

THE JOURNAL OF
ALLERGY
AND
CLINICAL IMMUNOLOGY

VOLUME 73

NUMBER 6

Continuing Medical Education

This continuing medical education self-assessment program is sponsored by The American Academy of Allergy and Immunology and supported by a grant-in-aid from Fisons Corporation.

Food hypersensitivity

Dean D. Metcalfe, M.D. Bethesda, Md.

The evaluation of reactions after ingestion of foods is one of the more challenging problems in allergy and immunology practice. The extensive differential diagnosis, absence of definitive diagnostic procedures, and lack of a satisfactory prophylactic therapy contribute to the difficulties. However, in the final analysis, the clinical management of food hypersensitivity (allergy) rests on the identification and removal of offending agents (foods) and the treatment of adverse reactions. In general, this approach to the clinical management of food hypersensitivity is the same as the approach to the management of allergic diseases of the skin and the upper and lower respiratory tracts.

The complexity of adverse reactions to foods has led to a confusion in terminology applied to allergic and nonallergic reactions. To standardize terminology, the American Academy of Allergy and Immunology Committee on Adverse Reactions to Foods has suggested definitions to be used in discussing aspects of food-induced reactions (Table I).¹ This terminology will be incorporated in this review.

The clinical expression of food hypersensitivity is

Abbreviations used

RAST:	Radioallergosorbent test
ELISA:	Enzyme-linked immunosorbent assay
PRIST:	Paper radioimmunosorbent test

the result of a series of interactions between ingested food antigens, the digestive tract, tissue mast cells and circulating basophils, and food antigen-specific IgE. In some food-induced diseases such as gluten-sensitive enteropathy and severe milk and soy allergy observed in newborn and older infants, additional immunologic mechanisms are involved. Because of the unique nature of these latter diseases, they will be discussed under separate headings.

INCIDENCE

In view of the extraordinary diversity of foods and substances within foods routinely ingested, it may be considered surprising that hypersensitivity reactions to these materials are relatively infrequent. Although the incidence of true food allergy in the general population is unknown, it is probably less common than perceived by the general public. Food allergy has been variously estimated from 0.3% to 7.5% in children, and the incidence decreases with age.^{2, 3} The incidence is higher in allergic children, approaching

From the Allergic Diseases Section, Laboratory of Clinical Investigation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md.

Reprint requests: Dean D. Metcalfe, M.D., Bldg. 10, Rm 11C210, National Institutes of Health, Bethesda, MD 20205.

TABLE I. Definitions relative to adverse reactions to foods

Term	Definition
Adverse reaction to a food	Clinically abnormal response believed caused by an ingested food or food additive
Food hypersensitivity (allergy)	Immunologic reaction resulting from the ingestion of a food or food additive
Food anaphylaxis	Classic allergic hypersensitivity reaction to food or food additives involving IgE and release of chemical mediators
Food idiosyncrasy	Quantitatively abnormal response to a food or food additive; response differs from its physiologic or pharmacologic effect and resembles a hypersensitivity reaction but does not involve an immune mechanism; anaphylaxis-like reaction may be called "anaphylactoid"
Food intolerance	General term describing an abnormal physiologic response to an ingested food or food additive that is <i>not</i> proved to be immunologic in nature; category includes idiosyncratic, pharmacologic, metabolic, or toxic responses to food or food additives
Food toxicity (poisoning)	Term implying an adverse effect caused by direct action of a food or food additive on host recipient without the involvement of immune mechanisms; nonimmune release of chemical mediators may take place; toxins may be either from the food itself or from microorganisms; anaphylaxis-like reaction may be called "anaphylactoid"
Anaphylactoid reaction to a food	Anaphylaxis-like reaction to a food or food additive as a result of nonimmune release of chemical mediators
Pharmacologic food reaction	Adverse reaction to a food or food additive as a result of a naturally derived or added chemical that produces a drug-like or pharmacologic effect in the host
Metabolic food reaction	Adverse reaction to a food or food additive as the result of the effect of the substance on the metabolism of the host recipient

25% of those with infantile eczema.⁴ Among adult atopic patients, 24% report allergic symptoms on eating or handling various foods.⁵ However, in both adults and children,^{6, 7} challenges with suspected foods have demonstrated that only approximately one third of the patients supposedly allergic to that food react on reexposure. Even so, one is left with a probability that as many as one in 10 atopic adult patients may have reproducible adverse reactions to foods or materials in foods.

GASTROINTESTINAL IMMUNE RESPONSES

Ingested antigenic molecules pass through the epithelium of the gastrointestinal tract by macromolecular transport in adsorptive epithelial cells⁸ and by membranous epithelial or "M" cells.⁹ These antigens then can interact with the mucosal immune system and also gain access to the circulation. A number of nonimmunologic and immunologic host defense mechanisms modulate the host's responses to ingested substances.^{10, 11} Normal bacterial and viral populations that inhabit the gastrointestinal tract¹² are important in preventing overgrowth of pathogenic organisms and maintaining gastrointestinal function. The normal growth of protective microorganisms may be altered by both antibiotics¹³ and diet.¹⁴ Bacterial overgrowth in the gastrointestinal tract is partially limited by normal peristalsis. As long as bacteria are eliminated from the system at a rate equal to their growth, the organism number remains constant. The "blind loop syndrome" with steatorrhea and anemia follows interruption of this normal process.¹⁵

Substances produced by the mucosal and submucosal glands of the gastrointestinal epithelium and by the liver have a role in preserving normal intestinal function. Gastric acidity limits access of organisms into the intestinal tract. Achlorhydria is associated with an increased incidence of gastrointestinal infection¹⁶ and an increase in circulating anti-bovine serum albumin antibodies.¹⁷ The latter observation suggests that certain food proteins are not degraded in achlorhydria and gain access to the small intestine where they are absorbed in greater quantities. Both lysozyme and bile salts affect bacteria. Lysozyme, with or without IgA and complement, may lead to bacterial lysis.¹⁸ The growth of some microorganisms is inhibited in bile salts.¹⁹

Mucous-coat glycoproteins on the gastrointestinal surface have defensive functions including the prevention of parasitic, bacterial, and viral attachment to the epithelium and interaction with allergens and enterotoxins to prevent their penetration across the epithelium.²⁰ A relationship between immunologic reactions and glycoprotein synthesis and release is suggested by two in vivo observations. First, intestinal anaphylaxis

in the rat is accompanied by increased mucus release.²¹ Second, adoptive immunization of *Nippostrongylus*-infected rats augments goblet cell differentiation in the intestinal epithelium.²²

The lining of the gastrointestinal tract is renewed as epithelial cells are lost through normal turnover. Cell renewal can be interrupted by drugs including methotrexate and alcohol and by disease states such as uremia and ischemia. Disruption of the mucosal lining is associated with diarrhea, malabsorption, passage of toxins into the circulation, and with bacteremia.

