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Reassessment of the temporal patterns of bronchial obstruction after exposure to occupational sensitizing agents

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*Typical asthmatic reactions after exposure to common or occupational allergens have been classified as isolated immediate, early late, late, and dual (Pepys and Hutchcroft, 1975⁶). Atypical reactions can also occur, but their temporal behavior and frequency are unknown. We analyzed 69 bronchospastic reactions after exposure to three types of occupational sensitizers in the laboratory: isocyanates, western red cedar, and IgE sensitizing agents. Graphs of the reactions were presented to three observers in a blind, randomized way. Reactions were defined as follows: (1) typical patterns, that is, isolated immediate, early late, late, and dual, as put forward by Pepys and Hutchcroft,⁶ and (2) atypical patterns including progressive (onset, during, or minutes after exposure, progressing to a maximum reaction 5 to 6 hours later) and square waved (similar to a dual reaction but with only partial recovery [$<10\%$] between the immediate and late falls in FEV₁). Some curves were also analyzed by polynomial regression. The three observers agreed in 59/69 cases (86%), and a consensus was reached after discussion for the remaining subjects. Fifteen of 63 (22%) reactions were atypical. IgE-mediated reactions and reactions to red cedar were, respectively, mainly of the immediate and late types. The distribution of reactions to isocyanates, however, was significantly different (chi-square, 6.1; $p = 0.01$), the "progressive" pattern occurring in 7/23 instances (30%). There was a satisfactory concordance between visual assessment and polynomial fit analysis in distinguishing dual from square-waved reactions. We conclude that isocyanates frequently cause atypical progressive bronchospastic reactions that are rarely observed after exposure to IgE agents and western red cedar. (*J ALLERGY CLIN IMMUNOL* 1991;87:630-9.)*

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Occupational asthma is becoming the most common occupational respiratory disease in the developed world.¹⁻⁴ Specific inhalation challenges with sensitizing agents are still regarded as the gold standard for confirming a diagnosis.⁵ This type of exposure that requires medical supervision can induce different temporal patterns of asthmatic bronchospastic reaction in the laboratory. Classic patterns were described by Pepys and Hutchcroft⁶ as being immediate, early late, late, and dual. High molecular weight agents generally cause isolated immediate or dual asthmatic reactions, whereas low molecular weight agents are mainly responsible for isolated late asthmatic reactions. However, atypical patterns can also occur^{7,8} after exposure to isocyanates, the most common cause of occupational asthma in North America.^{9,10} However, these studies^{7,8} can be considered as anecdotal since the temporal behavior and frequency of these reactions have not been determined in a systematic way.

The aim of this study was to describe and assess the frequency of the different bronchospastic reactions caused by three types of occupational sensitizers: isocyanates, western red cedar, and IgE sensitizing agents (flour, psyllium, and guar gum). The hypothesis is that the frequency of temporal patterns is different depending on the group of agents. A total of 69 positive reactions were analyzed, 23 for each group of sensitizers.

METHODS

Subjects

This study includes 69 subjects who were referred for investigation of occupational asthma in the laboratory of Hôpital du Sacré-Coeur in Montreal and who underwent specific inhalation challenges with positive results.

Sensitizing agents

The three groups of sensitizing agents were

1. *Isocyanates*: This group included all subjects with positive tests (N = 23) between 1986 and 1989 in which an isocyanate monitor (MDA 7100 monitor, MDA Scientific, Inc., Glenview, Ill.) had been used during inhalation challenge test. The level of exposure to isocyanates was lower than 20 ppb (irritant threshold). TDI was used for challenge in the six foam-industry workers (25%); HDI, in 10 spray painters (44%); and MDI, in seven employees in various industries (plastics, foundries) (31%).
2. *Western red cedar*: This group included all the 23 most recent subjects to have had positive specific inhalation challenges in the laboratory between 1983 to 1989, thus overlapping the interval for which the positive challenges with isocyanates were selected; they worked in various plants manufacturing windows and doors.
3. *Sensitizing agents inducing IgE-mediated reactions*: This

Abbreviations used

HDI: Hexamethylene diisocyanate
MDI: Diphenylmethane diisocyanate
PC₂₀: Provocative concentration of histamine or methacholine causing a 20% fall in FEV₁
TDI: Toluene diisocyanate

group included randomly (alphabetic order of the subject's name) chosen subjects who had undergone specific inhalation challenges during the same period as subjects with reactions to isocyanates. Eleven bakers were challenged with flour, eight (35%) subjects, including seven nurses and one pharmaceutical worker, with psyllium, and four (17%) workers (one in a pharmaceutical company and three in carpet producing plants) with guar gum.

