

Fatalities from immunotherapy (IT) and skin testing (ST)

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The Committee on Allergen Standardization of the American Academy of Allergy and Immunology obtained information about 46 fatalities that had occurred during immunotherapy (IT) or skin testing (ST) since 1945. Sufficient information for complete analysis was provided for 30 patients (six for ST and 24 for IT). Of the 30 fatalities, there were 15 male and 15 female fatalities, ranging in age from 7 to 70 years ($x = 33$ years). Known errors of administration accounted for three and possibly an additional three fatalities. Ten fatalities occurred during seasonal exacerbation of the patient's disease, four in patients who had been symptomatic at the time of the injection, two of whom had been receiving β -adrenergic blockers. Of the 24 fatalities associated with IT, four had experienced previous reactions, 11 manifested a high degree of sensitivity, and four had been injected with newly prepared extracts. Fifteen of the 30 fatalities had received pollen extracts as part of the fatal injection. Of the six fatalities associated with ST, five were due to intradermal testing without prior puncture testing. The signs and symptoms were variable and did not indicate that death was imminent nor predict the cause of death. The time to onset of the reaction was less than 30 minutes in 22/30, more than 30 minutes in 3/30, and not reported in 5/30. The cause of death in 14/16 patients with asthma was respiratory. Epinephrine had been administered to 18, not administered to three, and was either not recorded or unknown in the remaining nine patients. Since seven to 10 million allergen injections are administered yearly, the risk of a fatal reaction is low and may be lessened even further as additional precautions are taken in the selection and treatment of allergic patients and in improved treatment of the anaphylactic reactions. (J ALLERGY CLIN IMMUNOL 1987;79:660-77.)

Six fatalities after IT have been reported since Lamson, in 1929, first described a death from anaphylaxis after IT.¹⁻⁷ Between 1895 and 1968, more than 70 deaths have been reported after ST, most caused by antigens no longer in common use (horse serum-derived tetanus or diphtheria antitoxin and pneumococcal antiserum).^{1, 4, 8-15} Nine of the 70 deaths were in patients tested with allergens similar to allergens used today.^{1, 4, 8, 10-15} There have been no published articles since 1980 of fatalities caused by IT or ST in the United States. The purpose of the present study was to ascertain, by questionnaire, whether fatalities attributable to IT and ST had been encountered by the 3400 members of the AAAI. The further objectives were (1) to analyze each fatality and evaluate the circumstances resulting in death, (2) to identify possible risk factors predisposing to death, i.e., medications,

Abbreviations used

AAAI: American Academy of Allergy and Immunology
IT: Immunotherapy
PPS: Prick, puncture, scratch
ST: Skin test

exercise, and other disease states, and (3) to assess therapeutic measures used to treat such reactions.

METHODS AND MATERIAL

This study was initiated in 1983 as a 10-year retrospective analysis of fatalities from ST and IT. Members of the AAAI were sent questionnaires on three separate occasions: January 1984, July 1984, and November 1984. Unsolicited reports of deaths submitted before 1973 are also included in this study. The names of patients, physicians, locations of the fatalities, and their dates were requested as a means of preventing duplication of reports. If two reports were submitted on the same patient, data were derived from the questionnaire with the highest reliability as rated by the respondent. Returned questionnaires that contained no specific information about the deaths were deemed insufficient and, although they are not included in this analysis, are listed in Table I. The complete data on the questionnaire were not available in every case because of the retrospective

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Received for publication Jan. 16, 1987.

Accepted for publication Jan. 20, 1987.

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TABLE I. Additional reports of deaths from ST or IT from 1984 to 1985 survey*

Before 1973		After 1973—Cont'd	
1	1945, hospital known Comment: fatality after ID cottonseed extract	10	1980-1985, city known
2	1956, city known Comment: fatality after IT injection in 30-year-old black man	11	Before 1981, city known Comment: fatality from house dust extract
3	1964, hospital known Comment: fatality after IT injection	12	1982, city known
4	1965, city known	13	1984, city known Comment: fatality after IT in a 30-year-old male subject
5	1967, or earlier, city known Comment: fatality after IT in a male child	14	Hospital known Comment: fatality after IT in a patient receiving β -blockers
6	1972, city known	15, 16	Mid-1970s, city known Comment: fatality after IT
7	1970-71, city known		
After 1973			
8	1974, city known Comment: fatality after IT in 18-year-old female subject		
9	1980-82, city known Comment: fatality after ST in a 7- to 10-year-old child		

ID = intradermal.

*No details provided by responders and therefore excluded from detailed analysis.

TABLE II. Patient profiles—ST F

Case	Sex	Age (yr)	Year	Clinical state(s)	Medication(s)	Data reliability
Before 1973						
1	M	11	1964	Asthma, atopic eczema	Unknown	High
2	F	10	1964	Asthma	Antihistamine	Moderate
After 1973						
3	M	50s	1980	Unknown	Unknown	High
4	F	40	1982	Asthma	Unknown	High
5	M	24	1982	Asthma	Unknown	High
6	M	38	1983	Asthma	Antihistamine	High

F = fatality.

nature of the study. Because of its sensitive nature, no attempt was made to solicit additional information from members who submitted case reports; there were two exceptions. One physician was contacted by phone to clarify two cases he reported on the same questionnaire, and the second physician was telephoned because the responding physician referred us to him. All information received was confidential.

The 64-item survey requested the following information: age, sex, medical diseases, and allergen sensitivity of the patient, specialty of physician involved, location of therapy, status of IT allergen(s) used for diagnosis and treatment, time since previous injection, known errors, time of onset of symptoms, type of symptoms, cause of death, type of treatment, and data reliability.*

*Copies of the questionnaire can be obtained by writing the principal author.

RESULTS

Sixty questionnaires were returned; 14 fatalities were reported on more than one questionnaire. Although the questionnaire specifically requested reports of fatalities from 1973 to 1983, some respondents included fatalities that had occurred before 1973, and these data were also included in the analysis. Fifteen reports provide knowledge of 16 fatalities but were excluded from detailed analysis because of insufficient data (Table I). None were believed to be duplicates.

The 30 remaining fatality reports contained sufficient information and also were not believed to be duplicates. The profiles of the six patients whose deaths were associated with ST are tabulated in Table II, and the 24 patients whose deaths were associated with IT are tabulated in Table III. Two of the six fatalities

TABLE III. Patient profiles—IT F

Case	Sex	Age (yr)	Year	Clinical state(s)	Medication(s)	Data reliability
Before 1973						
7	F	35	1959	None	None	High
8	M	Adult	1960	Blank	None	Blank
9	M	18	1964	Asthma	None	Moderate
10	M	Blank	1966	Cardiovascular	Blank	High
11	M	38	1971	Blank	Blank	High
12	M	9	1971	Asthma	Prednisone, 17.5 mg, qod; Elixo-phyllin*; Actifed†	High
After 1973						
13	M	7	1974	Asthma	Asthma medications	Moderate
14	F	27	1974	Coronary artery disease	Blank	Moderate
15	M	20	1975	Blank	Blank	Blank
16	F	Blank	1978	Unknown	Unknown	Minimal
17	F	50	1979	None	None	High
18	M	18	1980	Asthma	Theo-Dur‡, 300 mg, every 8 hours; terbutaline, 5 mg, tid; tapering prednisone	High
19	F	19	1981	Asthma	Dimetapp§; Alupent ; oral contraceptive	High
20	M	50	1981	Cardiovascular, diabetes mellitus, asthma, hypertension	Theo-Dur‡; terbutaline; prednisone, 20 mg qod; Ventolin*** insulin; Hygroton#; Bronkosol¶	Moderate
21	F	50	1981	Blank	Blank	High
22	F	70	1982	Cardiovascular, degenerative joint disease, glaucoma, asthma, hypertension	Bronchodilators; Isordil**, nonsteroidal anti-inflammatory drug; diuretic; Timoptic††; pilocarpine; Diamox‡‡	High
23	F	27	1982	Unknown	Nasalide§§; Medrol , 4 mg; Ke-flex¶¶, 250 mg qid	High
24	M	52	1983	Reflux esophagitis, asthma	Somophyllin-CRT###, 500 mg qd; Ventolin Inhaler***	High
25	F	Blank	1983	Asthma	None	High
26	F	11	1983	Unknown	Unknown	High
27	F	29	1983	Asthma	Ventolin***; Dimetapp§; Marax†††	Blank
28	F	19	1984	Blank	Blank	High
29	F	61	1984	Hypertension, obesity, asthma	Aldoril†††, 25 mg, tid	High
30	M	58	1984	Cardiovascular, COPD, hypertension	Inderal‡‡‡; Atrovent, two puffs as needed	High

F = fatality; qod = every other day; tid = three times a day; COPD = chronic obstructive pulmonary disease; qid = four times a day; qd = every day.

