

Systemic allergic reactions to ingested antigens

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Fifteen cases of systemic allergic reactions to ingestant antigens are reported. The causative antigens were identified through exhaustive exploration of historical details. These antigens were penicillin, pinto bean, halibut, rice, potato, Brazil nut, shrimp, milk, a cereal mix, garbanzo bean, tangerine, salicylsalicylic acid, and demethylchlortetracycline. The importance of determining the causative antigen is emphasized. Before the cause was determined, 8 patients had recurrent anaphylaxis. These reactions were studied by certain immunologic methods. Cutaneous tests were positive in all patients tested except the salicylsalicylic acid and the demethylchlortetracycline reactors. Monkey P-K or human P-K reactions were performed with sera from 9 patients who had positive skin tests. All were positive. Specific release of histamine from leukocytes was detected in 7 of 9 patients studied. These methods are useful for studying immunologic reactions, but they do not establish or confirm a definitive diagnosis of clinically significant food allergy. The clinical and immunological characteristics of the cases are discussed.

Allergic shock is the human clinical counterpart of anaphylaxis in animals. The term *anaphylaxis* could also be applied to these human responses. The most common cause of human anaphylaxis is the injection of antigenic materials used for therapeutic purposes, of which penicillin and foreign sera predominate.¹ Anaphylaxis may also occur from the ingestion of antigens.²⁻⁸ Although these reactions are rare,⁹ they constitute a highly significant risk for the patient who develops this type of hypersensitivity.

This report describes a series of patients having explosive allergic reactions to ingested antigens. From Jan., 1967, through Dec., 1967, 8 patients with possible allergic reactions entered the emergency rooms of the Northwestern

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University Hospitals. By seeking patients of this type, 7 additional cases were found. The proven or presumptive etiology was established in all but 2 cases. This series represents an unusually large group of patients with this problem seen in a short period of time. This is thought to result from coincidence, the availability of a large medical center, and a unit in allergy which receives many consultations for complex allergic diseases.

Although reactions of this type are uncommon in the individual physician's practice, awareness of such problems is important. Causative factors in anaphylaxis to ingested antigens must be determined promptly to prevent a lethal recurrence. For this reason and to describe certain immunologic studies, these cases of anaphylaxis caused by foods and ingested drugs are described in detail.

CASE REPORTS

The clinical characteristics of the reactions of each patient are summarized in Table I.

Case 1

This case has been reported in detail elsewhere.¹⁰ A 52-year-old Caucasian male attorney entered the emergency room on May 3, 1967, with dyspnea, angioedema, urticaria, abdominal "cramping," nausea, emesis, and an oppressive sensation of the thorax. Blood pressure was 80/60 mm. Hg.

The causative antigen was determined to be benzyl penicillin which was erroneously dispensed as ascorbic acid. Anaphylaxis occurred a total of 3 times before the patient admitted use of the medication despite specific questioning by 4 examiners.

This patient subsequently had generalized urticaria and angioedema following a sting

Table I. *Clinical characteristics of the reactions*

Patient	Age	Sex	Blood pressure (mm. Hg)	Syncope	Cyanosis	Dyspnea	Angioedema	Urticaria	Abdominal distress	Chest pain
1	52	M	80/60	—	—	+	+	+	+	+
2	37	F	95/30*	+	+	+	Tracheal intubation	+	+	+
3	27	M	0/0	—	—	+	+	+	+	—
4	21	F	N.T.†	—	+	+	+	+	+	—
5	17	M	N.T.‡	—	+	+	+	—	+	+
6	28	M	N.T.‡	—	+	+	+	—	+	—
7	24	M	N.T.‡	+	N.K.§	+	+	+	—	—
8	5 mo.	M	N.T.‡	—	+	—	—	+	N.K.§	N.K.§
9	49	M	70/0	—	+	+	+	+	—	—
10	39	M	110/60	—	—	+	+	+	—	—
11	33	F	110/70	—	—	+	+	+	+	—
12	37	M	60/0	—	—	+	+	—	—	+
13	34	M	N.T.‡	+	N.K.§	+	+	+	—	+
14	22	M	0/0	+	+	+	+	+	—	+
15	40	M	80/60	—	+	+	+	+	—	—

*After epinephrine was administered.