Immunologic defense systems of the gastrointestinal tract include the reticuloendothelial cells (Kupffer cells) of the liver, immunoglobulin production, cell-mediated immunity, and mast cell activation. The liver is important in that both intact microorganisms and molecules including toxins that cross the intestinal epithelium generally enter the portal system and the liver. The liver, by virtue of an abundance of reticuloendothelial cells, has the capacity to remove these materials. If this system is interrupted in certain liver diseases, entry of unwanted materials may cause symptoms.²³ Furthermore, both humoral and cellular immune responses to antigens injected into the portal circulation differ from those after injection of antigen into the inferior vena cava,²⁴ demonstrating an effect of liver cells upon the immunologic response.

The humoral immune system of the gastrointestinal tract includes the local production of IgA and IgM. In adults, IgA-producing cells predominate, with IgM-producing cells being the next most common (6% to 18%), then IgG-producing cells (3% to 4%), and, finally, IgE and IgD isotypes (less than 1%).^{25, 26} The levels of IgA in adult human jejunal secretions have been reported as 27.6 mg/100 ml.²⁷ In contrast, exocrine fluids of newborn infants are devoid of IgA and IgM. Immunoglobulins in intestinal secretions then increase with exposure of the individual to bacterial and food antigens. IgM production appears particularly important in infants as judged from antibody response to oral vaccination with *Escherichia coli*.²⁸ Measurement of fecal IgA antibodies in bottle-fed, healthy infants suggests that the intestinal IgA-producing cell system may reach maturity as early as 1 to 2 mo.²⁹

Induction of the humoral immune response appears to occur primarily in the Peyer's patches. Here, antigens enter through the epithelium into the subepithelial zone where lymphocyte sensitization occurs. Primed lymphocytes leave via the efferent lymphatics, pass through the mesenteric nodes and thoracic duct, and then pass into the systemic circulation.³⁰ These cells migrate through the spleen and other organs and return to the lamina propria³¹ where

B-lymphocytes complete their differentiation into plasma cells. IgA synthesized by these cells in the mucosa is dimeric, and IgM is pentameric, as determined by the incorporation of polypeptide "joining" or "J" chains.³² When J chains containing IgA and IgM are released into the interstitial fluid, each molecule is joined to an epithelial glycoprotein termed "secretory component" or "secretory piece." The secretory piece in turn aids in the transport of immunoglobulin across the epithelial cells to the lumen and helps the immunoglobulin to resist proteolysis.

Gut-associated immunoglobulins function in the defense against microorganisms and control of antigen absorption. Secretory IgA prevents bacterial adherence to mucosal surfaces.³³ Secretory immunoglobulins against viruses including polio aid in host defense against these agents.³⁴ IgE develops in association with certain parasitic infections and may play a role in parasite expulsion. Local immunization in rats with horseradish peroxidase or bovine serum albumin results in reduction in antigen absorption.²³

Cell-mediated immunity can be demonstrated in the gastrointestinal tract. This immunity may be independent of a comparable systemic immunity.³⁵ Priming of T cells to luminal antigens can occur in Peyer's patches.³⁶ These cells may also travel via the thoracic duct to the bloodstream and return to the lamina propria as T-effector cells. Cell-mediated immunity probably participates in the protection of the gastrointestinal tract against infection, especially against organisms where the response of the immune system is that of delayed hypersensitivity.

The majority of allergic reactions to foods is believed to be IgE-mediated, mast cell-dependent immediate hypersensitivity reactions. The first requirement in the development of an immediate hypersensitivity reaction is the inherited ability of a given individual to form IgE to specific substances in the environment. In food hypersensitivity, the specific substances are food-derived antigens. This presence of IgE on mast cell surfaces which reacts with food antigens has been demonstrated by immediate wheal and erythema reactions in the skin after local injection of minute amounts of food antigen.⁷ Such reactions have been passively transferred by intracutaneous injection of allergic sera into the skin of normal recipients followed by local injection 24 hr later of food antigen to which the donor is sensitive (Prausnitz-Kustner test). This test, useful in demonstrating the passive transfer of a sensitizing agent in the serum, was discovered by injecting the serum of Kustner, who was allergic to fish, into Prausnitz and eliciting a positive response on local challenge with fish antigen.³⁷ Similar local reactions have been reported when the food antigen was

administered orally 24 hr after injection of serum into the skin.³⁸

Food antigen-specific IgE indirectly has been demonstrated to lead to the degranulation of mast cells in the gastrointestinal tract. Local mucosal reactions reminiscent of those that follow mast cell degranulation in human skin have been reported in vivo after passive sensitization of human ileum and colonic mucosa.³⁹ Local reactions after passive sensitization could be induced by ingestion or by direct application of the antigen. Human mucosal mast cells have also been reported to degranulate in vitro in IgE-dependent reactions.⁴⁰

Mast cells, reportedly observed in gastrointestinal tissue as early as the third fetal month, gradually increase in number during infancy and childhood until adult levels are reached.⁴¹ While human skin contains, on the average, 7000 mast cells per cubic millimeter, the human duodenal mucosa contains approximately 10,000 to 20,000 mast cells per cubic millimeter. Mast cells are particularly found in the mucosa and submucosa in the gastrointestinal tract.⁴² Mast cells in the mucosa tend to be distributed randomly throughout the lamina propria. Mast cells are especially prominent in the loose connective tissue in the duodenal mucosa in and around Brunner's glands. Mast cells in the submucosa, muscular layer, and serosa appear both in approximation to small blood vessels and nerves and at sites distant from the vessels. The number of cells found within the mucosa varies considerably depending on the level of the gastrointestinal tract examined. Thus the mucosa of the stomach, duodenum, and ileum contains more mast cells than do the esophagus, colon, and rectum. Variations in submucosal, muscular, and serosal mast cells are less extreme among biopsy sites.