*Berlex Laboratories, Inc., Cedar Knolls, N. J.

†Burroughs Wellcome Co., Research Triangle Park, N. C.

‡Key Pharmaceuticals, Inc., Miami, Fla.

§A. H. Robins Co., Richmond, Va.

||Boehringer Ingelheim, Ridgefield, Conn.

¶Winthrop-Breon Laboratories, New York, N. Y.

#USV Laboratories, Inc., Tarrytown, N. Y.

**Ives Laboratories, Inc., New York, N. Y.

††Merck Sharp & Dohme, West Point, Pa.

‡‡Lederle Laboratories, Pearl River, N. Y.

§§Syntex Laboratories, Inc., Palo Alto, Calif.

|||Upjohn Co., Kalamazoo, Mich.

¶¶Dista Products Co., Indianapolis, Ind.

###Fisons Corp., Bedford, Mass.

***Glaxo, Inc., Research Triangle Park, N. C.

†††Roerig, New York, N. Y.

‡‡‡Ayerst Laboratories, New York, N. Y.

TABLE IV. ST: Background information

Case No.	Method of ST	Extract	No. of tests applied	Location of therapy	Extenuating circumstances	Error
Before 1973						
1	Scratch and ID	ID: egg, corn, beef, lamb, milk, wheat, kapok, oat, feather, wool Scratch: oak, <i>Alternaria</i> , maple, timothy, June, ragweed	20	Clinic	Patient was hysterical during testing	No
2	ID	Pollens	20-40	Office same	Reaction occurred after second set of 20; spring allergen season	No
After 1973						
3	ID	Pen G and PPL	2-5	Office same	Prick tests not done	Incorrect dose?
4	ID	Walnut	16	Office same	Patient highly sensitive to peanut and coconut	No
5	ID	Dust, mold, tobacco, epidermal	10-20	Office same	Wheezing at time of injection; respiratory arrest after previous skin test to nuts	Unknown
6	ID	Flaxseed	10-20	Office same	None	Prior PPS test not done

ID = intradermal; Pen G = penicillin G; PPL = Penicilloyl polylysine.

TABLE V. IT: Background information

Case No.	Degree of sensitivity	Allergen(s) dose, mode of administration	Status of IT	Time since previous injection	Extenuating circumstances	Location of therapy	Error
Before 1973							
7	3+ PPS	AQ ragweed 100 PNU/ml SQ	↑ (3 mo to 1 yr)	1-2 wk	? Excessive dose of Levophed*	Office same	? Excessive dose of Levophed*
8	NA	NA	Maintenance (2 yr)	NA	Patient refused to wait after injection	Office different	No (? part of dose administered IV during SQ injection)
9	4+ PPS	<i>Alternaria</i> , 2000 PNU SQ	Maintenance (2-3 yr)	1-2 wk	Allergy season; recurrence of asthma after a course of prednisone	Office same	No
10	NA	SQ	NA	Unknown	None	Hospital allergy laboratory	NA

↑ = larger dose than preceding one; ↓ = lesser dose than preceding one; AQ = aqueous; SQ = subcutaneous; NA = not answered or available; IV = intravenously; IM = intramuscularly; ER = emergency room; mod = moderate.

*Winthrop-Breton Laboratories, New York, N. Y.

†Miles Pharmaceuticals, West Haven, Conn.

continued

TABLE V. Cont'd

Case No.	Degree of sensitivity	Allergen(s) dose, mode of administration	Status of IT	Time since previous injection	Extenuating circumstances	Location of therapy	Error
11	4+ PPS	SQ	↑	Unknown	Previous reaction to IT; patient went home after injection	Office same	NA
12	MOD PPS	Trees/grasses/weeds, 1:50, 0.45 ml; dust/ <i>Alternaria</i> /mold, 1:50, 0.45 ml SQ	↑	1 wk	Grass-pollen season; prior history of respiratory failure 2 mo before death	Office same	NA
After 1973							
13	Unknown	Ragweed, 10,000 PNU/ml, 10 ml (10 ml administered) IM	Maintenance	Unknown	Allergy season	Hospital	Dose incorrect Incorrect dose of epinephrine
14	Minimal ID	Unknown	Unknown	Unknown	Chest pain 1 wk before death	Office same	Unknown
15	NA	Stinging insects, 5000 PNU, 2 cc; timothy, 5000 PNU, 3 cc; ragweed, 5000 PNU, 3 cc; <i>Alternaria</i> , 1000 PNU, 1 cc; dust, 1 cc (extract mix)	↑	NA	None	Office same	Unknown
16	NA	NA	Maintenance	NA	None	Hospital	No
17	4+ PPS	Grasses, ragweed and sage, chenopod, 1:10,000 w/v, 0.15 cc each, SQ	↑ (last, 0.1 cc) (<3 mo)	1 to 2 wk	Pollen season; rage over motor vehicle accident	Office same	No
18	4+ PPS	Dust/grass, 18 PNU/ml, 0.2 ml SQ; Oak/ <i>Alternaria</i> , 20 PNU/ml, 0.2 ml SQ	First injection	NA	Respiratory arrest secondary to asthma (2 mo before death)	ER	No
19	Unknown	Ragweed, 500 PNU, 0.8 ml; Dog/cat, 100 PNU, 0.4 ml; Dust/mold, 500 PNU, 0.8 ml SQ	↑ (3 mo-1 yr)	1-2 wk	Many ER visits for asthma	Student health	Allpyral† to AQ

TABLE V. Cont'd

Case No.	Degree of sensitivity	Allergen(s) dose, mode of administration	Status of IT	Time since previous injection	Extenuating circumstances	Location of therapy	Error
20	4+ PPS	Grass, ragweed, 1:50, 0.5 cc; molds, 1:100, 0.5 cc	Maintenance (1-2 yr)	2-3 wk	Fall pollen season	Office different	No
21	NA	NA	NA	NA	None	Office same	Blank
22	Minimal ID	Ragweed, 1,000 PNU, 0.8 ml SQ	↑ (last, 600 PNU) (19 yr receiving IT)	2-3 wk	Respiratory distress at time of injection; previous reaction	Medical clinic	No
23	RAST, 101.9%	AQ ragweed mixture, 1:20, 0.4 cc SQ	↑ (1 yr)	3 days, shorter	Previous reaction to IT, local; pollen season	Office same	Allpyral† to AQ
24	Unknown	Mixed grasses, ragweed, dust mite, chenopod, 1:500 w/v, 0.5 SQ	Unknown (3 mo-1 yr)	Unknown	Ragweed season	Office same	No
25	4+ PPS	AQ pollen, 1:100 w/v, SQ	Maintenance (2 mo)	3 wk, longer	Seasonal exacerbation	Office same	No
26	Unknown	Dust, 4000 PNU; grass, 150 PNU; ragweed, 150 PNU; tree, 3000 PNU; English plantain, 150 PNU	↓ because of previous reaction (2-3 yr receiving IT)	Unknown	Change in manufacturer; previous reaction to IT	Office different	No
27	4+ PPS	Allerdust, house dust, mites, ragweed, cat dander	NA	Unknown	Patient administered the injection at home	Home	Unknown
28	Unknown	NA	NA	NA	NA	Office different	Unknown
29	Unknown	Pollen mix of giant and short ragweed, 0.2 cc, 1:20 w/v	Maintenance (2-3 yr)	4-8 wk, longer	Extract was 4 yr old	Office same	No
30	4+ PPS	Ragweed extract and other inhalants	↑ (3 mo-1 yr)	<1 wk	Experienced systemic reaction with skin tests; small local reaction on preceding injection of same dose; pollen season	Office different	Unknown

