

Fever and leucocytosis accompanying asthmatic reactions due to occupational agents: frequency and associated factors

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Fever and leucocytosis accompanying asthmatic reactions due to occupational agents: frequency and associated factors. C. Lemière, D. Gautrin, C. Trudeau, H. Ghezzi, A. Desjardins, A. Cartier, J-L. Malo. ©ERS Journals Ltd 1996.

ABSTRACT: Fever is sometimes associated with asthmatic reactions following specific inhalation challenges with occupational agents. Our aims were to estimate the prevalence of fever in subjects with occupational asthma confirmed by specific inhalation challenge and to examine the characteristics and clinical correlates of subjects who develop fever on specific inhalation challenge.

We performed a retrospective analysis of 317 subjects who had positive specific inhalation challenge to occupational agents and a comparison of subjects who developed fever after specific inhalation challenge with a random sample of those who did not. Fifteen subjects (5%) developed fever associated with positive specific inhalation challenge. They were compared with a random sample of 60 subjects who did not develop fever. The fever group: 1) showed a larger increase in absolute number of blood neutrophils, and a larger decrease both of blood lymphocytes and forced vital capacity after specific inhalation challenge; 2) included fewer atopics; 3) had been exposed more frequently to low rather than high molecular compounds; and 4) always experienced a late reaction and had more atypical reactions.

We conclude that after positive specific inhalation challenge; fever occurs infrequently, and is associated with an increase in blood neutrophils and a decrease in blood lymphocytes and forced vital capacity. Such reactions seem more likely to occur in nonatopic subjects exposed to low molecular weight agents.

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Occupational asthma is currently the most common type of occupational lung disease [1]. Specific inhalation challenges consisting of replicating the subject's exposure in a controlled fashion in a hospital laboratory, are used in conjunction with other means to confirm the diagnosis [2]. During specific inhalation challenge, functional indices derived from forced expiratory manoeuvres are monitored to detect asthmatic reactions. As parenchymal or systemic reactions may occur in these challenges, other indices are also monitored such as oral temperature and white blood cell counts. Such systemic reactions, suggestive of hypersensitivity pneumonitis after exposure to occupational agents, have been reported with isocyanates [3] and metals [4]. However, the association of asthmatic and systemic reactions has been described more recently and only in isolated cases [5].

The frequency of fever and leucocytosis accompanying asthmatic reactions to occupational agents and the predictive factors are unknown. We hypothesized that such an association would be more common with non-immediate reactions, that are usually non-immunoglobulin E (IgE)-mediated and occur on exposure to low molecular weight chemicals. We therefore examined spirometry, oral temperature and white blood counts in 317

subjects who developed significant changes in forced expiratory volume in one second (FEV₁) ($\geq 20\%$) after exposure to occupational agents to assess the frequency of accompanying systemic reactions and the predictive factors, if any.

Subjects and methods

Subjects

All subjects (n=317) who had a positive specific inhalation challenge with occupational agents ($\geq 20\%$ fall in FEV₁) in our laboratory from 1981 onwards were included in this retrospective study. From these subjects, those who experienced fever 1 h or more after the end of specific inhalation challenge were selected. This group is referred to as the fever group. A control group, representative of the cohort, was selected in a randomized way from subjects who did not develop fever after specific inhalation challenge in order to make a satisfactory comparison with the fever group. The number of subjects allocated to the control group was four times the number included in the target group, as it was considered that this would increase the power of the analysis

and make comparisons more satisfactory. The randomized group was comparable to the cohort concerning baseline data (see below in analysis of results).

As the occurrence of fever is associated with a nonimmediate pattern of asthmatic reaction (see below), another control group (one subject of the fever group for four subjects of the control group) was also randomized among the subjects who experienced a nonimmediate asthmatic reaction. It was also ensured that this second control group was comparable to the whole group for baseline data.

Relevant data collection

Demographic and clinical information (sex, age, smoking habits, medication, nature of occupational agent, duration of exposure before the onset of symptoms, duration of symptoms before removal from work) were collected, as well as spirometric values at the time of specific inhalation challenge. The atopic status was ascertained by skin-prick testing with a battery of 16 common inhaled allergens. A subject was defined as atopic if he/she had at least one positive skin test, with a negative control.

