

Life-threatening inhalant allergy: typical anaphylaxis induced by inhalational allergen challenge in patients with idiopathic recurrent anaphylaxis

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Summary

Eight patients, referred to an allergy service because of anaphylactic syndromes, were investigated for the usual causes (drugs, foods, insect stings etc.) without satisfactory results. All were atopic by history and/or allergy skin testing. Inhalation challenges, using nebulized common inhalant allergens to which the patients were positive by skin tests, were performed to test whether such inhaled allergens could be causing the anaphylactic episodes. Four of the eight patients developed anaphylactic episodes similar to the spontaneous attacks. Two of the other four patients developed precipitous asthma with some suggestion of non-pulmonary anaphylactic features.

It is suggested that inhaled allergens may be a common cause of recurrent anaphylaxis where other recognized causes have been excluded.

Introduction

Anaphylaxis is a broad term used to cover minor localized phenomena such as an allergen-induced positive immediate prick skin test through to the life-threatening anaphylactic shock syndrome seen in, for instance, a hypersensitive individual stung by a bee. Whatever the magnitude of the reaction it involves mast cells and/or basophils, sensitized by homocytotropic antibodies, induced to degranulate and release mediators such as histamine by allergens specifically bound by these cell-fixed antibodies (Gell, Coombs & Lachmann, 1975). For the purposes of this paper the term anaphylaxis refers to clinical syndromes which may or may not include asthma but do include non-pulmonary problems such as laryngeal oedema, pruritus, urticaria, angioedema, hypotension, and abdominal symptoms.

In our clinics we regularly see patients who complain of such recurrent anaphylactic phenomena and in whom the well-recognized causes such as drugs, insect stings, food allergy, injection therapies etc (Freedman & Gold, 1976) have been

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excluded. We have observed (Broom & Fitzharris, in prep.) that patients with precipitous life-threatening asthma sometimes develop minor, non-pulmonary anaphylactic symptoms, in addition to precipitous asthma, when subjected to allergen bronchial challenge. This lent support to our suspicion that inhalant allergens may cause florid anaphylaxis.

In this study patients, primarily presenting with unexplained anaphylactic syndromes, were subjected to inhalant challenge with common air-borne allergens. The challenge allergen was selected on the basis of a suggestive clinical history where this was available and/or prick skin testing.

Patients and methods

Prick skin testing (PST) and intra-dermal skin testing (IDST) were performed using allergen extracts obtained from Bencard (U.K.). All skin test results refer to weal sizes in excess of reactions to control solutions. Intra-dermal skin tests were performed using 0.02-ml volumes of dilutions of the Bencard provocation testing solutions. Where reference is made to grass and tree skin testing the Bencard B₂ grass pollen and B₃ tree pollen mixture were used. Inhalation challenges utilized Bencard Provocation Testing solutions in ten-fold dilutions ranging from 1/10⁵ through to neat extract. Normal saline was used as the diluent. Occasionally Bencard PST extracts were used diluted in the same way. The allergen solutions were delivered in 1-ml volumes via a Hudson nebulizer (Model No. 1720) at oxygen flow rates of 7 l/min. Peak expiratory flow rates were measured with a Wright peak flow meter both before challenge and at regular intervals thereafter. The patients were asked to describe their symptoms, if and as they developed. Leading questions were avoided. All challenges were on a single blind basis. Control challenges utilised Bencard provocation testing control solution. Though the majority of patients were or had been mild asthmatics, none were on or needed therapy at the time of the challenges. The end point of a challenge series was discretionary based on clinical judgement and peak flow falls.

Patient 1

Patient 1, a 21-year-old male student reported episodic rhinorrhoea and cough after exposure to barley chaff dust up to the age of 11 years. Cat-induced allergic conjunctivitis has been a problem until aged 13 years. After that he had been well until December 1979 when, while jogging in a park, he suddenly developed rhinorrhoea, facial angioedema, and 'tightness' of the throat with dyspnoea. There was no further problem until November 1981 when during an evening out-of-doors party he suddenly developed rhinorrhoea, generalized urticaria, facial and palatal angioedema, laryngeal stridor with dyspnoea (but no chest rhonchi), and nausea with vomiting. He was not exercising at the time.