Clinical investigation

An open respiratory and occupational questionnaire was first completed by trained physicians. Information on sex, age, height, smoking habits, duration of exposure at work, onset of symptoms at work, and types of sensitizing agents handled at work was obtained. These results are presented in Table I.

Immunologic tests

Skin prick tests were performed with a battery of 15 common inhalant allergens. For subjects with occupational asthma mediated by an IgE-dependent mechanism, we also did skin tests with appropriate extracts. Extracts of cereals (wheat, oats, barley, corn, and rye, Hollister-Stier Laboratories, Rexdale, Ontario) were used in bakers; psyllium (Omega Laboratories, Montreal, Quebec) and guar gum (1 mg/ml) extracts were used on the other subjects according to the job.¹¹ All subjects in the group with IgE-mediated reactions had immediate positive reaction to the relevant allergen present in the workplace, defined by a >3 mm wheal (in subjects without dermographism as assessed by skin testing with phosphate-buffered saline) and a >2 mm wheal to histamine phosphate at a concentration of 1 mg/ml.

Specific IgE and IgG antibodies were measured in a blind way to ensure that there was no knowledge of specific inhalation-challenge results. Specific antibodies to isocyanates were assessed in all 23 workers.¹² Specific antipneumococcal IgE antibodies were assessed in only 13/23 workers exposed to western red cedar¹³ for whom sera were still available.

Functional investigation

Spirometry was measured with a Collins 9-L spirometer (Warren Collins, Inc., Braintree, Mass.) according to American Thoracic Society standards.¹⁴

Nonspecific bronchial responsiveness to histamine or methacholine was determined in all subjects except for one

TABLE I. Baseline anthropometric, clinical, and functional characteristics

	Group I	Group II	Group III
	Isocyanate-exposed (n = 23)	Western red cedar-exposed (n = 23)	IgE-mediated reactions (n = 23)
Sex (M/F)	20/3	23/0	14/9
Age (yr)	42.9 ± 10.9	38.8 ± 13.2	33.2 ± 9.9
	ANOVA <i>F</i> , 4.2; <i>p</i> = 0.02; Scheffé's <i>F</i> (I-III), 4.7; <i>p</i> < 0.05		
Atopy (present/absent)	9/14	13/10	19/4
	Fisher's <i>F</i> , 13.0; <i>p</i> = 0.001		
Smoking habits			
Smokers/exsmokers/nonsmokers	3/11/9	1/9/12	6/7/10
Duration of exposure (yr)	8.6 ± 7.8	6.8 ± 6.4	8.7 ± 7.3
Duration of symptoms (yr)	2.5 ± 3.0	3.4 ± 3.8	3.6 ± 2.7
FEV ₁ (% pred)	97.9 ± 14.3	97.2 ± 18.3	98.7 ± 13.5
FEV ₁ /FVC ₁ (% pred)	86.3 ± 11.7	93.2 ± 8.9	88.7 ± 9.4
PC ₂₀ (mg/ml)			
<2	12	13	5
2-16	8	7	14
>16	3	3	3

ANOVA, Analysis of variance.

Mean ± SD results or the actual number of subjects are presented; significant statistical comparisons only are presented. Results of the one-way analysis of variance are listed together with contrasts and pairs of comparisons.

subject in the group with IgE-mediated reactions. Also, changes in PC₂₀ were assessed after specific inhalation challenges in 21 workers in the isocyanate-exposed group, 20 in the western red cedar-exposed group and 22 in the group exposed to IgE-mediated agents. The tests were performed with a Wright's nebulizer (output, 0.14 ml/min) at tidal volume breathing for 2 minutes with a standardized procedure.¹⁵

Specific inhalation challenges

These tests were performed in a challenge room as proposed by Pepys and Hutchcroft.⁶ The following sequence of tests was performed on each subject. On the first day of nonexposure (control day), spirometry, oral temperature, and white blood count were first assessed. FEV₁ was monitored every 10 minutes for 1 hour, every 30 minutes for 2 hours, and hourly for the next 6 hours. Maximum daily fluctuations in FEV₁ had to be <10% for a subject to continue with the tests. At the end of the day, a blood sample was taken, and the serum was kept at -20° C for determination of specific antibodies. A methacholine or histamine inhalation test was also performed in all subjects but two. On the second day, the isocyanate-exposed subjects were exposed to the control product (i.e., the product usually mixed with isocyanates) for a total of 15 minutes. For HDI, the control product was an enamel containing aromatic hydrocarbons, ketones, and aliphatic and ether ester; for MDI, various aromatic hydrocarbons and fluorocarbons were used. The diluent for TDI was a commercial preparation made of polyol (99%) and aliphatic amine (1%). FEV₁ and