For all subjects, spirometry (FEV₁ and forced vital capacity (FVC)) had been monitored on a control day to ensure stability of asthma (changes in FEV₁ ≤10%). This control day was a nonexposure day in 21 subjects and a day of exposure to a control product (paint, lactose, resin, wood dust) in 54 subjects. Spirometry was performed according to proposed standards [6] on a Vitalograph (Vitalograph Ltd, Buckingham, UK) or Collins spirometer (W.E. Collins, Inc. Braintree, MA, USA). FEV₁ was monitored at baseline, and then every 10 min for the first hour, every 30 min for 1 h, and hourly for a total of at least 7 h after the end of the exposure. Bronchial responsiveness to methacholine was assessed at the end of the control day, using a Wright's nebulizer (output = 0.14 L·min⁻¹) at tidal volume breathing for 2 min, according to the procedure outlined by COCKCROFT *et al.* [7].

A blood sample for white cell counts (total count, leucocytes, neutrophils, eosinophils and lymphocytes) was generally obtained on the morning and at the end of the control day. Only the white blood cell count obtained at the end of the control day was compared to the one obtained at the end of the challenge day. Therefore, the time of blood collection was similar on the control and challenge days.

On the days of exposure to the suspected offending agent, specific inhalation challenges were carried out in an 8 m³ challenge room, according to a proposed methodology [8], or using a closed circuit apparatus to generate isocyanates [9] or particles [10]. The duration of exposure was progressive (one breath, 15 s, 1 min, 2 min, 5 min, *etc.*) either on the same day (high molecular weight agents) or different days (low molecular weight agents) for a maximum period of 2 h [2]. FEV₁ was assessed immediately after each exposure period and at the same intervals as for the control day (see above). FVC and oral temperature were assessed before challenge and then hourly after the end of exposure. Bronchial responsiveness to methacholine was reassessed at the end of the last day or on the following day if FEV₁ was not back to ±10% of the value obtained on the day of the first

methacholine testing. A blood sample was also obtained at the end of the day on which a significant fall in FEV₁ occurred, or on the following day in a few cases.

Analysis of results

Reference values for spirometry were taken from KNUDSON *et al.* [11]. Values for provocative concentration of agonist causing a 20% fall in FEV₁ (PC₂₀) equal to or less than 16 mg·mL⁻¹ represented significant bronchial hyperresponsiveness [12]. Changes in PC₂₀ ≥3.2 fold from one assessment to the next were considered to be significant [13]. A specific inhalation challenge was considered to be positive if subjects developed significant changes in FEV₁ (≥20%) after exposure to occupational agents.

Patterns of reaction were defined as follows. Classical or typical reactions: immediate, late, early late, dual, according to the definition of PEPYS and HUTCHCROFT [8]. Atypical reactions, according to PERRIN *et al.* [14]: 1) "progressive", progressive fall in FEV₁, in the first minutes after or during exposure with a maximum fall reached 5–6 h after the end of exposure; 2) "square waved", immediate and maximum fall in FEV₁ in the first minutes after exposure without significant recovery (<10% fluctuation from the maximum fall) thereafter (up to 8 h); 3) "prolonged immediate", similar to immediate but slower recovery (several hours). Fever was defined by an oral temperature above 37.2°C on at least two occasions during specific inhalation challenge. Indeed, HENDRICK *et al.* [15] have demonstrated that a body temperature above 37.2°C was one of the six objective measurements showing a good sensitivity-specificity balance in subjects suffering from hypersensitivity pneumonitis.

The two randomized groups (four randomized subjects for one subject in the fever group) were first compared with the whole group, to ensure that it was a representative sample of the cohort, using several variables. Three statistical tests were used: 1) Chi-squared for dichotomous variables (*i.e.* sex, atopic status, smoking habits, medication, molecular weight of the occupational agent PC₂₀ before and after specific inhalation challenge); 2) t-test for continuous variables (age, duration of exposure before symptoms, duration of symptoms before removal from work, FEV₁, FVC, temperature); and 3) Mann-Witney test for biological variables that did not have a normal distribution according to Lilliefors test (leucocytosis, neutrophilia, lymphocytosis, eosinophilia).