TABLE VI. Signs, symptoms, and treatment of reactions to STs

Case No.	Onset of symptoms	Symptoms	Resuscitation measures	M.D. present at onset of reaction	Cause of death
Before 1973					
1	10-20 min	Pruritus, vomiting	Epinephrine 0.3 cc SQ; IV; ICd	No (ST done by R.N.; M.D. present within 3 min)	Anaphylactic shock, aspiration of vomitus, bron- chospasm
2	3-10 min	Pruritus, angioedema, lower airway obstruc- tion, shock/unconscious	Epinephrine, fluids, glucocorticoids, O ₂ , Benadryl*	No (M.D. present within 3 min)	Anaphylactic shock, asthma
After 1973					
3	3-10 min	Hypotension	O ₂ , epinephrine, volume ex- pander, gluco- corticoids, dopamine†	Yes	Anaphylactic shock, arrhythmia
4	3-10 min	Lower airway obstruction, unconscious	Epinephrine, the- ophylline	Yes	Asthma, anaphylac- tic shock
5	Unknown	Lower airway obstruction, unconscious, myocar- dial infarction	CPR, O ₂	Unknown	Asthma, arrhythmia
6	10-20 min	Pruritus, angioedema, up- per airway obstruction, shock	Benadryl* Medrol‡	Yes	Anaphylactic shock, airway obstruc- tion, arrhythmia

SQ = subcutaneously; IV = intravenously; ICd = intracardiac; CPR = cardiopulmonary resuscitation.

*Parke-Davis, Morris Plains, N. J.

†Astra Pharmaceutical Products, Inc, Westboro, Mass.

‡Upjohn Co., Kalamazoo, Mich.

from ST occurred before 1973, and four occurred after 1973. Six of the 24 fatalities from IT occurred before 1973, and 18 occurred after 1973. The respondents considered the information submitted in the questionnaire to be highly reliable in 21 fatalities, moderately reliable in five, minimally reliable in one, and of either unknown reliability or not provided in the remaining three fatalities. The physicians who observed the fatalities supplied the information in 10 of the 30 fatalities. The other 20 fatalities were reported by physicians who had knowledge of the fatalities but who had not been directly involved in the cases.

There were four male and two female fatalities from ST and 11 male and 13 female fatalities from IT. The average was 33 years for fatalities whose age had been provided (30 years for ST and 34 years for IT) with a range of 10 years to the 50s for ST and 7 to 70 years for IT. The indications for IT (allergic rhinitis and/or asthma and insect hypersensitivity) were not requested in the questionnaire. Diseases in these 30 subjects included asthma in 16 (associated with cardiovascular disease in two), cardiovascular disease alone in three, and either no disease or insufficient information in the remaining 11 subjects. Eleven of

the 16 subjects with asthma had been receiving anti-histamine and antiasthmatic drugs, and five subjects were either not receiving drug therapy or its usage was unknown or not provided. Two of the subjects with asthma had histories of respiratory failure; one subject had experienced severe bronchospasm after skin tests to nuts, and one subject had required repeated emergency room visits for control of asthma. Two patients were receiving a β -adrenergic blocking agent: propranolol in a patient with chronic obstructive pulmonary disease, hypertension, and cardiovascular disease, and timolol in a patient with glaucoma.

Five of the six fatalities associated with ST were tested intradermally alone (it is unknown if any were tested with more than one intradermal concentration of extract), and the sixth fatality was tested intradermally and by scratch test (Table IV). No allergen concentrations, injection volumes, or reaction sizes were reported. Many different extracts were used during testing (Table IV). The possibility of an error was reported by two respondents (a questionable incorrect dose of penicillin G or penicilloyl polylysine and failure to have done a PPS test before the intradermal ST [Table IV, Nos. 3 and 6]). Possible circumstances

contributing to the skin test fatalities were reported as (1) skin tests done during allergy season, one patient, (2) a patient hysterical during skin testing, one patient, and (3) a patient with a prior clinical history of sensitivity to peanut and coconut who was tested with walnut, one patient. One subject (Table IV, No. 5), wheezing at the time of ST, had previously suffered a respiratory arrest associated with ST.

Nine of the 24 fatalities after IT had been reported to be extremely sensitive by ST (3+ or greater reaction by PPS test), one had a high titer of allergen-specific IgE by RAST (No. 23), one had moderate sensitivity (No. 12), and two subjects had minimal intradermal sensitivity (Nos. 14 and 22). The information of the remaining 11 subjects was either unknown or not provided (Table V). Allergens injected in the fatal IT cases consisted of mixtures in 10, single or ragweed allergen(s) in seven, and were not identified by the respondents in the remaining seven subjects. Pollen extracts had been administered to 16 of the fatalities either alone or in combination with other extracts. Thirteen of the pollen extracts included ragweed and/or grass. Seven IT subjects had been receiving maintenance, nine subjects had been receiving increasing doses, one subject had received the initial dose, and one subject had received a decreased dose because of a previous large local reaction. Information was not available in the remaining six subjects. The interval between the fatal injection and the preceding injection was not different from the previous injection interval in nine subjects, longer in two subjects, and shorter in one subject; information was not available in 12 subjects.

A known error in administration of allergen extract was reported in three subjects: an incorrect dose in one and a change from Allpyral (Miles Pharmaceuticals, West Haven, Conn.) to aqueous extract in two subjects. A questionable error was reported in one subject, i.e., speculation on the part of the respondent that part of the extract had been inadvertently administered intravenously. One subject may have died from an overdose of a drug used to treat the reaction. No known errors were reported in 10 cases, and errors were either unknown or not reported in nine cases.

Listed extenuating circumstances reported were as follows: IT during patients' allergy season, nine patients; previous local and/or systemic reactions to IT or ST, five patients (Nos. 11, 22, 23, 26, and 30) (two of these patients also had received injections during the pollen season and are also included under "IT during patients' allergy season"); wheezing or respiratory distress at the time of the injection, one patient; administration of resuscitative medication that may have contributed to the fatality, two patients (one

for IT and one for ST); chest pain for 1 week preceding the injection, one patient; minor motor vehicle accident after the injection, one patient (this patient also included under "IT during patients' allergy season"); first IT injection, one patient; injection from a new vial from a different manufacturer, one patient; extract was 4 years old, one patient; injection administered at home, one patient; recurrence of asthma after a course of prednisone, one patient (this patient also included under "IT during patients' allergy season"); many emergency room visits for asthma, one patient; previous respiratory arrest secondary to asthma, two patients (Nos. 12 and 18) (this patient also included under "IT during patients' allergy season"); and patient refused to wait after injection or went home after injection, two patients.