oral temperature were monitored after exposure as on the first day. On the third and subsequent days, if this were required, subjects were exposed to isocyanate in one of the following ways: (1) approximately 100 ml of pure commercial TDI (80% 2,4-TDI and 20% 2,6-TDI) was deposited in a small cup, (2) HDI, which was used for the challenge, was the commercial preparation to which the subject was exposed at work (from 20% to 75% of HDI/HDI biuret, depending on the product), nebulized with the diluent (1:3 concentration) with an Inspiron nebulizer (Inspiron, Division of C. R. Bard, Inc., Rancho Cucamonga, Calif.), and (3) commercial MDI containing 40% to 50% of MDI and 50% to 60% of polymethylene polyphenyl isocyanate was heated in a metal cup to approximately 80° C. On the isocyanate-challenge day(s), subjects were asked to remain in the challenge room for progressively longer periods of time: one breath, 15 and 45 seconds for a total of 1 minute on the first day; 1 minute, 2 minutes, and 2 minutes for a total of 5 minutes on the second day; and total periods varying from 15 to 120 minutes on the subsequent days.

For the other agents, western red cedar, flour, psyllium, and guar gum, either a realistic test (n = 33) as proposed by Pepys and Hutchcroft⁶ or a special apparatus (n = 13) was used. This recently described apparatus guarantees that exposure is to low (<10 mg/m³) and steady concentrations of dusts.¹⁶ On the second day, subjects were exposed to a control dust: wood dust of local species (spruce, fir, or pine) not containing white or red cedar or lactose powder for the others agents (flour, psyllium, or guar gum).

The duration of the control exposure was 15 to 30 minutes. On the third day, the exposure to flour, psyllium, or

TABLE II. Characteristics of challenges and reactions

	Group I	Group II	Group III
	Isocyanate-exposed (n = 23)	Western red cedar-exposed (n = 23)	IgE-mediated reactions (n = 23)
Duration of exposure on challenge day (min)	39 ± 59.4	52.9 ± 70.6	8.2 ± 14.2
	ANOVA <i>F</i> , 3.6; <i>p</i> = 0.04; Scheffé's <i>F</i> (II-III), 3.4; <i>p</i> < 0.05		
Maximum fall in FEV ₁ (%)	33.5 ± 13.9	26.6 ± 6.2	27.2 ± 7.3
	ANOVA <i>F</i> , 4.2; <i>p</i> = 0.02; Scheffé's <i>F</i> (I-II), 3.4; <i>p</i> < 0.05		
Interval after which maximum fall in FEV ₁ occurred (min)	220 ± 179	357 ± 142	99 ± 163
	ANOVA <i>F</i> , 14.2; <i>p</i> = 0.001		
	Scheffé's <i>F</i> (I-II), 4.0; <i>p</i> < 0.05; Scheffé's <i>F</i> (II-III), 14.2; <i>p</i> < 0.05		
Time during which the FEV ₁ remained <20% baseline (min)	138 ± 126	96 ± 92	83 ± 160
Changes in PC ₂₀			
<2-fold	13	13	11
2-3.2-fold	0	3	7
>3.2-fold	8	4	4

ANOVA, Analysis of variance.

Mean ± SD results or the actual number of subjects are presented; significant statistical comparisons only are presented. Results of the one-way analysis of variance are listed together with contrasts and pairs of comparisons.

guar gum was progressive: one breath, 10, 15, 30 seconds, 1, 2, and 5 minutes; exposure was increased during the following days to a maximum of 2 hours divided in intervals of 30 minutes. For western red cedar, the exposure was as follows: 5 minutes, 30 minutes, and 120 minutes on 3 consecutive days.

Bronchial responsiveness was reassessed at the end of the day of reaction in the case of isolated immediate or prolonged immediate reactions provided that FEV₁ had returned to ±10% of baseline value determined during the first histamine/methacholine test or the following day(s) (i.e., as soon as FEV₁ had returned to ±10% of baseline).

Graphs of the specific inhalation challenge reactions were drawn demonstrating time on the abscissa and percent of changes in FEV₁ on the ordinate.