In rodents where gastrointestinal mast cells have been carefully studied, mast cells in the lamina propria differ from mast cells in the submucosa and skin as reviewed elsewhere.⁴³ They stain less intensely with toluidine blue and contain fewer and more heterogeneous granules. These mast cells demonstrate a T-lymphocyte dependent increase during parasitosis. Mucosal mast cells are thus termed "atypical mast cells." Similar differences may exist in man, although this is far from certain.

There is evidence that gastrointestinal mast cells degranulate not only to IgE-mediated stimuli but to complement-derived anaphylatoxins C3a and C5a as well. It is known that IgA, IgG, and IgM, some of which are directed against specific food determinants, are present in gastrointestinal secretions.⁴⁴ Interaction of food with IgM or IgG may lead to complement deposition in gastrointestinal tissues as observed in patients with cow's milk sensitivity.⁴⁵ Such comple-

ment activation and the concomitant generation of anaphylatoxins could lead to mast cell degranulation. An IgG antibody, termed heat-stable, short-term sensitizing antibody, has been reported in sera from children developing symptoms approximately 24 hr after milk ingestion.⁴⁶ Such IgG antibodies reportedly sensitize monkey skin at 2 to 4 hr, have agglutinating activity, and do not compete with IgE reagents for cell receptors. The clinical significance of such observations is not clear. Finally, in evaluating reactions involving the gastrointestinal tract, it should be remembered that mast cells may also degranulate to pharmacologic agents such as codeine.

The possible sequence of events after mast cell degranulation within gastrointestinal tissues includes: local changes in vasopermeability, stimulation of mucous production, increase in muscle contraction, stimulation of pain fibers, and recruitment of inflammatory cells. Local intestinal anaphylaxis has been demonstrated to facilitate the passage of macromolecules through the gastrointestinal barrier.¹⁰ The local reaction increases mucosal permeability and the entry of food antigen into the body where it may be distributed to other target organs, initiating degranulation of mast cells at those sites. The gastrointestinal tract, by virtue of its food processing, is also in a position to alter the timing of type I reactions. Antigenic sites on food antigens may be unmasked or degraded as food is digested. As food passes through the digestive tract, additional antigen sites may be exposed for interactions with specific IgE on epithelial, mucosal, and submucosal mast cells.

CLINICAL FEATURES

Immunologically mediated reactions to foods and materials within foods are expressed by a spectrum of signs and symptoms from abdominal pain to generalized anaphylaxis. These expressions of food allergy are influenced by factors including the age and awareness of the patient, the quality and quantity of food ingested, and the type and extent of associated medical problems. With such modulating factors in mind, the clinical reflection of food allergy can be divided into that resulting from the action of offending foods on the initial contact organ, which is the digestive tract, and on secondary contact systems including skin, lungs, and blood vessels.

The oropharynx and gastrointestinal tract are the initial sites of exposure to food antigens. Edema and pruritus of the lips, oral mucosa, and pharynx may be reported as the food contacts the mucosa. Such reactions are transient and not necessarily followed by other allergic manifestations. Entry of offending foods into the stomach and subsequently into the intestine may result in nausea, cramping, pain, abdomi-

TABLE II. Differential diagnosis of food hypersensitivity*

I. Additives and contaminants	2. Pesticides
A. Dyes	3. Antibiotics
1. Tartrazine	II. Gastrointestinal diseases
B. Flavorings and preservatives	A. Structural abnormalities
1. Nitrites and nitrates	1. Hiatal hernia
2. Monosodium glutamate	2. Internal obstruction
3. Sulfiting agents	B. Enzyme deficiencies
4. Sodium benzoate	1. Lactase deficiency
C. Toxins	2. Glucose-6-phosphate dehydrogenase deficiency
1. Bacterial	3. Galactosemia
a. Botulism	C. Malignancy
b. Staphylococcal intoxication	D. Other
2. Mushroom toxins	1. Peptic ulcer disease
3. Mycotoxins (aflatoxins)	2. Gallbladder disease
4. Seafood-associated	3. Cystic fibrosis
a. Saxitoxin (shellfish)	III. Endogenous pharmacologic agents
b. Scombroid poisoning (histamine)	A. Caffeine
c. Ciguatera poisoning (fresh reef fishes as grouper, snapper)	B. Theobromine
D. Infectious organisms	C. Histamine
1. Bacteria	D. Tyramine
a. Salmonellosis	E. Tryptamine
2. Parasites	F. Dopamine
a. Giardiasis	G. Norepinephrine
b. Trichinosis	H. Serotonin
c. Diphyllbothriasis	I. Phenylethylamine
3. Viruses	J. Alcohol
a. Hepatitis	K. Hallucinogenic alkaloids
E. Insect parts	IV. Psychological reactions
F. Mold antigens	V. Other
G. Accidental contaminants	A. Collagen vascular diseases
1. Heavy metals	B. Endocrine disorders

*The list is not comprehensive. Examples only are given.

nal distension, vomiting, flatulence, and diarrhea. Gastrointestinal problems are prominent in infants where milk antigens are often incriminated. These symptoms of gastrointestinal involvement can be the only expression of food allergy. Gastrointestinal complaints may be accompanied by hyperactive bowel sounds and a change in abdominal girth. Occult fecal blood loss, malabsorption, protein-losing enteropathy, functional intestinal obstruction, and eosinophilic infiltrates have all been associated with gastrointestinal allergy.⁴⁷

Food allergy may also be expressed in one or more extraintestinal target tissues. The basis of the preferential reactivity of one system over another is unknown. The skin is a common target organ in food allergy. Skin reactions are evidenced by acute urticaria and/or angioedema and much less frequently by chronic urticaria.⁴⁸ In one report of 554 patients with urticaria, food allergy was demonstrated as the cause in only 1.4%.⁴⁹ Atopic eczema exacerbated by foods has been demonstrated in children.⁵⁰ Adult

eczema appears less frequently to be related to food sensitivity. Asthma and rhinitis caused by food allergy are more common in children⁷ than in adults.⁵¹

Systemic anaphylaxis as a result of allergy to ingested foods generally occurs within minutes but occasionally has been reported hours after ingestion of the offending food.⁵² The first anaphylactic episode may be unexpected or may be preceded by minor symptoms such as abdominal discomfort or urticaria on previous exposure to the food. Systemic anaphylaxis involves multiple target organs as evidenced by abdominal pain, nausea, emesis, diarrhea, dyspnea, cyanosis, chest pain, urticaria, angioedema, arrhythmias, hypotension, and shock.