The two control groups were not significantly different from the whole "negative" population. Therefore, the fever group could be compared with the control group representing the whole "negative" population and with the control group who experienced nonimmediate asthmatic reactions only. The same variables as listed above were examined. Variables were compared in the two groups according to criteria set for the previous analysis (see above). As the hypothesis had been made that the fever group had been exposed to low molecular weight agent more often (so the null hypothesis had not been set), a confidence interval test was used to compare the proportions of subjects exposed to low and high molecular weight agents in the two groups and to assess that the difference

between these proportions was not null [16]. Significance was accepted at the 95% level for all statistical tests. Statistical tests were carried out using Statistical Package for the Social Sciences (SPSS) (Chicago, IL, USA).

Results

Characterization of the fever group and reactions

Fifteen subjects of the 317 cases studied (5%) experienced fever. Twelve of the 15 subjects who developed fever also had an increase of temperature after the specific inhalation challenge greater than one SD above the mean of changes in temperature. Figure 1 shows the distribution of temperatures for the whole cohort.

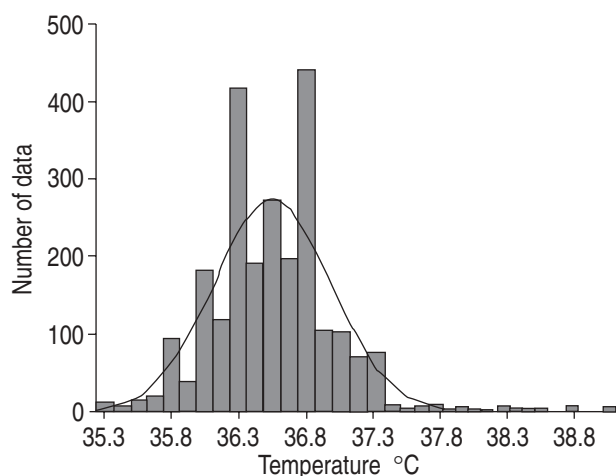


Fig. 1 – Distribution of temperature in the whole cohort. The normal distribution curve is illustrated.

The baseline anthropometric, clinical and functional results of the 15 subjects are listed in table 1. Most subjects were males who had been exposed to low molecular weight agents and three, to high molecular weight agents. None of these subjects experienced isolated immediate reactions. Five subjects had isolated late reactions and three subjects had a dual reaction (immediate and late). Seven subjects demonstrated an atypical reaction of the progressive or of the square-waved pattern [14]. Six of the 15 subjects reported chills and malaise during specific inhalation challenge. Of these six, three had been exposed to isocyanates, two to metal fumes and one to polyester.

The changes in functional tests at the time of specific inhalation challenge are presented in table 2. Eleven subjects had a $\geq 15\%$ fall in FVC. Blood was drawn before and after specific inhalation challenge in 11 of the 15 subjects. Nine out of 11 developed a significant increase in neutrophil count (increase in circulating neutrophils ($\geq 2.5 \times 10^9$ cells \cdot L $^{-1}$ ($\geq 2,500$ cells \cdot mm $^{-3}$)). Seven out of 11 showed a fall in lymphocyte number of (0.5×10^9 cells \cdot L $^{-1}$ (500 cells \cdot mm $^{-3}$)) or more; with, for 6 of the 7 subjects, an absolute lymphopenia ($< 1.5 \times 10^9$ cells \cdot L $^{-1}$ ($< 1,500$ cells \cdot mm $^{-3}$)). There were no significant changes in eosinophil count.

Comparison between fever and nonfever groups (tables 3 and 4)

Variables such as age, sex, smoking habits, medication, duration of exposure before symptoms, duration of symptoms before removal from work, and duration of exposure during the specific inhalation challenges were not different in the two groups (age and medication are

Table 1. – Anthropometric, clinical, functional and biological data of the fever group on the control day