A careful history and food skin testing failed to reveal an obvious cause such as drugs, diet, salicylates etc. Common inhalant PST showed: mixed grasses, 9 mm; *D. farinae*, 9 mm; *D. pteronyssinus*, 4 mm; cats, 3 mm; dog, 3 mm; *Cladosporium herbarum*, 2 mm. Assuming the possibility an inhalant allergen was involved, the circumstances and skin testing most suggested grass pollens. Figure 1 shows the result of a bronchial challenge with dilutions of grass pollen allergen (Bencard, B₂). There was no hint of a reaction until 1/10 dilution was reached. A total of 2 cc was given resulting in an anaphylactic syndrome of sudden onset which included asthma, urticaria and angioedema. The failure of higher dilutions to give milder symptoms is at least

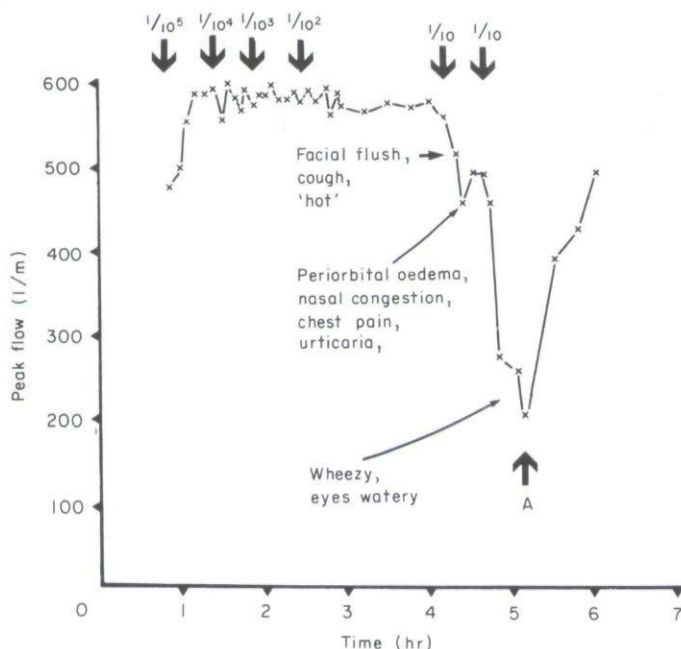


Fig. 1. Patient 1, inhalation challenge with grass pollen extract (PST = 9 mm) dilutions. A, adrenaline given.

compatible with the clinical history which was that of major episodes of anaphylaxis occurring at very infrequent intervals. It might be surmised that only very occasionally does he inhale enough grass pollen to reach a putative threshold level triggering him into anaphylaxis. No other challenges were performed in this patient because of the dramatic and convincing multiple symptomatology in response to the grass challenge.

Patient 2

Patient 2, a 21-year-old male (hospital orderly) gave a history of 'wheezy bronchitis' through childhood until 12 years of age, but was subsequently well. At 19 years of age an upper respiratory tract infection was complicated by wheeze. Since then he has had ten episodes of inspiratory stridor, most of them leading to hospital admission. Many possible factors such as diet, salicylates, food colourings, food preservatives, CIQ esterase inhibitor deficiency, organic obstruction, and conversion hysteria had been excluded by the relevant investigations including single blind challenges, bronchoscopy and psychiatric consultation. On one occasion in the Accident and Emergency Department, adductor spasm was observed on laryngoscopy by a medical Registrar. The ninth episode was associated with minor sneezing and urticaria over the trunk. The tenth episode involved hypoxia causing coma and was nearly fatal.

Prick skin testing with common inhalants showed: *D. pteronyssinus*, 8 mm; *D. farinae*, 5 mm; *Alternaria*, 4 mm; mixed grasses, 2 mm; *Penicillia*, 2 mm.

Inhalation challenge results are shown in Fig. 2. No symptoms and no drops in peak flow were observed in response to placebo or grass pollen (Bencard, B₂) challenge though PST showed a minimal positive weal to this allergen. In contrast, *D. pteronyssinus* challenge caused a desire to clear his throat at high allergen dilutions. Stridor, with the other symptoms listed in the figure, followed 1/10 allergen challenge.