The symptoms, signs, and treatment of all systemic reactions from ST and IT are summarized in Tables VI and VII, respectively. Symptoms or signs of anaphylaxis were reported to have occurred in 20 minutes or less in 20 patients, between 20 and 30 minutes in two, 30 minutes or more in three, and unknown in the remaining five patients. Anaphylactic shock or shock was listed as cause of death in 18 of the 30 patients. The initial symptoms and/or signs were related to the respiratory tract in 16/30 patients of which 14/16 were asthmatic. The causes of the 16 fatalities with asthma were respiratory in nine, anaphylactic shock in six (in five of these six, a contributing cause of death was respiratory), and ventricular fibrillation in one fatality. The symptoms and/or signs included vascular reactions in 5/6 patients with cardiovascular disease by history. The cause of death in these patients was associated with shock and/or arrhythmia. With respect to treatment of anaphylaxis, epinephrine had been administered to 18 subjects by various routes, had not been administered to three subjects, and its administration was unknown in the remaining nine subjects. Oxygen was administered in 14 subjects, not administered in four subjects, and was unknown in 12 subjects. Intubation was reported to have been attempted in seven subjects. An autopsy was performed in 11 fatalities, and when information was provided, it was incorporated into this article.

A physician had been present at the time of 15 of the fatal reactions and had not been present in 12 fatalities when the reaction began, and this information was not known or the question was not answered in the remaining three subjects. The respondents stated that a physician was present within 3 minutes of the initiation of the fatal reaction in three of the 12 fatalities in which a physician was not initially present. The IT had been administered in a physician's office in 17 fatalities (12 in the office of the physician who

TABLE VII. Signs, symptoms, and treatment of reactions to IT

Case No.	Onset of symptoms	Symptoms	Resuscitation measures	M.D. present at onset of reaction	Cause of death	Extenuating circumstances
Before 1973						
7	<3 min	Pruritus, hypotension, lower airway obstruction	Epinephrine, O ₂ , Benadryl*, Levophed†	Yes	Rupture of berry aneurysm, arrhythmia, seizure, subdural hematoma	
8	3-10 min	Symptoms of anaphylaxis	None	No (patient did not wait after injection)	Anaphylactic shock	
9	<3 min	Lower airway obstruction	Epinephrine, O ₂ , theophylline	Yes	Asthma	
10	<3 min	Shock	Epinephrine	No (M.D. present within 3 min)	Arrhythmia, anaphylactic shock	
11	20-30 min	NA	NA	No (patient went home after injection)	NA	
12	<3 min	Upper/lower airway obstruction, shock, unconscious	Epinephrine, O ₂ , CPR	Yes	Asthma, anaphylactic shock	
After 1973						
13	Unknown	Lower airway obstruction, hypotension	Epinephrine, 1 ml IV	Yes	Ventricular fibrillation (secondary to epinephrine), anaphylactic shock, asthma	
14	20-30 min	Faint	Blank	Yes	Arrhythmia/? myocardial infarction, shock	
15	30 min	NA	NA	NA	Anaphylactic shock	
16	3-20 min	Unconscious	Unknown	No (patient died on elevator on the way to ER)	Anaphylactic shock	
17	>30 min	Pruritus, flush, unconscious	Epinephrine, O ₂ , bretylium	No (patient waited in office for 20 min)	Anaphylactic shock, ventricular fibrillation, minor motor vehicle accident	

NA = not answered or available; CPR = cardiopulmonary resuscitation; IV = intravenously; ER = emergency room;

*Parke-Davis, Morris Plains, N. J.

†Winthrop-Breon Laboratories, New York, N. Y.

‡Merck Sharp & Dohme, Rahway, N. J.

§Astra Pharmaceutical Products, Inc., Westboro, Mass.

||Upjohn Co., Kalamazoo, Mich.

TABLE VII. Cont'd

Case No.	Onset of symptoms	Symptoms	Resuscitation measures	M.D. present at onset of reaction	Cause of death	Extenuating circumstances
18	<3 min	Lower airway obstruction, pruritus	Atropine, theophylline, epinephrine, D ₅ W (2.5 L), O ₂ , NaHCO ₃	No (patient was in ER lobby)	Airway obstruction, asthma	
19	10-20 min	Short of breath, lower and upper airway obstruction, shock, unconscious	NaHCO ₃ , theophylline, Isuprel†, epinephrine, Decadron‡, Ringer's lactate, O ₂	Yes	Upper airway obstruction, asthma, anaphylactic shock, arrhythmia	
20	3-10 min	Lower airway obstruction, unconscious, hypotension	Epinephrine, Decadron‡, O ₂	No (M.D. was in another suite)	Anaphylactic shock, airway obstruction	
21	Unknown	NA	NA	Yes	Lower airway obstruction	
22	<3 min	Short of breath	Epinephrine, Benadryl*	Yes	Airway obstruction	
23	<3 min	Hypotension, seizures, unconscious	Dopamine§, theophylline, atropine, defibrillation, epinephrine, Solu-Medrol , Ringer's lactate (2 L), O ₂	No (injection administered by an L.P.N.)	Airway obstruction, aspiration	
24	Unknown	Chest pain, short of breath, seizures/coma, myocardial infarction	Unknown	Yes	Asphyxia/aspiration	

continued

had prepared the allergens for an injection; five with allergens for IT prepared within a different office), five in a hospital, one in a student health facility, and one at home.

DISCUSSION

Seven fatalities from IT were reported in the literature between 1929 and 1980.¹⁻⁷ Although more than 70 deaths during ST had been reported between 1895 and 1968, many of the antigens then used are no longer used for diagnostic ST.^{1,4,8-15} The present retrospective study by questionnaire analyzes six fatalities from ST (1964 to 1983) and 24 from IT (1959 to 1984). Sixteen additional fatalities from ST and IT are also presented with information not sufficiently detailed to permit inclusion in this analysis.

The mean age of death after ST and IT in this survey was 30 and 34 years, respectively. The mean age of death of the cases reported in the literature with ST

and IT to allergens similar to those in current use was 35 and 34 years, respectively. The age range in this study was 7 to 70 years; the age range reported in the literature was 5 months to 78 years (Tables VIII and IX), confirming that any age may be affected. The absence of a sexual predilection for fatalities is similar to previously published articles.

Sixteen of 30 (53%) fatalities were subjects with asthma, consistent with the percentage of subjects with asthma in the fatalities reported in the literature (nine of 16 [56%], Tables VIII and IX). Subjects with asthma, therefore, appear to be disproportionately represented among fatalities, since patients receiving IT have allergic rhinitis more than twice as often as asthma or bronchitis.¹⁶ Patients with asthma also have more severe anaphylactic reactions and account for more than an expected proportion of the allergic population who experience severe anaphylactic reactions after Hymenoptera stings.¹⁷ Patients whose histories

TABLE VII. Cont'd

Case No.	Onset of symptoms	Symptoms	Resuscitation measures	M.D. present at onset of reaction	Cause of death	Extenuating circumstances
25	>30 min	Cough, lower airway obstruction	Epinephrine, O ₂ , terbutaline	Yes	Asthma	
26	Unknown	Unknown	Unknown	No (reaction occurred after patient left office)	Unknown	
27	3-10 min	Unknown	Unknown	No	Anaphylactic shock	Patient's mother gave injection at home
28	<3 min	Unknown	NA	Unknown	NA	
29	3 min	Pallor, hypotension, unconscious, lower airway obstruction	Epinephrine, 1-2 cc; dexamethasone, 24 mg IV; O ₂ , 7 L/min	Yes	Anaphylactic shock, asthma	
30	10-20 min	Lower airway obstruction, unconscious, hypotension, ventricular fibrillation	Epinephrine, 0.75 ml SQ and additional IV; Solu-Cortef , Dopamine [§] , O ₂ , lidocaine, aminophylline, NaHCO ₃	Yes	Anaphylactic shock, asthma	

(e.g., cases Nos. 12, 18, 19, and 22) suggest severe episodes of airway obstruction or unstable asthma therefore require special precaution to assess the severity of their disease before allergen administration. The clinical status of the patient with respect to underlying airway obstruction is of special relevance, since the injection of allergen via IT or the inhalation of allergen via atmospheric exposure may, independently or in combination, produce increased airway obstruction. A catastrophic outcome may result when airway obstruction induced by IT is superimposed on already significant and increasing obstruction, hyperinflation, or on an airway that has been primed by prior aeroallergen challenge.