Analysis

Reference values for spirometry were obtained from Knudson et al.¹⁷ The PC₂₀ was interpolated from individual dose-response curves drawn on a semilogarithmic non-cumulative scale. Significant bronchial hyperresponsiveness was set at a PC₂₀ value <16 mg/ml.¹⁸ Changes in PC₂₀ ≥3.2-fold from 1 day to the next were considered to be significant and changes from twofold to 3.2-fold borderline, since this corresponds to the upper limit of the 95% confidence interval for reproducibility of the test in our laboratory,¹⁹ as well as in another laboratory.²⁰

The FEV₁ fall had to be ≥20% of baseline and of control days to be considered significant, except for dual reactions in which the late component of the reaction was present if a fall in FEV₁ of 15% or more occurred. Types of temporal reactions were defined, before they were interpreted blind

(i.e., without consultation between the readers and the name of the subject remaining unknown to readers), as follows:

1. Classic reactions, according to the definition of Pepys and Hutchcroft⁶: *immediate or isolated early*: onset of reaction 10 to 20 minutes after exposure ended with a maximum decrease in FEV₁ occurring within 10 to 20 minutes and progressive recovery in the first or second hour; *late*: onset 3 or 4 hours, maximum 8 hours after exposure ended, and lasting 3 or more hours; *early late*: onset 1 to 2 hours, maximum 3 hours, after exposure ended, and lasting 3 or more hours; and *dual*: a combination of both early and late reactions with almost complete recovery (±10% of baseline FEV₁) after the first reaction.
2. Atypical reactions, according to our experience: *progressive*: progressive fall in FEV₁ in the first minutes after or during exposure with a maximum fall being reached 5 to 6 hours after the end of exposure; *square waved*: immediate and maximum fall in FEV₁ in the first minutes after exposure without significant (<10% fluctuation from the maximum fall) recovery thereafter (up to 8 hours); and *prolonged immediate*: similar to immediate but with slower (several hours) recovery.

For dual, square-waved, and progressive reactions, curves relating time on the abscissa and the percentage fall in FEV₁ on the ordinate were analyzed by a second degree polynomial fit to describe further the trend of reactions and to test the existence of a peak effect. The rationale for the use of up to a second degree polynomial fit was that the larger degree polynomial fits will represent what we consider oscillation caused by noise (patients, instability, etc.).

TABLE III. Type of reactions as assessed by physicians

	Group I	Group II	Group III
	Isocyanate-exposed (n = 23)	Western red cedar-exposed (n = 23)	IgE-mediated reactions (n = 23)
Typical			
Isolated immediate	7	0	15
Early late	1	0	0
Late	5	17	1
Dual	1	2	5
Total	14	19	21
Atypical			
Prolonged immediate	1	1	0
Progressive	7	2	0
Square-waved	1	1	2
Total	9	4	2

Chi-square (comparing the number of atypical reactions in the isocyanate-exposed group, 9/23, with the other two groups, 6/46), 6.1; $p = 0.01$.

Statistical analysis

Fisher's exact probability (if n was <5 by cells), chi-square, Mann-Whitney U test, analysis of variance with Scheffé's contrasts, and Student's unpaired t test were used in the analysis of the clinical, immunologic, and functional results.

RESULTS

The anthropometric, clinical, functional, and immunologic results for the three groups of subjects are presented in Table I. The distribution of sex, age, and atopy was statistically different; that is there were more women, the subjects were younger, and more of the subjects were atopic in the group with IgE-mediated reactions. The duration of exposure, the duration of symptoms, the baseline FEV₁, and the presence of significant bronchial hyperresponsiveness did not differ among the three groups. However, the group with IgE-mediated reactions generally had a lower degree of bronchial hyperresponsiveness ($PC_{20} > 2$ mg/ml) (chi-square, 6.0; $p = 0.01$). The characteristics of the reactions are presented in Table II. The duration of exposure on the day of the test was significantly shorter for the group with IgE-mediated reactions. The maximum fall in FEV₁ was significantly more pronounced for isocyanates, especially compared with western red cedar. The interval after which the maximum fall in FEV₁ occurred was shorter for the group with IgE-mediated reactions than for the other two groups. Significant changes (≥ 3.2 -fold difference) in PC_{20} after the reaction were not significantly different in the three groups.

