

Survey of fatalities from skin testing and immunotherapy 1985-1989

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Background: The Committee on Allergen Standardization of the American Academy of Allergy and Immunology (AAAI) began a study of fatalities associated with skin testing and immunotherapy in an effort to identify risk factors and to ascertain whether any additional precautions are required to prevent and treat serious reactions.

Methods: Questionnaire data was obtained from members of the AAAI and the American College of Allergy and Immunology, regarding 17 fatalities associated with immunotherapy for the years 1985 to 1989. In this period, no fatalities were reported with skin testing. The mean age of patients who died was 36.0 years (range: 10 to 77 years), and 69% were female. Of the patients who died, 76% had asthma, and most were reported to have had factors associated with severity (i.e., lability, required steroids, and/or prior hospitalizations). The only patient who had rhinitis alone had cardiovascular disease and was receiving a β -blocker. High sensitivity by skin test or RAST was reported by 71%, and 36% reported prior systemic reactions. Sixty-five percent of the patients were undergoing build-up therapy. Fatalities involved use of allergen doses between 1:1 million to 1:10 wt/vol. Other factors associated with fatalities were: changing to a new vial of extract, 5; dosing error or inappropriate dose adjustment, 5; allergen season, 5; symptomatic before injection, 4; not waiting after injection, 2; and home injection, 1. Onset of anaphylaxis occurred within 20 minutes in eleven patients, within 20 to 30 minutes in one, and after more than 30 minutes in one. In eleven cases the cause of death was associated with respiratory compromise. These data reinforce the need for special precautions in treating high-risk patients with asthma. The annual fatality rate from administration of allergenic extracts in the United States remains very low: 1 fatality per 2 million doses, but additional educational efforts to further reduce the fatality rate are needed. (*J ALLERGY CLIN IMMUNOL* 1993;92:6-15.)

Key words: Skin testing, immunotherapy, asthma, anaphylaxis

In 1983 the Committee on Allergen Standardization of the American Academy of Allergy and Immunology (AAAI) began a study of fatalities associated with skin testing and immunotherapy. A questionnaire was mailed to each member of the AAAI asking members to report cases they

Abbreviations used

AAAI:	American Academy of Allergy and Immunology
ACAI:	American College of Allergy and Immunology
FEV ₁ :	Forced expiratory volume in 1 second

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encountered. In 1987 Lockey et al.¹ reported 46 fatalities that had occurred during immunotherapy or skin testing since 1945. Sufficient information for complete analysis was reported on 30 of these cases for the period 1959 to 1984. Six of those fatalities were associated with skin testing, and 24 were associated with immunotherapy.

We now report a further study of 17 fatalities associated with immunotherapy for the period

1985 to 1989, as reported by the members of both the AAAI and the American College of Allergy and Immunology (ACAI). The details of each episode were reviewed in an effort to identify risk factors and to ascertain whether any additional precautions are required to prevent and treat serious reactions. The results suggest that special precautions need to be taken for patients with asthma.

METHODS

Questionnaires that were sent to all members of the AAAI and ACAI in July and September 1989, respectively, requested a report of any fatalities known to have been associated with skin testing or immunotherapy. The completed questionnaires, which were returned to one of the authors, were kept confidential.

The following information was requested: name, address, phone number of reporting physician and whether he or she could be contacted, age and sex of the patient, and location at which the fatality occurred. The clinical history was requested, particularly details of the presence and status of asthma, use of β -blockers and other medications, reliability of the information, whether death was associated with skin testing or immunotherapy, specialty of attending physician, number of extracts injected, location of administration, whether a physician was present, whether injections had been given in another physician's office, and whether that physician had been present when the reaction began or whether another physician was responsible for coverage. Also questioned was whether the correct dose had been given, the time interval since the last dose was given, number of injections, initial dose of immunotherapy, sensitivity of patient, whether a fresh vial of extract had been used, whether extract was aqueous or alum precipitate, whether maintenance or build-up therapy was given, how long patient had been receiving the same extract, whether there was a switch of manufacturers, whether the injection was given during the allergy season, whether a switch from one form to another (e.g., alum precipitate to aqueous) was made, and occurrence of prior local or systemic reactions.