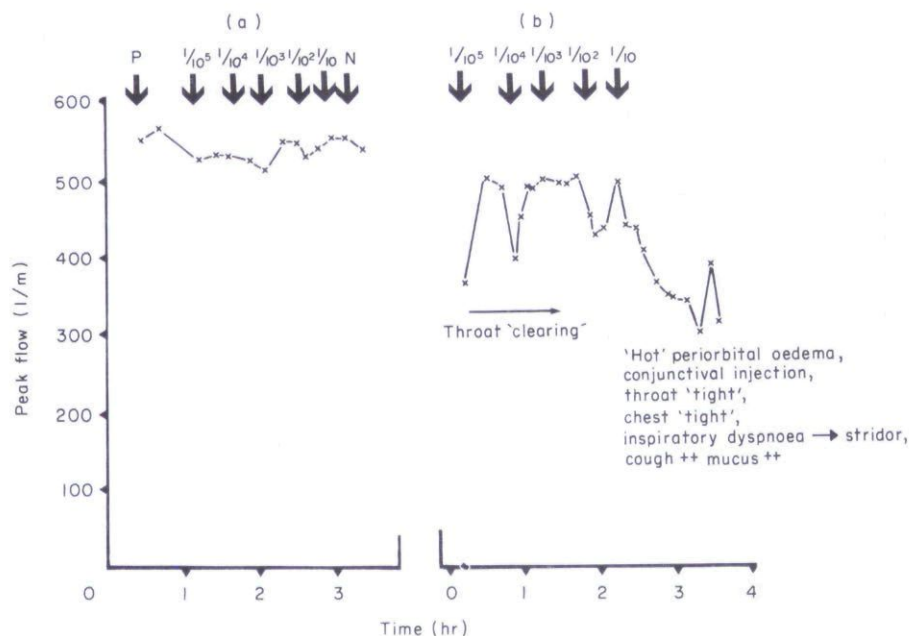


Fig. 2. Patient 2, inhalation challenge with grass pollen extract (a, PST = 2 mm) and *D. pteronyssinus* extract (b, PST = 8 mm). P, placebo challenge; N, neat extract.

Though the other symptoms were clearly obvious the throat symptoms and stridor dominated the clinical picture. It is noteworthy that the patient tolerated inhalation challenge with grass pollen even down to neat extract concentration.

Patient 3

Patient 3, an 11-year-old boy, had had asthma since infancy but this had become quite mild in recent years requiring little therapy. At age 6 years, he developed urticaria occurring initially at 2-month intervals. By age 7 years the frequency and severity had increased. Marked facial angioedema had become a problem. From 9 years of age he was suffering from recurrent anaphylaxis once or twice per week. Symptoms included an initial feeling of being 'hot all over' followed by pruritus and perhaps urticaria. Abdominal pain with nausea and vomiting could occur. There was often lacrimation, rhinorrhoea, and dyspnoea with some uncertainty as to whether the latter was predominantly originating in the throat or in the chest. He remained a vexing problem for 2 years, not yielding to elimination diets, food challenges (using all positive food skin tests as a guide), or salicylate and other chemical challenges. Investigations for CIQ esterase inhibitor deficiency and mastocytosis were negative.

Prick skin tests with common inhalant allergens showed: *D. farinae*, 5 mm; *D. pteronyssinus*, 5 mm; *Alternaria*, 7 mm; grass, 5 mm; *Aspergillus fumigatus*, 3 mm.

Figure 3 shows the results of inhalation challenge. A $1/10$ dilution of *D. pteronyssinus* caused minor symptoms greatly accentuated by neat extract challenge. He spontaneously offered the information that 'this is like my attacks at home'. Lack of co-operation prevented us from returning to the grass and *Alternaria* challenges to see whether neat extracts of these would cause similar problems. It should be noted from

