

Late asthmatic reactions and bronchial variability after challenge with low doses of allergen

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(Received in original form 7 December 1987 and in revised form 23 May 1988; accepted for publication 24 May 1988)

Summary

Late allergic inflammatory reactions are probably of major importance for the development of asthma. In order to study the occurrence of early and late asthmatic reactions after challenge with different doses of allergen, inhalation provocation tests were performed in 13 patients with mild or moderate symptoms of allergic asthma. The provocation series was started with a low allergen dose (0.1–10 BU), which was then increased in successive ten-fold increments at intervals of 1 week until a pronounced bronchial reaction developed. Three different reaction patterns were observed. Six patients showed an isolated late reaction to relatively low doses of allergen. In four patients an immediate reaction was followed by a late reaction—a so-called dual response, and in three patients only an immediate reaction occurred. In four of the six patients who showed only a late reaction a higher allergen dose was given and this resulted in dual reactions in all four. One patient was challenged with an even higher dose, to which she reacted with an immediate response alone. After a late reaction, bronchial variability with low PEF values was observed over a period of several days. It is thus possible for an isolated late asthmatic reaction to be provoked by a low dose of inhaled allergen. This can be of clinical importance, repeated small doses of allergen may be unnoticed but still give bronchial inflammation and asthmatic symptoms.

Introduction

Bronchial asthma is a disease characterized by varying degrees of bronchial obstruction, with bronchial hyperreactivity as a predominant feature. Immediate allergic responses that usually resolve rapidly cannot explain the protracted course in allergic asthma. In recent years attention has been drawn to the fact that in addition to the immediate allergic reaction there is also a late inflammatory phase, which occurs 3–10 hr after provocation. Apart from contributing directly to symptoms after allergen exposure, the occurrence of late reactions has also been linked to eosinophil activation

[1-3], development of bronchial hyperreactivity [4-7] and the effect of immunotherapy [8,9]. The clinical picture and the degree of severity of the asthmatic condition are related to the tendency to develop late reactions [10,11]. Persistent bronchial hyperreactivity may thus be due to late reactions in the airways after repeated exposure to allergens.

For immediate allergic reactions there is a clear dose-response relationship in both the skin and the airways [12,13]. In skin tests, high allergen doses and high RAST titres that result in a strong immediate reaction are also associated with an increased frequency of late reactions [14,15]. The prerequisites for the occurrence of late reactions in the respiratory tract are not completely known. At bronchial challenge it is usual to give increasing doses of allergen at 15-30 min intervals until bronchial obstruction occurs. After such provocation a late bronchial reaction can be seen in some patients. Greatly varying frequency figures have been reported for the occurrence of a late asthmatic reaction [1,10,16]. A high IgE level probably facilitates the development of such a reaction [17, 18]. However, the importance of the allergen dose is controversial. Some findings indicate that a large dose of allergen can result in a late reaction [16,17], whereas in other studies isolated late reactions have been observed after small doses (R. Dahl, pers. comm. [19]).

In the present investigation we submitted patients with allergic asthma to a series of inhalation challenges in order to study the importance of the size of the allergen dose for the occurrence of late asthmatic reactions. A total of 13 patients participated in the study and six of them exhibited a late reaction alone to relatively low doses of an allergen extract.

Patients and methods

Thirteen patients, nine women and four men, aged 16-41 years (mean 25) referred for investigation of asthma, took part in the study. All patients had a history of allergic asthma, a positive prick test and positive RAST for the allergens investigated. Nine patients were sensitized to several allergens. The allergen considered to be of greatest clinical importance was chosen. All patients except two had high RAST titres for the allergen tested, i.e. Phadebas RAST units (PRU/ml) class III or IV (3.9-170 PRU/ml). The other two patients were challenged with *Alternaria* (RAST class I, 0.6 PRU/ml) and weeping fig sap extract (RAST class II, 3.2 PRU/ml), respectively. All patients had only mild or moderate asthmatic symptoms and they were in a stable phase of their disease when the study began. None of them was using asthma medication continuously, only β -II stimulants occasionally, nor was any of them using inhaled steroids or disodium cromoglycate. Beta-II stimulants were withdrawn at least 12 hr before every challenge. Nine patients were challenged with standardized freeze-dried allergen extracts (birchpollen, timothy grass pollen, *Alternaria* or *Dermatophagoides pteronyssinus*) labelled in biological units BU/ml (Pharmalgen®, Pharmacia Diagnostic AB, Uppsala, Sweden); 100 000 BU/ml of timothy grass pollen allergen extract corresponds with 2000 international units/ml (IU/ml), 100 000 BU/ml of birch pollen allergen extract to 5000 IU/ml and 100 000 BU/ml of *Dermatophagoides pteronyssinus* corresponds with 660 000 IU/ml. In seven patients pollen extracts were used, these provocations were performed in the non-pollen season. Four patients were challenged with extract of weeping fig sap extract. Sap (latex) was diluted to 1/100 w/v with physiological saline containing 0.3% human serum albumin (Albumin diluent®, Pharmacia Diagnostic, Uppsala, Sweden). In a study of plant workers exposed to