Information was also requested regarding technique of injection, how long patient waited, initial symptom, symptoms in order of importance, time of onset of symptoms, how soon physician was contacted, treatment, cause of death, what if anything could have been done to prevent death, extenuating circumstances, and results of autopsy (if done).

RESULTS

Patient details and nature of injection

Information was collected on the 17 fatalities associated with immunotherapy during the study period of January 1, 1985 to December 31, 1989. No fatalities were associated with skin testing.

Duplicate reports were received on three fatalities. When reports were received that were incomplete or secondhand, individuals were contacted by mail or telephone. One physician did not wish to provide additional information. The ages of the patients ranged from 10 to 77 years with a mean of 36.0 years. Six fatalities occurred in 1985, two in 1986, two in 1987, six in 1988, and one in 1989. There were eleven female and five male patients; the sex of one patient was unreported. Sixteen of the 17 physicians who reported the data considered the information to be highly valid (Table I).

Asthma was reported in 13 of the 15 patients (87%) for whom clinical history was provided (77% of all fatalities). Hay fever was reported in 53% of the patients who died. Only one patient was reported to have had hay fever only, and he had coexisting hypertension, cardiovascular disease, and was receiving a β -blocker. All patients with asthma except one (i.e., 12 of 13) were reported to be either labile or steroid-requiring or to have had a history of hospital or emergency room care. In 10 cases the patients had required oral administration of steroids or hospital visits. The one patient with asthma not included in the above group was a 57-year-old with coexisting cardiovascular disease. Three other fatalities were among patients with asthma (57, 60, and 77 years old) with coexisting medical problems: cardiovascular disease, 2; diabetes, 1; and chronic obstructive pulmonary disease, 1. Three of the patients with asthma were reported to have had symptoms just before they received the fatal injection. One had received Sus-Phrine with the allergen dose because of prior respiratory symptoms.

The degree of sensitivity to allergens was reported to be high in 13 of 15 patients; this was based on skin testing in 14 cases and in vitro test results in one case. For patients for whom relevant information was reported, 42% had had prior systemic reactions (36% of all fatalities). All patients had received aqueous extracts. One patient was receiving weekly alum-adsorbed house dust in addition to aqueous dust mite but received only the aqueous extract in the fatal dose. Of the 16 patients in whom an immunizing extract was described, 15 were receiving pollen extracts (93% of which contained ragweed and/or grass). Five were receiving dust mite (Table II).

In 11 of 15 patients the fatal reaction occurred during build-up therapy (65% of all fatalities). Of the 17 fatalities, allergen dose was referred to in 12. Half of them occurred at concentrations be-

TABLE I. Patient profiles

Patient No.	Sex	Age (yr)	Year	Reliability	Clinical state(s)*	Asthma status	Medications*	β -blockers
1	F	18	1985	High	Unknown	Unknown	No other medication	No
2	F	57	1985	High	Asthma, CVD, hay fever	Nonsteroid-dependent	Diet pills, vitamins	No
3	M	57	1985	High	Asthma, hay fever, diabetes	Steroid-dependent, resp. arrest, asthma hospitalizations & ER visits	Theophylline, terbutaline tablets, metaproterenol, beclomethasone, prednisone	No
4	M	40	1985	Moderate	Unknown	Unknown	Unknown	?
5	F	20	1985	High	Asthma, hay fever	Steroid-dependent & labile, attack the night before, asthma hospitalization & ER visits	Theophylline, albuterol MDI, other medications unknown	No
6	F	13	1985	High	Asthma	Labile, just finished 10 days of steroids	Theophylline	No
7	M	48	1986	High	Hay fever, BP, CVD	—	Unknown	Yes
8	F	36	1986	High	Asthma	Nonsteroid-dependent, labile	Unknown	No
9	M	24	1987	High	Asthma, hay fever	Steroid-dependent & labile & prior hospitalizations	Beclomethasone, cromolyn, metaproterenol by nebulizer Atrovent, Theo-Dur	No
10	F	60	1987	High	Asthma, hay fever, diabetes	Severe, steroid-dependent, & labile; asthma hosp & ER visits	Theophylline, albuterol MDI, beclomethasone, cromolyn, prednisone, NPH insulin	No