†N.T.; not taken.

‡Not seen by physician during acute episode.

§N.K.; not known.

||A morbilliform rash was present.

by one of the Hymenoptera insects. He had cutaneous reactivity with extracts of bee, wasp, hornet, and yellow jacket.

Case 2

A 37-year-old Negro woman entered the emergency room on Feb. 22, 1967, with dyspnea, generalized urticaria and angioedema, and syncope. Similar episodes, without syncope, occurred in 1964 and in Jan., 1967, but she did not seek medical aid.

She had a history of allergic rhinitis.

On physical examination the patient was unconscious with laryngeal stridor, pulmonary wheezing, cyanosis, angioedema of the face and oropharynx, and generalized urticaria. The blood pressure, pulse, and respiratory rate were 95/30 mm. Hg, 100, and 20, respectively, after epinephrine chloride and diphenhydramine hydrochloride were administered.

The hemoglobin (Hb) was 13.0 Gm. per 100 ml. The leukocyte count (WBC) was 19,000 with 72 per cent neutrophils, 10 per cent bands, 15 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophiles.

The patient received epinephrine, diphenhydramine, and hydrocortisone parenterally, tracheal intubation and intravenous hydration. She promptly recovered and was discharged the next morning.

She was seen for consultation by the allergy service for the first time on March 16, 1967, one week after having a recurrent reaction. She was unaware of any relationship of these reactions to any specific food although both reactions followed a meal. Cutaneous tests with numerous foods including those ingested before the recent reaction were negative except for slight reactivity (1+) to soy bean. A diet diary was instituted, and the patient was instructed to carry medication for emergency use.

Subsequently, 4 reactions of varying severity occurred. Correlation with pinto bean became apparent from observation of the diet diary. A prick test with extract prepared from fresh, raw pinto bean caused a large local cutaneous reaction and was followed by mild generalized symptoms of dyspnea, wheezing, pruritus, and flushing. This reaction cleared immediately after subcutaneous administration of epinephrine.

Case 3

A 27-year-old Negro man entered the emergency room on Oct. 27, 1967. While ingesting halibut and toast, he abruptly developed dyspnea, generalized urticaria, facial angioedema, dizziness, "faintness," diarrhea, nausea, and emesis.

The blood pressure and pulse were not detectable with the patient in the upright position and were 90/80 mm. Hg and 70, respectively, with the patient supine. The respiratory rate was 20 after administration of epinephrine. The rectal temperature was 99.6° F. Wheezing, generalized urticaria, and facial angioedema were present. The remainder of the examination was normal.

The Hb and Hct were 13.8 Gm. per 100 ml. and 46.0 per cent, respectively. The WBC was 12,600 with 75 per cent neutrophils, 1 per cent bands, 21 per cent lymphocytes, 1 per cent monocytes, and 2 per cent eosinophiles. Urinalysis, chest roentgenogram, blood urea nitrogen (BUN), blood glucose, and serum sodium, potassium, and chloride, and carbon dioxide were normal.

Complete recovery promptly followed treatment with epinephrine and diphenhydramine. The patient was discharged the next day and referred to our clinic for further evaluation.

Additional history revealed that a similar reaction occurred several months earlier while ingesting halibut. The patient also had seasonal allergic rhinitis. A cutaneous prick test was strongly positive to halibut extract.

Case 4

A 21-year-old Caucasian woman had allergic rhinitis and asthma since childhood. She entered the emergency room on Dec. 15, 1967, with dyspnea, dizziness, pruritus, swelling of the face, weakness, headache, and abdominal cramps. These symptoms developed while

the patient was ingesting rice. Similar reactions, including syncope, had previously occurred during ingestion of rice.

She had a previous psychiatric hospitalization.

Physical examination revealed facial angioedema, generalized urticaria, cyanosis, and wheezing. Vital signs were not taken in the emergency room.