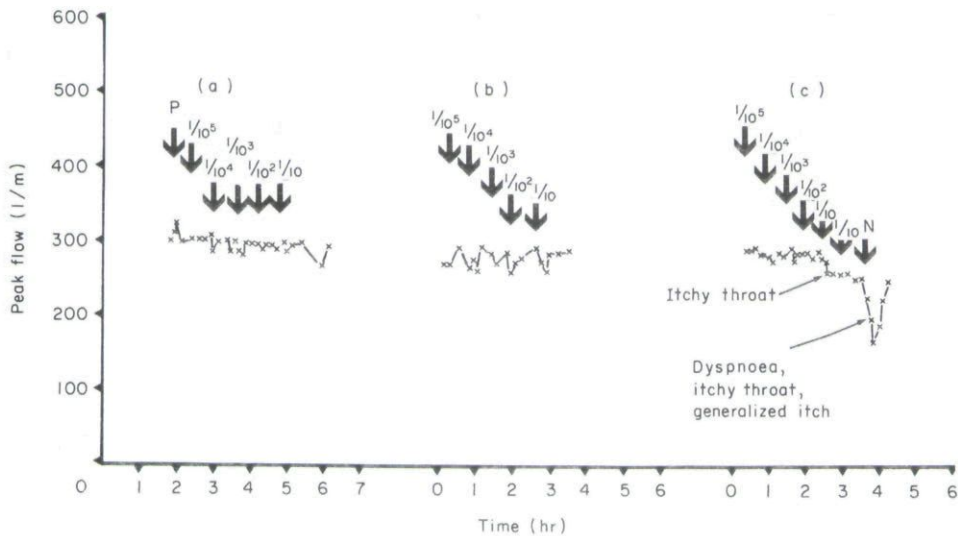


Fig. 3. Patient 3, inhalation challenge with grass allergen (a, PST = 5 mm), *Alternaria* allergen (b, PST = 7 mm) and *D. pteronyssinus* allergen extracts (c, PST = 5 mm).

the history that generalized pruritus was one of his initial symptoms in his spontaneous episodes and this was so in the challenge response as well.

Patient 4

Patient 4, a 23-year-old female computer operator, had had asthma since age 2 years, worse in association with horses, long grass, housedust, winter, smoke, fumes and temperature changes. There was a mild nocturnal dipping tendency. She had had severe infantile eczema and some minor residual flexural problems as an adult. She suffers from grass, cat and horse-induced allergic rhinitis.

In August 1981 while at work she suddenly developed facial angioedema, generalized pruritus, crampy abdominal pain, ear ache, diarrhoea, vomiting, severe asthma, dizziness and collapse. She hadn't eaten for 7 hr. In November 1981 at 2.30 a.m. having awakened for a football telecast and following ingestion of a flavoured commercial dairy food product, she developed an identical serious syndrome. Normally she can take acetylsalicylic acid, flavoured and preserved foods with no problems. She has taken salicylates since that time with no adverse effect and oral challenge with the identical dairy food caused no difficulty.

Prick skin testing showed: *D. pteronyssinus*, 10 mm; *D. farinae*, 10 mm; mixed grasses, 20 mm; horse, 20 mm; haydust, 10 mm; *Cladosporium herbarum*, 4 mm; dog, 0 mm; *Alternaria*, 0 mm. These latter two allergens were shown to be positive by intradermal skin testing (Fig. 4). Inhalation challenge (Fig. 4) showed marked asthmatic reactions to grasses (A), alternaria (B), and *D. pteronyssinus* (D), but a much smaller reaction to dog (C) with no reaction to placebo (P). The mite response involved inspiratory stridor but no other non-asthmatic anaphylactic symptoms. The two spontaneous anaphylactic episodes included severe asthma. In this patient then, the inhalational challenges showed that grass, *Alternaria* and mite challenge could cause severe precipitous asthma. Apart from mild hypotension during one response and