Four subjects in this study were symptomatic at the time of their fatal ST or IT injection: two were wheezing (Nos. 5 and 9), one was in respiratory distress (No. 22), and one had unstable angina (No. 14). The state of health of the subjects at the time of the fatal injection was not reported in the cases from the literature. Altering or postponing IT injections has been recommended for the symptomatic subject,^{18, 19} and this study suggests that the ill subject, especially with

asthma, probably is at a greater mortality risk during ST and/or IT.

Respondents volunteered that 10 patients died from ST or IT during the season when their allergic disease was exacerbated. No similar information is available from the case reports in the literature, although as early as 1941, the staff members of the Cleveland clinic²⁰ had advised that the number of ST be modified according to the season of the year. Others have suggested modifying the dose of IT during the active pollen season.^{18, 21} This clinical concern appears well founded because increases in specific IgE²² and skin test reactivity²³ have both been observed during or shortly after the peak of allergen exposure, suggesting that patients may be more sensitive during or after atmospheric allergen exposure.

Bronchial hyperactivity is also increased in highly atopic patients²⁴ after natural atmospheric allergen challenge of the bronchi,²⁵ certain viral infections,²⁶ drugs²⁷ (e.g., β -blockers), or air pollutants (e.g., ozone and SO₂).^{28, 29} Furthermore, subjects with "stable" asthma may have substantial airway obstruction not manifested by clinical symptoms but demonstrable

by pulmonary function tests.³⁰ The physician administering allergen extracts must therefore take into account many variables in assessing the tolerance of allergic (especially patients with asthma) patients undergoing IT in order to diminish or to avoid the risk of a severe reaction to the injected extract.

Two fatalities in this survey with obstructive airway disease were receiving β -adrenergic blockers. The precise contribution of β -blockers is not certain in these patients. The use of β -blockers may aggravate anaphylaxis and asthma and also impair response to β -adrenergic agents, thus diminishing their effectiveness in the treatment of asthma and anaphylaxis.^{31, 32}

The degree of skin sensitivity provides an important risk factor influencing the incidence of anaphylactic or systemic adverse reactions during IT.^{33, 34} Nine of the 24 fatalities after IT had a high degree of skin sensitivity (3+ or greater on previous PPS test), one had a high RAST value, one had moderate sensitivity, two had minimal ST sensitivity, and 11 fatalities were not reported. There is a higher risk of systemic reactions among exquisitely skin-sensitive patients (i.e., who react positively to high dilutions $\geq 1:10$ million) of the immunizing allergen.³⁴ A high degree of skin sensitivity may also be associated with more severe allergic disease.^{35, 36} Thus, knowledge of the skin sensitivity of the patient is a critical element in predicting the risk of developing a systemic reaction during allergen injection treatment.

The risk of an adverse effect after IT or ST is also related to the dose of allergen administered. Dosage or administration errors were believed to account for four of the 24 IT fatalities, i.e., incorrect dose in one (No. 13 received an entire vial of 10 ml), change from Allpyral (Miles Pharmaceuticals) to aqueous extracts in two, and the possibility of inadvertent intravenous injection of a subcutaneous dose in one. One subject succumbed after the initial injection of IT (No. 18). Three subjects had been receiving IT and succumbed after receiving an injection from a new vial (Nos. 19, 23, and 26 [listed as change in manufacturer, therefore counted as a new vial]). Two of these four subjects (Nos. 19 and 23) received an aqueous instead of Allpyral (Miles Pharmaceuticals) extract. Extra precaution is appropriate whenever new vial(s) are prescribed or begun. It is not necessarily the new vial(s), per se, that increase the risk of anaphylaxis but the increased possibility of injecting too large a dose from new vial(s).

The dose resulting in seven of the 24 IT fatalities was the maintenance dose (i.e., had been administered previously without reaction); nine of the remaining 17

subjects had been receiving increasing doses (the initial dose in one), one was receiving decreasing doses, and data on six subjects were not reported. The length of time between the previous injection and the fatal injection was the usual interval in most cases, since only two subjects had received injections at a longer than usual interval and one subject at a shorter interval. Data about these factors (status of IT or length of time between injections) have not been reported in case reports from the literature.

At least one of the allergens used in IT was a pollen extract in 16 of the 24 IT fatalities (ragweed and/or grass in 15); one subject had been injected with a mold extract, *Alternaria*. The data in the remaining seven subjects were not reported (Table V). Pollen allergens had been administered to five of the seven fatalities reported in the literature; there was insufficient information as to the allergen(s) involved in the remaining two cases (Table VIII). The incidence of fatal reactions to pollen extracts (especially grass and ragweed) may be related to the high skin reactivity to these extracts in comparison to other pollen and non-pollen extracts,^{37, 38} suggesting either the higher potency of these extracts or the higher sensitivity of the population to these allergens.

There were known or questionable errors reported in six fatalities (two with ST and four with IT). There were no known errors in 11 subjects, and errors are either unknown or not reported in the remaining 13 subjects. Although 20% of the fatalities were attributable to errors or possible errors, errors have not been reported in the literature to explain either IT or ST fatalities. This suggests that, although mistakes occur, most fatalities may not be due to recognizable errors or not reported as errors. Since five of six ST fatalities had followed with intradermal ST without previous PPS tests, it is advisable that the latter tests should always precede intradermal testing. The clinical rationale for this is well founded because the intradermal test requires a thousandfold to more than 10,000-fold lower allergen dose to produce wheal³⁹ or erythema⁴⁰ responses equal to that produced by the puncture test with the allergen. When the puncture test is negative, an intradermal dose that is hundredfold lower than the puncture test dose may produce many positive intradermal reactions.⁴¹ Initial use of intradermal testing (especially in patients whose puncture tests could later prove strongly positive) may therefore expose such patients to allergen doses thousands of times higher than that required to produce a positive puncture test that increases the risk of an adverse reaction caused by overdosage.

The introduction of standardized extracts may de-

TABLE VIII. Case reports from the literature: Fatalities from IT

Author	Sex	Age (yr)	Medical disease	Allergen	Status of IT	Onset of symptoms
Lamson ¹ 1929	M	34	Asthma	Bermuda-grass pollen, 0.05 cc, 1:100	(because of "nervousness" with preceeding reaction)	<3 min
Waldrott ² 1932	F	40		Ragweed extract, 1400 units	Unknown	<3 min
Vaughn, Black ³ 1939			Unknown	Unknown	Unknown	Unknown
Vance, Strassmann ⁴ 1942	M	35	Asthma	Ragweed extract	Unknown	<1 hr
James, Austen ⁵ 1964	M	56		Hay fever desensitization injections	Unknown (11 of 21)	<45 min
Rands ⁶ 1980	F	19	Asthma	Pollinex, Migen†	Maintenance	3-10 min
Pollard ⁷ 1980	M	24	Asthma	Bencard‡ product	Unknown (fifteenth injection)	25 min

*Autopsy confirmed anaphylactic shock.

