

Late bronchial obstructive reaction to experimental inhalation of house dust extract

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Summary

This study was undertaken to confirm the high incidence of the 'late' bronchial reaction after house dust inhalation and to assess whether symptoms and signs of these 'late' reactions were comparable with the clinical features of the classic Type III (Gell and Coombs) allergic reactions in the lung as shown by extrinsic allergic alveolitis.

Although the time sequence of this late reaction is in agreement with the classic Type III reaction (Arthus phenomenon), other features of alveolitis are absent. There were no crepitations on physical examination, no fever, no leucocytes, no decrease of the Pa_{O_2} , and no abnormal radiological findings. These results were related to the protective effects of some drugs. The protective effect of disodium cromoglycate and prednisolone is probably the same in both types of late reactions. The protective effect of antihistamine drugs, which is found in this late obstructive reaction, is, according to the literature, absent in the classical Type III reaction. There seem to be no valid arguments to ascribe the 'late' bronchial obstructive reaction to the toxic complex syndrome.

Theoretical and practical implications of the late obstructive bronchial reaction are mentioned.

Introduction

It is still an open question whether late bronchial reactions due to inhalation of house dust are of the same nature as other late reactions that have been described after inhalation of fungi and other organic dusts (Williams, 1963; Longbottom & Pepys, 1964; Hilvering, de Vries & Orie, 1966; Pepys, 1969; Schlueter, Fink & Sosman, 1969; Stevens, Hilvering & Orie, 1970), although the time-sequence of both reactions is very similar.

We therefore studied a number of patients with these late obstructive reactions,

particularly in respect to the presence of the relevant clinical features of the classic Type III reaction of Gell & Coombs (1968).

We assessed: physical signs, body-temperature reactions, reaction of the blood leucocytes, blood eosinophils, arterial oxygen tension, late intracutaneous skin tests, ventilatory lung function tests, and X-ray pictures. We have not measured blood precipitins in our patients; the results in the literature are contradictory (McAllen, Assem & Maunsell, 1970; Holford-Strevens *et al.*, 1970).

The protective effect of disodium cromoglycate, prednisolone, and an antihistamine—the latter results were obtained in previous studies (Booij-Noord, Orie & de Vries, 1971)—was also taken into consideration in assessing the identity or non-identity of the two late reactions.

We also performed some protection tests with a sympathomimetic drug, Diphenyl-oricrenaline (Berotec®), because the suggestion has been made (Assem & Schild, 1969; Lichtenstein & Margolis, 1968; Assem, 1971) that catecholamines prevent histamine release in the allergen reaction. Protection tests were also used in order to elucidate some details in the pathophysiology of the obstructive late reaction.

Many patients are sensitive to house dust. Our house dust extract of the present study was made from house dust gathered from a hundred different houses scattered all over the Netherlands (prepared by Pharmacy: Diephuis, Groningen).

Mite extracts from *Dermatophagoides pteronyssinus* (Voorhorst *et al.*, 1967; Spieksma, 1970) were inhaled for comparison with house dust, to see if they have the same effects in producing immediate and late reactions.

Patients and methods

Fifty-five hospitalized patients with chronic obstructive lung disease with a history of attacks of dyspnoea, good functional reversibility and not on prednisolone treatment in general, except that prednisolone was given to three patients (who gave only an immediate reaction), were challenged with a house dust extract. Data on these patients and methods (analytical and statistical) are published elsewhere (Booij-Noord *et al.*, 1970, 1971).

The effect of the inhalation was measured by assessing vital capacity (VC) and forced expiratory volume in 1 sec (FEV₁) before, directly after the allergen inhalation, and at 5, 10, 15, 20, 30, 40, 50 and 60 min intervals, and thereafter each hour until 10 p.m. The measurements were repeated on the next day at 8 a.m., 10 a.m. and 5 p.m. in some patients.

Skin-tests. End point titrations were performed with tenfold dilutions, starting with 0.5 mg/ml house dust extract. The intracutaneous injections were given at 9.40 a.m., evaluated at 10 a.m., and thereafter every hour till 10 p.m. They were carried out in eighteen patients with an immediate bronchial reaction only, and in nineteen patients with both immediate and late bronchial reactions after house dust extract inhalation.

Physical examination of the chest was made in fifteen patients, who had a late obstructive reaction after inhalation of house dust.

Body-temperature. Rectal temperature was taken at 11 a.m., 1 p.m., 3 p.m. and 5 p.m. in ten patients, both on challenge and control days.

White blood count. Leucocytes were counted in the capillary blood at 8 a.m., 11 a.m., 1 p.m., 3 p.m., 5 p.m. and at 8 a.m. on the next day. This was also done in ten patients after allergen and Coca solution inhalation.

Blood eosinophils were measured before the allergen inhalation, and at 3 p.m., 5 p.m. and at 8 a.m. on the next day, after Coca solution inhalation for control and after inhalation of the allergen.

Blood gases. Arterial oxygen tension was measured in seven patients before the house dust inhalation, during the immediate reaction, 10–15 min after the inhalation, during the late reaction and 7–8 hr thereafter. The measurements were made during the second house dust extract inhalation; the patients were not receiving drugs.

Radiography. X-ray pictures were taken at 8 hr, 24 hr and 10 days after the allergen inhalation in ten patients.

Drugs and doses used in protection tests in patients giving the late reaction after house dust inhalation

Prednisolone was given orally 15–20 mg daily for 9–16 days before and continued on the test day.