CVD, Coronary vascular disease; *resp.*, respiratory; ER, emergency room; MDI, metered dose inhaler; BP, blood pressure; NPH, neutral protamine Hagedorn; COPD, chronic obstructive pulmonary disease; NTG, nitroglycerine.

*Triamcinolone = triamcinolone acetonide MDI; beclomethasone = beclomethasone dipropionate MDI; cromolyn = cromolyn sodium MDI.

tween 1:10 to 1:100 wt/vol. In addition, doses were reported at each of the following dilutions: 1:1,000; 1:10,000; 1:100,000; and 1:1 million wt/vol. During build-up therapy, additional factors reported with fatal reactions were: dosage errors, 4; switching to a new vial of extract, 3; presence of symptoms before injection, 2; allergen season, 1; and home injection, 1. Among the four reactions that occurred during maintenance therapy, two occurred with the first injection from a new vial of extract, two occurred in patients who had symptoms before injection, and two occurred during the allergy season.

Details of reaction and treatment

The time to onset of symptoms was specified in 14 cases and in 12 cases occurred within 20

minutes of the injection, and one fatality was reported to have started between 20 to 25 minutes afterward. The one patient who had steroid-dependent asthma had an attack the night before the onset of the reaction; this reaction was unwitting but was reported to have started more than 30 minutes after the injection. Eight of the injections associated with fatalities were given in offices other than that of the prescribing allergist; seven were given in the office of the prescribing allergist; one was given at home; and the location of one was not reported. A physician was present at 11 of the 17 reactions. No physician was present in two instances, and in four the presence of a physician was not known or unreported (Table III). Epinephrine was reported to be used in 92% of the patients who died for whom treatment was

TABLE I. Cont'd

Patient No.	Sex	Age (yr)	Year	Reliability	Clinical state(s)*	Asthma status	Medications*	β -blockers
11	F	77	1988	High	Asthma/COPD, hay fever, CVD	Lable, 8 hospitalizations for asthma/bronchitis in past year	Theophylline, albuterol MDI, cromolyn, oral and transdermal NTG	No
12	M	41	1988	High	Asthma, hay fever	ER visit	Theophylline, albuterol MDI, inhaled triamcinolone	No
13	F	22	1988	High	Asthma	Nonsteroid-dependent, labile, 3-4 hospitalizations in past 3 years	No medications	No
14	—	—	1988	High	Unknown	Unknown	Unknown	?
15	F	12	1988	High	Asthma	Labile, 2 prior hospitalizations	Theophylline, albuterol MDI, inhaled triamcinolone	No
16	F	41	1988	High	Asthma	Nonsteroid-dependent, labile	Theophylline, albuterol tablets, albuterol MDI, Tegretol	No
17	F	10	1989	High	Asthma, hay fever	Nonsteroid-dependent, labile, visits to ER	Theophylline, albuterol MDI	No

prescribed. Terbutaline was used in one additional case. Causes of death were listed as: respiratory, 9; both respiratory and cardiovascular, 5; unknown, 2; other, 1. In no case was death reported as being cardiovascular alone (Table IV).

DISCUSSION

Anaphylaxis is well recognized as a complication of allergen-specific immunotherapy, but fatal reactions are rare (i.e., ~1:2.5 million injections). In the present series and in previous series, the risk of fatal reactions appears to be increased in patients with asthma, presumably because the response of the lungs to mediators released by allergen is exaggerated. The results suggest that the risk is further increased when the patient with asthma is steroid-dependent; has required hospital or emergency room visits for treatment; is experiencing increased bronchospasm; or has compromise of another vital system (e.g., the cardiovascular system). The only patient in this series who had rhinitis only had a history of cardiovascular disease and was receiving a β -blocker, a medication known to interfere with sympathomimetics in the treatment of anaphylaxis.