The urinalysis, hemogram, blood glucose, BUN, and a serologic test for syphilis (VDRL) were normal. Chest roentgenogram showed calcification in the right lower lobe and right hilus. A skull roentgenogram and electroencephalogram were normal.

Signs and symptoms of the reaction cleared promptly after parenteral administration of epinephrine and diphenhydramine. Because of withdrawn, agitated behavior, she was admitted to the hospital. The psychiatric diagnosis was paranoid schizophrenic reaction. The question arises whether this psychotic episode in a latent schizophrenic patient may have been precipitated by the allergic shock reaction. Our service was requested to give allergy consultation.

A cutaneous prick test was strongly positive with a dilute solution of rice extract.

Case 5

A 17-year-old Caucasian boy was referred to our clinic because of reactions which occurred repeatedly after ingestion of potato. These reactions were characterized by wheezing, dyspnea, angioedema, dizziness, weakness, and chest pain described as "tightness." Cutaneous scratch tests were positive to extracts of potato, ragweed, and house dust. He had no symptoms due to inhalant allergy.

Case 6

A 28-year-old Caucasian man came to our clinic because of seasonal allergic rhinitis and asthma since 3 years of age. Systemic allergic reactions occurred numerous times after ingestion of Brazil nut, pistachio nut, and cashew. These reactions occurred immediately after ingestion and were characterized by rhinorrhea, dyspnea; cyanosis; angioedema of face, tongue, and pharynx; abdominal cramps; weakness; and dizziness.

Prompt improvement followed administration of epinephrine and antihistamines. Inadvertent ingestion occurred because these nuts are concealed in many pastries and candies. A cutaneous scratch test with Brazil nut extract was performed elsewhere and caused a large local reaction and wheezing.

Case 7

A 24-year-old Caucasian man came to our clinic on Aug. 31, 1967, because of allergic rhinitis and asthma. Ingestion of shrimp and lobster had repeatedly caused rhinorrhea, angioedema of face and oropharynx, urticaria, dyspnea, wheezing, dizziness, and syncope. A cutaneous prick test with shrimp extract was markedly positive.

On Jan. 14, 1968, the patient ingested homemade shrimp casserole to avoid insulting a girl friend despite knowledge of his sensitivity to this food. Pruritus, generalized urticaria, swelling of the face and neck, dyspnea, dysphagia, laryngeal stridor, weakness, and dizziness developed immediately.

In the emergency room the pulse was 100, temperature 98.6° F. orally. Generalized urticaria, facial angioedema, and wheezing were present. All manifestations cleared promptly after administration of epinephrine and diphenhydramine.

Case 8

A 5-month-old Caucasian boy was referred to us because of reactions which invariably followed ingestion of pasteurized but otherwise uncooked milk. These reactions were characterized by pallor, cyanosis, muscle flaccidity, and generalized urticaria. Prompt alleviation of signs and symptoms followed administration of epinephrine. On one occasion, milk was accidentally spilled on him; urticaria developed at all sites of contact. Further cutaneous testing was deferred. The patient tolerated milk in baked foods.

Case 9

A 49-year-old Caucasian man entered the hospital in Aug. 22, 1964. Dyspnea, swelling of the face and oropharynx, pruritus, urticaria, and dyspnea had developed while he was ingesting a cereal mix.

There was a past history of allergic rhinitis.

The blood pressure was 70/0 mm. Hg; pulse, 120 and regular; respiratory rate, 20; and temperature, 97.2° F. orally. Angioedema of the face, generalized urticaria, cyanosis, and wheezing were present. The remainder of the physical examination was normal.