The types of reactions within each group are presented in Table III. There was agreement between the three observers in 59/69 (86%) of cases. They disagreed about the distinction between dual and square-waved reactions. However, after discussion, a consensus was reached. Typical patterns (immediate, late, or dual) were found mainly in the group with IgE-mediated reactions and the western red cedar-exposed group, 21/23 (91%) and 19/23 (83%), respectively. The distribution of reactions was significantly different for isocyanates as compared with the other two types of agents: 9/23 (40%) atypical patterns compared with 4/23 (17%) for red cedar and 2/23 (9%) for IgE-mediated agents. Isocyanates caused atypical progressive bronchospastic reactions more frequently (7/23 or 30%). There were atypical reactions for all types of isocyanates (TDI, $n = 4$; HDI, $n = 4$; MDI, $n = 1$). Atypical reactions induced significant changes in bronchial responsiveness (changes in $PC_{20} \geq 3.2$ -fold difference) more frequently than typical reactions (7/15 instances as compared to 9/48 instances; chi-square, 4.7; $p = 0.03$). This could not be accounted for by more pronounced changes in FEV₁ (falls of $28.4\% \pm 9.8\%$ and $29.0\% \pm 6.8\%$ in the case of typical and atypical reactions, respectively; Student's t test, 0.3; $p > 0.05$). Moreover, atypical reactions tended to cause more changes in bronchial responsiveness than reactions of the late, dual, and early late types (7/15 instances as compared to 5/26 instances; chi-square, 3.5; $p = 0.06$).

After analyzing the immediate reactions, we found that two reactions were not classic (i.e., with recovery

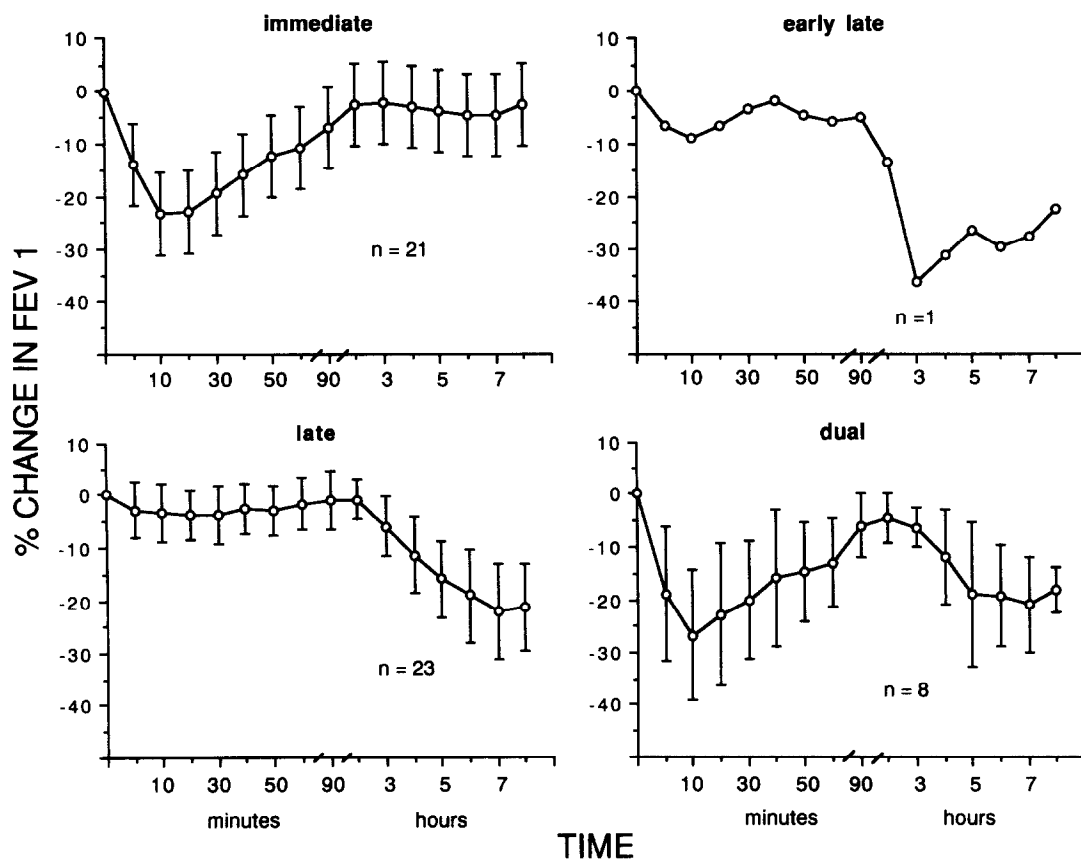


FIG. 1. Mean $\pm$ SD or individual values of the percent change in FEV₁ (on the ordinate) as a function of time since exposure (on the abscissa) for the four typical patterns of reactions (see text for definition). The numbers of individuals for each pattern are presented.

within 1 to 2 hours). Indeed, there was progressive recovery in the 7 to 8 hours after exposure. We therefore classified these reactions as atypical. Graphs of typical and atypical reactions are illustrated in Figs. 1 and 2.