Thirty-one fatalities (15 additional fatalities had inadequate documentation to be included

with the 31) associated with immunotherapy have been reported in the United States from 1925 to 1984.¹⁻⁸ The present study adds 17 cases from 1985 through 1989. More than 70 deaths associated with skin testing were reported between 1895 and 1968.^{2, 5, 9-16} Many of these were associated with biologic products that are no longer used. The present study reported no fatalities associated with skin testing. Since only six deaths that resulted from skin testing were reported in a 20-year period (1964 to 1984),¹ the absence of skin-test fatalities in the last 4 years may not indicate a decreased fatality rate. However, widespread adoption of the recommendation to use percutaneous testing to screen for immediate hypersensitivity before intradermal testing has probably led to a reduction in the risk of fatal reactions after allergy skin tests.

The mean age of patients who died was 36 years, which is similar to the results of the AAAI (34 years) and the British surveys (31 years).^{1, 17} Although female subjects were reported to receive immunotherapy slightly more often during this reporting period (54%) than male subjects¹⁸ and were disproportionately reflected in the fatalities (69%), neither the AAAI nor the British survey reported a difference in fatalities on the

TABLE II. Background information

Patient No.	Sensitivity	Extract	Maintenance	Prior systemic reactions	Circumstances
1	High	Weed, tree, grass, dust mite, mold, dust 1:50	No	Unknown	10× previous dose, left immediately after injection
2	Moderate	7-Antigen mix including ragweed	No	No	Obese, multiple extracts (3), first injection from new vial
3	High	Grass, tree, weed, mold, dust, 1:20	No	Yes	Multiple extracts (3), dosage increased despite prior asthmatic systemic reaction, charted as IM injection
4	Unknown	Ragweed, others unknown	Unknown	Unknown	Given ragweed extract at height of ragweed pollen season
5	High	Pyrethrum 1:50, tobacco & mite 1:100, weed, grass, mold, tree, & dust 1:20	Yes	Unknown	Severe asthma attack the night before, did not tell, non-compliant with medications and visits, multiple extracts
6	High	Grass, weed, tree 1:200,000 wt/vol & tree 1:200,000 wt/vol	No	Unknown	Probable error in dose, delay in treatment
7	High	Grass, mold, dust dilution unknown	No	No	Obese, did not wait, first dose from new vial that was lower in concentration, prior local reaction
8	High	Pollen (high concentration) dilution unknown	No	4 Anaphylactic	Home injections, had previously used epinephrine, found dead at home
9	High	Grass, tree, weed, house dust, mold, dust mite 1:50,000	No	Hives after first dose (8 days before fatal third dose)	Constant daily medication for asthma including nebulizer, dose doubled, shorter interval (q 4-5 days)
10	High	Tree-mite 1:100, grass-weed 1:100	Yes	Mild bronchospasm after preceding injection	First injection from new maintenance vials, despite mild wheezing & chest tightness on preceding injections, dose from new vial only decreased 50%, during allergy season

IM, Intramuscular; Resp, respiratory.

*Multiple extracts (>3), 5 injections, busy office/double patient load, possible dose error: 0.5 ml written rather than 0.05 ml, last dose 0.45 ml of 1:10,000 ragweed mix, next dose from new vial: 0.5 of 1:1,000, dosed during grass pollen season, prior local and systemic reactions, injections administered into back.

basis of sex.^{1, 17} During 1980 to 1984 when 17 fatalities were reported,¹ there were an estimated 47.1 million allergen doses administered in the United States,¹⁸ yielding an annual fatality rate of 1 fatality for every 2.8 million injections.^{1, 8} During 1985 to 1989, there were an estimated 33.1 million doses of allergenic extract administered in the