The Hct was 48 per cent, and the WBC was 9,500 with 88 per cent neutrophils, 6 per cent bands, and 7 per cent lymphocytes. Chest roentgenogram revealed minimal linear atelectasis in the left lower lobe. The admission electrocardiogram (ECG) revealed depression of the S-T segment in Leads I, II, aV_F, and V₂ through V₆. ECGs obtained the next day and on the 3 successive days showed atrial fibrillation and nonspecific ST-T changes. The ECG of Aug. 29 demonstrated sinus rhythm and ST-T changes consistent with digitalis effect. Urinalysis, BUN, serum creatinine, serum proteins, sodium, potassium, chloride, bicarbonate, a serologic test for syphilis (VDRL), 3 serial determinations of serum glutamic oxaloacetic acid (SGOT), and 2 determinations of lactic dehydrogenase (LDH) were normal.

Oxygen, parenteral epinephrine, cortisone, diphenhydramine, aminophylline, and adrenocorticotrophic hormone (ACTH), and intravenous fluid support were administered in the emergency room. The blood pressure rose to 110/70 mm. Hg; pulse was 100 and regular, and the other clinical manifestations of the reaction cleared within one hour. He was admitted to the hospital, and our service was requested to investigate the etiology of the reaction.

The next day, the patient's pulse was irregular. The ECG showed atrial fibrillation and nonspecific ST-T changes. He was treated with digitoxin and ACTH. Sinus rhythm returned 6 days later.

Cutaneous prick tests were positive with the specific lot of cereal mix which the patient was ingesting at the onset of the reaction. Cutaneous tests with individual ingredients of the cereal mix and a different lot of the same brand of cereal mix were negative. Cutaneous tests with all other foods temporally related to the reaction were also negative. The patient has subsequently ingested all these foods except the cereal mix without adverse reaction. The reaction is attributed to the specific lot of cereal mix and may have been caused by a contaminant.

Case 10

A 39-year-old Caucasian man entered the emergency room on July 26, 1967. Dizziness, dyspnea, wheezing, generalized pruritus, and swelling of the face and oropharynx developed while he was ingesting supper.

The blood pressure was 110/60 mm. Hg with the patient supine; pulse, 108; respiratory rate, 16; temperature, 98.0° F. orally. Positive findings included rhinorrhea, lacrimation, generalized urticaria, and angioedema of the face and oropharynx. All manifestations of the reaction cleared promptly after parenteral administration of epinephrine and diphenhydramine. He left the emergency room 3 hours after admission; his blood pressure was 110/60 mm. Hg; pulse, 88, and respiratory rate, 16.

Subsequent investigation revealed that partially cooked garbanzo bean (chick-pea) was ingested immediately prior to his reaction. A cutaneous prick test with this food was positive. All other foods ingested before the reaction produced negative cutaneous tests and were subsequently ingested without adverse effect. He tolerated well-cooked beans.

The patient had allergic rhinitis and atopic asthma.

Case 11

A 33-year-old Caucasian woman entered the emergency room on Dec. 17, 1967. While ingesting a meal, she suddenly developed generalized pruritus, dyspnea, abdominal "cramps," nausea, and dizziness.

Positive physical findings included generalized urticaria, angioedema of face and

oropharynx, and wheezing. Blood pressure, pulse, and temperature were obtained after parenteral administration of epinephrine and diphenhydramine and were 110/70 mm. Hg, 104, and 97.4° F. orally. The blood pressure was 136/80 mm. Hg 25 minutes later. All manifestations cleared promptly after treatment, and the patient was referred to our clinic.

Tangerine was among the foods ingested before the reaction. The patient has subsequently ingested all of the other foods without adverse effect. A cutaneous prick test with fresh tangerine juice was positive, and cutaneous tests with all other foods temporally related to the reaction were negative.

She subsequently ingested lemonade and fresh orange without adverse effect. Cutaneous tests with fresh orange juice were negative.

She had seasonal allergic rhinitis.

Case 12

A 37-year-old Caucasian man was receiving salicylsalicylic acid and acetylsalicylic acid (Persistin) and prednisone for treatment of lupus erythematosus and rheumatoid arthritis. He entered the hospital on Feb. 23, 1968, because of fever. Chills and other symptoms were not present.

The rectal temperature was 104.6° F.; blood pressure, 110/76 mm. Hg; pulse, 100 and regular; and respiratory rate, 20. The patient appeared flushed but in no apparent distress. There were typical generalized changes of rheumatoid arthritis. The remainder of the physical examination was normal.