Disodium cromoglycate was given as follows: (1) (DSCG, Lomudal®, Intal®) aerosol: a 2% solution dissolved in distilled water inhaled for 3 min (approximately 12 mg) 10 min before the allergen inhalation. (2) DSCG aerosol was administered before the allergen inhalation and before the expected late reaction and then at 3-hourly intervals. (3) DSCG aerosol was not administered before the allergen inhalation but only before the expected late reaction and then at 3-hourly intervals.

Antihistamine. Mepyramine (Antallergan®, Pyrilamine®) 25 mg i.m. was given before the expected late reaction and 5 hr later.

Sympathomimetic drug. Diphenyl-orciprenaline (Berotec®, Th 1165a) 0.08 mg i.m. was given before the house dust inhalation, before the expected late reaction, and 5 hr later in two patients. Diphenyl-orciprenaline inhalation (400 µg) before the allergen inhalation and before the expected late reaction and at 4-hourly intervals only in one patient.

Rank tests were performed with the data on leucocyte counts and body temperature changes in the late reaction.

Results

Fifty-five patients had an immediate reaction after the inhalation of house dust, and in twenty-six of them a late reaction was also observed. Isolated late reactions, i.e. without an immediate reaction (van Lookeren Campagne, Knol & de Vries, 1969) were not observed in this series. In fifteen patients with an evident immediate reaction to other different allergens no late reactions were observed. The immediate reaction appeared rapidly after the allergen inhalation, was maximal at 10–20 min and disappeared within 1½–2½ hr.

The onset of the late reaction was mostly 4 (3–5) hr after the challenge, maximal at 7–12 hr and persisted up to 26–33 hr after the inhalation. Sometimes the FEV₁ decreased to such a low level that orciprenaline (metaproterenol, Alupent®) inhalation (5% aerosol for 30 sec) was indicated. During the late reaction no crepitations were noted and the chest radiographs showed no abnormal shadows.

Ten out of nineteen patients with a late obstructive reaction had no positive late skin reactions (Table 1). No significant rise in body temperature and no leucocytosis was noted in the late reaction (Tables 2 and 3). Patients with immediate and late obstructive bronchial reactions had comparable numbers of eosinophils 7 and 9 hr

Table 1. Immediate and late skin test reactions to house-dust, in relation to effect of house dust inhalation

Inhalation test	No. of patients	Intracutaneous tests*				
		20 min		6 hr		8 hr
		Wealing reaction	Oedematous reaction	Erythema	Oedematous reaction	Erythema
Immediate reaction: +	12	+	—	—	—	—
and late reaction: +	1	+	+	—	—	—
and late reaction: —	2	+	—	+	—	—
Immediate reaction: —	3	+	+	—	+	—
Immediate reaction: +	5	+	+	+	+	+
and late reaction: +	4	+	+	—	—	—
and late reaction: —	2	+	—	+	—	—
Immediate reaction: +	8	+	—	—	—	—

* Extracts of house-dust were used in concentrations 0.0005, 0.005, 0.05 and 0.5 mg/ml.

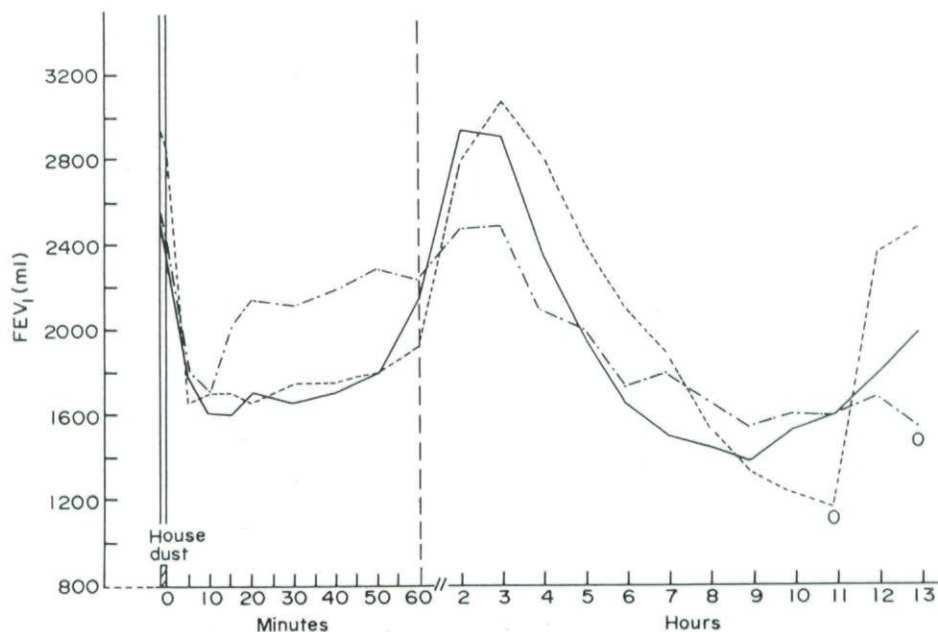


Fig. 1. The inhalation of house dust mite extract in comparison with the inhalation of house dust extract. Male, 21 years old; predicted FEV₁ 4540 ml; blood eosinophils 520/mm³. —, Inhalation of house dust 10 mg/ml (I); ---, inhalation of house dust 10 mg/ml (II); —, inhalation of house dust mite 200 N µg/ml (*Dermatophagoides pteronyssinus*). O: orciprenaline aerosol 5%.