DIAGNOSIS

The diagnostic process in food allergy starts with a careful medical history and physical examination directed at distinguishing food hypersensitivity from other causes of adverse reactions to foods (Table II). Skin tests and in vitro tests for antigen-specific IgE

TABLE III. Characteristics of purified water-soluble food allergens

Allergen	Source	Molecular weight	Composition	Characteristics
Antigen M	Codfish	12,328	113 Amino acids to 1 glucose	Parvalbumine, chelates calcium, relatively acid and protease resistant
Antigen II	Shrimp	38,000	96% Protein; 4% carbohydrate	Heat stable
Peanut I	Peanut	—	91% Protein; 9% carbohydrate	Relatively acid and protease resistant
Soybean trypsin inhibitor	Soybean	20,500	Polypeptide chain, two disulfide bridges	Relatively acid and protease resistant

are used in selected cases to support the clinical diagnosis. When skin tests are required and judged safe, confirmation of the diagnosis may be obtained by oral challenge with suspected foods.

History

A detailed report of the reaction including the presentation must be obtained. Symptoms and signs of food reactions include pruritus, hives, eczema, angioedema, abdominal pain, nausea, vomiting, diarrhea, asthma, hypotension, and rhinitis. One or several symptoms and signs may occur with the same food on different occasions. The severity of the reaction may be gauged by the extent and duration of symptoms and the treatment required for control. The patient should be specifically questioned to determine the setting of the reaction; for example, did reactions occur only when exercise followed eating?

Foods of particular interest are identified by their ingestion in some proximity to the reaction. With the use of food challenge, a number of foods have been implicated in immediate allergic reactions in children and adults. These foods include peanuts, nuts, egg, milk, soy, fish and other seafood, banana, and chicken.⁵³ However, many additional foods have the potential to cause food allergies, although less frequently.

A limited number of specific food antigens responsible for immediate hypersensitivity reactions have been isolated and characterized as reviewed elsewhere.⁵⁴ These include allergens from codfish,^{55, 56} shrimp,⁵⁷ peanut,⁵⁸ and soybean⁵⁹ (Table III). Protein fractions from cow's milk and egg have also been examined for antigenicity. Cow's milk consists of casein (80%) and whey proteins (20%). Beta lactoglobulin is the principal protein in whey, appears to be the most allergenic of the milk proteins, and is relatively resistant to heating and to proteases. It is a glycoprotein with a molecular weight of 36,000 and contains two identical polypeptide chains, each with a

molecular weight of 18,000. Other proteins in milk include alpha lactalbumin, bovine serum albumin, and bovine gamma globulins. Casein and beta lactoglobulin are synthesized in the mammary gland and do not appear to have a relationship to bovine plasma proteins. Individuals reactive to egg are usually sensitive to the egg white. Ovalbumin and ovomucoid are the primary allergens in egg white protein. Both are present in uncooked and cooked egg. Conalbumin (ovotransferrin) is also allergenic. Lysozyme appears to be much less allergenic.⁶⁰

Allergenic food proteins, although generally heat and enzyme resistant, may be altered by food preparation. Factors such as whether the food was raw, cooked, or otherwise processed are of importance. Food antigens capable of inducing allergic responses may be limited to only part of the food, such as the skin from an apple, or may only be transiently present at a certain stage of ripeness. A suspected food may fail to consistently lead to an allergic reaction. Reasons for this inconsistency include the amount consumed (larger amounts are more likely to induce reactions), the presence of other simultaneously ingested foods that may delay digestion, the state of the food, and the possibility that concomitant medications such as antihistamines may have masked the reactions. It has been suggested that in some cases food reactions are noticed only when the individual is suffering from other allergic problems. Certain foods appear more likely to cause problems in patients with specific inhalant allergies. Thus ragweed-sensitive patients are more likely to react to camomile tea.

Foods may be contaminated by other foods as well as contain a wide variety of substances that lead to reactions that may be confused with food allergy (Table II). Cross contamination of one food by another may take place before processing, during processing, and during food preparation. Mold contaminants are prominent in fermented food products such as cheese, dried fruits, yogurt, and wine. Insect parts

can contaminate spices and other foods. Drugs, dyes, additives, bacteria, and bacterial products occasionally contaminate foods. Milk from cattle has been contaminated with bacitracin, penicillin, and tetracycline used to treat bovine diseases. Dyes such as tartrazine yellow (Food, Drug, and Cosmetic No. 5) cause non-IgE-mediated hypersensitivity reactions in some individuals who are sensitive to aspirin.⁶¹ The amount of natural salicylates in foods is small, and for that reason it is unlikely that they provoke problems even in aspirin-sensitive patients.¹ Sulfiting agents used to reduce spoilage of such foods as lettuce and shrimp, to inhibit undesirable microorganisms during fermentation such as in wine making, to sanitize food containers, and to prevent oxidative discoloration of foods have been demonstrated to induce problems reminiscent of allergic diseases. Foods that may have higher amounts of sulfiting agents include salads, dehydrated potatoes, fruits, vegetables, wines, shrimp and other seafood, baked goods (especially pizza crust and tortilla shells), tea mixes, and vegetable and fruit juices. Several asthmatic patients had the onset of severe wheezing and associated anaphylactoid symptoms and signs after challenge with potassium metabisulfite in one report.⁶² Monosodium glutamate in sufficient quantity (usually 3 to 6 gm) can lead to the "Chinese restaurant syndrome" consisting of a warmth or burning sensation, especially over the head and shoulders, stiffness or tightness, weakness in the limbs, pressure, tingling, headache, light-headedness, and gastric discomfort occurring approximately 15 minutes after ingestion.⁶³ Bacteria and bacterial toxins may cause both gastrointestinal and systemic symptoms and may be confused with food allergy. The diagnosis of botulism or fish, shellfish,⁶⁴ and mushroom poisoning must not be overlooked in the emergency room when a patient presents with a "food reaction." Scombroid poisoning, caused by the ingestion of tuna, mackerel, and related fish containing high levels of histamine resembles food allergy and can be confirmed by high levels of histamine in the implicated fish. Persons on isoniazid (a histaminase inhibitor) may be especially sensitive. Giardiasis may be accompanied by cramping, diarrhea, flatulence, malabsorption, and urticaria.