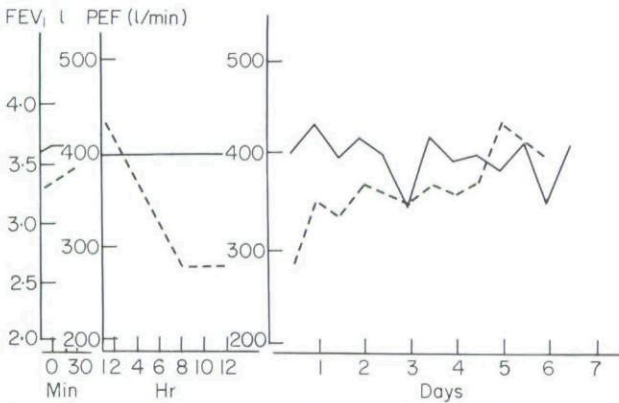


Fig. 1. An isolated late reaction (patient 2) after inhalation of 1 BU birch pollen extract (---). The subsequent days PEF values were low and not restored to normal until the fourth day. Inhalation with diluent (—) gave no reaction.

weeping fig, a concentration of $1/10^6$ w/v of this extract was approximately equal to 1 BU [20]. Bronchial challenge were performed by nebulization of 1 ml of the extract in a jet nebulizer (Aiolos, Medicinsk Teknik AB, Karlstad, Sweden). At a driving pressure of 220 kPa it generated an aerosol with about 65% of the particles less than $6 \mu\text{m}$ and an output of $0.83 \text{ ml/min} \pm 0.03$. One millilitre of the extract was inhaled through a mouthpiece by tidal breathing without use of a nose clip. In eight patients the series of challenges were started with a run-in period with a check of peak expiratory flow (PEF) using a Mini Wright Peak flowmeter (Clement Clarke Int. Ltd) morning and evening for 1 week, to assess the individual variation in the basal PEF values. Before every challenge forced expiratory volume in 1 sec (FEV₁) (Vitalograf®) was checked, at least 80% of predicted normal value was required for the challenge to proceed. FEV₁ was then recorded immediately and 15, 30, 45 and 60 min after the allergen provocation. In eight patients PEF was also measured at the same intervals. All subjects checked their PEF once hourly during their waking hours on the day of the challenge and in the morning and evening of the remaining days up to the next challenge. At the first challenge albumin diluent was inhaled and after 1 week the allergen challenges were begun with an initial dose of 1 BU Pharmalgen extract and $1/10^5$ or $1/10^7$ w/v weeping fig sap extract. Only one dose was inhaled at each challenge. The dose was increased ten-fold at each step at intervals of 1 week, until a significant reaction occurred or up to a maximum dose of 10 000 BU or $1/100$ w/v, respectively. The criterion for a positive immediate reaction was 20% fall in PEF and/or FEV₁ within 30 min of the challenge. A fall in PEF 3–10 hr after the challenge by more than 15% of the pre-challenge value, and a typical change in the PEF curve with progressively decreasing values, was regarded as a late reaction. In the five patients in whom only FEV₁ was checked initially, the PEF values during the day of challenge were compared with the PEF value 1 hr after the challenge.

The study was approved by the local Ethics Committee of the Karolinska Hospital.