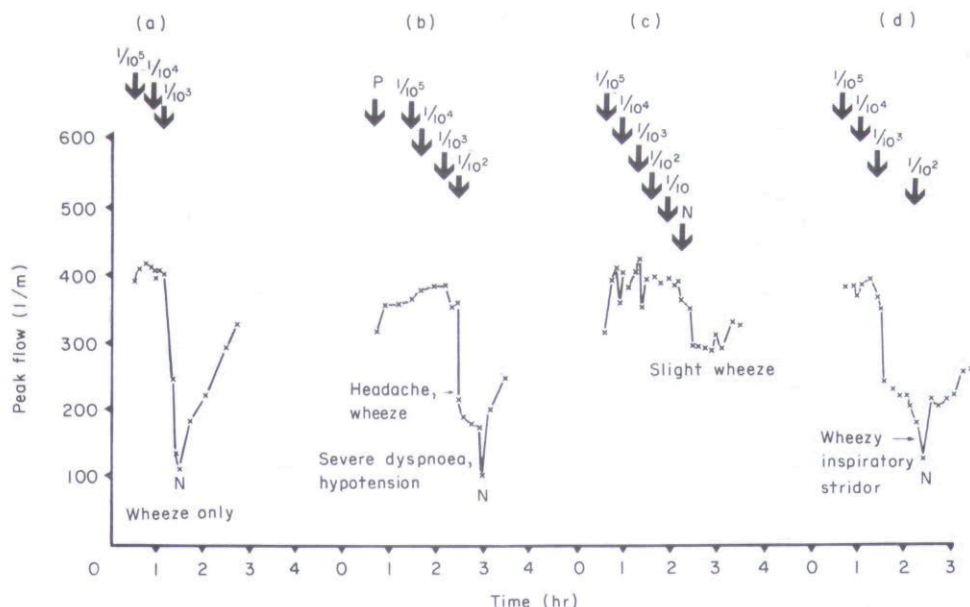


Fig. 4. Patient 4, inhalation challenge with grass allergen (a, PST=20 mm), *Alternaria* allergen (b, IDST $1/10^5$ extract dilution=6 mm), dog dander allergen (c, IDST $1/10^5$ extract dilution=6 mm), and *D. pteronyssinus* allergen (d, PST=10 mm) extracts. P, placebo challenge. NS, nebulized salbutamol administered.

inspiratory stridor during another, the doses given did not cause florid non-pulmonary symptoms.

Patient 5

Patient 5, a 9-year-old school boy, suffered one episode of anaphylaxis in October 1981 while playing football in a grassed area surrounded by trees during an evening barbecue. Symptoms included urticaria, angioedema, severe dyspnoea and dizziness with a tendency to faint. A careful history and food skin testing revealed nothing helpful but inhalant prick skin testing showed: grass, 5 mm; trees, 2 mm. Figure 5 shows a negative challenge with grass extract right up to neat concentration. He has had no further episodes in the 6 months since the first attack. The cause of the anaphylaxis remains undefined.

Patient 6

Patient 6, a school boy aged 14 years, presented with a past history of congenital adrenal hyperplasia, flexural eczema as a young child, and a 2-year history of sudden episodes of laryngeal oedema, conjunctivitis, rhinitis, facial angioedema, urticaria, and vomiting. These occurred about every second week and appeared to be much more frequent during the summer months. Peanut ingestion regularly led to tightness in the throat and he wondered whether several attacks followed the ingestion of raisins. Some of the attacks had been associated with swimming. Food prick skin testing showed large reactions to beans, peanuts, soyabeans, lentils and parsley. We accepted the peanut reactions as clinically significant and he was not challenged with peanut. Single blind oral challenge with soyabean, lentil, and parsley in capsules resulted in

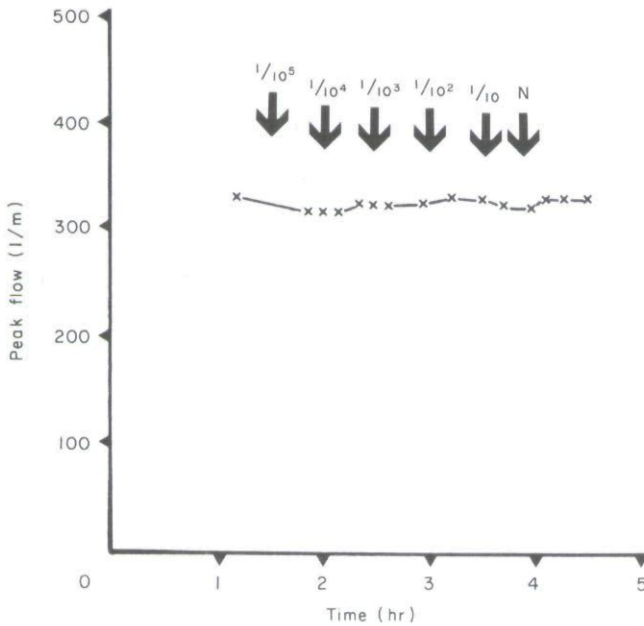


Fig. 5. Patient 5, inhalation challenge with grass allergen (PST = 5 mm).

anaphylaxis following the parsley. He developed conjunctivitis, urticarial rash, cough and wheeze with a 45% drop in his peak flow rate. Over the next year he had only one anaphylactic episode while on a diet eliminating beans, peanuts and parsley. This one attack occurred in October at a time when both tree and grass pollens can be prevalent. The episode occurred while he was skate-boarding in a tree-lined square. Inhalant prick-skin testing showed: trees, 4 mm; *D. pteronyssinus*, 3 mm. Placebo and tree inhalation challenge down to extract at neat concentration caused no symptoms. *Dermatophagoides pteronyssinus* challenge down to neat concentration caused a gradual 25% drop in peak flows though the patient had no symptoms of any sort.