United States for an annual fatality rate of 1 fatality for every 2 million injections.¹⁸ Patients who were receiving immunotherapy in the United States during this time period were diagnosed with rhinitis four to five times more often than with asthma.¹⁸ The high percentage of patients with asthma among fatalities (77%) is consistent

TABLE II. Cont'd

Patient No.	Sensitivity	Extract	Maintenance	Prior systemic reactions	Circumstances
11	High	Mite 1:1,000,000 wt/vol	No	No	FEV ₁ (52% pred) 9 mo earlier, not skin tested, patient received mite 2×/wk & Center Al dust 100 pnu/ml weekly, new vial
12	High	Tree 1:20, grass-weed-dust mix 1:1000	No	No	During allergy season
13	High	Ragweed mix, dust & mold 1:1000 wt/vol, grass & weeds 1:50	No	Resp & chest discomfort after inject 2 wk earlier	See footnote*
14	Unknown	Unknown	Unknown	Unknown	Unknown
15	High	Grass mix 1:50, tree-weed mix 1:5,000, 0.2 ml each	No	No	Sick at time of injection, did not wait
16	Minimal	Ragweed 1:20, house dust-dust mite, molds 1:10	Yes	No	New ragweed vial, dose was to be reduced 40%, injection during ragweed pollen season
17	High	Grass-tree-weed mix 1:100, house dust + house dust mite mix 1:1,000	Yes	No	Increased dust-mite mix dose, Sus-Phrine for recurrent wheezing after prior injections & in syringe w/antigen, resp infection w/wheezing 24-48 hr earlier

with the results of the previous AAAI (53%) and British (62%) reports.^{1, 17}

It has been reported that systemic reactions during rush immunotherapy occur more frequently in patients with asthma with a forced expiratory volume in 1 second (FEV₁) less than 80% of the predicted value.¹⁹ It is likely that more severe adverse reactions will occur in patients who have more difficulty with asthma. On the basis of those results, Hejjaoui et al.²⁰ suggested that FEV₁ measurements be performed before immunotherapy and that injections be withheld if these measures of airway obstruction are below 70% of the predicted value. Whether routine screening of peak flow before each injection and before departure from the physician's office after each injection, as recommended in Europe,²¹ or longer waiting periods (i.e., 30 minutes) would be effective in reducing serious reactions should be evaluated.

The previous AAAI report found β -blockers to

be associated with two fatalities.¹ The present survey identified an additional fatality in a patient who was receiving β -blockers (patient no. 7). This patient represents the only reported nonasthmatic fatality, and he may have died of a myocardial infarction rather than anaphylaxis. The other drugs associated with the fatalities in this report are consistent with the predominance of patients with asthma who require continuous treatment. Although not specifically solicited, none of the patients reported in this survey were taking angiotensin-converting enzyme inhibitors.

Skin sensitivity or RAST score was reported to be high in 71% of all cases. This is in agreement with other reports that subjects with high degrees of skin sensitivity are at greater risk of anaphylaxis¹ and is consistent with the high frequency (50%) of highly sensitive patients reporting prior systemic reactions in this group. In keeping with the previous U.S. report and with normal practice in the United States, the majority of fatal reac-

