%)	7 (53.8%)
Duration of service in company, yr*	5.5 ± 4.6	5.6 ± 4.7	7.0 ± 4.1	5.7 ± 4.0
Asthma or occupational asthma from the questionnaire	48 (36.9%)	41 (38.0%)	5 (100%)	9 (69.0%)
Smokers	47 (36.2%)	36 (33.3%)	2 (40%)	4 (30.8%)
Rhinoconjunctivitis	46 (35.4%)	39 (36.1%)	5 (100%)	6 (46.2%)
FEV_1/FVC , %	85.5 ± 6.5	85.7 ± 6.1	86.5 ± 5.1	88.2 ± 7.1
Significant eosinophilia	2/125 (1.6%)	7/100 (7.0%)	1 (20%)	1/11 (9.1%)
Atopy	74/120 (61.7%)	67/101 (66.3%)	5 (5.6 $\pm$ 0.5)	9 (2.4 $\pm$ 2.4) [†]
Specific IgE, cpm $\geq 515^*$	31/118 (26.3%)	26/102 (25.5%)	5 (5,511 $\pm$ 3,360)	3 (494 $\pm$ 184) [‡]
Positive skin reaction to psyllium	23/120 (19.2%)	19/101 (18.8%)	5 (5)	4 (0) [§]
$\text{PC}_{20} \leq 16$ mg/ml	16/42 (38.1%)	12/35 (34.3%)	4 (80%)	9/11 (81.8%)
Changes in FEV_1 , $> 10\%$	—	13 (12.0%)	3 (60%)	7 (53.8%)
Significant changes in PEFR	—	3/33 (9.1%)	3 (60%)	0/7 (0%) [¶]
Significant changes in PC_{20}	—	4/35 (11.4%)	2 (40%)	2/8 (25%)
4 or 5 of the last 5 features	—	3 (2.8%)	3 (60%)	0 (0%)

* Values are mean $\pm$ SD.

[†] Mean $\pm$ SD number of positive skin tests to a battery of 7 common inhaled allergens are shown in parentheses; significantly different ($t = 4.6$, $p < 0.001$) in the 2 groups.

[‡] $t = 3.3$, $p < 0.01$.

[§] Chi-square = 6.9, $p < 0.01$; figures in parentheses refer to the number of subjects who were found to be positive when repeating the skin tests.

[¶] Chi-square = 5.6, $p < 0.02$.

production period. At that time, skin tests were repeated and subjects were questioned and examined by one of the physicians in charge of the study. Specific inhalation tests were performed in a challenge room of the hospital laboratory as described by Pepys and Hutchcroft (14). On the first day, the subject was asked to tip lactose dust from one tray to another for 30 min; FEV₁ was recorded before the exposure, every 10 min for 1 h after the challenge, then every 30 min for 1 h, and hourly for as long as 8 h after the challenge. The PC₂₀ was obtained at the end of the day. On the second day, psyllium dust was used instead of lactose for the following intervals: 5, 15, and 45 s and 2 min for 2 consecutive exposures; FEV₁ was recorded immediately and 10 min after the end of each exposure and then at the same intervals as on the day of exposure to lactose. The exposure was stopped if the FEV₁ had dropped by 20% or more. If no significant change in FEV₁ had been recorded on that day, exposure was prolonged to 30 min on a third day, and PC₂₀ was reassessed at the end of that day. We measured the amount of psyllium dust at the mouth and nose level of a control subject who handled psyllium dust in a manner similar to that in our subjects. The concentration of dust was monitored during an interval of 5 min with a PCAM-TX photometer (PPM Inc, Knoxville, TN).

Contingency tables, chi-square and *t* tests were used for the analysis of results. A *p* value of less than 0.05 was considered significant.