Results

During the series of bronchial provocation tests, three different patterns of response were observed. Six patients displayed an isolated late reaction, as exemplified in Fig. 1. In four patients there was an immediate reaction followed by a late one—a dual

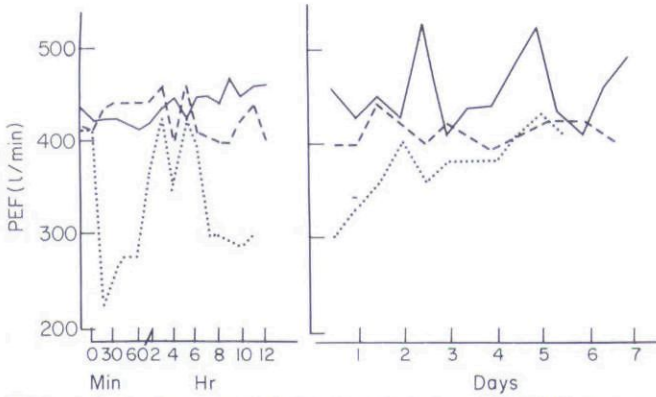


Fig. 2. A dual response (patient 10) after inhalation of 1000 BU. *D. pteronyssinus* (....). Inhalation of 100 BU (---) and diluent (—) gave no reaction. Following the reaction PEF values were low and progressively returned to normal on the fourth day.

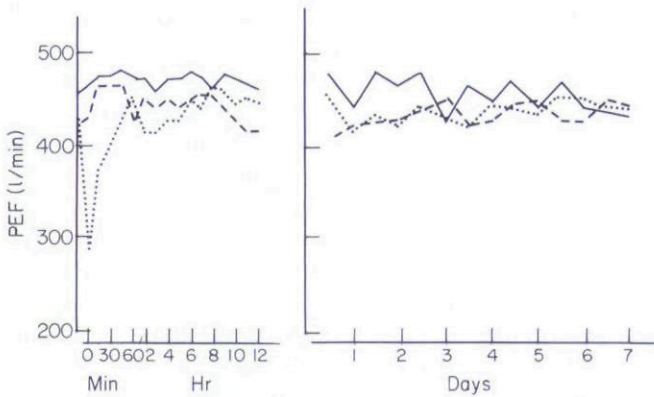


Fig. 3. An immediate response (patient 11) after inhalation of 10 000 BU of timothy grass pollen extract (....). No late reaction followed and the subsequent days PEF values remained unchanged. Inhalation of diluent (—) and 100 BU (---) gave no reaction.

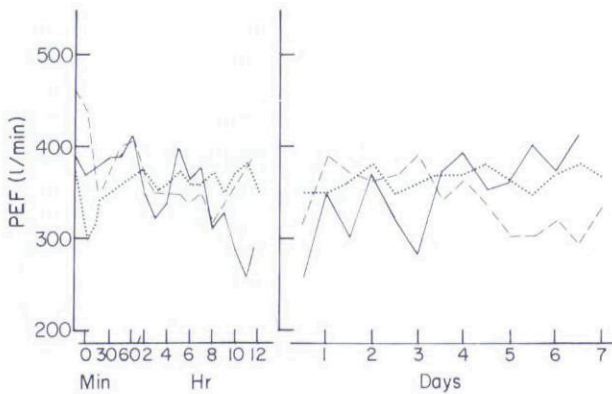


Fig. 4. In Patient 6, inhalation of 1 BU of birch pollen extract (solid line) resulted in an isolated late reaction. After inhalation of 1000 BU (---) a dual reaction occurred while 10 000 BU (....) resulted in an early reaction.