The hematocrit and hemoglobin were 43 per cent and 13.7 Gm. per 100 ml, respectively. The WBC was 7,850 per cubic millimeter with 37 per cent neutrophils, 41 per cent bands, 19 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophiles. The sedimentation rate was 35 mm. per hour. Lactic dehydrogenase was 850 units, and SGOT was 50 units. Normal or negative studies included blood glucose, total and direct bilirubin, BUN, serum creatinine, chest roentgenogram, intravenous pyelogram, ECG, creatine phosphokinase, and cultures of sputum, urine, cerebrospinal fluid, and 4 blood specimens. Protein, chloride, glucose, VDRL, and colloidal gold determinations of the cerebrospinal fluid were normal. The hemogram, lactic dehydrogenase, and SGOT were normal when the patient was discharged. Tests for rheumatoid factor, lupus erythematosus preparations, and antinuclear factor were previously positive. Serum complement had been 31 units (normal 35 to 50 units).

The patient became afebrile within 16 hours after the salicylsalicylic acid and acetylsalicylic acid were discontinued. These drugs were returned to the therapeutic regimen 6 days later. Nasal stuffiness, rhinorrhea, sneezing, flushing, angioedema and paresthesias of the face, headache, myalgia, dyspnea, sneezing and a generalized erythematous, raised, punctate rash developed 1½ hours after oral administration of the first dose. The blood pressure was 60/0 mm. Hg; pulse, 128 and regular; respiratory rate, 28; and rectal temperature, 104.2° F. The patient recovered after treatment with parenteral diphenhydramine, metaraminol (Aramine), hydrocortisone, and intravenous fluid support. Consultation from our service was subsequently requested. This reaction and the fever which led to hospital admission were attributed to salicylsalicylic acid. Aspirin was cautiously returned to the therapeutic regimen, and all other temporally related antigens (except salicylsalicylic acid) were subsequently ingested without adverse effect.

Case 13

A 34-year-old Caucasian male physician entered the hospital on Jan. 3, 1968. The evening before admission, he ingested 300 mg. of demethylchlortetracycline (Declomycin) for vague, nonspecific symptoms. Within 20 minutes, headache, transient syncope, dyspnea, "tightness in the chest," angioedema of the face and hands, and generalized urticaria developed. He injected hydrocortisone acetate, 50 mg., intramuscularly, and the next day, he sought medical help. He had previously taken demethylchlortetracycline without adverse reaction.

He had a previous history of allergic rhinitis, urticaria once after ingestion of straw berries, and hepatitis.

The blood pressure was 140/90 mm. Hg, and pulse rate was 80 and regular. Positive

findings were generalized urticaria, periorbital edema, and edema of the hands and feet.

The admission ECG showed nonspecific ST-T changes, and a subsequent ECG was normal. Normal or negative studies included a hemogram, urinalysis, sedimentation rate, blood urea nitrogen (BUN), serologic test for syphilis, flocculation studies, SGOT, alkaline phosphatase, lactic dehydrogenase, serum proteins, bilirubin, blood glucose, serum uric acid, and calcium and phosphorus.

Complete recovery followed treatment with prednisone and diphenhydramine.

Case 14

A 22-year-old Caucasian man entered the emergency room on Jan. 1, 1967. Chest pain, dyspnea, swelling of the face, generalized pruritus, and syncope developed while he was ingesting a meal. Similar reactions had occurred 5 times previously.

The blood pressure was 0/0 mm. Hg. The apical rate was 115, respiratory rate, 18; and temperature, 99.6° F. orally. Positive findings were wheezing, cyanosis, angioedema of the face and generalized urticaria. The admission Hb, Hct, and WBC were 20.7 Gm. per 100 ml., 60 per cent, and 26,250 per cubic millimeter, respectively, with 56.5 per cent neutrophils, 12 per cent bands, 4 per cent eosinophils, 1.5 per cent basophils, and 26 per cent lymphocytes. The admission ECG showed sinus tachycardia. A subsequent hemogram and ECG were normal. Normal or negative studies included the urinalysis, VDRL, platelet count, lupus erythematosus preparation, uroporphyrins, serum phosphorus, alkaline phosphatase, electrolytes, protein electrophoresis, SGOT, and chest roentgenogram. Cutaneous prick tests were strongly positive to extracts of molds, house dust, chocolate, tomatoes, and potatoes.