Results

Initial Assessment

A summary of the results of the initial assessment in which 92.8% of the employees participated is presented in table 1. Among them were 100 white subjects (including 7 from Pakistan or India, 7 from the Philippines, and 8 from other areas) and 30 black subjects from the West Indies. Results of the initial questionnaire are detailed in table 2. The questionnaire gave a history suggestive of occupational asthma and asthma in 39 and 9 subjects, respectively (table 2). Only 3 employees had a FEV₁/FVC ratio < 70%. Of the 48 subjects with a history of asthma and/or occupational asthma from the first questionnaire, 42 underwent methacholine inhalation challenges before the production period, 4 refused to participate, and a methacholine challenge was felt to be unsafe in 2 others who had heart conditions. The PC₂₀ was < 2 mg/ml in 5 subjects, between 2 and 8 mg/ml in 6, and between 8 and 16 mg/ml in 5 others, these intervals corresponding respectively to moderate, mild, and borderline airway hyperresponsiveness (13). Of 6 of 8 subjects with symptoms of chronic bronchitis but normal

TABLE 2
ANSWERS TO QUESTIONNAIRES DURING THE DIFFERENT STEPS OF THE STUDY

	Number of Workers	
	Yes	No
Before the production period, n = 130		
Wheezing or whistling in the last year	20	110
Tightness in the chest in the morning	13	117
Shortness of breath in the last year	26	104
Cough at night in the last year	16	114
Number of workers with positive answer to none, 81; one, 28; two, 16; three, 5; four, 0		
At work		
Wheezing or whistling	4	126
Tightness in the chest	14	116
Shortness of breath	18	112
Cough	14	116
Number of workers with positive answer to none, 101; one, 16; two, 6; three, 6; four, 1		
Runny or stuffy nose	34	96
Sneezing	34	96
Itchy or watery eyes	26	104
At the time of production at work, n = 108		
Wheezing or whistling	7	101
Tightness in the chest	18	90
Shortness of breath	11	97
Cough	16	92
Number of workers with positive answer to none, 80; one, 12; two, 10; three, 4; four, 2		
Runny or stuffy nose	33	75
Sneezing	30	78
Itchy or watery eyes	25	83

spirometric results who had PC₂₀ assessed, none showed significant bronchial hyperresponsiveness; table 3 gives the association between skin reactivity to psyllium, English plantain, and grass. As shown in table 4, there was a close association between the level of specific IgE and skin reactivity to psyllium. There was a significant association (chi-square = 9.7, *p* < 0.01) between the presence of a positive skin test to psyllium and atopy. There was also a significant association between a history of asthma and/or occupational asthma and the presence of a positive immediate reaction to psyllium (chi-square = 14.7, *p* < 0.001). The skin reactivity to psyllium of the employees

was not associated with their department of work (chi-square = 3.5, *p* > 0.05).

Second Assessment

In tables 1 and 2, the characteristics of the 108 subjects and the present results of the questionnaire administered at the time of the second assessment are summarized. Of the 22 subjects who were lost at this step, 7 had left the company, 8 were absent, and 7 refused to participate. Thirty-five subjects had methacholine tests repeated at the time of the production period (2 workers were absent, 4 others had left, and the remaining 2 refused). The PC₂₀ dropped by ≥ 3.2-fold (increase in airway responsiveness) in 4

TABLE 3
SKIN TEST REACTIONS TO PSYLLIUM, ENGLISH PLANTAIN AND GRASS

	+	-	Total	Chi-square	p Value
English plantain					
Psyllium					
+	14	9	23		
-	7	90	97		
Total	21	99	120	37.1	< 0.001
Grass					
Psyllium					
+	13	10	23		
-	13	84	97		
Total	26	94	120	20.4	< 0.001

TABLE 4
SPECIFIC IgE AND SKIN REACTIVITY TO PSYLLIUM

	Specific IgE to Psyllium (cpm)			Chi-square	p Value
	< 515	≥ 515	Total		
Skin reactivity to psyllium*					
< 3 mm	77	15	92	24.6	< 0.001
≥ 3 mm	7	15	22		
Total	84	30	114		

employees and by 2.5-fold in another subject. Monitoring of PEFR was performed in 33 subjects before and during production. Readings were uninterpretable in 6 subjects, normal in 24, and abnormal in 3 others. Thirteen subjects had a drop $\geq 10\%$ in FEV₁ during the processing period.