Table 1. Detailed description of the bronchial provocation series

Patient no.	Challenge doses	RAST class	RAST (PRU/ml)	Total IgE (kU/l)	FEV ₁ before provocation	FEV ₁ after 1 hr	PEF before provocation	PEF after 1 hr	Maximum decrease of			PEF variation		Reaction type	
									PEF/FEV ₁ within 30 min (%)	PEF within 3-10 hr (%)	Run-in period (%)	The week after provocation (%)	Early	Late	
1 F 30 years	Diluent birch pollen 1 BU 10 BU 100 BU	3	14	92	3.7	3.65	n.d.	450	*	0	0	10	34		
					3.85	3.75	n.d.	520	3	3	26		11	—	+
					3.8	3.65	n.d.	470	4	13	13		10	—	—
					3.75	3.45	n.d.	500	14	20	20		25	—	+
2 F 30 years	Diluent birch pollen 1 BU	4	43	360	3.6	3.65	n.d.	400	*	0	2	n.d.	19		
					3.3	3.45	n.d.	430	0	35	35	19	24	—	+
3 F 20 years	Diluent birch pollen 1 BU 10 BU 100 BU 1000 BU	3	8.1	180	3.35	3.3	n.d.	450	1	2	2		9	—	—
					3.25	3.2	n.d.	450	2	0	—		9	—	—
					3.2	3.25	n.d.	n.d.	0	—	—		9	—	—
					3.3	3.25	n.d.	420	2	—	—		12	—	—
					3.2	3.35	n.d.	400	30	25	25		24	+	+
4 M 41 years	Diluent weeping fig 1 × 10 ⁻⁷ w/v 1 × 10 ⁻⁶ w/v 1 × 10 ⁻⁵ w/v	4	30	100	2.7	2.7	n.d.	510	0	15	15	n.d.	28		
					2.7	2.75	n.d.	590	0	32	32		26	—	+
					2.5	2.7	n.d.	560	0	36	36		31	—	+
					2.6	2.65	n.d.	550	40	38	38		30	+	+
									*			n.d.			
5 M 25 years	Diluent Weeping fig 1 × 10 ⁻⁷ w/v 1 × 10 ⁻⁶ w/v 1 × 10 ⁻⁵ w/v 1 × 10 ⁻⁴ w/v	4	170	400	4.95	5.0	n.d.	600	2	9	9	14			
					5.25	5.4	n.d.	650	0	15	15		12	—	—
					5.35	5.2	n.d.	610	5	34	34		25	—	+
					5.20	5.0	n.d.	610	17	35	35		26	—	+
					5.15	4.0	n.d.	550	48	45	45		23	+	+

Table 1 (continued)

Patient no.	Challenge doses	RAST class	RAST (PRU/ml)	Total IgE (kU/l)	FEV ₁ before provocation	FEV ₁ after 1 hr	PEF before provocation	Maximum decrease of				PEF variation		Reaction type		
								PEF after 1 hr	PEF/FEV ₁ within 30 min (%)	PEF within 3-10 hr (%)	Run-in period (%)	The week after provocation (%)	Early	Late		
6 F	16 years	4	32	260	3.9	4.1	380	375	3	21	12	27				
	Diluent															
	birch pollen															
	1 BU				4.05	3.7	390	420	5	33		32	-	+		
	10 BU				4.1	4.1	390	400	5	36		30	-	+		
	100 BU				3.85	3.85	350	380	0	0		18	-	-		
	1000 BU				4.1	3.7	460	410	23	27		26	+	+		
	10 000 BU				3.9	3.5	370	370	19	5		8	+	+		
7 F	22 years	1	0.6	140	3.55	3.35	380	410	5	5	10	7				
	Diluent															
	<i>Alternaria</i>															
	1 BU				3.4	3.35	375	390	0	5		5	-	-		
	10 BU				3.6	3.6	425	440	4	4		7	-	-		
	100 BU				3.4	3.15	430	450	3	2		7	-	-		
	1000 BU				3.15	3.2	460	440	4	17		15	-	+		
	10 000 BU				3.0	2.65	425	370	19	21		19	+	+		
8 M	22 years	4	150	2900	5.8	5.5	700	700	5	9	12	11				
	Diluent															
	Timothy grass															
	1 BU				5.3	5.5	700	700	0	4		9	-	-		
	10 BU				5.4	5.35	700	700	0	11		13	-	-		
	100 BU				5.4	5.3	600	700	7	7		14	-	-		
	1000 BU				5.45	5.35	670	675	1	3		7	-	-		
	10 000 BU				5.4	4.2	670	600	43	36		10	-	+		
9 M	28 years	3	7	93	3.85	4.1	475	575	0	9	23	15				
	Diluent															
	Timothy grass															
	1 BU				3.75	4.5	530	590	0	2		25	-	-		
	10 BU				4.45	4.4	660	640	15	12		15	-	-		
	100 BU				3.7	3.9	530	580	15	10		32	-	-		
	1000 BU				3.65	3.15	570	475	37	30		26	+	+		
10 F	16 years	3	5.4	97	3.2	3.25	430	410	5	2	23	21				
	Diluent															
	<i>D. pteronyssinus</i>															
	1 BU				3.1	3.2	430	460	9	0		11	-	-		
	10 BU				3.35	3.2	440	440	0	9		15	-	-		
	100 BU				3.2	3.05	420	440	2	5		9	-	-		
	1000 BU				3.0	1.65	410	275	46	30		23	+	+		