†Not in article. Listed only as Pollinex, pollen extract; Migen, house dust-mite extract.

‡Bencard Allergy Unit, Brentford, Middlesex, U. K.

TABLE IX. Case reports from the literature: Fatalities from ST

Author	Age (yr)	Sex	Medical disease	Injected extract	Onset of symptoms
Baagoe ¹⁰ 1928	Unknown			Egg white, 0.1 cc	Sudden
Lamson ¹ 1929	5 mo	M	Eczema	Ovomucoid, 0.05 cc	2 min
Lamson ¹ 1929	34	M	Asthma	Buckwheat 1:500, ID	2-3 min
Vance, Strassmann ⁴ 1942	4	F		Silkworm, sheep's wool, kapok extracts, IC	5 min
Wiseman, McCarthy-Brough ¹¹ 1945	78	F	Asthma	17 environmental allergens, 0.01 cc, IC	5 min
Swineford ¹² 1946	49	F	Asthma	56 food extracts, 8-9 inhalant extracts, IC	3 min
Blanton, Sutphin ¹³ 1949	57	F	Asthma	56 STs, scratch and IC	Sudden
Harris, Shure ¹⁴ 1950	25	F	Asthma	Environmental substances, ID	1 min
Dogliotti ¹⁵ 1968	35	M		Penicillin scratch	4-5 min

ID = intradermally; IC = intracutaneously.

*Autopsy confirmed anaphylactic shock.

Symptoms	Cause of death
Flushing, athetoid movements, dyspnea	Anaphylactic shock*
Dyspnea, urticaria	Anaphylactic shock
Unknown	Unknown
Unknown	Anaphylactic shock*
Dyspnea	Anaphylactic shock*
Flushing, tachycardia	Anaphylactic shock*
Unknown	Status asthmaticus

Initial symptoms	Cause of death
Dyspnea	Unknown
Cyanosis	Respiratory arrest
Lacrimation, cyanosis, respiratory difficulty	Anaphylactic shock
Shock/unconscious	Anaphylactic shock*
Cough, asthma	Respiratory arrest
"Not feeling well," dyspnea	Cardiovascular collapse
Air hunger	Anaphylactic shock*
Dyspnea	Respiratory arrest*
Flush, abdominal pain	Anaphylactic shock

crease the risk of ST and IT fatalities because standardization will remove speculation regarding potency and dose. Extracts will be labeled with defined potency units, and instructions for use will be related to the dose of allergenic extract. With more uniform potency there should be a reduction of errors caused by switching extracts, vials, and manufacturers. Because standardized extracts are as potent as many of the extracts already commercially available, the risk of inadvertent overdosage should not be increased over the risk already inherent in treatment with existing extracts.

Some of the fatalities during IT and ST were associated with injection of a low dose of extract (≤ 100 PNU or $<1:1000$ w/v). Therefore, the patient's sensitivity and clinical status before administration will always be important factors in assessing the patient's tolerance to an extract, regardless of the dose injected. No allergenic extract can be considered absolutely safe for a specific patient who is allergic to that extract. All extracts, at any dose, must be injected with appropriate precaution and supervision. In this context, many systemic reactions in highly sensitive patients have been observed with a potent ragweed extract diluted up to hundredfold.⁴²

A previous systemic reaction, either to ST or IT, probably increases the likelihood of a subsequent fatal reaction because a systemic reaction in the absence of a dose error suggests a highly sensitive patient, a patient with severe, labile, or coexistent diseases, or a patient receiving a medication that may adversely influence the response to the allergen(s). One subject, who succumbed while the subject was being skin tested, had required epinephrine for reactions after allergy injections in past time (No. 5). Five subjects who died from IT had previously reacted to IT injections (two local reactions and three reactions not further defined).

The signs and symptoms occurring as a result of immunization were variable and included localized pruritus, hypotension, chest pain, and obstructed airway. The character or severity of the initial symptoms did not appear to predict the fatal outcome nor the cause of death.

The signs and symptoms of a systemic reaction appeared in less than 20 minutes in 20 subjects, in 20 to 30 minutes in two subjects, and in more than 30 minutes in three subjects (five were unknown or not reported) (Tables VI and VII). One of the subjects who expired more than 30 minutes after the injection had waited for 20 minutes in the physician's office and, on the way home 10 minutes later, was involved

TABLE X. Summary of data on fatalities associated with ST

Total fatalities	No screening or PPS tests	Attributed to food allergen	Symptoms present when tested	Error in dose	Tested during season
6	5 (2-6)*	1 (4)	1 (5)	1 (3?)	1 (2)

*Numbers in parentheses refer to patient numbers.

TABLE XI. Summary of data on fatalities associated with IT

Total		Total	
Prior degree of sensitivity		Place of injection	
3+, 4+, or high RAST	10 (7, 9, 11, 12, 17, 18, 20, 23, 25, 27, 30)*	Prescribing M.D.'s office	12 (7, 9, 11, 12, 14, 15, 17, 21, 23-25, 29)
Moderate	1 (12)	Other M.D.'s office	6 (8, 20, 22, 26, 28, 30)
Minimal	2 (14, 22)	Hospital	4 (10, 13, 16, 18)
Unknown	6 (13, 19, 24, 26, 28, 29)	Home	1 (27)
NA	5 (8, 10, 15, 16, 21)	Student health office	1 (19)
Injected allergens		Extenuating circumstances	
Ragweed alone	5 (7, 13, 22, 23, 29)	Injection during allergen season	9 (9, 12, 13, 17, 20, 23-25, 30)
Molds alone	1 (9)	Patient did not wait in office	2 (8, 11)
Mixed inhalants		Others	5 (7, 14, 18, 19, 22)
Alone	10 (12, 17-20, 24-27, 30)	None	3 (15, 16, 21)
With insect allergens	1 (15)	Unknown	5 (10, 11, 15, 16, 28)
NA	7 (8, 10, 11, 14, 16, 21, 28)	Error in treatment	
Status of IT		Change AQ to Allpyral†	2 (19, 23)
At maintenance	7 (8, 9, 13, 16, 20, 25, 29)	Dose incorrect	1
Doses increasing	9 (7, 11, 12, 15, 17, 19, 22, 23, 30)	Partly IV	1 (8)
Doses decreasing	1 (26)	Overdose Levophed‡	1 (7)
First injection	1 (18)	No error	10 (9, 16-18, 20, 22, 24-26, 29)
NA	6 (10, 14, 21, 24, 27, 28)	NA	4 (10-12, 21)
Time since previous injection		Unknown	5 (14, 15, 27, 28, 30)
<1 wk	2 (23, 30)		
1-2 wk	5 (7, 9, 12, 17, 19)		
>2 wk	4 (20, 22, 25, 29)		
NA	13 (8, 10, 11, 13-16, 18, 21, 24, 26-28)		

IV = intravenously; NA = not answered or available.

*Numbers in parentheses refer to patient numbers.

†Miles Pharmaceutical, West Haven, Conn.

‡Winthrop-Breton Laboratories, New York, N. Y.

in a minor vehicle accident. She was taken to the emergency room with cardiopulmonary resuscitation in progress. The accident may have exacerbated the systemic reaction or resulted from the systemic reaction.