Three respirable dust samples revealed dust concentrations of 0.6, 0.8, and 1.2 mg/m³ during the mixing operations. Two total dust samples collected on separate days during the same operations yielded concentrations of 12.0 and 25 mg/m³. Two respirable dust samples obtained during the packaging operation showed concentrations of 0.5 and 1.2 mg/m³. Finally, 1 sample of total dust collected during these operations yielded a concentration of 2.8 mg/m³.

Specific Inhalation Challenges

Twenty-one subjects who had a PC₂₀ ≤ 16 mg/ml and immediate skin reactivity to psyllium ($n = 10$) and/or diminished their PC₂₀ by a ≥ 3.2 -fold difference ($n = 4$) and/or changed their FEV₁ by $\geq 10\%$ ($n = 13$) during the processing period were referred for inhalation challenges to psyllium in the laboratory. One subject refused the tests. He most probably had occupational asthma, as he showed a strong positive immediate skin reaction to psyllium, had a PC₂₀ of 1.1, and changed his FEV₁ by 11% during the processing of psyllium. It was decided not to perform the tests in 2 other subjects, as their history obtained by the investigators via an open questionnaire did not suggest asthma nor occupational asthma. They also had no immediate skin reactivity to psyllium. During a challenge performed in a similar manner with a control subject, the mean concentration of dust was 12.96 mg/m³, the maximal and minimal values being 28.5 and 4.0 mg/m³, respectively. Maximal levels were obtained early (first minute) during the recording, as fine particles were then dispersed into the air. The results are illustrated in figure 1 in the 5 subjects who had only an isolated immediate bronchoconstriction, with a FEV₁ drop vary-

ing from 21.9 to 37.8%. In these 5, PC₂₀ assessed at the end of the day of exposure to lactose and on the last day of exposure to psyllium showed no significant change; table 1 lists the characteristics of these 5 subjects compared with the 13 other subjects who had negative challenges. Those with positive challenges had a greater number of positive skin tests. Four subjects with negative challenges initially showed a wheal 3 to 4 mm in diameter to psyllium, but these tests were negative (< 3 mm) when they were repeated at the time of the inhalation challenges. There was no overlap in the specific IgE values, these ranging from 1,465 to 9,438 cpm in subjects with positive challenges and from 344 to 926 cpm in those with negative challenges. Changes in FEV₁ and PC₂₀ occurred at work in a similar proportion of employees in both groups. Changes in PEFR were significantly more frequent in those with positive challenges although they were absent in 2 subjects with positive inhalation challenges.

Discussion

Psyllium contains a gum composed of a mixture of polysaccharides without proteins (15). There have been reports of occupational asthma caused by psyllium in nurses, in employees of pharmaceutical companies, and in 1 user handling psyllium (1-8). In the only epidemiologic survey of a pharmaceutical company that we could trace (3), 28 of 64 (44%) exposed workers had positive intracutaneous tests to psyllium. This proportion was only 19% in the present study. This might be explained by the fact that we used the prick method, which is less sensitive but more specific than are intracutaneous tests to detect immunologic sensitization (10). Also, our employees were not constantly exposed to psyllium at work. Combining the results of skin tests with those of specific IgE antibodies increased the prevalence of IgE sensitization to 32% in our survey. Eighteen of the 64 subjects (28%) in the above-quoted study (3) had positive inhalation challenges, although it is not known which proportion