TABLE III. Signs, symptoms, and treatment of reactions to immunotherapy

Patient No.	Onset of Rx (min)	Physician present	Sx in order of importance	Treatment
1	20	No	Lower airway obstruction	Epinephrine SQ & IV, dexamethasone IV, methylprednisolone IV, dopamine, verapamil, intubation, oxygen, NaHCO ₃ , atropine
2	2-5	Yes	Upper/lower airway obstruction	Epinephrine SQ, 0.3-0.5 ml, $\times 3$; diphenhydramine IV; cimetidine; methylprednisolone; lactated Ringer's; epinephrine IV; oxygen
3	3-10	Yes	Upper airway obstruction, loss of consciousness, shock	Epinephrine SQ; dexamethasone IM; albuterol MDI, 2 puffs
4	Unknown	Yes	Unknown	Unknown
5	> 30	Unknown	Unknown	Unknown
6	3-10	Yes	Lower airway obstruction	Epinephrine, 0.3-0.5, $\times 2$; H ₂ antihistamine; steroid; oxygen, difficulty ventilating
7	20-25	Yes	Shortness of breath, cold, clammy, chest pain	Epinephrine, 0.5 ml, $\times 2$ or 3
8	Unknown	No	Unknown	None
9	3-5	Yes	Upper/lower airway obstruction, urticaria/angioedema	Epinephrine, 1 ml, SQ $\times 2$ & 2 ml intracardiac; total of 6 ml; methylprednisolone, 1.5 ml; D ₅ W; intubation and emesis
10	3-10	Yes	Lower airway obstruction, urticaria/angioedema	Terbutaline, 0.4 ml, SQ $\times 1$; IV fluids; oxygen; atropine IV; epinephrine, 1 ampule through ET tube; NaHCO ₃ IV, xylocaine IV; defibrillation, difficult to intubate
11	8	Yes	Lower airway obstruction	O ₂ ; epinephrine 0.5 ml, $\times 3$; D ₅ 1/2 normal saline, diphenhydramine IV; aminophylline 500 mg, IV; atropine 1 mg, IV; CPR; tracheostomy
12	0-3	Yes	Hypotension, loss of consciousness, lower airway obstruction	Epinephrine, 0.3-0.5 ml, $\times 3$ IM; dexamethasone, 20 mg; dobutamine; isoproterenol; oxygen; atropine; NaHCO ₃
13	Unknown	Yes	Respiratory arrest	Epinephrine given, details unknown
14	Unknown	Unknown	Unknown	Unknown
15	15	Unknown	Found without respiration or pulse	Delay in institution of CPR, epinephrine SQ $\times 6$; oxygen; NaHCO ₃ ; dopamine; atropine, lidocaine
16	0-3	Unknown	Upper/lower airway obstruction	Intubation, otherwise unknown
17	10-20	Yes	Lower airway obstruction	Sus-Prine, 0.3 ml, SQ; normal saline; oxygen; metaproterenol by nebulizer; epinephrine, 0.35 ml

Epinephrine: 1:1000, volume given when known.

Rx, Reaction; Sx, symptoms; SQ, subcutaneous; IV, intravenous; IM, intramuscular; MDI, metered dose inhaler; ET, endotracheal; CPR, cardiopulmonary resuscitation.

tions occurred with the use of aqueous extracts that contained ragweed and grass pollen.¹ The high frequency of ragweed and grass pollen extracts involved in fatalities probably reflects the

high prevalence of reactivity to these allergens in the U.S. population and their high biologic potency.²²

In keeping with previous reports, most fatalities

TABLE IV. Cause of death

Patient No.	Cause of death	Autopsy findings
1	Asthma, shock	Unknown
2	Edema of airway, shock, asthma	Unknown
3	Edema of upper airway, shock, anoxic encephalopathy	Unknown
4	Unknown	Unknown
5	Lower airway obstruction with extensive mucous plugging	Extensive mucous plugging of lower airway
6	Asthma	Unknown
7	Anaphylaxis and pulmonary edema	Anaphylaxis and pulmonary edema
8	Laryngeal edema	Laryngeal edema
9	Possible epinephrine overdose	Acute anaphylaxis
10	Asthma, seizure, cardiac arrest	Unknown
11	Acute eosinophilic laryngotracheobronchitis	Acute laryngotracheobronchitis
12	Anaphylactic shock, asthma	Not reported
13	Edema of the upper airway, asthma, cardiac arrhythmia	Acute edema of larynx, congestion of lungs
14	Unknown	Unknown
15	Lower airway obstruction	Changes consistent with asthma: mucous plugging, etc.
16	Edema of upper airway, asthma, airway obstruction	Unknown
17	Asthma	Lower airway obstruction