Complete recovery promptly followed treatment with epinephrine, diphenhydramine, and intravenous fluid support. He was admitted to the hospital for further evaluation.

The patient subsequently ingested all foods and drugs temporally related to the reaction, including chocolate, potatoes, and tomatoes, without apparent adverse reaction. Reactions have occurred after he left the hospital. The causative antigen was undetermined, but all reactions followed ingestion of various foods containing a large mold content.

Case 15

A 40-year-old Caucasian man entered the hospital on May 27, 1967. Dyspnea, generalized pruritus, lightheadedness, and swelling of his face and tongue occurred while he was ingesting a meal.

The past history revealed allergic rhinitis and asthma.

The blood pressure was 80/60 mm. Hg. The pulse and respiratory rate were 84 and 20, respectively, after treatment. Positive findings were cyanosis, wheezing, generalized urticaria, and facial swelling.

The hemogram, urinalysis, VDRL, ECG, and chest roentgenogram were normal. Cutaneous tests with extracts of all foods ingested at the time of the reaction were negative.

Complete recovery promptly followed treatment with epinephrine and diphenhydramine, and he was discharged from the hospital on May 29.

The causative antigen remains undetermined. All foods and drugs temporally related to the reaction have subsequently been ingested without adverse effect. He has not had repeated anaphylaxis, but he has had recurrent urticaria without any consistent relation to foods or drugs.

CLINICAL SUMMARY

Of the 15 patients, 14 were between the ages of 17 and 52 years, and one was 5 months of age. All had acute, potentially fatal reactions with cutaneous, respiratory, and hypotensive manifestations (Table I). All patients whose blood pressures were recorded had hypotension except Cases 10 and 11. Those whose blood pressures were not recorded and Cases 10 and 11 had various manifestations of hypotension including weakness, dizziness, pallor, cyanosis,

flaccidity, and syncope. Cases 10 and 11 may have had postural hypotension, but the blood pressure was obtained in the supine position.

Syncope occurred in 4 patients, cyanosis in 8, and dyspnea in 14. One required tracheal intubation. Angioedema, urticaria, or both occurred in all. Abdominal distress was present in 6, and 4 had chest pain. All reactions cleared after treatment with sympathomimetic and antihistaminic drugs.

All reactions occurred following a meal. Each case was evaluated by a complete medical and allergic history of possible exposure to antigens. Positive cutaneous tests demonstrated presence of reaginic antibody in 10 of the 12 patients tested.

In 8 patients (Table II) the etiology was proven by recurrence with repeated inadvertent ingestion. The causative ingestants were penicillin, pinto bean, halibut, rice, potato, Brazil nut, shrimp, and milk. The patient with a penicillin reaction had taken benzyl penicillin tablets which were erroneously

Table II. *Cases of proven etiology**

<i>Patient</i>	<i>Etiology</i>	<i>Comment</i>	<i>Other atopic diseases</i>
1	Penicillin	Recurrence 3 times from mislabeled drug	Systemic allergic reaction due to Hymenoptera sting
2	Pinto bean	Systemic reaction to prick test	Allergic rhinitis
3	Halibut		Allergic rhinitis
4	Rice		Allergic rhinitis, Asthma
5	Potato		None; skin test positive to ragweed and dust
6	Brazil nut, pistachio, cashew	Systemic reaction to scratch test	Allergic rhinitis, Asthma
7	Shrimp, lobster		Allergic rhinitis, Asthma
8	Milk, raw	Tolerates baked foods	None

*All had recurrence with repeated inadvertent ingestion. Other temporally related antigens have subsequently been ingested without adverse reaction.