Patient 7

Patient 7, a female student aged 23 years, has a family history of asthma. She had suffered from summer-time allergic rhinitis since early childhood. She gave a history of four episodes of anaphylaxis over 13 years. The first attack was at age 10 years while playing cricket in the summer in the early evening and she recalls facial angioedema, generalized urticaria and inspiratory dyspnoea. This episode was attributed to bananas ingested 2 hr before. At age 20 years the second episode occurred while sitting out-of-doors in mid-summer. The same symptoms occurred but in addition she was dizzy and became semi-comatose. The third episode occurred at age 23 years in early spring on a fine day while jogging in a heavily forested park. This time the symptoms included conjunctivitis, cough, urticaria, facial angioedema, laryngeal obstruction and unconsciousness. In late spring of the same year while jogging in the same park she developed a similar but not quite so severe episode.

Further interrogation revealed occasional waking in the early hours of the morning with sneezing and coughing, sneezing on bed-making, and probable asthma on

exposure to a lot of housedust. She reported some sneezing in early summer. Dogs would make her sneeze.

Common inhalant prick skin testing showed: trees, 15 mm; *D. farinae*, 10 mm; *D. pteronyssinus*, 3 mm; mixed grasses, 10 mm; horse, 4 mm; dog, 0 mm (intradermal skin testing showed 10-mm weal to 1/10 dilution of the Bencard bronchial provocation solution). A methacholine intradermal skin test was negative.

Inhalation challenge results are shown in Fig. 6. The response to all the allergen challenges have common features. The patient spontaneously stated that the reaction to the grass challenge was very like her spontaneous attacks. Intradermal skin testing revealed positive reactions to all common inhalants and therefore a skin test negative inhalant challenge was not obtained.

Patient 8

Patient 8, a male computer engineer aged 25 years, had had no allergic problems until aged 22 years. In the 3 years since then he has had six major anaphylactic episodes including feeling hot all over his body, generalized pruritus, facial angioedema sometimes, conjunctivitis, throat tightness, severe dyspnoea, vomiting, giddiness and disorientation. Most occurred out of doors. Only one involved moderate exercise. He also described perhaps thirty medium severity episodes and these included symptoms such as sore throats, urticaria, conjunctivitis, nasal congestion, dyspnoea and throat tightness. He described numerous minor episodes which were essentially the symptoms of allergic rhinitis and conjunctivitis. His symptoms had only ever occurred over the New Zealand summer from September through to March. He appeared to develop contact urticaria when sitting on certain grasses. He claimed that his attacks could be