Sub. No.	Sex	Age yrs	Atopy	Smoking habits	Pattern of reaction	Occupational agent	FEV1 L	% pred	FVC L	% pred	PC20 mg \cdot mL $^{-1}$	Blood cells $\times 10^9$ cells \cdot L $^{-1}$			T $^{\circ}$ C
												Leu	Neu	Lymph	
1	M	47	+	ES	SW	MDI	3.2	93	3.6	86	2.4	10.0	5.6	3.1	36.8
2	F	25	-	NS	Dual	Psyllium*	3.5	94	4.5	103	37	6.3	4.4	1.1	36.2
3	M	37	+	S	SW	Rabbit proteins*	3.1	97	3.7	96	16	9.1	4.6	3.4	36.8
4	F	36	-	S	EL	MDI	3.5	107	4.0	104	>128	13.5	9.9	3.1	36.2
5	M	50	-	S	P	Polyester	3.7	109	4.9	118	0.65	6.1	2.6	2.7	36.3
6	M	24	-	NS	Late	Galvanized metal	2.2	45	3.8	66	0.9	ND	ND	ND	36.9
7	M	59	-	ES	Late	Amine	3.3	114	4.9	138	6.6	8.8	6.8	1.3	36.9
8	M	29	-	NS	Late	MDI	4.0	103	4.5	96	>128	9.3	4.6	4.0	36.8
9	M	48	-	S	SW	PPI	3.0	82	4.3	95	13.5	5.7	3.2	1.9	36.7
10	M	59	-	S	SW	Galvanized metal	2.1	72	2.8	78	1.7	12.3	8.7	2.2	36
11	M	58	-	S	Dual	Steel	2.8	104	4.0	119	3.0	5.0	2.8	1.5	36.1
12	F	35	-	ES	Late	Polypropylene	2.6	76	3.2	77	0.3	ND	ND	ND	36.3
13	M	34	-	ES	P	PPI	3.6	88	4.3	88	ND	ND	ND	ND	ND
14	M	35	-	ES	SW	HDI	3.6	89	4.8	100	1.5	6.6	5.0	1.5	37.2
15	F	23	+	NS	Dual	Cereals*	3.4	119	3.8	118	0.5	ND	ND	ND	35.8
Mean		40					3.2	93	4	99		7.8	4.5	2.2	36.4
SD		13					0.5	19	0.6	19		2.0	1.6	1.0	0.12

Sub: subjects; M: male; F: female; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PC20: provocative concentration causing a 20% fall in FEV1; Leu: leucocytes; Neu: neutrophils; Lymph: lymphocytes; T: body temperature; S: smoker; NS: nonsmoker; ES: ex-smoker; MDI: diphenylmethane diisocyanate; HDI: hexamethylene diisocyanate; PPI: polymethylene polyphenylisocyanate; SW: square-waved; P: progressive; EL: early late; ND: not done; *: high molecular weight agent.

Table 2. – Functional and biological data of the fever group following specific inhalation challenges

Pt No.	FEV ₁ % fall	FVC % fall	PC ₂₀ mg·mL ⁻¹	Blood cells ×10 ⁹ cells·L ⁻¹						T °C
				Leu Δ	Neu Δ	Lymph Δ				
1	47	38	ND	19.8	+9.8	17.0	+11.4	1.4	-1.7	38.4
2	26	7	14	10.7	+4.4	8.7	+4.3	1.5	+0.4	37.6
3	29	16	16	17.6	+8.5	15.4	+10.8	1.1	-2.3	38.0
4	29	22	>128	16.6	+3.1	14.0	+4.1	1.2	-1.9	38.7
5	41	30	0.4	16.7	+10.6	14.7	+12.1	1.2	-1.5	39.0
6	24	32	1.4	10.3	-	8.1	-	1.0	-	38.0
7	21	15	6.6	8.0	-0.8	6.0	-0.8	1.1	-0.2	37.6
8	23	17	>128	10.0	+0.7	7.9	+3.3	1.6	-2.4	38.8
9	17	-	1.3	10.7	+5.0	8.6	+5.4	1.1	-0.8	38.1
10	27	16	0.15	14.5	+2.2	11.7	+3.0	0.4	-1.8	38.5
11	36	32	2.7	9.8	+4.8	7.8	+5.0	1.6	+0.1	38.5
12	33	24	0.1	6.6	-	4.2	-	1.7	-	37.5
13	48	-	0.7	6.6	-	4.4	-	1.7	-	37.4
14	46	34	0.8	8.9	+2.3	5.8	+0.8	2.1	+0.6	37.4
15	28	14	1.2	ND	-	ND	-	ND	-	37.3
Mean	31	23		12.3	+4.6	10	+5.4	1.4	-1.0	38.0
SD10	10		4.3	3.7	4.3	4.3	0.5	1.1	0.15	

For further abbreviations see legend to table 1.