(73%) occurred during dose build-up. Additional factors that may have been relevant included inadvertent errors in dosage, 3; switch to a new vial of extract, 3; inappropriate dose increase despite recent symptoms or prior systemic reaction, 3; and dosing during the allergy season, 1. Switching to a new vial of extract and errors in dose were associated frequently with fatalities in both our study and the previous AAI report.¹ Although dose errors or inappropriate dose escalation had occurred with several of these reactions, it is important to note that no dose was absolutely safe, because fatalities occurred with doses as low as 1:1 million wt/vol. Standardization of extracts may reduce reactions associated with switching to a new vial of extract. Clinical experience with standardized Hymenoptera venom extracts suggests that these extracts are safe.^{23, 24} Stability of extracts is important to assure that the values on the label accurately reflect the extract potency. Use of freeze-dried or 50% glycerinated concentrates, albumin-saline diluents, and separate formulations of pollen and nonpollen extracts is likely to enhance the stability of extract potency.²⁵

In the present survey 5 of 17 (29%) fatalities occurred during an exacerbating pollen season. This was not as marked as in the previous report in which 9 of 24 cases (38%) occurred during

pollen season¹ but still suggests the need to be cautious in allergen dose escalation or repetition during the pollen season.²⁶

Eight of the 17 fatalities occurred in places other than the office of the prescribing allergist. It is important to ensure that medical personnel who administer allergen injections understand the need to monitor both the response to prior injections and the patient's current clinical status. Instructions from the prescribing physician should specifically cover detailed precautions. However, the present results do not allow any conclusion about whether injections are more or less dangerous in another physician's office.

The time to onset of fatal or severe anaphylactic reactions is a matter of great importance, because it defines the appropriate waiting period after injections. The AAI has recommended that "... the usual time interval is 20 minutes for allergen immunotherapy or skin testing to prevent serious and possible fatal reactions. This may be extended for high risk patients."²⁷ The Food and Drug Administration has made a similar recommendation.²⁸ In the present survey all but two reactions started within 20 minutes. The one patient in whom the reaction was reported to have started after 30 minutes had had a recent attack of asthma. Thus the results of the survey could be interpreted as showing that patients with

labile or steroid-dependent asthma are "high risk patients" and should remain in the office for 30 minutes. The British experience with fatal reactions to immunotherapy reported 76% of reactions within 20 minutes; 15% between 20 and 120 minutes; 4% between 2 and 4 hours; and 4% between 6 and 36 hours.²⁹ With the longer delays in patients with asthma, the causal relationship to the injection becomes less convincing. In addition, the British experience involved a variety of adsorbed extracts so that the time to onset may not be directly comparable to results in the United States.²⁷

Respiratory compromise was reported to be the primary or associated cause of death in 14 of the 17 cases. This is in keeping with the high proportion of patients with significant asthma. In turn, this suggests that patients with inflamed or hyper-reactive airways are at increased risk for fatal reactions because the airways can respond dramatically during anaphylaxis. Cardiovascular response alone was unusual as a reported cause of death, which may explain why there was an apparent lower incidence of fatalities in patients who were being treated for rhinitis alone. The results certainly reinforce the need for care with patients with asthma and adequate training of both physicians and ancillary personnel in managing anaphylaxis.

In summary, an analysis of questionnaire reports revealed that 17 deaths from anaphylaxis after allergen injection occurred from 1985 through 1989. The overall risk is estimated to be approximately 1 fatality for every 2 million injections. Most of the fatalities occurred in patients with steroid-dependent or labile asthma. Indeed, the results of the survey leave little doubt that the risk of immunotherapy is higher among patients with asthma. The survey reinforces previous conclusions about precautions to prevent inappropriate dosage or mistakes in dosage. Immunotherapy should be prescribed and given by physicians who are aware of the risks and skilled in the treatment of anaphylaxis. Patients should be informed of the risks and the necessity to remain in the physician's office for the designated length of time after the injection. A waiting period of 20 minutes is recommended for all patients, but longer intervals (i.e., 30 minutes) are appropriate for high-risk patients.

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