Table 2. Rectal temperature taken after house dust inhalation in comparison with rectal temperature after Coca solution inhalation

Patient	Test	Rectal temperature (°C)				
		8.30 a.m.	11 a.m.	1 p.m.	3 p.m.	5 p.m.
1	I	37.1	37.2	37.4	37.1	
	II	36.4	36.9	37.6	36.9	
	IV	36.2	36.9	37.1	37.1	
2	I	37.2	37.3	37.5	37.3	
	II	37.1	37.1	37.3	37.5	
	IV	37.0	37.0	37.7	37.4	
3	I	ND†	ND	ND	ND	
	II	ND	37.4	37.2	37.4	
	IV	36.4	36.7	36.5	36.8	
4	I	37.2	37.3	37.3	37.3	
	II	36.9	36.8	36.9	37.3	
	IV	37.0	37.0	37.6	37.3	
5	I	ND	ND	ND	ND	
	II	37.2	37.2	37.2	37.4	
	IV	ND	ND	ND	ND	
6	I	37.0	37.5	37.8	37.3	
	II	37.5	37.0	37.2	37.5	
	IV	36.9	37.4	37.4	37.4	
7	I	37.2	37.1	37.3	37.0	
	II	37.3	37.2	37.2	37.2	
	IV	37.3	37.6	37.5	37.4	
8	I	37.1	37.3	37.5	37.2	
	II	37.2	37.1	37.4	37.2	
	IV	37.5	37.6	37.5	37.4	
9	I	ND	ND	ND	ND	
	II	37.1	37.2	37.1	37.1	
	IV	ND	ND	ND	ND	
10	I	37.6	37.6	38.2	37.4	
	II	37.8	38.2	38.2	37.8	
	IV	37.7	37.7	37.4	37.3	
Mean	I	37.2	37.3	37.6	37.2	
	II	37.2	37.2	37.3	37.3	
	IV	37.0	37.2	37.3	37.3	

Rank-test: difference between Coca solution and house dust extract inhalation not significant.

* Test I: Coca solution inhalation; Test II: house dust extract inhalation; Test IV: Second house dust extract inhalation for control.

† ND: not done.

Table 3. Leucocytes counted in the capillary blood before and after house dust extract inhalation in comparison with Coca solution inhalation

Patient	Test*	Leucocytes/mm ³					
		8 a.m.	11 a.m.	1 p.m.	3 p.m.	5 p.m.	8 a.m. following day
1	I	5900	6700	6600	6800	8500	5300
	II	7300	9600	9600	7400	9000	6400
	IV	9600	10000	10000	8600	10100	7500
2	I	8600	9400	8900	8100	9100	9000
	II	7900	7700	7400	8000	7700	6800
	IV	8100	8200	10200	9900	8500	8000
3	I	7400	8100	7100	5700	6300	5100
	II	5100	5200	5500	6300	6100	7100
	IV	4000	4600	5200	5300	5300	5300
4	I	4600	8100	6700	6600	5000	ND†
	II	6000	9700	8300	7900	10700	7200
	IV	5400	7000	9600	9200	7300	8000
5	I	6300	7300	6900	7200	8500	7400
	II	5500	6700	8200	8400	8400	5700
	IV	4800	6800	7400	8800	7500	5000
6	I	6300	7300	6900	7200	8500	7400
	II	5500	6700	8200	8400	8400	5700
	IV	4800	6800	7400	8800	7500	5000
7	I	5000	5800	6200	6800	7600	5400
	II	5200	6000	5700	7100	7600	5600
	IV	5000	5600	7800	7100	7200	6200
8	I	4900	5800	6800	7400	9100	5300
	II	4600	4900	5900	8000	7600	4300
	IV	3900	7000	6600	6400	6300	5200
9	I	7800	7800	8200	7400	7100	ND
	II	5900	6500	8000	8300	8400	ND
	IV	6600	7200	9600	8100	8000	ND
10	I	7200	7900	10300	10500	13200	7700
	II	ND	5000	7400	7600	9000	8200
	IV	7000	7100	9500	10200	11300	9000
Mean	I	6400	7420	7460	7370	8290	6575
	II	5889	6800	7420	7740	8290	6333
	IV	5920	7030	8330	8240	7900	6778

Rank-test: difference between Coca solution and house dust inhalation not significant.

* Test I: Coca solution inhalation; Test II: house dust extract inhalation; Test IV: second house dust extract inhalation for control.

† ND: not done.

Table 4. Blood eosinophilia

	Before inhalation	After house dust extract inhalation		
	(/mm ³)	7 hr (%)*	9 hr (%)*	24 hr (%)*
Patients with immediate reaction: +	451	80.5	90.1	90.7
and late reaction: -	748	32.4	38.1	98.8
	308	78.6	103.6	103.6
	418	39.9	82.3	105.3
Mean		62.4	78.5	101.3
SD		22.4	28.4	3.4
Patients with immediate reaction: +	3344	65.5	79.6	129.8
and late reaction: +	1320	75.0	115.0	177.5
	297	92.6	103.6	344.5
	341	74.2	80.5	193.4
	121†	118.2	200.0	309.1
	880	86.3	102.5	146.3
	660	65.0	120.0	151.7
	759	78.3	92.8	107.1
	825	124.0	128.0	150.7
	242	45.5	95.5	172.6
	154‡	78.4	150.0	221.0
Mean		82.1	115.4	191.2
SD		22.9	35.0	74.1
Patients§ with Coca solution inhalation	3289	75.3	81.5	95.9
for control	1265	102.5	108.7	73.1
	352	93.8	109.4	84.4
	374	142.0	168.0	58.7
	110†	90.0	140.0	80.0
	1012	101.9	135.9	108.6
	594	111.7	122.7	109.7
Mean		102.5	123.7	87.2
SD		20.9	27.7	18.8

* In per cent of blood eosinophilia before inhalation.