Table 3. – Comparison of anthropometric, clinical and functional results in fever group and control non fever group

Variables	Fever group	Control group	P-value
Sex	M 11 (73)	46 (77)	
	F 4 (27)	14 (23)	0.78†
Smoking	+ 11 (73)	35 (58)	
	- 4 (27)	25 (42)	0.28†
Atopy	+ 3 (20)	38 (63)	
	- 12 (80)	22 (37)	0.002†
Molecular weight of agent			
Low	12 (80)	35 (58)	
High	3 (20)	25 (42)	0.04‡
Duration of exposure to agent before symptoms yrs*	7.5±7.5	10.2±10.4	0.26‡
Duration of symptoms yrs*	3.7±4.9	3.4±3.9	0.85‡
Pattern of reaction to challenge			
Isolated immediate	0	27 (45)	0.001†
Nonimmediate	15 (100)	33 (55)	
Typical	8 (53)	53 (88)	0.001†
Atypical	7 (47)	7 (12)	
FEV ₁ L*	3.18±0.51	3.36±0.78	0.38‡
FVC L*	4.1±0.6	4.4±1.0	0.11‡
% fall in FEV ₁ *	31±10	30±12	0.63‡
% fall in FVC*	23±10 (n=13)	13±9 (n=48)	0.001‡
Duration of exposure during specific challenge min [†]	15 (3–120)	31 (0.08–4.80)	0.53¶
PC ₂₀ before SIC			
<16 mg·mL ⁻¹	10 (71)	48 (87)	
≥16 mg·mL ⁻¹	4 (29) (n=14)	7 (13) (n=55)	0.15†
PC ₂₀ after SIC			
<16 mg·mL ⁻¹	11 (79)	42 (91)	
≥16 mg·mL ⁻¹	3 (21) (n=14)	4 (9) (n=46)	0.19†

All data is pre specific inhalational challenges. Percentage values are given in parentheses. *: mean±SD. †: median (range). ‡: Chi-squared; ‡: t-test or confidence interval test; ¶: Mann-Whitney test. n=15 for the target group and n=60 for the control group, otherwise stated in parenthesis. SIC: specific inhalation challenge. For further abbreviations see legend to table 1.

Table 4. – Comparison of laboratory results in the fever and non fever control group

Variables	Fever group	Control group	P-value
Leucocytes×10 ⁹ cells·L ⁻¹			
Before SIC	7.8±2.0 (n=11)	7.2±2.0 (n=52)	0.44
After SIC	11.7±5.3 (n=14)	9.0±2.6 (n=44)	0.03
Difference	5.1±5.1 (n=11)	1.7±2.4 (n=43)	0.0005
Neutrophils×10 ⁹ cells·L ⁻¹			
Before SIC	4.5±1.6 (n=11)	4.5±1.6 (n=52)	0.94
After SIC	9.6±5.0 (n=14)	6.1±2.6 (n=44)	0.009
Difference	6.2±5.5 (n=11)	1.5±2.5 (n=43)	0.0007
Lymphocytes×10 ⁹ cells·L ⁻¹			
Before SIC	2.2±1.0 (n=11)	1.9±0.8 (n=52)	0.51
After SIC	1.3±0.6 (n=14)	2.0±0.9 (n=44)	0.01
Difference	-0.9±1.0 (n=11)	0.1±1.0 (n=43)	0.008
Eosinophils×10 ⁹ cells·L ⁻¹			
Before SIC	0.3±0.3 (n=9)	0.3±0.3 (n=50)	0.52
After SIC	0.2±0.2 (n=12)	0.3±0.3 (n=44)	0.06
Difference	-0.2±0.3 (n=8)	0.0±0.3 (n=41)	0.055

Value are presented as mean±SD. Mann-Whitney test was used for level of significance. Comparing values before and after SIC. SIC: specific inhalation challenge.

not listed in table 3). However, the proportion of atopic subjects was lower and exposure to low molecular weight agents was more frequent in the fever group. No subject from the fever group developed an isolated immediate reaction, whereas 45% of the control group did. Subjects in the fever group more often developed reactions of an atypical pattern. Analysis of changes in spirometry data revealed that the fever group had a more significant fall in FVC. The comparison of FEV₁, maximum fall of FEV₁ after specific inhalation challenge and bronchial responsiveness before and after specific inhalation challenge showed no differences between the two groups.