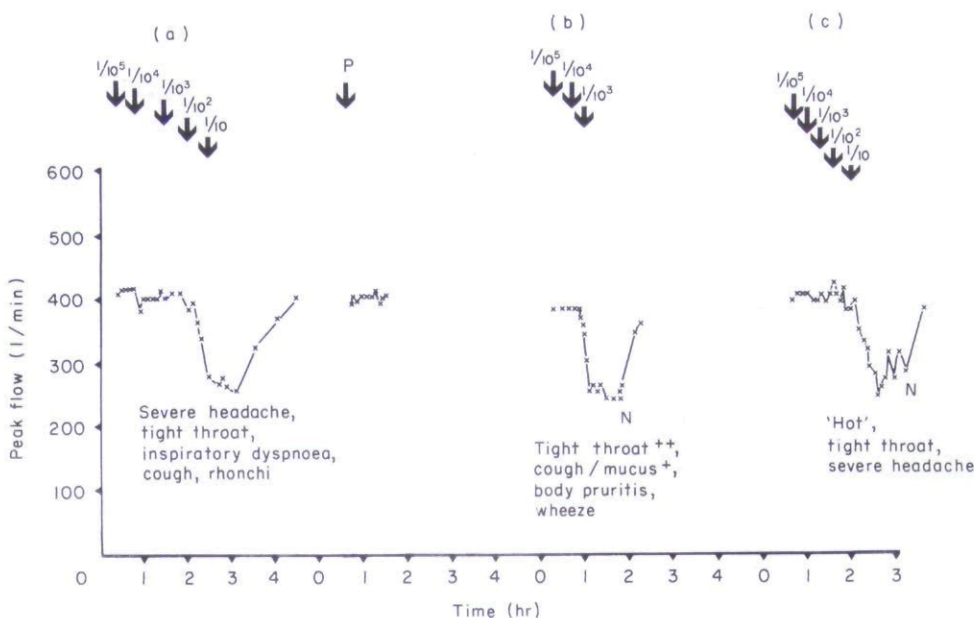


Fig. 6. Patient 7, inhalation challenge with tree allergen (a, PST = 15 mm), grass allergen (b, PST = 10 mm), and *D. farinae* allergen (c, PST = 10 mm) extracts. P, placebo challenge. NS, nebulized salbutamol administered. Each challenge series given on separate days.

consistently induced by going near certain lawn areas on the local University campus. He was convinced grasses were the cause of his problem.

Common inhalant prick skin testing showed: mixed grasses, 16 mm; haydust, 3 mm; trees, 2 mm. Figure 7 shows negative reactions both to placebo and a skin test negative allergen, *D. farinae*. A $1/10^2$ dilution of the grass extract caused a significant peak flow drop but not convincing anaphylaxis. It was decided, in retrospect unwisely, to proceed cautiously with a half-a-dose of the next concentration. As can be seen from the figure, the reaction was extreme, anaphylactic, and fortunately very responsive to adrenaline and oxygen.

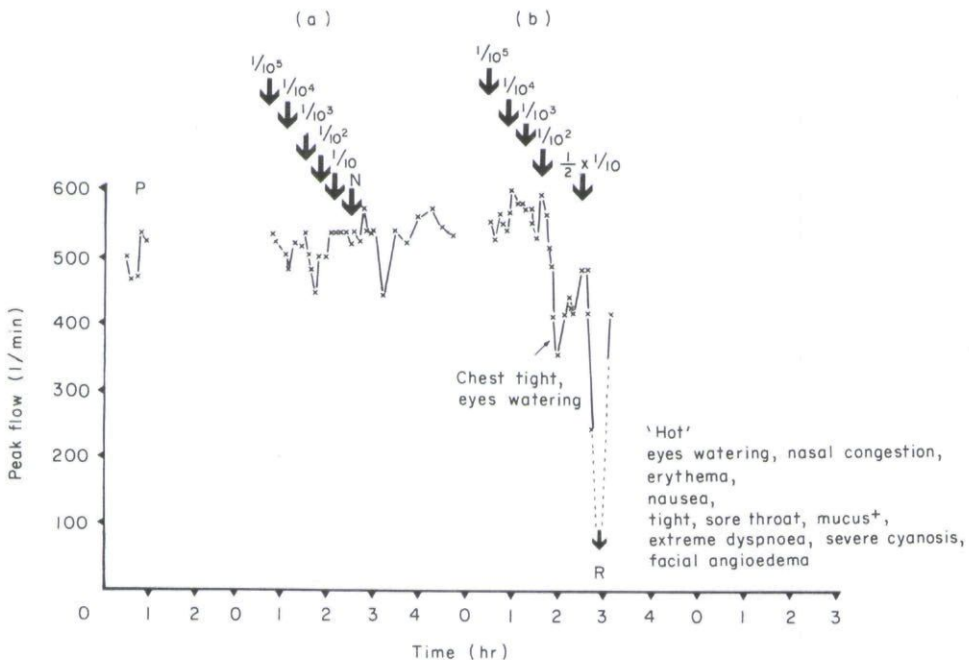


Fig. 7. Patient 8, inhalation challenge with *D. farinae* allergen (a, prick and intradermal skin test negative) and grass allergen (b, PST=16 mm) extracts. R, urgent resuscitation (rapid response to Adrenaline and oxygen). P, placebo challenge.

Discussion

All of the patients described in this study were referred to the clinic for management of anaphylaxis which in all cases but one was recurrent. Five out of the eight had a past or present history of asthma. All are clearly atopic and during the course of these studies no patient presented with anaphylaxis of unknown cause who did not have a positive skin test to an inhalant allergen with which he could be tested. In each patient dietary, drug, and other common causes of anaphylaxis have been reasonably excluded by careful history-taking, food skin testing, elimination diets and food and drug challenges where thought to be appropriate.