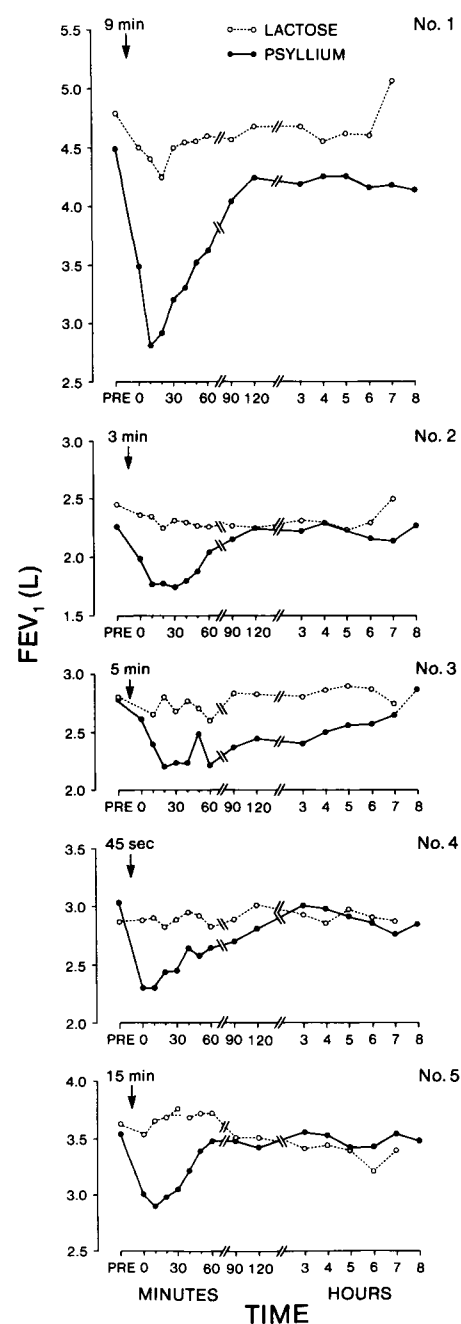


Fig. 1. Results of specific inhalation challenges in the 5 subjects who showed significant immediate bronchoconstriction. The duration of exposure to psyllium is indicated by the arrow.

had nasal, conjunctival, or bronchial challenges nor which criteria were set to define a positive challenge. In the present study, we found that at least 3.6% (5 of 140) of the exposed workers were affected with occupational asthma. Immunologic sensitization and occupational asthma to psyllium seemed more frequent in atopic subjects. Atopy also is an accompanying factor in other types of occupational asthma caused by enzyme detergents and by laboratory animals (16). Interestingly, those 5 workers with occupational asthma also had the

highest values of specific IgE to psyllium, in the range of values found in nurses with occupational asthma caused by this agent (17).

We found an association between skin reactivity to psyllium, English plantain, and grass. Rosenberg and coworkers (2) found cross-reactivity between psyllium and plantain, which was not confirmed by Busse and Schoenwetter (1) and, recently, by Gauss and coworkers (18).

The present study raises interesting questions about the investigation of immunologic sensitization and occupational asthma in epidemiologic surveys. As fully discussed elsewhere (16), most studies that have documented the prevalence of occupational asthma in workers exposed to a specific agent have been of the screening type and did not confirm the diagnosis through objective means. The design of such screening studies has to rely on a nonexposed control population to compare the prevalence of an indicator in the exposed and the nonexposed population. Very few studies have tried to go beyond this screening step and have the diagnosis confirmed by objective means. This is what we have attempted to do here, as in previous studies (19, 20), first by the combined monitoring of peak expiratory flow rates and hyperresponsiveness to methacholine, and, second, through specific inhalation challenges. This confirmatory step was particularly relevant for the following reasons. Thirty-nine subjects had questionnaire responses suggestive of occupational asthma. However, the diagnosis of occupational asthma caused by psyllium was confirmed through objective means in only 5 of 35 of these subjects. Questionnaires apparently are biased instruments as they might not be sensitive enough or not specific enough depending on the conditions of use. If workers want to be compensated they may exaggerate their symptoms. This may have been the case in this study, as occupational asthma is a compensated condition in the province of Quebec. As we thought that our questionnaire probably gave rise to many false positives because of this information bias, we felt that objective measurements should be obtained only in those reporting a history of asthma or occupational asthma, as it was unlikely that subjects would tend to negate their symptoms. Nearly one third of the subjects gave a history suggestive of occupational asthma, and this proportion corresponds to what we obtained in crab-processing workers in the same province (19).

Among the objective means to confirm the diagnosis, some investigators (21) have proposed assessing FEV₁ before work and at work, and that any fall in FEV₁ $\geq$ 10% would be suggestive of work-related asthma. From the results of the present study and the findings of others (22), this threshold of 10% is probably not sensitive or specific enough as it did not differentiate those who later had positive from those who had negative specific inhalation challenges.