Table III. *Cases of presumed etiology**

<i>Patient</i>	<i>Etiology</i>	<i>Comment</i>	<i>Other atopic diseases</i>
9	A specific lot of a cereal mix	Skin test negative with other lots	Allergic rhinitis
10	Garbanzo bean (Chick-pea)	Tolerates well-cooked beans	Allergic rhinitis Asthma
11	Tangerine	Tolerates aspirin (See text)	Allergic rhinitis
12	Salicylsalicylic acid	Tolerates orange	
13	Demethylchlortetracycline		Allergic rhinitis

*Other temporally related antigens have subsequently been ingested without adverse reaction.

Table IV. *Etiology not established*

<i>Patient</i>	<i>Method of diagnosis</i>	<i>Comment</i>	<i>Other atopic diseases</i>
14	Recurrent reactions after ingesting foods having high mold content; prick test strongly positive	Etiology ingested molds (?)	None
15	Implicated foods have been ingested without recurrent anaphylaxis; skin tests were negative		Allergic rhinitis, asthma

identified as ascorbic acid; he received them directly from a practitioner. The patients with pinto bean and Brazil nut reactions had systemic reactions to cutaneous testing. Collateral inhalant allergy was present in 5; and, in addition, one was skin-reactive to ragweed and house dust.

In 5 patients (Table III) the etiology was presumed on the basis of clinical correlation and subsequent ingestion of other temporally related antigens without adverse reaction. The causative ingestants were a cereal mix, garbanzo bean, tangerine, salicylsalicylic acid, and demethylehlortetracycline. Four patients had collateral inhalant allergies, and one had lupus erythematosus and rheumatoid arthritis.

The etiology was not established in 2 patients (Table IV). One had recurrent reactions following ingestion of various foods having a large mold content. A prick test with mold antigen was strongly positive. These data suggest the possibility that ingested mold antigens in high concentration may be the cause of his anaphylaxis; this remains a speculation. The other has had recurrent urticaria, but anaphylaxis has not recurred. Cutaneous tests with all foods ingested prior to his systemic reaction were negative. His recurrent urticaria had no consistent relation to foods or drugs. He also had allergic rhinitis and asthma.

METHODS AND MATERIALS

Extracts

Allergenic extracts were obtained from commercial sources (Hollister-Stier, Downers Grove, Ill.) or prepared by standard methods.^{11, 12} Cutaneous tests with all extracts were negative in normal volunteers.

Cutaneous testing

Cutaneous tests were performed by the "prick" technique¹³ and begun with very dilute solution of antigen.

Monkey Prausnitz-Küstner (P-K)

The skin of rhesus monkeys was sensitized with 0.1 ml. of serial fivefold dilutions of sera. Evans blue dye was injected intravenously¹⁴ 24 hours later. The sensitized sites were then injected with 0.02 ml. of the highest concentration of antigen which did not produce a nonspecific reaction. Reactivity was read by the lowest concentration of serum which produced a blue reaction.¹⁴

Table V. *Immunologic studies*

<i>Patient</i>	<i>Antigen</i>	<i>Cutaneous test</i>	<i>Monkey P-K</i>	<i>Histamine release</i>
1	Penicillin	+	Undiluted	-
2	Pinto bean	+ and systemic reaction	1:5	+
3	Halibut	+	Undiluted	+
4	Rice	+	1:5	+
5	Potato	+	1:125	+
6	Brazil nut	+ and systemic reaction	No transfer to monkey 1:125 to human	+
7	Shrimp	+	1:125	+
9	Cereal mix	+	N.D.*	N.D.*
10	Garbanzo bean	+	Undiluted	-
11	Tangerine	+	1:25	-
12	Salicylsalicylic acid	-	N.D.*	N.D.*
13	Demethylchlortetracycline	-	N.D.*	N.D.*

*N.D.; not done.

Human P-K

The skin of a normal volunteer was injected with 0.1 ml. of sterile, five-fold dilutions of the Brazil nut reactor's serum. The volunteer ingested a raw Brazil nut 24 hours later. Reactivity was determined as the lowest concentration of serum required to produce a wheal and flare reaction.