Table 1 (continued)

Patient no.	Challenge doses	RAST class	RAST (PRU/ml)	Total IgE (kU/l)	Maximum decrease of					PEF variation		Reaction type		
					FEV ₁ before provocation	FEV ₁ after 1 hr	PEF before provocation	PEF after 1 hr	PEF/FEV ₁ within 30 min (%)	PEF within 3-10 hr (%)	Run-in period (%)	The week after provocation (%)	Early	Late
11 F 26 years	Diluent	4	38	360	2.5	2.6	455	470	0	0	4	11		
	Timothy grass													
	1 BU				2.45	2.5	440	450	0	7		11	-	-
	10 BU				2.55	2.5	425	450	0	7		11	-	-
	100 BU				2.6	2.55	420	420	0	2		7	-	-
12 F 25 years	1000 BU				2.55	2.35	470	420	9	13		9	-	-
	10 000 BU				2.55	2.25	440	450	34	9	n.d.	13	+	-
	Diluent	3	3.9	54	2.7	2.55	460	430	0	9		14		
	Weeping fig				2.75	2.6	460	460	0	0		14	-	-
	1 × 10 ⁻⁵ w/v				2.65	2.75	480	460	6	8		15	-	-
13 F 21 years	1 × 10 ⁻⁴ w/v				2.6	2.6	470	440	15	6		9	-	-
	1 × 10 ⁻³ w/v				2.65	2.25	470	400	28	7		n.d.	+	-
	1 × 10 ⁻² w/v	2	3.2	380			510	570	0	4	n.d.	11		
	Diluent				3.0	3.0	490	540	0	4		6	-	-
	Weeping fig				3.0	3.0	490	500	2	2		6	-	-
	1 × 10 ⁻⁴ w/v				3.0	2.8	490	460	20	3		4	+	-
	1 × 10 ⁻³ w/v				3.0	2.4	490	460	20	3		4	+	-

* The percentage decrease is calculated on FEV₁.

M = male, F = female, n.d. not done.

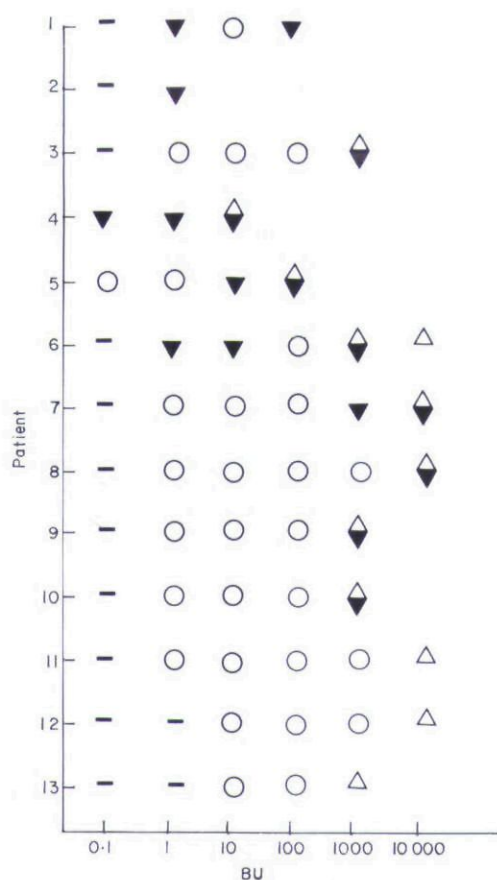


Fig. 5. An overview of the types of reaction after various doses of allergen inhaled. In patients 4, 5, 12 and 13, $1/10^6$ w/v of weeping fig extract is equalled to 1 BU. (○) Negative, (△) immediate, (▼) late, (◄) dual, (—) not done.

response (Fig. 2), and in three patients only an early reaction occurred (Fig. 3). Isolated late reactions were produced by relatively low doses of allergen. One patient reacted to a dose of 0.1 BU, three patients to 1 BU and one to 10 BU, whereas one patient reacted to 1000 BU. Four of these patients were submitted to bronchial provocation with further, higher allergen doses, and all four then showed a dual response. One patient was given a further higher dose and this resulted in an immediate reaction alone (Fig. 4). After a late reaction, both isolated and following an immediate response, the PEF values were generally low (eight out of 10 cases) during the subsequent days. They then rose progressively to be normalized after 2–4 days. The two other patients, nos 8 and 9, did not show any certain decrease in PEF values or change in PEF variability. After an immediate reaction the PEF values were normalized within 1 hr and then remained normal during the following week.