Proceeding on the premise that inhaled allergens might cause anaphylaxis and choosing challenge allergens which could conceivably be relevant because of a positive skin test and appropriate environmental circumstances, we have shown that four of the

eight patients (Patients 1, 2, 6 and 8) developed unquestionable anaphylaxis after challenge. The symptoms corresponded fairly closely to the spontaneous episodes. Of the other four patients, two (Patients 5 and 7) did not develop symptoms. One of these had only had one anaphylactic episode and the other had well-established food-induced anaphylaxis in addition to an unexplained episode. The remaining two patients (Patients 3 and 4) developed prominent asthmatic reactions, though Patient 3 complained of an itchy throat and generalized whole body pruritus, and Patient 4 became slightly hypotensive after one challenge and developed a distinct inspiratory stridor after another. Whether higher doses of allergen would have caused more distinctive anaphylactic syndromes in these two patients is of course uncertain.

The appearance of symptoms and signs outside the respiratory tract make it extremely unlikely that these reactions were due to respiratory tract irritation. Neat grass extract caused no reaction in Patient 2 in whom *D. pteronyssinus* extract (1/10 dilution) caused clear anaphylaxis. On the other hand Patients 1 and 8 developed severe anaphylactic reactions to higher dilutions of grass extract. The reactions appear therefore to be immunologically specific.

The dose response curves, constructed on the basis of ten-fold dilutions, generally show precipitous onset of symptoms and peak flow falls once a certain dosage is reached. Admittedly this might not be so obvious if the dilution steps were less than ten-fold. In Patient 1 for example there was no hint of an impending reaction until a 1/10 dilution of grass allergen extract was reached. This patient had had two anaphylactic episodes in 2 years in seasonal and environmental circumstances very compatible with grass-induced anaphylaxis. It is tempting to speculate, on the basis of the dose-response curve, that the infrequency of his attacks is due to the fact that only rarely does he reach an adequate threshold level of inhaled grass pollen. One of his spontaneous episodes occurred while he was jogging as did two of the episodes experienced by Patient 6. It might be that the increased ventilation with exercise leads to an increased inhalation of aerial allergen. In this way, exercise-related anaphylaxis may in some patients be related to the ease with which a threshold dose of allergen is reached. Recently Kaplan *et al.* (1981) have reported exercise-induced anaphylaxis in association with cholinergic urticaria. Neither of our patients had a history of cholinergic urticaria. In addition Sheffer and Austen (1980) have reported on sixteen patients with exercise-induced anaphylaxis and in most there was no suggestion of cholinergic urticaria. Though they state that skin testing was performed it is not clear whether inhalant allergen skin tests were included. Their patients certainly did not develop symptoms everytime they exercised. It would be interesting to relate the exercise-associated episodes of anaphylaxis in their patients to the common inhalant allergen skin tests, and the atmospheric allergen levels at the times of the episodes.

The significance of these challenge results is a major question. Assuming their validity, it is now possible to go back over the histories of these patients and perceive previously unrecognized relationships between inhalant allergen exposure and their symptoms. For instance, house mite challenge-positive Patient 2 has had several anaphylactic episodes following visits to the hospital mattress room. More objectively though, our basic finding is that in anaphylactic patients in whom conventional approaches have not revealed a cause, inhalation of a nebulized allergen to which the patient is skin-test positive can cause clinical anaphylaxis very similar to the spontaneous episodes. Definitive proof that inhaled allergens are, as we suspect from these results, a major cause of anaphylaxis rests on further studies of the results of

allergen exposure reduction measures (applicable to house mites), specific allergen desensitization, and consequent clinical improvement assessed over a period of time.

In the meantime we believe that inhalant allergens should be very seriously considered in cases of apparent idiopathic recurrent anaphylaxis. Our experience with Patient 8 demonstrates the potential risks involved when inhalation challenge is undertaken. Clearly other possible precipitants must be scrupulously excluded initially. Where this has been done we believe it is justifiable to consider inhalation challenge with appropriate allergens. There is certainly not yet enough conclusive data to justify blind desensitization of patients with idiopathic anaphylaxis on the basis of highly positive skin tests to common inhalant allergens.

Acknowledgments

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