White blood cell count analysis showed a significant increase in leucocytosis after specific inhalation challenge with neutrophilia and lymphopenia in the fever group but no significant changes in eosinophils (table 4). There was also a significant increase in leucocyte and neutrophil counts after specific inhalation challenge in the control group, but this increase was significantly lower than the one observed in the fever group. We observed a decrease in lymphocyte count in the fever group but not among the control group before and after specific inhalation challenge. There were significant differences in leucocytosis, neutrophilia and lymphocytosis between the fever and control groups after specific inhalation challenge, whereas they had similar values at baseline.

Comparison between fever group and nonfever control subgroup with late reactions only (control LAR n=60)

No significant differences were found between the two groups for the following variables: gender, mean age, smoking habits, medication, molecular weight of the offending agent, duration of exposure before symptoms and duration of symptoms, baseline FEV₁ and FVC, maximum fall of FEV₁ and FVC during the specific inhalation challenge. There were fewer atopic subjects in the fever group (3 out of 15; 20%) than in the control LAR group (60%) (p=0.006). There was a higher proportion of subjects with hyperresponsiveness to methacholine in the control LAR group than in the fever group before (97% as compared with 71%; p=0.01) and after (100% compared to 78%; p=0.008) specific inhalation challenge. The increase in leucocytosis was significantly higher in the fever group (from 7.8±2.0 to 11.7±5×10⁹ cells·L⁻¹) than in the control LAR group (from 7.2±1.7 to 8.3±2.6×10⁹ cells·L⁻¹; p<0.05). The increase in neutrophils in the fever group was also greater (from 4.5±1.6 to 9.6±5.0×10⁹ cells·L⁻¹) than in the control LAR group (from 4.5±1.6 to 5.3±2.6×10⁹ cells·L⁻¹; p<0.05). There was a significant decrease in lymphocytosis in the fever group (from 2.2±1.0 to 1.3±0.6×10⁹ cells·L⁻¹) as compared to the control LAR group (from 1.9±0.8 to 2.1±0.9×10⁹ cells·L⁻¹); p<0.05. There was also a significant decrease in the number of eosinophils in the fever group (from 0.3±0.3 to 0.1±0.2×10⁹ cells·L⁻¹) as compared to the control LAR group (from 0.3±0.3 to 0.4±0.2×10⁹ cells·L⁻¹; p<0.05).

Discussion

This retrospective study in 317 subjects with occupational asthma shows that 5% of them developed both asthmatic reaction and fever after exposure to the occupational agent that they reacted to. Subjects who developed fever had been exposed more often to low molecular weight agents and experienced late or atypical asthmatic reactions.

From a physiological point of view, it is difficult to set the frontier between an airway reaction and a parenchymal involvement after specific inhalation challenge. Parenchymal involvement is classically accompanied by systemic manifestations, such as fever and leucocytosis. Some airway involvement in hypersensitivity pneumonitis due to bird proteins has been described by HARGREAVE and PEPYS [17]. Among the 36 subjects who experienced a reaction on bronchoprovocation test with bird sera, 5 (14%) showed late reactions consisting of fever and asthma according to HARGREAVE and PEPYS [17]. VANDENPLAS *et al.* [3] described eight subjects who developed a hypersensitivity pneumonitis-type response after being exposed to diphenylmethane diisocyanate (MDI). These authors reported some degree of airway obstruction, but only one subject had evidence of bronchial hyperresponsiveness to methacholine.

Among the approximately 250 agents causing occupational asthma [18], only metal fumes [4] and isocyanates [19], had been, to our knowledge, identified as causing a mixed reaction, with evidence of asthma and parenchymal

involvement principally manifested by fever and leucocytosis. MALO and co-workers [5] reported the case of a subject who developed both fever due to an alveolitis and asthma after exposure to hexamethylene diisocyanate (HDI). MALO and CARTIER [4] also described such a mixed reaction in two solderers who developed a late asthmatic reaction after exposure to fumes of galvanized metal. One of the two subjects also demonstrated a significant increase in oral temperature and peripheral neutrophils.