Naturally occurring substances in some foods may cause problems confused with food allergy. Prunes, cucumbers, beans, fruits, soybeans, and onions contain substances that may lead to gastroenteric symptoms by irritation or pharmacologic activity. Amines such as tyramine and phenylethylamine, nitrates and nitrites, and alcohol may cause headaches in susceptible individuals. Methylxanthines (caffeine, theobromine, and theophylline) are found in coffee, tea,

cola, and chocolate. These substances cause nervousness, tremor, and tachycardia in large amounts. Vasoactive amines (epinephrine, norepinephrine, tyramine, dopamine, histamine, and 5-hydroxytryptamine) are found in bananas, tomatoes, avocados, cheeses, pineapples, and wines. Patients on monoamine oxidase inhibitors are susceptible to hypertension if they ingest foods high in such amines. Chocolate also contains phenylethylamine. Histamine may be present in wine.

Primary gastrointestinal diseases can lead to acute symptomatology after food ingestion. Examples are hiatal hernia, gastric and duodenal ulcers, cholelithiasis, gastric malignancy, diverticulosis, and vascular insufficiency. Gastroesophageal reflux may cause bronchial irritation, chronic cough, and wheezing in young children and infants. Collagen vascular diseases such as scleroderma and systemic lupus erythematosus can have associated gastrointestinal manifestations. Functional gastrointestinal reactions can be confused with adverse reactions to foods.⁶⁵

A deficiency of lactase or other enzymes can resemble food allergy. Lactase deficiency may be familial or acquired and can be associated with gastrointestinal infections and inflammatory bowel diseases. It may develop during infancy, childhood, or adulthood. Lactose is the principal carbohydrate of milk, and individuals with lactase deficiency demonstrate milk intolerance. Symptoms include bloating, cramping, and diarrhea. These effects result from the persistence of lactose in the gut, which exerts an osmotic effect that brings fluid into the intestinal lumen. In addition, colonic bacteria produce lactic acid and fatty acids from fermentation of the lactose that decreases the pH of the stool. Lactase deficiency has been estimated to occur in 5% to 20% of white North Americans, but the incidence may approach 80% to 90% in Asiatic people, black North Americans, Africans, Greenland Eskimos, and some Arab populations. A lactose tolerance test can be performed by the oral administration of approximately 0.75 to 1.5 gm of lactose per kilogram of body weight. In a positive test, blood glucose increases less than 20 mg/dl above the fasting glucose level. False-positive and false-negative results occur in approximately 20% of normal subjects. The determination of breath hydrogen after 50 gm of lactose is more specific. Colonic bacteria produce hydrogen from unadsorbed lactose with an increase in breath hydrogen.

The use of diets in diagnosis

When the relationship between ingestion of certain foods and resulting symptoms is unclear, the use of an elimination diet may be warranted. The likelihood of

TABLE IV. Common food groupings*

Animal			
Crustacea	Pelecypoda	Cephalopoda	Osteichthyes
Shrimp	Oyster	Octopus	Sardine
Crab	Clam	Squid	Trout
Lobster	Scallop		Salmon
Crayfish	Abalone		Whitefish
Vegetable			
Bromeliaceae	Gramineae	Leguminosae	Rutaceae
Pineapple	Barley	Kidney bean	Lemon
Chenopodiaceae	Corn	Lima bean	Grapefruit
Spinach	Oats	String bean	Orange
Compositae	Rye	Pea	Solanaceae
Lettuce	Wheat	Peanut	White potato
Cruciferae	Rice	Soybean	Chili pepper
Horseradish	Juglandaceae	Liliaceae	Tomato
Cabbage	English walnut	Garlic	Sterculiaceae
Mustard	Pecan	Onion	Chocolate
Cucurbitaceae	Lauraceae	Asparagus	Cola
Squash	Cinnamon	Palmaceae	Umbelliferae
Cantaloupe	Bay leaf	Coconut	Carrot
Watermelon		Polygonaceae	Caraway seed
Cucumber		Buckwheat	Dill
Drupaceae		Pomaceae	Celery
Almond		Apple	
Plum		Pear	
Peach		Rosaceae	
Apricot		Strawberry	
Cherry			

*Examples only.

establishing a diagnosis by use of elimination diets is higher when fewer foods are responsible for the symptoms. Elimination diets followed by the return of suspect foods to the diet should be applied only in situations where symptoms are not life-threatening, such as in chronic hives or rhinitis. It should be remembered throughout the diet-testing procedure that changing the type and amount of foods may also alter the symptoms of diseases such as disaccharidase deficiency, gluten-sensitive enteropathy, and cystic fibrosis. Before any diet is initiated, it is useful for the patient to remain on the usual diet for 1 to 2 wk. During that time the patient records the type and amount of foods ingested and the occurrence and character of adverse reactions. This record is useful in searching for suspect foods and in establishing baseline symptoms against which the success or failure of elimination diets can be measured. If symptoms fail to appear within this baseline period, the occurrence of symptoms is too infrequent to be appreciated during the period of an elimination diet. If no more than a few foods are suspects as the cause of symptoms, the initial elimination diet can consist simply of removing these foods. Such an approach is more likely to be of

benefit in pediatrics where allergy to such foods as milk, egg, or soy is common in early life. Care must be taken that suspected foods are not inadvertently consumed while they are hidden in other foods. For example, common foods such as eggs and corn are found in such food mixtures as margarine, mayonnaise, and salad dressing. Furthermore, biologic cross-reactivity between foods in food groups may occur in some instances (Table IV). Detailed food classifications are available elsewhere.¹