† 5 mg prednisolone daily.

‡ 2.5 mg prednisolone daily.

§ The same patients as the first seven patients with a late reaction.

Table 5. Arterial blood gas tensions (mmHg)

Patient	Age (yr)	Sex	Immediate reaction in 10-15 min after the inhalation						Late reaction in 7-8 hr after the inhalation		
			FEV ₁ *	Pa,O ₂	Pa,CO ₂	FEV ₁ †	Pa,O ₂	Pa,CO ₂	FEV ₁ †	Pa,O ₂	Pa,CO ₂
1	18	M	50	93	42	77	93 (0)	40	83	93 (0)‡	42
2	26	M	54	88	32.5	61	86 (-2)	37.5	57	85 (-3)	36
3	23	M	64	85	36	65	83 (-2)	38	48	80 (-5)	41
4	24	M	93	93	42	43	91 (-2)	36	67	92 (-1)	39
5	20	F	99	97	39	55	77 (-20)	34.5	50	71 (-26)	36
6	18	F	90	90	32	63	80 (-10)	32	80	88 (-2)	32.5
7	24	M	52	72	36	55	66 (-6)	35	58	64 (-8)	35

* Initial value in % predicted.

† In per cent of initial value.

‡ In parentheses difference from initial value.

Table 6. Bronchial reaction to inhalation of extract of house dust mite (*D. pteronyssinus*) in comparison with the reaction after house dust extract

Patient	Age (yr)	Challenge tests					
		Immediate reaction			Late reaction		
		HD ₁ *	Mite	HD ₂ †	HD ₁ *	Mite	HD ₂ †
1	23	-27.6‡	-20.6	-21.7	-48.9‡	-52.9	-43.5
2	28	-36.6	-33.3	-42.5	-46.1	-30.5	-46.9
3	18	-25.1	-31.9	-41.7	-58.3	-61.6	-65.6
4	24	-56.4	-52.4	-48.2	-51.3	-60.8	-48.2
5	21	-27.3	-36.6	-31.5	-44.3	-53.6	-60.3
6	26	-46.2	-34.8	-43.7	-53.7	-62.3	-57.5
7	15	-56.3	-44.5	-59.2	-12.5	-13.7	-14.9
8	14	-37.3	-39.7	-40.0	-7.4	-9.3	ND
9	17	-33.4	-40.0	-50.6	-1.2	-1.4	ND
10	16	-33.4	-23.5	-16.8	-7.2	-5.0	ND
11	35	-49.7	-35.7	-45.6	-3.1	-5.2	ND
12	30	-30.0	-38.3	-40.9	-5.1	-6.3	ND
Seven patients with a late reaction							
Mean					45.0	47.9	48.1
SD					15.1	18.7	16.7
Twelve patients							
Mean		38.3	35.9	40.2	28.3	30.2	—
SD		11.2	8.5	11.8	23.6	25.9	—

* HD₁ = first house dust inhalation.† HD₂ = second house dust inhalation for control.‡ Decrease of FEV₁ in per cent of initial value.§ Decrease of FEV₁ in per cent of spontaneous recovery 3 hr after the provocation.

Table 7. The results of protection tests of different drugs in immediate and late obstructive reactions after house dust inhalation; the results have been arranged according to the time of application of the drug, before and after the challenge

	Drug given		No. of patients	Protective effects of the drug on:		
	Before the challenge	After the challenge		Immediate reaction	Late reaction	
DSCG	+	+	11	++±	++±	cf. Fig. 3
	+	—	10	++±	+±	cf. Fig. 2
	—	+	6		—	cf. Fig. 4
Mepyramine	—	+	10		+±	cf. Fig. 3
	+	—	11	+±		
Prednisolone	+	—	10	—	++	cf. Fig. 2
Diphenyl-orci-prenaline (Th1165a)	+	+	3	+++	±	cf. Fig. 5

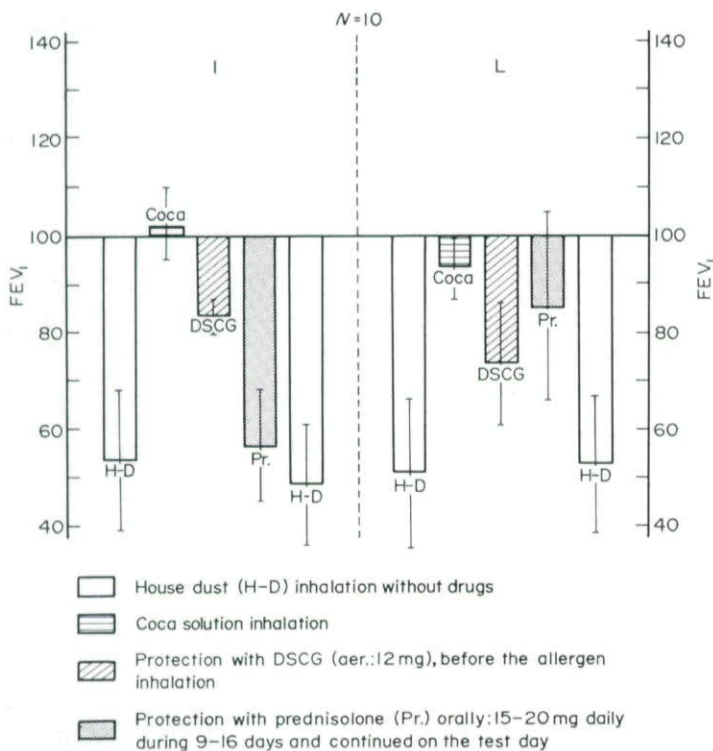


Fig. 2. Mean results of protective effect of DSCG, inhaled only before the allergen inhalation, and prednisolone in ten patients. I = immediate reaction, results in per cent of initial value; L = late reaction, results in per cent of spontaneous recovery 3 hr after allergen inhalation.