In the current study, evidence of a mixed bronchial and alveolar reaction was found. The proportion of subjects who had bronchial hyperresponsiveness to methacholine before specific inhalation challenge and the proportion of subjects who increased the level of their bronchial responsiveness to methacholine were similar to the results obtained by MALO and co-workers [20], who showed that 41 out of 101 subjects (40%) demonstrated a change in PC₂₀ after a late reaction on specific inhalation challenge. Moreover, the frequency of changes in PC₂₀ was the same among the fever group and the control group that did not experience fever. Therefore, our subjects in the fever group, in all likelihood, experienced an alveolar reaction in addition to their asthmatic reaction. We found that subjects who experienced fever more often have normal responsiveness to methacholine pre- and post-specific inhalation challenges than subjects who experienced nonimmediate asthmatic reactions without fever.

In this study, evidence of a "hypersensitivity pneumonitis reaction" relied mainly on the identification of fever and leucocytosis. However, three of our six patients exposed to isocyanates and three other subjects exposed to other agents experienced the combination of an oral temperature >37.2°C, a fall in FVC ≥15%, a significant increase in absolute number of neutrophils (≥2,500 cells·mm⁻³), and a significant fall in the number of blood lymphocytes (<500 cells·mm⁻³) together with absolute lymphopenia after specific inhalation challenge. We did not perform other tests to document the "alveolar component" except in a few cases. Nevertheless, HENDRICK *et al.* [15] have shown that a temperature above 37.2°C, an increase in leucocyte count of ≥2,500 cells·mm⁻³, and a fall in FVC of 15% with absolute lymphopenia were sensitive indices of a positive alveolar response after specific inhalation challenge; chest radiograph and transfer factor were less sensitive indices. Comparison of our fever group with the control group showed significant differences in the fall in FVC, increase of neutrophils and decrease in lymphocytes, suggesting that these subjects experienced a hypersensitivity pneumonitis-type reaction. However, some of our subjects did not meet all the criteria set by HENDRICK [15].

In the current study, we examined the variables associated with the development of fever. Fever occurred more often in subjects exposed to low molecular weight agents: 12 of the 15 patients who experienced fever had been exposed to low molecular weight agents. If occupational asthma caused by the exposure to high molecular weight compounds is, in most cases, IgE-mediated, occupational asthma due to low molecular weight agents is not usually

so [21]. The mechanism of action of low molecular weight agents on the airways and lung remains largely unknown. If some of these agents act through immunological mechanisms, other factors, such as the intrinsic chemical properties and pharmacological mechanisms, are probably involved [21, 22]. Some of these properties might explain the induction of hypersensitivity pneumonitis or acute lung reaction. It is also interesting to note that none of the patients who experienced fever developed an isolated immediate reaction, whereas 45% of the control group's subjects did.

Our fever group included 15 subjects, 12 of whom had been exposed to low molecular weight agents, which are more likely to cause nonimmediate reactions. The development of fever in subjects exposed to high molecular weight agents is more difficult to explain as it is IgE-mediated, whereas the mechanism of reactions due to low molecular weight agents is unknown for the majority of agents. Nevertheless, the three subjects who developed fever following exposure to high molecular weight agents also developed late or dual asthmatic reactions, which further suggests that the type of reaction and not the nature of the agent *per se* conditions the likelihood of developing fever. The association of asthmatic reactions and fever reported in the literature concerns subjects who developed a late type of reaction [17]. Subjects of the fever group more often experienced atypical nonimmediate reactions of the square-waved or progressive patterns [14]. The mechanism of these reactions is unknown. Fever was also more frequently observed among nonatopic patients. This cannot only be explained by the fact that subjects who experienced fever were more often exposed to a low molecular weight agent. Indeed, there was no significant difference in the molecular weight of the offending agent between the fever group and the control group of subjects with nonimmediate reactions and no fever.

In conclusion, fever was found to be associated with asthmatic reactions in 5% of subjects with positive challenges to occupational agents. Exposure to a low molecular weight agent and the occurrence of a late, especially atypical, pattern of reaction are, therefore, risk factors for the development of fever accompanying an asthmatic reaction. The pathogenesis of fever and leucocytosis accompanying these reactions remains to be explored.

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