If removal of one or several foods from the diet is not successful in eliminating symptoms, if multiple food sensitivities are suspected, or if symptoms are unlikely to be caused by foods such as is the case in chronic urticaria, initiation of a severely limited diet is sometimes warranted. Severe elimination diets, especially in children, can be used for only short periods of time. Extensive elimination diets for infants under 3 mo of age include milk substitute alone; 3 to 6 mo of age, milk substitute and rice cereal; 6 mo to 2 yr, milk substitute with vitamin supplement, rice cereal, applesauce, pears, carrots, squash, and lamb;⁶⁶ and for older children and adults, lamb and rice. Caution must be taken to instruct the patient to take nothing by

mouth but the foods on the diet and water. Both oral and topical medications including aspirin, vitamins, laxatives, and creams must be avoided when it is possible. Continuation of symptoms while patients are on restricted diets indicates that the symptoms are not caused by foods. The unlikely possibility that the individual foods on the restricted diets themselves cause symptoms may be eliminated by substituting other foods that are known not to correlate with symptoms. If symptoms resolve on the restricted diet, resumption of a normal diet should be accompanied by a return of symptoms; subsequent resumption of the restricted diet should alleviate these symptoms. Such cycling should reproducibly eliminate or provoke symptoms in order to allow the conclusion that symptoms are secondary to foods. If a relationship to diet is established, foods representing food groups eaten by the patient during the control period should be returned individually to the diet in normal amounts at intervals of 3 to 4 days. Foods returned to the diet without induction of symptoms may remain in the diet. Foods provoking symptoms should be removed until the procedure is completed. If resumption of symptoms is associated with the introduction of specific foods, then this cause-and-effect relationship must be verified by the disappearance of symptoms on elimination of that food. Although the procedure described is lengthy, it is direct and applicable to either inpatient or outpatient evaluations with a minimum of confusion.

Techniques by use of food extracts

A number of in vivo and in vitro procedures use food extracts in the diagnosis of food allergy. These techniques include skin testing, RAST, ELISA, and basophil histamine release.

1. *Skin testing.* Skin testing with foods involves the application of dilute water-soluble suspensions of food extracts to the dermis.^{7, 67} If the recipient has IgE antibody to the food antigen, local wheal-and-flare reactions typical of type I hypersensitivity are produced. Individuals may have positive skin tests in the absence of food allergy (false positive). However, allergic reactions to foods appear unusual in the face of negative skin tests (false negative).⁷ Skin testing with food extracts is performed by use of scratch or puncture techniques. Intradermal testing is avoided generally because of a greater danger of systemic reactions; nonspecific irritant reactions are also more frequent. Selected food extracts including nuts, egg, milk, soy, and fish correlate fairly reliably with allergic manifestations. However, patients should never be advised that they are allergic to certain foods solely on the basis of positive skin tests. Because of the risk

of anaphylaxis, skin testing with food extracts should be performed only by a physician experienced in this procedure. Recent pediatric studies have demonstrated that food extracts in a concentration of 1:20 w/v applied by the puncture technique give 3-millimeter or larger wheals in subjects having allergic reactions to foods verified by oral food challenge.⁶

2. *RAST and ELISA.* The RAST and ELISA are directed at an in vitro demonstration of IgE directed to specific antigens. The RAST is the most commonly used in vitro diagnostic test. It has also proved useful as a research tool in the identification of antigens in foods to which patients may react and as a tool in the standardization of allergenic extracts. Clinically, the RAST is used where skin testing with extracts might pose a hazard, particularly of anaphylaxis, in patients suspected of being exquisitely sensitive to a particular antigen. It may also be used both in patients with skin disease such as eczema so extensive as to preclude skin testing or in patients with severe dermatographism. The RAST is, however, less sensitive than direct skin testing⁶⁸ and more expensive. The ELISA, developed after the RAST, may also be used to measure antigen-specific IgE. The ELISA has similar potential to the RAST in the identification of food antigen-specific IgE.⁶⁹

3. *Basophil histamine release.* Peripheral blood basophils from individuals with suspected food allergies can be examined in vitro to determine if they degranulate to dilute suspensions of food antigens. Degranulation requires the presence of IgE on the basophil specific to the suspected food. Such degranulation can be monitored by histamine released into the supernatant fluid. Basophil-degranulation testing procedures correlate with skin tests but do not establish a diagnosis of food allergy, are time consuming, and appear to have no advantage over skin testing.⁷⁰ A high, spontaneous in vitro release of histamine from basophils taken from subjects allergic to foods has been reported.⁷⁰

4. *Controversial techniques.* Cytotoxic testing, provocative subcutaneous testing, and provocative sublingual testing use food extracts to diagnose food sensitivity. Cytotoxicity testing is based on the claim that a specific allergen added in vitro to whole blood or to serum leukocyte suspensions will result in reduction in white cell count or death of the leukocytes. Provocative subcutaneous testing and provocative sublingual testing involve subcutaneous injection or sublingual administration of sufficient antigen to elicit symptoms corresponding to the patient's complaints. A 1981 position statement issued by the American Academy of Allergy and Immunology held all three techniques to be unproven and stated that their use

should be limited to well-constructed diagnostic trials.⁷¹

Oral challenge in diagnosis

Oral food challenge may be used occasionally for the diagnosis of food intolerance if the correlation between specific foods and symptoms remains unclear. It need not be used if the medical history, physical examination, skin testing, and dietary studies have resulted in a diagnosis. The use of oral challenge to reproduce symptoms should be avoided in cases where there is a history of severe generalized anaphylaxis to the suspected food. Furthermore, no food challenge is without the risk of side effects, and the patient must be made aware of these dangers. Such procedures should be done only under the supervision of a physician.