Although occupational asthma without airway hyperresponsiveness has been described by some (23, 24), this is not the rule. Airway hyperresponsiveness persists in most workers with occupational asthma even if they are removed from their workplace for some years (25, 26). Its absence in one affected worker may be related to the fact that the first assessment was done at a time employees had not been exposed for 2 months. The situation might well be different in subjects who are continuously exposed to a sensitizing agent at work. However, 9 of the 11 workers without occupational asthma also had bronchial hyperresponsiveness. Bronchial hyperresponsiveness is also present in asthma of nonoccupational origin as well as in other chronic obstructive respiratory conditions.

Monitoring of PEFR has been described as a sensitive and specific means of confirming occupational asthma, as compared with specific inhalation challenges (27, 28). The fact that this monitoring was negative in 2 subjects might be due to the relatively short duration of the exposure period. We have previously shown that PC₂₀ monitoring is an important adjunct to serial monitoring of PEFR in the investigation of occupational asthma (19, 29). However, the fact that 3 subjects with occupational asthma did not change their PC₂₀ might be linked with the sole occurrence of immediate bronchospastic reactions after specific inhalation challenges. These reactions do not change bronchial hyperresponsiveness to histamine (30). On the other hand, the occurrence of such changes in 2 subjects without occupational asthma is perplexing. The second assessment was done during the tree pollen season, but none of the subjects who changed their PC₂₀ showed immediate skin reactivity to tree pollens. It has to be remembered that 5% of an asthmatic population might have changes in PC₂₀ falling outside the 95% confidence interval (a 3.2-fold difference being allowed for between-day reproducibility of the tests in our laboratory) for tests done on different days.

As the results of this study strongly suggest that the mechanism was IgE-mediated, the interpretation of the immunologic data is particularly interesting. First, every subject with occupational asthma had a positive immediate skin reaction to psyllium, whereas no subject without occupational asthma had this feature. Second, the highest values for specific IgE antibodies to psyllium were found in the 5 workers with occupational asthma. Thus, it is our opinion that assessment of skin reactivity and/or specific IgE levels in the investigation of occupational asthma seems, when feasible, a specific and sensitive tool. The fact that only those workers with skin reactivity to psyllium had positive immediate bronchospastic reactions contrasts with the results of the study by Goransson and Michaelson (3), who found 6 subjects with negative skin tests to psyllium but positive nasal and conjunctival provocation tests.

This study brings forth another interesting point. We showed that there was an association between atopy on the one hand and skin reactivity and occupational asthma to psyllium on the other hand. Although this study was not a longitudinal one, we may suppose that atopy preceded the sensitization to psyllium and may be a predisposing factor, although this warrants confirmation. Indeed, although we had no control group of nonexposed subjects, we found a higher prevalence of atopy in the studied population than what is usually found in random populations (31). It is not excluded that the development of atopy might be enhanced by continuous exposure to sensitizing agents. These subjects were also exposed to other pharmaceutical products besides psyllium at work. Two of these products contained methyl dopa and ampicillin, which have also been reported as causing occupational asthma (16).

The workers directly involved in the psyllium processing (i.e., mixing and packaging departments) were exposed to respirable dust concentrations below the standard level of 5 mg/m³ for nuisance dust during the second part of our survey. Two of the 5 workers with occupational asthma had never worked in the processing areas. Their exposure can be assumed to have been much less than that of the production workers. This observation shows that occupational asthma can be caused by low level exposure to psyllium dust carried away from the production area either by the ventilation system or on the workers' clothes. Clear-

ly, the threshold limit value adopted for nuisance dust is inappropriate for allergenic substances. Because it has been shown that reducing the airborne concentration of allergen can be an effective measure for preventing sensitization (7, 32), all available means to reduce exposure to psyllium to the lowest possible levels should be considered by pharmaceutical industries producing psyllium-containing laxatives.

In conclusion, the prevalences of occupational asthma and IgE sensitization to psyllium were at least 3.6 and 27.9%, respectively, in this pharmaceutical company, and atopy and IgE sensitization to psyllium were associated with occupational asthma.

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