Two of the 13 subjects for whom specific IgE to plicatic acid were assayed had significantly increased (values >2). These two subjects demonstrated isolated late reactions. Nine of 23 subjects (39%) had specific IgG to isocyanates (index >2) and two of these subjects also had increased IgE. Five of the nine subjects had typical reactions (two with immediate and three subjects with isolated late) and four had atypical reactions (three progressive and one square waved). This proportion is not different from the proportion of patterns observed in the 14 individuals with normal specific IgG (eight with typical reactions and six with atypical reactions).

Polynomial regression analysis was performed to confirm the visual classification for the atypical reactions, dual, square-waved, progressive, and pro-

longed immediate in which the pattern could have been misclassified by the observers. The general formula of the polynomial regression and the individual results are presented in Table IV. The r^2 was generally (6/8 instances) >0.90 for dual reactions (including 12 to 14 points between the maximum falls in FEV₁ of the early and late components of the reactions), the coefficient b^2 (quadratic component) being negative, which means a downward parabolic curvature of the fit between the points of maximum falls in FEV₁ at the time of the immediate and late components of the reactions. Square-waved curves all yielded not, or poorly significant r^2 , suggesting that these curves were flat. Furthermore, the number of points on each curve for which FEV₁ remained $<10\%$ of the maximum fall was significantly greater for the square-waved pattern (mean, 11; range, 9 to 13) as compared with the dual pattern (mean, 5.25; range, 1 to 9) (Mann Whitney U test, $p = 0.004$), again suggesting that the square-waved curves were flat. Finally, the percentage fall in FEV₁ at intervals of 90, 120, 180, and 240 minutes

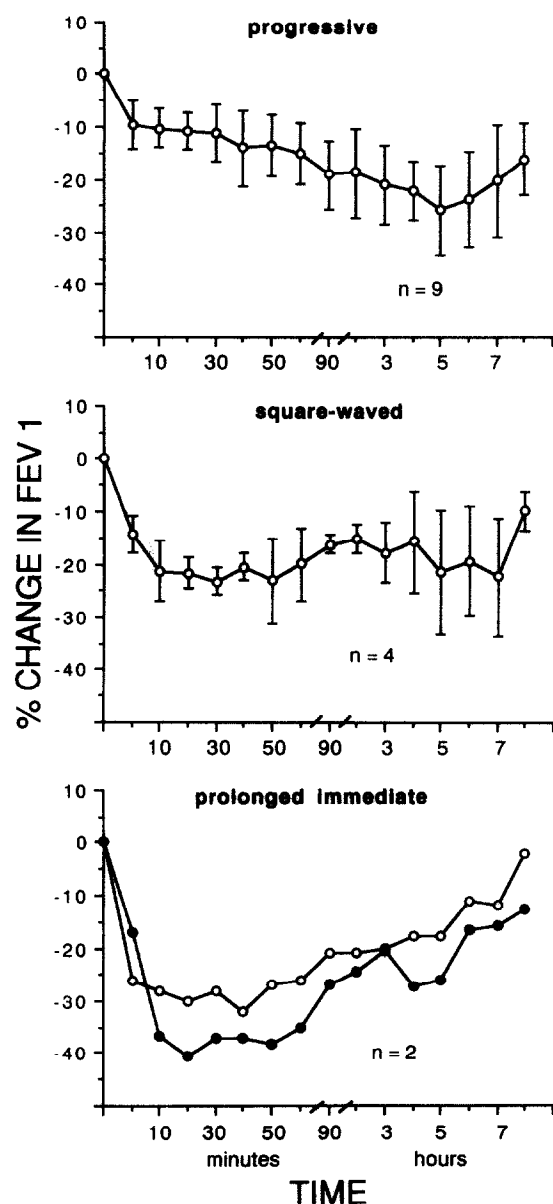


FIG. 2. Mean $\pm$ SD or individual values of the percent change in FEV₁ (on the ordinate) as a function of time since exposure (on the abscissa) for the three atypical patterns of reactions (see text for definition). The numbers of individuals for each pattern are presented.

after the exposure ended (between the immediate and late parts of the reactions) was also significantly less for the dual responders (mean $\pm$ SD, 7.1% $\pm$ 0.7%; $n = 8$) as compared to the square-waved pattern (mean $\pm$ SD, 16.1% $\pm$ 0.5%; $n = 4$) (Student's t test, 3.31; $p < 0.001$). Curves of progressive and prolonged immediate reactions yielded fits >0.6 in all instances with either negative (for progressive re-

actions) or positive (for prolonged immediate reactions) coefficients b_1 (linear component of the fit) (Table IV).