Food challenge may be performed in an "open," a "single-blind," or a "double blind" manner. In an open food challenge, both patient and physician are aware that a specific food is being administered. In a single-blind food challenge, only the patient is unaware of what food is being administered. In a double-blind food challenge, the patient remains unaware of whether a specific food or a placebo is being administered and a "neutral" observer such as a physician or nurse is also unaware of what is being administered. The results are scored by the patient and the medical observer. This last technique must be used if a positive challenge requires only a subjective response on the part of the subject. During challenge procedures, the patient should remain on a limited diet with foods that are known not to cause symptoms. The food being tested should be prepared preferably in the same state as the food that may have led to a reaction. The amount of food administered as a test dose is governed by the apparent degree of the suspected hypersensitivity. An initial dose of 10 to 100 mg is reasonable in most cases. The patient should be observed preferably for a period of time exceeding the time determined in the history between food ingestion and symptoms. If no symptoms are reproduced by the test dose, the challenge should be repeated with the use of increasingly larger doses (twofold to tenfold increments) until the amount of food ingested exceeds that taken by history. This procedure is repeated until all suspected foods have been examined.

In blinded procedures, suspected foods may be administered by being masked within other foods, placement within an opaque gelatin capsule, or insertion via a nasogastric tube. The last procedure is poorly tolerated by most patients and generally is not used. Any food or capsule used to hide material being

administered must itself be demonstrated not to induce symptoms. Not all foods are masked by the same foods. For example, up to 8 gm of shrimp may be blended into a 250-milliliter vanilla milkshake without the shrimp being detected. In contrast, the taste of peanuts blended into a similar milkshake is easily detected. A single 00 gelatin capsule holds from 300 to 600 mg of dried food. When calculating equivalent doses of dried foods, it must be remembered that water content varies widely. Eight grams of dried milk is equivalent to 62 gm (2 oz) in the liquid state.

In a double-blind food challenge, an unequivocal positive reaction such as hives or asthma is reasonable evidence of an adverse reaction to a food. In cases of subjective complaints, a number of positive tests to a suspect food along with negative placebo tests are necessary to substantiate the diagnosis. Acceptance of a positive test does not prove that an immunologic mechanism is responsible.

No blind oral food challenge can be perfect for a number of reasons. Presentation of food in capsules omits the possibility of reactions in the mouth, pharynx, and esophagus as well as effects on the food of early digestion by salivary enzymes. Small amounts of foods may be regurgitated or eructated and identified by the subject's sense of taste and smell. The significance of negative challenge tests needs to be established clearly by long-term clinical follow up. A positive response is clearly diagnostic, but one or even several negative responses may not absolutely exclude sensitivity to that food in some complicated situations. There may be unknown relationships between suspected foods and periods of abstinence from that food before challenge. The presence of other foods eaten with a suspected food may have facilitated or inhibited digestion and absorption.

DELAYED REACTIONS TO FOODS

In addition to immediate reactions to foods, examples exist of chronic gastrointestinal conditions associated with specific foods in certain individuals. These conditions include gluten-induced enteropathy, food protein-induced gastroenteropathy, and hyper-eosinophilic gastroenteritis. In such diseases the immunologic mechanisms involved may include delayed hypersensitivity, antigen-antibody complex formation with complement activation, and IgE-mediated mast cell degranulation.

Gluten-induced enteropathy, or nontropical sprue, is a disorder characterized by intolerance to gluten, a protein found especially in wheat. There is a marked increase in the prevalence of the major histocompatibility antigens, HLA-B8 and HLA-Dw3, in patients with this disorder. The toxic component of gluten

appears to be gliadin, the alcohol-soluble component of gluten. Peptides of gliadin obtained by proteolytic digestion are also toxic. These peptides are rich in proline and glutamine and poor in aromatic amino acids and carbohydrates. The mechanism by which gluten damages the intestinal mucosa of susceptible individuals has been the subject of intense study. One early suggestion was that the disease was caused by a deficiency of specific enzymes required to degrade gluten. Later it was postulated that celiac disease followed an abnormal immunologic response to gluten. Recently, an enterocyte cell-surface abnormality has been suggested that allows gluten to bind to its surface and induce toxicity. In gluten-sensitive patients, the ingestion of gluten generally leads to a blunting and flattening of the mucosal surface, a villous atrophy, and a dense infiltration of the lamina propria with inflammatory cells. Clinically these changes are reflected in malabsorption characterized by diarrhea, bloating, steatorrhea, and weight loss. The diagnosis requires evidence of malabsorption, an abnormal jejunal biopsy specimen with characteristic changes, and clinical and histologic improvement on a gluten-free diet. A few patients require prolonged adherence to a gluten-free diet before improvement.

An associated asymptomatic gluten-sensitive enteropathy is observed in most patients with dermatitis herpetiformis that mimics gluten-induced enteropathy both morphologically and in response to gluten. This disease is histologically characterized by dermal papillary collections of neutrophils and subepidermal vesicle formation. IgA and complement deposits are reported at the epidermal-dermal junction. Dermatitis herpetiformis is characterized by itchy, chronic, papulovesicular eruptions, usually symmetrically distributed on extensor surfaces. The buttocks, sacrum, shoulders, posterior nuchal area, and scalp may be involved. There is a marked increase in patients who are positive for the HLA-B8 and HLA-Dw3 antigens and in certain B cell antigens. The sulfones or sulfapyridine has been the mainstay of therapy. However, it is now clear that the skin disease often responds to strict adherence to a gluten-free diet.

Food protein-induced gastroenteropathy is a disease of infants and children where chronic gastrointestinal disease appears caused by a sensitivity to, in most cases, milk or soy protein.^{72, 73} Such patients clinically express diarrhea and malabsorption. The identification and removal of the offending protein from the diet result in improvement. Reintroduction of the protein is followed by an exacerbation of the problem. Changes vary from minor inflammatory changes to villous atrophy in mucosal biopsy specimens. This problem does not appear permanent with

many children able to tolerate the milk or soy proteins in later life. The immunologic mechanisms responsible are not clear, although there is some evidence for the participation of immediate hypersensitivity reactions or concurrent viral infections.⁴⁵

A combination of peripheral blood eosinophilia and eosinophilic infiltration of the gastrointestinal wall without evidence of vasculitis is observed in eosinophilic gastroenteritis.⁷⁴ Immediate hypersensitivity mechanisms appear to be involved in some patients as evidenced by elevated serum IgE levels, multiple positive skin tests to inhalants and foods, and exacerbation of abdominal pain and diarrhea after ingestion of specific foods. Even in cases where foods are believed to be involved, the institution of a severe elimination diet is frequently ineffective. Steroids are effective in selected cases.