The results are presented in detail in Table 1 and the dose–response relationship is summarized in Fig. 5.

Discussion

Factors influencing the occurrence of late allergic responses have been much discussed

[18, 21, 22]. In this study we found that isolated late bronchial reactions can occur after inhalation of relatively low doses of allergen, in accordance with observations of Orié and Dahl (R. Dahl, pers. comm. [19]). This is best illustrated by the four patients with isolated late reactions who were challenged with increased allergen doses. All reacted with a dual response to a higher dose than that which induced their isolated late reaction. One patient showed an immediate reaction alone when given a yet higher dose. The observation that a late reaction in the airways can be produced by a low allergen dose is contrary to the findings at cutaneous tests, where late reactions are observed only after higher doses than those that produce an isolated early reaction. A possible reason for this is that a low allergen dose does not induce immediate obstruction in central airways, and the allergen is then able to reach further peripherally and give rise to an isolated late reaction with obstruction mainly of the small airways. Support for this is offered by the fact that allergen provocation tests that have resulted in late reactions are associated with an increased hyperinflation [10,23]. The increased prevalence of late reactions reported after challenge of patients pre-treated with an inhaled β -II agonist [16] fits with such an explanation. In the present study we used PEF and FEV_1 as measures of bronchial obstruction, but as they mainly reflect obstruction in central airways they are not well suited for measuring peripheral airway obstruction. Further information may possibly be obtained with the use of more specific methods.

The late bronchoconstriction was observed at home by letting patients check their PEF values. This might lead to difficulties in judging the late reactions. However, we have earlier used the method of letting patients measure PEF themselves at home and then checked the accuracy of their measurements by letting them stay at the hospital, and we found that it worked well. In addition we had no reason to believe that the patients had any further contact with allergens during the provocation day.

An allergen challenge in patients with asthma should not only be observed for the occurrence of immediate and late reactions, but also additional information may be obtained by following the response for several days after challenge.

The late response is considered to be an inflammatory reaction following mast cell release, but the mediators and mechanism may be partly different from the immediate response. Support for this is the fact that β_2 -adrenoreceptor stimulants, which are known to be mast cell stabilizers [24,25] do not block the late bronchoconstriction or increases in bronchial responsiveness [26]. The reaction, however, most probably originates from mast cell release since several mast cell releasing agents may lead to late skin responses [27].

Patients with allergic asthma are often unaware of the direct relationship between exposure to an allergen and their asthmatic condition and bronchial hyperreactivity. Based on assumptions that high allergen doses are necessary for development of late reactions in the airway, Platts-Mills and collaborators have proposed the theory that as inhaled allergens are bound to small particles, the concentration of an allergen can be so high locally where the particles are deposited that both an immediate and a late allergic reaction can occur there. The local reaction is unnoticed by the patient and cannot be observed objectively. If allergen particles are inhaled during a longer period of time, this will give rise to repeated allergic reactions in the bronchial wall with increased hyperreactivity as a result [28]. Our findings give reason to propose an alternative explanation for the discrepancy of an asthmatic condition: the allergen concentration in the air might be too low for causing an immediate response but still

give rise to a general late reaction, probably due to peripheral deposition of the inhaled allergen. If small doses of allergen are inhaled repeatedly over a long period, with isolated late reactions as the result, this can lead to the development of bronchial hyperreactivity, which in turn has an impact on the clinical features of the asthmatic disease.

Acknowledgments

We are grateful to Helene Johansson and Margit Mohlin for their assistance with the provocation tests and Tove Bångstad for secretarial assistance. This study was supported by grants from the Swedish Work Environment Foundation (grant No. 841302), the Foundation of King Gustaf V's 80th Anniversary and the Swedish Heart-Lung Foundation.

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