Most anaphylactic reactions have occurred within 30 minutes after injection, inducing some allergists

to require at least a 30-minute wait after injection,^{19, 21, 29, 43} whereas other allergists require a 20-minute wait.^{18, 45} Since the 20-minute wait is not adequate for some patients, the longer period appears desirable. The onset of symptoms in the ST fatalities was less than 20 minutes in 5/6 (one unknown). Because ST doses are usually less than IT doses, a

TABLE XII. Summary of data on signs, symptoms, treatment, and cause of death from ST and IT

	ST	IT		ST	IT
Symptoms and signs			Resuscitation treatment		
Pruritus	3 (1, 2, 6)*	3 (7, 17, 18)	Oxygen	3 (2-4)	11 (7, 9, 12, 17-20, 23, 25, 29, 30)
Angioedema	2 (2, 6)	0	Epinephrine	4 (1-4)	14 (7, 9, 10, 12, 13, 17-20, 22, 23, 25, 29, 30)
Airway obstruction and/or asthma	4 (2, 4-6)	12 (7, 9, 12, 13, 18-20, 22, 24, 25, 29, 30)	Volume expander	2 (2, 3)	3 (18, 19, 23)
Shock	2 (2, 6)	4 (8, 10, 12, 19)	Glucocorticoids	3 (2, 3, 6)	5 (19, 20, 23, 29, 30)
Coma	3 (2, 4, 5)	9 (12, 16, 17, 19, 20, 23, 24, 29, 30)	Dopamine† or Levophed‡	0	3 (7, 23, 30)
Hypotension	1 (3)	6 (7, 13, 20, 23, 29, 30)	Theophylline	1 (4)	5 (9, 18, 19, 23, 30)
Myocardial infarction	1 (5)	1 (24)	Antihistamine	2 (2, 6)	2 (7, 22)
NA or unknown	0	6 (11, 15, 21, 26-28)	CPR	1 (5)	1 (12)
			NA or unknown	0	10 (8, 11, 14, 15, 16, 21, 24, 26-28)
Time to onset to SR					
<20 min	5 (1-4, 6)	15 (7-10, 12, 16, 18-20, 22, 23, 27-30)			
20-30 min	0	2 (11, 14)			
>30 min	0	3 (17, 15, 25)			
Unknown	1 (5)	4 (21, 24, 26)			
M.D. present at onset					
Yes	3 (3, 4, 6)	12 (7, 9, 12-14, 19, 21, 22, 24, 25, 29, 30)			
No	2 (1, 2)	10 (8, 10, 11, 16-18, 20, 23, 26, 27)			
NA or unknown	1 (5)	2 (15, 28)			
Cause of or contributing to death					
Airway obstruction and/or asthma	5 (1, 2, 4-6)	13 (9, 12, 13, 18-25, 29, 30)			
Cardiovascular	3 (3, 5, 6)	6 (7, 10, 13, 14, 17, 19)			
Anaphylactic shock	5 (1-4, 6)	13 (8, 10, 12-17, 19, 20, 27, 29, 30)			
Others	2 (1, 7)	4 (7, 17, 23, 24)			
NA or unknown	0	3 (11, 26, 28)			

NA = not answered or available; CPR = cardiopulmonary resuscitation.

*Numbers in parentheses refer to patient numbers.

†Astra Pharmaceutical Products, Inc., Westboro, Mass.

‡Winthrop-Breon Laboratories, New York, N. Y.

20-minute waiting period appears to be adequate after completion of ST.

Although epinephrine was injected in 18 of 30 subjects without preventing the fatality, it is the treatment of choice for anaphylaxis and must be administered in adequate doses and as frequently as clinical conditions demand.⁴³⁻⁴⁵ Oxygen was mentioned in 14 instances without description of the patency of the airway or adequacy of ventilation; thus, there may not have been optimal management of the airways or of ventilation in some cases. There may be great difficulty oxygenating patients with upper airway obstruction, e.g., laryngospasm or laryngeal edema; in these circumstances, endotracheal intubation may fail, and tracheostomy or cricothyrotomy may be necessary.⁴⁶

Hypotensive patients who are unresponsive to the usual dose of epinephrine may require intravenous epinephrine, other vasopressors in doses higher than usually administered, and volume expanders.⁴⁷ Because cardiac arrhythmias may complicate the treatment of patients experiencing anaphylaxis, cardiac monitoring, where it is possible, may be advisable.⁴⁸ Patients with anaphylaxis with associated unresponsive asthma may also require intravenous glucocorticosteroids as well as β -adrenergics and theophylline.⁴⁹

Subjects with persistent asthma are more likely to die from asthma during ST and/or IT because respiratory failure caused or contributed to death of 14 of 16 subjects with asthma. Respiratory failure was listed as the primary cause of death of nine of the 16 subjects with asthma and as the secondary cause of death in an additional five of six subjects whose primary cause of death was anaphylactic shock. Death in a 7-year-old child with asthma (No. 13) was not respiratory but resulted from ventricular fibrillation after, and perhaps resulting from, an intravenous injection of 1 ml of 1:1000 epinephrine.⁴⁸ The two cases with cardiovascular disease and asthma died from respiratory complications. The patient with unstable angina succumbed from a myocardial infarction/arrhythmia.

Information was adequate to indicate whether a physician had been present at the time of 27 of the 30 fatalities. A physician was present at the time of the onset of 15 of the 27 fatalities, and a physician was present within 3 minutes of the onset of the symptoms in three of the other fatalities. The presence or absence of a physician had not been indicated in the case reports from the literature. Several authors^{18, 19} have previously recommended that ST and IT should be carried out only in the presence of a physician and that appropriate drugs and equipment be available to treat any reactions that may occur. The data in this study support such a recommendation.

Because fatalities from ST and IT occur, despite direct physician supervision, such testing and therapy should be prescribed and/or administered by physi-

cians who are trained to do so, are aware of the risks, and are skilled in treatment of systemic allergic reactions. Patients to be skin tested or to receive IT should be informed of the risks of ST and IT, screened to assess their clinical status before ST or each injection, and asked to report any change in their clinical status and any symptoms or signs after their previous IT injection.

Although 46 fatalities have been reported in this survey with ST and IT during the past 39 years, the risk of fatality should be considered in the context of the large number of patients skin tested and receiving IT in the United States. One estimate of allergen usage, based on annual studies from a panel of 2000 physicians in the United States, indicates that in each of the previous 5 years, seven to 10 million allergen injections had been administered.⁵⁰

The risk of a fatal reaction is, therefore, very low and may be lessened as additional precautions are taken in the selection and treatment of allergic patients and in improved treatment of the anaphylactic reactions.

Tables X, XI, and XII are a summary review on the data base. It is evident that ST and IT of patients of any age and of either sex may result in fatal reactions. Patients suffering asthmatic symptoms (especially patients with unstable asthma that are prone to do so) are at a greater risk of fatal reactions than are patients without asthma. IT during seasonal exacerbations of the patients' disease, especially asthma, or of individuals with exquisite skin test sensitivity is more likely to result in fatality. Errors in dosage can and must be avoided by the most scrupulous attention to the kind of extract selected for injection, its concentration, and the volume withdrawn for injection. The probable contributing role of treatment with β -adrenergic blockers also appears to be significant. As indicated in a position statement by the Executive Committee of the AAAI⁵¹: "... the undeniable fact [is] that no matter what precautions are taken, systemic reactions inevitably will occur at some time in some patients." This is certainly in agreement with our experience and mandates the need to institute appropriate procedures to permit early detection of, and optimal treatment of, systemic reactions in order to avoid a fatal outcome.

We thank Mrs. Patricia Ann Walsh for secretarial assistance and AAAI for printing and mailing the questionnaires.

REFERENCES

1. Lamson RW. So-called fatal anaphylaxis in man. *JAMA* 1929;93:1776.
2. Waldbott GL. The prevention of anaphylactic shock. *JAMA* 1932;98:446.
3. Vaughan WT, Black JH. Practice of allergy. St. Louis: The CV Mosby Co, 1939.