DISCUSSION

Typical asthmatic reactions after exposure to common or occupational allergens have been classified as isolated immediate, early late, late, and dual by Pepys and Hutchcroft.⁶ Atypical reactions caused by isocyanates have been described by Zammit-Tabona et al.⁷ Séguin et al.⁸ described atypical reactions, principally of the square-waved type. However, atypical reactions were not identified as such by these authors and remained anecdotal. The aim of this work was therefore to determine the frequency of these reactions and to determine if they were more frequent after exposure to one or the other of the agents. Reactions to western red cedar were mainly of the late type, confirming other studies.²¹ IgE-mediated reactions were primarily immediate and late, as in the case for common allergens. The major findings of this study are that atypical reactions represent a significant proportion of all reactions (22%) and that they occur more frequently after exposure to isocyanates. These atypical reactions can occur after exposure to all types of isocyanates and cause changes in bronchial responsiveness more often. Although we acknowledge that the square-waved pattern can be identified as dual by amplifying the criteria of identification of these two types of reactions and that early late can be incorporated in the late type, such patterns as the progressive and prolonged immediate are original because they have not been described systematically before.

It is unlikely that these atypical reactions were caused by nonspecific irritation since exposure levels of isocyanates were kept at <20 ppb, the accepted irritant threshold. Exposing subjects to concentrations of isocyanates <20 ppb does not cause irritant reactions as demonstrated by other investigators.²² It is furthermore unlikely that a difference in baseline airway caliber or bronchial hyperresponsiveness between subjects would explain the different patterns. Although the isocyanate-exposed group was different from the group with IgE-mediated reactions in several aspects (sex, age, atopy, more pronounced bronchial hyperresponsiveness, and duration of exposure on the day of the test), they were not different from the western red cedar-exposed group. Neither do we think that the presence of atypical reactions, which was more frequent with isocyanates, was due to longer exposure during the challenges. Exposures to isocyanates were longer than to IgE-mediating agents but not significantly longer than the exposures that caused

TABLE IV. Polynomial regression analysis

Type of reaction	Agent	Polynomial regression			
		Coef b_1	Coef b_2	Intercept (b_0)	r^2
Dual (n = 8)	IgE, Flour	0.9	-4.0	-53	0.97
	IgE, guar gum	0.3	-0.8	-24	0.90
	IgE, psyllium	0.2	-0.8	-21	0.91
	IgE, psyllium	0.5	-2.0	-39	0.70
	IgE, Flour	0.4	-1.6	-27	0.97
	Western red cedar	0.5	-1.7	-30	0.96
	Western red cedar	0.5	-1.5	-58	0.97
	Isocyanate	0.4	-3.0	-18	0.24
Square-waved (n = 4)	IgE, psyllium	0.2	-0.4	-30	0.64
	IgE, flour	0.1	-0.7	-25	0.25
	Western red cedar	0.2	-0.6	-24	0.39
	Isocyanate	0.1	-0.4	-25	0.49
Progressive (n = 9)	Isocyanate	-0.04	0.07	-8	0.69
	Isocyanate	-0.05	0.03	-10	0.84
	Isocyanate	-0.03	0	-11	0.67
	Isocyanate	-0.17	0.3	-4	0.96
	Isocyanate	-0.14	0.34	-8	0.71
	Isocyanate	-0.18	0.36	-9	0.63
	Isocyanate	-0.10	0.16	-6	0.89
	Western red cedar	-0.14	0.23	-19	0.67
	Western red cedar	-0.10	0.18	-9	0.71
Prolonged immediate (n = 2)	Isocyanate	0.08	0.01	-29	0.91
	Western red cedar	0.08	0.07	-39	0.85

b_0 , Intercept; b_1 , coefficient of the linear component; b_2 , coefficient of the quadratic component.
General formula of the polynomial regression: $Y = b_0 + b_1X + b_2X^2$. For each subject, the indices are presented together with the squared value of the regression coefficient (r^2) according to the types of reactions and specific agents. The number of points for each curve varied from 12 to 14.

significant reactions to western red cedar. Indeed, as the temporal pattern was determined after the end of exposure, the fact of exposing individuals for various time intervals from one breath to 2 hours could have altered the pattern of reaction described thereafter.