Table 8. Clinical and laboratory data of patients with immediate inhalation reaction with and without late obstructive reactions

Patients	Age	Sex	Attacks of dyspnoea at rest or all day*	Chronic cough on rising or all day*	Chronic phlegm on rising or all day	Vasomotor rhinitis or pollinosis	Wheezing		Blood eosinophils (/mm ³)†	Histamine threshold value‡ (mg/ml)	Intracutaneous tests with inhalant allergens				
							At rest	With exertion			House dust	Moulds	Pollen	Epidermals	
Patients with an immediate reaction and no late reaction															
18	M		+	+	+	+	+	+	508	16	+	+	-	+	
18	M		+	-	-	-	+	+	341	16	+	+	-	+	+
35	M		+	-	-	-	+	+	286	8	+	+	-	+	+
53	M		+	+	+	-	+	+	253	32	+	+	+	+	+
22	M		+	-	-	-	-	+	440	8	+	+	-	+	+
25	F		+	+	+	-	-	+	297	1	+	+	-	+	+
20	M		+	-	-	+	+	+	1177	32	+	+	+	+	+
22	M		+	+	+	+	-	+	187	16	+	+	-	+	+
17	M		+	-	-	+	-	+	341	32	+	+	-	+	+
15	M		+	+	-	-	-	+	1265	8	+	+	+	+	+
17	M		+	+	-	-	-	+	1485	8	+	+	-	+	+
19	F		+	-	-	-	-	+	495	16	+	+	+	+	+
Mean									589.4	16.1					
SD									449.0	10.0					
Patients with an immediate reaction and also a late reaction															
25	F		+	+	+	-	+	+	440	2	+	+	-	+	+
21	M		+	+	+	-	+	+	517	2	+	+	+	+	+
24	M		+	+	-	+	+	+	1650	8	+	+	+	+	+
23	M		+	-	-	+	+	+	869	8	+	+	-	+	+
27	M		+	-	-	+	-	+	561	1 1/2	+	+	+	+	+
30	M		+	+	+	+	+	+	517	8	+	+	-	+	+
17	M		+	+	+	+	-	+	385	16	+	+	-	+	+
16	M		+	+	-	-	+	+	1452	8	+	+	+	+	+

18	M	++	-	-	-	+	902	$\frac{1}{2}$	++	+	+	+
14	M	+++	+	-	+	+	990	8	++	-	+	+
18	F	+++	-	-	+	+	760	8	++	+	+	+
16	F	++	+	+	+	+	715	4	++	+	+	+
16	M	-	-	-	+	+	850	16	++	+	+	+
19	F	++	-	-	-	+	470	2	++	+	+	+
22	F	+++	-	-	-	+	430	4	++	+	+	+
21	F	++	-	-	-	+	200	2	++	+	+	+
46	M	+++	+	+	-	+	330	2	+++	+	+	+
14	M	++	-	-	-	+	560	1	++	+	+	+
Mean							699.9	5.5				
SD							378.3	4.8				

* On most days of at least 3 months of the year, for at least 2 consecutive years.

† Measured only in the morning in the fasting condition before the first allergen inhalation.

‡ Histamine aerosols in a spray with an airflow of 8 l/min containing exponentially increasing concentrations are inhaled for 30 sec; the degree of bronchial obstruction is measured by spirometry. The lowest concentration exponentially increasing causing a decrease in WC and/or FEV₁ of 10% or over is called the threshold value, if this or the following concentrations give a further decrease of at least 25%. The concentrations used are: $\frac{1}{8}$, $\frac{1}{4}$, $\frac{1}{2}$, 1, 2, 4, 6, 16 and 32 mg/ml (histamine diphosphate). This threshold value is considered to be an index for the reactivity of the bronchial tree. In normal subjects the histamine threshold value is over 32 mg/ml.

Table 9. Lung function data of patients with immediate inhalation test reactions with and without late obstructive reactions