Histamine release from human leukocytes

Specific antigen was added to suspensions of washed peripheral leukocytes from each patient tested. The quantity of histamine released was determined by standard methods.¹⁵

RESULTS

Cutaneous testing

Cutaneous tests (Table V) were performed in 12 patients in whom the causative antigen was determined. Wheal and erythema reactions occurred in all except the patients with salicylsalicylic acid and the demethylchlortetracycline reactions.

Monkey P-K and human P-K

Passive transfer reactions to rhesus monkey were attempted with sera from 9 patients (Table V). In titers varying from undiluted serum to 1 to 125, 8 produced positive reactions.

The patient with the Brazil nut reaction did not transfer to monkey but transferred to a human in a dilution of 1 to 125.

Histamine release from human leukocytes

Leukocytes from 9 patients were challenged with specific antigen. Significant release was obtained from 7. There was no release from leukocytes from a normal donor.

DISCUSSION

Food allergy is sometimes diagnosed without objective criteria and other times ignored despite clinical evidence. This general problem is discussed in detail elsewhere.¹⁶ The positive cutaneous tests, monkey P-K reactions, and histamine release do not establish or confirm a definitive diagnosis of clinically significant food allergy. They are useful methods for studying clinical allergy by immunologic parameters.

Although anaphylaxis to ingestant antigens is rare,⁹ identification of the causative antigen is imperative in order to prevent a subsequent lethal reaction. Among our 15 patients, 6 had recurrent anaphylaxis before coming to our attention, and 2 others had recurrent anaphylaxis before the cause could be identified. Both of the latter failed to admit ingestion of the antigen despite specific inquiry. The penicillin reactor was one of them, and he was questioned specifically about drug ingestion by 4 examiners. No patient has had recurrence after the cause was considered proved or presumed.

Failure to admit ingestion of drugs was not a purposeful attempt to deceive but rather inability of the patient to understand the question related to drug ingestion. Either the patient did not consider the drug as a "drug" or had forgotten the exposure. This occurred despite awareness by the examining physician that such omissions by patients are common.

Identification of the antigen is often difficult. In this series, the 8 who entered the emergency rooms were diagnostic problems, and the diagnosis remains undetermined in 2. The cause was determined in 6.

Eosinophils are frequently associated with allergic reactions.¹⁷ Peripheral eosinophilia was not apparent among these patients with anaphylaxis. The reactions may have been too brief for eosinophilia to develop, or the blood specimens were obtained too early to demonstrate it. Studies utilizing the skin window technique¹⁸ have demonstrated maximum infiltration of eosinophils 24 hours after intradermal injection of antigen in atopic patients. Our patients improved, and blood samples were obtained within minutes after onset and treatment. Case 1 had a WBC of 9,100 with 7 per cent eosinophilia 45 hours after admission. This specimen may have been obtained during the decline of a possibly larger peripheral eosinophilia.

Most of the patients had other atopic diseases, demonstrating their propensity to produce reaginic antibody against a variety of antigens. The data suggest that they had large amounts, but not necessarily unusually high titers, of reaginic antibody against the antigens which caused anaphylaxis. The monkey P-K titers of these patients were equivalent to those of patients with inhalant allergy.¹⁴ Unaltered food antigens are absorbed from the gastrointestinal tract.¹⁹⁻²⁰ Anaphylactic sensitivity may result from various combinations of several possible factors. These include a large amount of antibody,²² high efficiency of antibody,²³ a large amount of antigen,²⁴ systemic absorption of intact antigen, release of increased quantities of mediators,²⁵ and differences in individual reactivity.

Atopic patients have been postulated to have increased mucosal permeability

to antigens.^{26, 27} A nonatopic person, passively sensitized with serum from the patient with the Brazil nut reaction, reacted after ingestion of the nut. Therefore, systemic absorption appears to be a property of this antigen not associated with a mucosal defect in this patient. Other authors¹⁹⁻²¹ have reported systemic absorption of intact food antigens in nonatopic persons.

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