4. Vance BM, Strassmann G. Sudden death following injection of foreign protein. *Arch Pathol* 1942;34:849.
5. James LP, Austen KF. Fatal systemic anaphylaxis in man. *N Engl J Med* 1964;270:597.
6. Rands DA. Anaphylactic reaction to desensitization for allergic rhinitis and asthma. *Br Med J* 1980;281:854.
7. Pollard RCH. Anaphylactic reaction to desensitization [Letter]. *Br Med J* 1980;281:1429.
8. Lamson RW. Sudden death associated with the injection of foreign substances. *JAMA* 1924;82:1091.
9. Vaughan WT, Pipes DM. On the probable frequency of allergic shock. *Am J Dig Dis Nut* 1936;3:558.
10. Baagoe KH. Case of allergic death due to intracutaneous injection of 10 cc of white of hen's egg. *Ugeskr Laeger* 1928;90:550.
11. Wiseman JR, McCarthy-Brough MP. Skin sensitivity in the aged-fatality following intradermal tests. *J ALLERGY* 1945;16:250.
12. Swineford O. Anaphylactic shock from skin testing. *J ALLERGY* 1946;17:24.
13. Blanton WB, Sutphin AK. Death during skin testing. *Am J Med Sci* 1949;217:169.
14. Harris MC, Shure N. Sudden death due to allergy tests. *J ALLERGY* 1950;21:208.
15. Dogliotti M. An instance of fatal reaction to the penicillin scratch test. *Dermatologica* 1968;136:489.
16. National Disease and Therapeutic Index. IMS America, Ltd.
17. Settiple GA, Klein DE, Boyd GK. Relationship of atopy and anaphylactic sensitization: a bee sting allergy model. *Clin Allergy* 1978;8:259.
18. Sheldon JM, Lovell RG, Mathews KP. A manual of clinical allergy. Philadelphia: WB Saunders, 1967:114-9.
19. Zeiger RS, Schatz M. Immunotherapy of atopic disorders. Present state of the art and future perspectives. *Med Clin North Am* 1981;65(5):987.
20. Thomas JW, ed. Allergy in clinical practice. Philadelphia: JB Lippincott, 1941:8-11.
21. Melam H. Principles of immunologic management of allergic disease due to extrinsic antigens. In: Patterson R, ed. Allergic diseases. Philadelphia: JB Lippincott, 1972:293.
22. Gleich AJ, Yunginger JW. Seasonal changes in IgE antibodies in patients with ragweed hayfever. In: Yamamura Y, head, ed. committee. Allergology. Proceedings of the VIII International Congress of Allergology. Tokyo: 1973. (International Congress series No. 323:44, 1974).
23. Gergen PJ, Turkeltaub PC. Percutaneous immediate hypersensitivity to eight selected allergens in the civilian noninstitutionalized population ages 6-74 years. United States—1976-1980. Hyattsville, Maryland: Data from the National Health Survey, series 11; DHHS publication, NCHS.
24. Cockcroft DW, Murdock KY, Berscheid BA. Relationship between atopy and bronchial responsiveness to histamine in a random population. *Ann Allergy* 1984;53:26.
25. Sotomayer H, Badier M, Vervloet D, Orehek J. Seasonal increase of carbachol airway responsiveness in patients allergic to grass pollen. *Am Rev Respir Dis* 1984;130:56.
26. Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA. Mechanisms of bronchial hyperactivity in normal subjects after upper respiratory tract infection. *Am Rev Respir Dis* 1976;113:131.
27. Ryo UY, Townley RG. Comparison of respiratory and cardiovascular effects of isoproterenol, propranolol, and practolol in asthmatic and normal subjects. *J ALLERGY CLIN IMMUNOL* 1976;57:12.
28. Holtzman MJ, Cunningham JH, Sheller JR, Irsigler GB, Nadel JA, Boushey HA. Effect of ozone on bronchial reactivity in atopic and nonatopic subjects. *Am Rev Respir Dis* 1979;120:1059.
29. Sheppard D, Wong WS, Vehara CF, Nadel JA, Boushey NA. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Respir Dis* 1980;122:873.
30. deBoeck C, Zinman R, Larson C, Fox Z. Importance of physician identification of airflow limitation in stable asthmatics. *Ann Allergy* 1984;53:30.
31. Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. *Ann Allergy* 1981;47:35.
32. Jacobs RL, Rake GW, Fournier DC, et al: Potential anaphylaxis in patients with drug-induced beta-adrenergic blockade. *J ALLERGY CLIN IMMUNOL* 1981;68:125.
33. VanderVeer A Jr, Cooke RA, Spain WC. Diagnosis and treatment of seasonal hay fever. *Am J Med Sci* 1927;174:101.
34. Turkeltaub PC, Baer H. The importance of patient skin sensitivity in evaluating dose-dependent adverse reactions during immunotherapy. *J ALLERGY CLIN IMMUNOL* 1985;75(Pt 2):163.
35. Norman PS, Lichtenstein LM, Ishisaka K. Diagnostic tests in ragweed hay fever. *J ALLERGY CLIN IMMUNOL* 1973;52:210.
36. Hunt KJ, Valentine MD, Sobotka AK, et al. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978;299:157.
37. Voorhorst R, Spijksma FThM, Varekamp H. House dust atopy and the house dust mite: quantitative aspects of skin tests with atopic allergens. Leiden, The Netherlands: Stafleu's Scientific Publishing, 1969:15-31.
38. Turkeltaub PC, Rastogi SC, Baer H. The use of quantitative skin testing to assign allergy units to allergenic extracts. *Ann Allergy* 1985;55(Pt 2):303.
39. Belin LGA, Norman PS. Diagnostic tests in the skin and serum of workers sensitized to *B. subtilis* enzymes. *Clin Allergy* 1977;7:55.
40. Turkeltaub PC, Rastogi SC, Baer H, Anderson MC, Norman PS. A standardized quantitative skin test assay of allergen potency and stability; studies on the allergen dose-response curve and effect of wheal, erythema, and patient selection on assay results. *J ALLERGY CLIN IMMUNOL* 1982;70:343.
41. Stenius B. Skin and provocation tests with *D. pteronyssinus* in allergic rhinitis: comparison of prick and intracutaneous skin test methods and correlation with specific IgE. *Acta Allergol* 1973;28:81.
42. Van Metre TE Jr, Adkinson NF Jr, Amodio FJ, Kagey-Sobotka A, Lichtenstein LM, Mardiney MR Jr, Norman PS, Rosenberg GL. A comparison of immunotherapy schedules for injection treatment of ragweed pollen hay fever. *J ALLERGY CLIN IMMUNOL* 1982;69:181.
43. Kelly JF, Patterson R. Anaphylaxis *JAMA* 1974;227:1432.
44. Lockey RF, Fox RW. Allergic emergencies. *Hosp Med* 1979;6:64.
45. Lockey RF, Bukantz SC. Allergic emergencies. *Med Clin North Am* 1974;58:147.
46. Iserson KV, Sanders AB, Kaback K. Difficult intubations: aids and alternatives. *Am Fam Physician* 1985;31:99.
47. Smith PL, Kagey-Sobotka A, Bleecker ER, et al. Physiologic manifestations of human anaphylaxis. *J Clin Invest* 1980;66:1072.
48. Sullivan TJ. Cardiac disorders in penicillin-induced anaphylaxis: association with intravenous epinephrine therapy. *JAMA* 1982;248:2161.
49. Littenberg B, Gluck EH. A controlled trial of methylprednisolone in the emergency treatment of acute asthma. *N Engl J Med* 1986;314:150.
50. National Disease and Therapeutic Index. IMS America, Ltd.
51. American Academy of Allergy and Immunology Executive Committee: personnel and equipment to treat systemic reactions caused by immunotherapy with allergenic extracts [Position statement]. *J ALLERGY CLIN IMMUNOL* 1986;77:271.