Patients		TLC	RV/TLC	VC	VC after	FEV ₁	FEV ₁ after	Viscous work	Viscous work	Compliance
		(% pred.)	(%)	(ml)	thiazinamium*	(ml)	thiazinamium†	(g.cm/ml)	thiazinamium†	(l/cmH ₂ O)
Age	Sex									
Patients with an immediate reaction and no late reaction										
18	M	82	15	5000 (88)	4900	4300 (86)‡	4300	1.6	0.9	0.26
18	M	118	27	5550 (107)	5550	3450 (62)	4500	2.4	1.3	0.33
35	M	127	30	6020 (115)	5980	4800 (80)	5150	2.3	2.3	0.30
53	M	108	25	4750 (114)	4900	2650 (56)	3650	4.9	3.6	0.33
22	M	98	27	6040 (99)	6020	3900 (65)	4300	4.8	2.9	0.28
25	F	96	33	1820 (47)	2340	1390 (76)	1720	4.0	2.4	0.12
20	M	107	20	5700 (110)	5950	3600 (63)	4700	1.5	1.5	0.12
22	M	97	25	5600 (97)	5610	5070 (91)	5300	5.2	2.6	0.11
17	M	112	33	4600 (92)	4580	2500 (54)	3980	2.7	1.2	0.28
15	M	98	25	2900 (90)	3000	1800 (62)	2500	4.7	4.0	0.17
17	M	102	24	5700 (95)	5880	4080 (72)	5450	2.8	2.8	0.24
19	F	103	21	3560 (100)	3820	1800 (51)	2400	3.3	2.6	0.17
Patients with an immediate reaction and also a late reaction										
25	F	104	22	3800 (92)	4600	2480 (65)	3100	3.4	3.4	0.30
21	M	97	40	4580 (78)	5200	2610 (57)	3650	3.8	3.3	0.25
24	M	100	19	4950 (94)	5150	4050 (82)	4800	2.5	2.3	0.19
23	M	111	26	6000 (109)	6000	4100 (68)	5150	5.4	6.0	0.35
27	M	104	20	6000 (108)	6400	3555 (59)	4750	3.3	0.7	0.46
30	M	95	29	4050 (80)	4950	2180 (54)	3380	3.8	2.8	0.30
17	M	111	20	5600 (103)	6150	3550 (64)	4500	2.0	2.3	0.24
16	M	81	25	4450 (70)	4700	3410 (76)	4020	3.1	2.0	0.16
18	M	95	31	5050 (82)	5300	2500 (49)	3500	3.18	1.53	0.23
14	M	91	29	3620 (78)	3750	2740 (75)	3100	4.8	2.1	0.31
18	F	125	26	3140 (91)	3400	2180 (69)	2820	3.5	1.5	0.15
16	F	85	32	3500 (87)	3370	2950 (84)	2900	3.2	1.5	0.14

16	M	74	24	3550 (68)	3820	1900 (53)	2380	4.0	2.5	0.13
19	F	111	29	3750 (112)	3960	2600 (68)	2850	7.0	7.0	0.19
22	F	107	33	3820 (98)	3810	2600 (68)	3200	2.5	2.5	0.13
21	F	106	21	4160 (99)	4150	2850 (68)	3140	2.0	1.8	0.22
46	M	87	34	4500 (100)	4480	2490 (55)	3000	2.3	0.6	0.43
14	M	81	19	3400 (70)	3700	2720 (80)	3400	2.4	2.4	0.10

* Thiazinamium (Multigan®; 25 mg i.m.) has antihistaminic and anticholinergic activities.

† The number in parentheses is percentage of the predicted value.

‡ The number in parentheses is percentage of VC.

Table 10. Late allergic reactions

	'Obstructive late reactions'	'Late reactions Arthus type'
Onset	3-5 hr	4-5 hr
Maximal	8-13 hr	7-8 hr
Duration	26-33 hr	24-36 hr
Physical examination	Prolonged expiration	Crepitations
Rise of temperature	—	+
Leucocytosis	—	+
Blood eosinophils	+ (24 hr)	±
Intracutaneous tests		
Immediate	+ (100%)	+ (92%)*
Late	+ (58%)	+ (93%)*
Decrease of art. PO_2	±	+
Chest X-ray lesions	—	+
FEV ₁	Definitely impaired	No change or less impaired, more individual variations
Viscous work of breathing	Definitely impaired	Less impaired, more individual variations
Influence of drugs: prednisolone	++ (15-20 mg, 10 days)	± (20 mg, 14 days)† ++ (40 mg)‡
Disodium cromoglycate	++ ±	++
Antihistamine	+ ±	—

Pulmonary aspergillosis: *Pepys (1969). Farmers' lung: †Hilvering *et al.* (1966), ‡Williams (1963).

after the inhalation. After 24 hr the number of eosinophils, however, was significantly higher in patients with a late obstructive reaction (Table 4).

The change in arterial Pa,O_2 was very similar both in the immediate and the late reaction. In most cases only minor changes were found (Table 5), in contrast to cases with organic dust disease (Stevens *et al.*, 1970). The reactions to house dust and mites were comparable, as may be seen in Table 6 and Fig. 1.

Discussion and conclusions

The occurrence of a late reaction of the obstructive type after house dust inhalation has been recognized by several authors (Herxheimer, 1952; ten Cate, 1954; van Geuns, 1956; Gronemeyer & Fuchs, 1959). In accordance with the observations of van Lookeren Campagne *et al.* (1969) in our experience the prevalence of this kind of reaction is rather high (47% of all positive inhalation reactions). Of his patients twenty-five (46%) children had a positive immediate reaction to the provocation with house dust, and eight (15%) children in addition had a late reaction with an interval of 8-13 hr after provocation. Many children—twenty-one (39%)—had an isolated late reaction, which did not occur in our adult patients in the present study.

The characteristics of the late obstructive reactions observed in our patients were compared with those of the typical Arthus reaction in the lung (extrinsic allergic alveolitis) (Table 10).