Other original findings of this study, which have not been explored previously, to the best of our knowledge, are (1) the reproducibility of interpretation by three independent observers and (2) the correspondence of this interpretation with the mathematical analysis of the curves that was performed in this study. We found that there was satisfactory agreement in interpreting the pattern of reactions among the three observers with rigid criteria set beforehand. The only exception was in distinguishing between dual and square-waved patterns; consensus was nevertheless reached after discussion. We also demonstrated that a distinction could be made between these two types of reactions with polynomial regression analysis by averaging the percentage fall in FEV₁ at 90, 120, 180,

and 240 minutes after exposure, that is, between the early and late components of the dual reaction, and counting the number of points with FEV₁ values <10% of baseline on the individual curves. We therefore think that a distinction can be made between these two reactions. Polynomial regression analysis also demonstrated that the nine progressive reactions interpreted as such by the three observers fitted a linear regression with a satisfactory correlation coefficient and a negative slope, whereas the two prolonged immediate reactions fitted a linear regression but with a positive slope. We do not think that the lack of recovery of the square-waved reaction as compared with the dual can be explained by a more pronounced immediate bronchospastic reaction. Indeed, the immediate maximum percentage fall in FEV₁ was 28.4% ± 10.4% for the dual reaction as compared with 27.0% ± 1.5% for the square-waved reaction (Student's *t* test, 0.36; not significant).

We did not find significant differences in the

changes in PC₂₀ before and after the reactions among the three groups. However, variations of PC₂₀ $\geq$ 3.2-fold were more frequent after atypical reactions than after typical reactions. There was even a tendency for the atypical reactions to cause changes in bronchial responsiveness more often than late, early late, and dual reactions. This finding suggests that atypical reactions can have even more physiologically significant consequences than the classic reactions.

The explanations for finding different types of temporal reactions are still speculative. The first explanation might be purely physical. The agents were physically different and were delivered with different methods (vapors, aerosol, mixture of particulates and vapors, or dust). It is not excluded that the physical type of the stimulus can alter the pattern of reaction. The second explanation might be related to the pathophysiological mechanism, although it is clear that mechanisms cannot be discussed on the basis of the results of specific inhalation challenges. In the group with IgE-mediated reactions, the mechanism was immunologic,^{23, 24} as suggested by the fact that all subjects had immediate positive skin reactions. In the other two groups, the mechanism of sensitization is not clearly understood, but an immunologic mechanism cannot be ruled out. Increased levels of specific IgE to western red cedar and of specific IgE or IgG to isocyanates were found in some of our subjects, as in other studies.²⁵⁻²⁹ Differences in the patterns of reactions with isocyanates as opposed to the two other types of agents might be linked with a different influx of cells, neutrophils³⁰ or eosinophils.^{31, 32}

Our results have practical implications. Atypical reactions, not related to a nonspecific irritant mechanism, are possible after exposing subjects with occupational asthma to isocyanates in the laboratory. The diagnosis of occupational asthma can still be made since we do not believe that atypical reactions reflect irritant or nonspecific mechanisms, but rather sensitization.

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Clinical and immunologic evaluations of reactive dye-exposed workers

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To evaluate type I hypersensitivity to reactive dyes, its prevalence, and its relationship to respiratory dysfunction, we studied clinical and immunologic features, including skin prick tests, RAST, and bronchoprovocation tests, of 309 employees working in a reactive-dye industry. Our survey revealed that 78 (25.2%) employees had work-related lower respiratory symptoms associated with or without nasal, skin, or eye symptoms. Among these employees, 38 (48.7%) had nonspecific bronchial reactivity. Thirteen demonstrated immediate (6), dual (6), or late only (1) asthmatic responses after inhalation of four kinds of reactive-dye solutions. Twenty-five employees demonstrated immediate skin responses to black GR dye, and 21 reacted to orange 3R. Fifty-three employees (17%) had specific serum IgE antibody against black GR and orange 3R-human serum albumin conjugate. Specific IgE was detected more frequently in symptomatic employees (30%) and smokers (100%). No association was found between atopy and specific IgE binding. The RAST-inhibition tests of black GR revealed significant inhibitions by black GR-human serum albumin conjugate and minimal inhibitions by unconjugated black GR. Orange 3R RAST-inhibition tests revealed significant inhibitions by conjugated forms of black GR and orange 3R and some inhibitions by two unconjugated dyes, suggesting an immunologic cross-reactivity between these dyes. These findings suggested that reactive dyes could induce immunologic responses, most likely IgE-mediated. (J ALLERGY CLIN IMMUNOL 1991;87:639-49.)

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