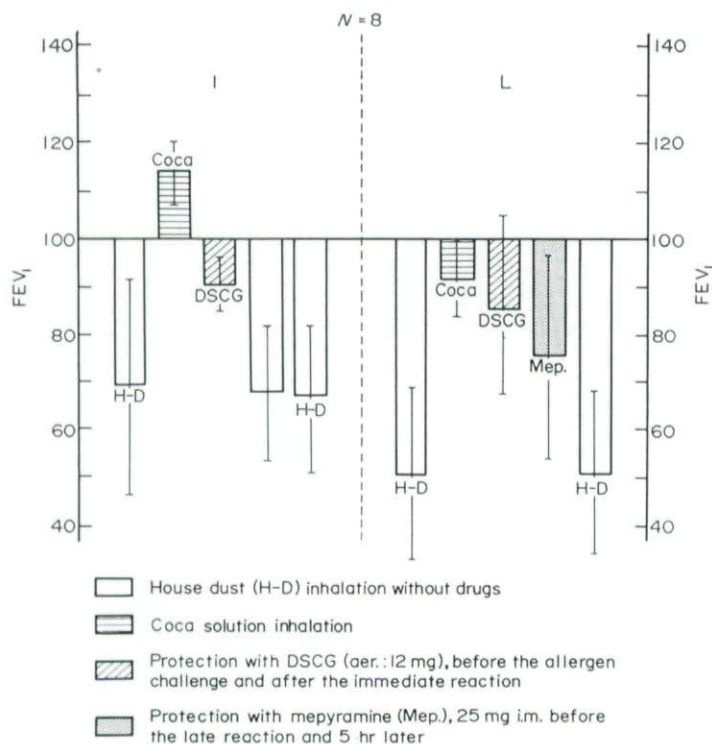


Fig. 3. Mean results of protective effect of DSCG, inhaled before the allergen inhalation and after the immediate reaction and mepyramine in eight patients. I = immediate reaction, results in per cent of initial value; L = late reaction, results in per cent of spontaneous recovery 3 hr after allergen inhalation.

Although the time characteristics for both types are about the same, the clinical features (physical examination, fever), laboratory tests (leucocytosis, eosinophilia, intracutaneous tests and blood gases) and radiological findings are quite different.

The clinical signs and the lung function changes in the late 'obstructive' reaction points to an involvement of the medium and large bronchi, whereas the late reaction (Arthus type) points to alveolar involvement with deposition of toxic antigen-antibody complexes. Why these two different phenomena have such sharply localized reaction areas remains in the dark.

It is also not clear whether the late obstructive reaction has the same immunological mechanism as the classic Type III reaction. Circulating, precipitating antibodies (IgG) that are essential in the classic Arthus reaction have not been assessed in our study. The findings in the literature are contradictory (McAllen *et al.*, 1970; Holford-Strevens *et al.*, 1970). The role of precipitins (IgG-antibodies) in the late bronchial obstructive reactions seems until now questionable. More recent studies (Pepys *et al.*, personal communication) have shown dual, Type I and Type III reactions to prick tests with *Dermatophagoides pteronyssinus*. They have also found IgG antibodies to this extract, prior to injection treatment. These findings suggest that such mechanisms which could be responsible for the speed of appearance of late bronchial reactions are present. They do not explain the localization and obstructive nature of the bronchial

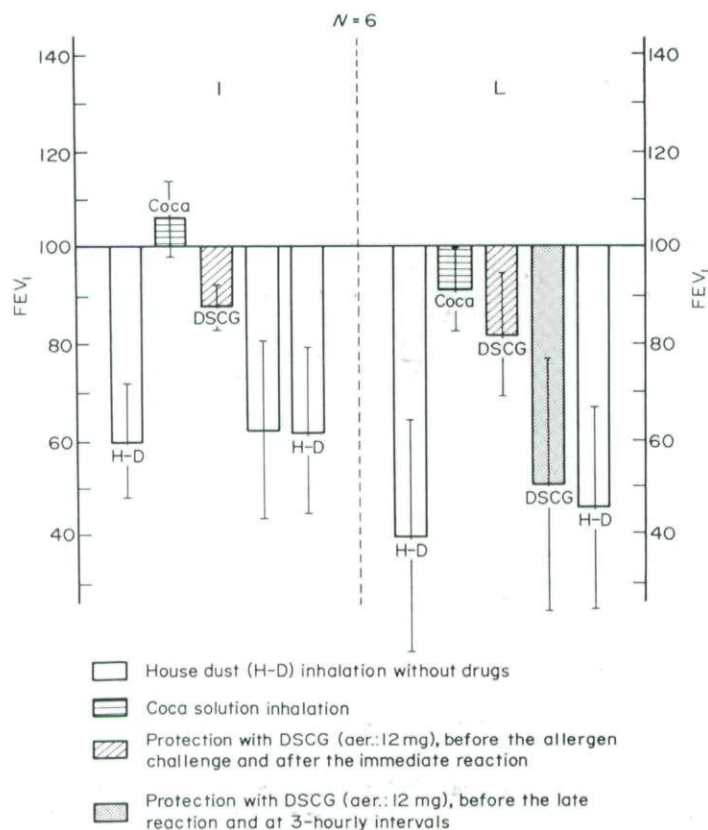


Fig. 4. Mean results of protective tests of DSCG inhaled before the expected late reaction and at 3-hourly intervals in comparison with DSCG inhaled before the allergen inhalation and after the immediate reaction in six patients. I = immediate reaction, results in per cent of initial value; L = late reaction, results in per cent of spontaneous recovery 3 hr after allergen inhalation.

reaction. In obstructive reactions reaginic antibodies play an important role. In all the patients with late bronchial obstructive reactions an immediate weal (reaginic) reaction could be demonstrated.

A difference between these two types of reaction seems also to be suggested by the protective effects of corticosteroids, which is more complete in this type of bronchial reaction than for example in the classical farmers' lung (Williams, 1963; Hilvering *et al.*, 1966).

The protective effect of DSCG cannot be compared so easily, but if conclusions may be drawn from Pepys *et al.* (1968) and our own results, again the effect of DSCG seems to be more complete in the obstructive late reaction than in the late reaction induced by toxic complexes. This might mean that in the classic Arthus reaction more—or other—components are involved than in the obstructive late reaction. This conclusion is also in agreement with the fact that antihistamines do not influence the late Arthus reaction (Rose, 1954; Gell & Coombs, 1968; Lunn & Hughes, 1967) by contrast with our results in the late obstructive reaction.

The effect of the protective drugs can be explained by the assumption that besides

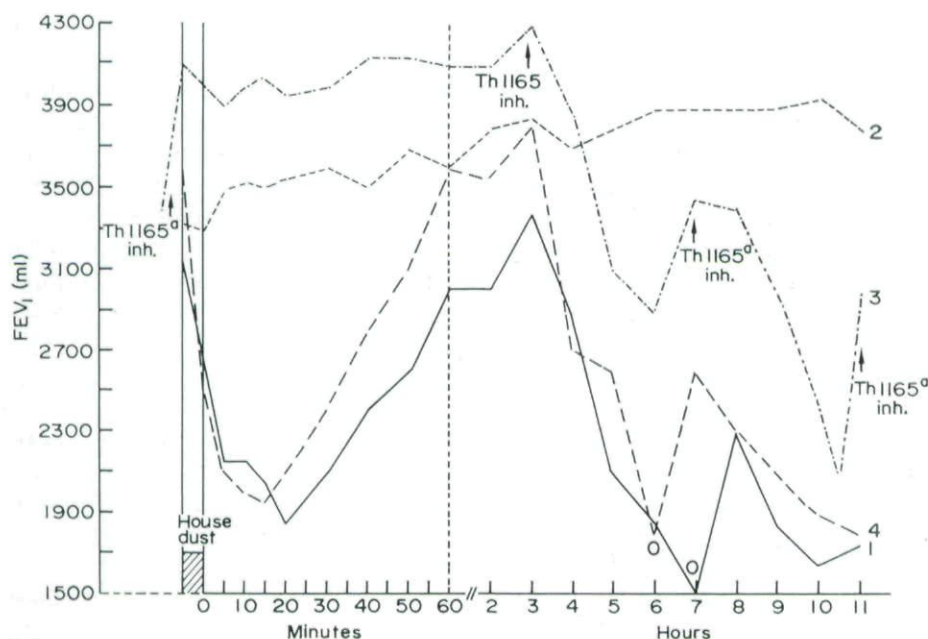


Fig. 5. Protection test with a sympathomimetic drug diphenyl-*o*-ciprenaline on the immediate and the late reaction. Female, 20 years old; predicted FEV_1 3424 ml. —, First house dust inhalation (Test 1); ---, Coca solution inhalation (Test 2); — · —, protection with Th1165^a 400 µg (Test 3); · · ·, second house dust inhalation (Test 4). O: *o*-ciprenaline.

the release of mediators from the mast cell responsible for the immediate reaction, other substances are released which give rise to cellular reactions. If the mediator release from the immediate reaction is prevented (DSCG) the late reaction is also influenced. If the effect of mediators inducing the immediate reaction is only blocked (sympathomimetic drug) no effect in the late reaction is to be expected. Drugs that prevent release of mediators from the polymorphonuclear neutrophil cells (corticosteroids) will block the late reaction even if the immediate reaction has not been prevented. Drugs that block some of these mediators, once released, will prevent a part of the late reaction (antihistamines). Drugs that neither influence release of mediators from polymorphonuclear leucocytes, nor block (part of) these mediators will have no effect on the late reaction (DSCG). DSCG has an influence on the mast cells (Cox, 1967; Cox & Altounyan, 1970), but little on the leucocytes (Lichtenstein & Adkinson, 1969; Assem & Mongar, 1970).

All these facts would be compatible with the suggestion that the immediate reaction is primarily the result of mediator release from mast cells, whereas in the late obstructive reaction an additional factor from the mast cell is involved, producing—probably via a leucocytic micro-infiltration—a vaso-active substance. This hypothesis does not explain why in some patients no late bronchial reaction occurs. A further identification and quantification of the proposed factors is necessary.

In our study the two groups of patients with and without a late obstructive reaction after an initial immediate obstructive reaction, show no clinical or functional differences that might explain the presence or absence of this reaction (Tables 7 and 8).

Another possibility which was investigated was the role of a specific pharmacological property of house dust causing late bronchial obstructive reactions. Late bronchial obstructive reactions to other allergens are seldom reported in the literature; in our own experience they were not found. In our patients the effect of house dust was comparable with that of house dust mite (*Dermatophagoides pteronyssinus*). It is not likely that late bronchial obstructive reactions can be attributed to non-antigenic properties of house dust. Further studies are necessary before a more definite conclusion can be drawn from these observations. Apart from the theoretical implications, the demonstration of a late obstructive reaction and the protective activity of some drugs seems to be of practical importance in patients with chronic obstructive airways ventilatory defect with an allergy to house dust.

Acknowledgments

We thank Miss M. G. E. v.d. Ham, Miss A. Edinger, Miss J. J. v.d. Staay, Mrs H. R. M. Overzet-de Preter, Miss L. J. Muller and Miss H. J. Buys for technical assistance. We thank Fisons Ltd for providing disodium cromoglycate (Lomudal®), Intal®, and Boehringer Sohn for providing the sympathomimetic drug, diphenyl orciprenaline (Berotec®, Th 1165a).

Supported by grants from the National Research Council TNO, The Netherlands (GO 623 C21) and the European Coal and Steel Community, Luxemburg (6240-21-081).

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