A number of complaints such as abdominal pain, headache, tension, fatigue, and depression are believed by some individuals to be caused by certain foods. Multiple foods are often suggested as the cause of any or all of the above complaints in these instances that occur hours to days after food ingestion. Such associations remain unproven. Several centers are currently investigating such claims to determine if there is a cause-and-effect relationship.

THERAPY

The preferable approach to the medical management of any disease is prevention. In the case of food allergy, this concept forms the basis for the recommendation that infants be breast-fed when it is possible. This is particularly important for children of atopic parents. Breast-feeding avoids exposure of the immature gastrointestinal system to foreign milk and other proteins. The question as to whether breast-feeding will decrease the likelihood of children of atopic parents developing other allergies in later life remains to be answered.

The management of an immunologically mediated food reaction consists of dietary avoidance and the pharmacologic treatment of symptoms resulting from inadvertent exposure. There is no evidence at present to support injection immunotherapy or oral desensitization in the treatment of food allergy. An individualized treatment plan must be established for each patient that takes into consideration the number of foods involved, the degree of sensitivity, and the severity of symptoms. In designing an elimination diet for long-term use, care must be taken to provide optimal nutrition while completely eliminating the offending foods. Hidden sources of foods must be explained to the patient to reduce the risk of unexpected exposure to the offending food. Knowledge of the

botanic families, as well as the classification of foods from animal sources, is important, since cross-reacting antigens may be found among foods in the same group (Table IV). For example, patients sensitive to shrimp often experience symptoms after the ingestion of other crustaceans. When treatment is first instituted, strict avoidance of all sources of the offending food should be observed. If the initial diagnosis is correct and compliance is maintained, improvement in the patient's condition should result. Eventually, in the absence of anaphylactic sensitivity, small amounts of the offending food may be tolerated on cautious reintroduction into the diet. For example, small amounts of egg may be tolerated when it is used as an ingredient in the preparation of other foods. In addition, certain foods not tolerated raw may be ingested without difficulty when they are completely cooked.

The later the onset of a food allergy the less likely that the sensitivity will be lost. Most infants sensitive to cow's milk outgrow this problem by 2 yr of age. Children diagnosed as having food allergy after 3 yr of age were also less likely to outgrow the allergy.⁷⁵

Even the most careful patient may inadvertently ingest the food to which he is sensitive. When the resulting symptoms of this exposure involve sites distant from the gastrointestinal tract, the treatment for each specific symptoms is no different than when other provocateurs are involved. For example, the treatment of food-induced urticaria is the same as the treatment of idiopathic urticaria, while asthma resulting from food ingestion is managed as asthma provoked by other allergens. Gastrointestinal symptoms after inadvertent food ingestion are usually treated with antihistamines. The treatment for anaphylaxis differs only slightly from the treatment of idiopathic anaphylaxis. If the patient does not respond to epinephrine administration and other initial resuscitative measures, gastric lavage may be indicated to decrease further antigen absorption. The patient with anaphylactic sensitivity should be taught how to self-administer epinephrine and should have an epinephrine-containing syringe and antihistamine available at all times. An identification tag stating the patient's sensitivity is also advised.

Clinical studies with use of cromolyn sodium to treat food allergy must be interpreted as inconclusive and have been reviewed elsewhere.¹ The difficulties in establishing the value of oral cromolyn sodium therapy are demonstrated by the following examples. Bronchospasm after ingestion of specific foods to which a subject was sensitive has been reported both to be prevented and not to be prevented by the prior ingestion of oral cromolyn sodium.^{76, 77} In the first

study, administration of cromolyn sodium before food challenge was also reported to reduce entry of antigen and the formation of immune complexes.⁷⁶ In a double-blind trial evaluating cromolyn sodium in preventing food allergy, the oral administration of cromolyn sodium was better than placebo. However, mean symptom scores for placebo and cromolyn sodium therapy were not significantly different.⁷⁸ Oral cromolyn sodium has not yet been approved for the treatment of food allergy by the Food and Drug Administration. The prophylactic use of nonsteroidal anti-inflammatory agents has been reported to prevent food-induced acute gastrointestinal symptoms.⁷⁹ This finding must be considered preliminary. Corticosteroids are used rarely in the treatment of food allergy. Eosinophilic gastroenteritis and protein-losing gastroenteropathy associated with food allergy are two conditions in which steroid use may be instituted and tapered as symptoms resolve. If prolonged steroid therapy becomes necessary, an alternate-day regimen should be attempted. The numerous side effects of steroids limit their use to severe cases.

I would like to thank Shirley Starnes for her help in the preparation of this manuscript.

REFERENCES

1. Anderson JA, Bahna S, Buckley J, Crawford L, Feingold B, Frick O, Furukawa C, et al: Adverse reactions to foods. American Academy of Allergy and Immunology Committee on Adverse Reactions to Foods. In Anderson JA, Sogn DD, editors: National Institute of Allergy and Infectious Diseases, United States Department of Health and Human Services, Public Health Service, National Institutes of Health. (in press)
2. Buckley RH, Metcalfe D: Food allergy. *JAMA* 248:2627, 1982
3. Fries JH: Factors influencing clinical evaluation of food allergy. *Pediatr Clin North Am* 6:867, 1959
4. Heiner DC: Allergy to cow's milk. *N Engl Soc Allergy Proc* 2:192, 1981
5. Eriksson NE: Food sensitivity reported by patients with asthma and hay fever. *Allergy* 33:189, 1978
6. Bock SA, Buckley J, Holst A, May CD: Proper use of skin tests with food extracts in diagnosis of hypersensitivity to food in children. *Clin Allergy* 7:375, 1977
7. Bock SA, Lee Y, Remigio LK, May CD: Studies of hypersensitivity reactions to foods in infants and children. *J ALLERGY CLIN IMMUNOL* 62:327, 1978
8. Cornell R, Walker WA, Isselbacher KJ: Small intestinal adsorption of horseradish peroxidase, a cytochemical study. *Lab Invest* 25:42, 1971
9. Owen RL, Jones AL: Epithelial cell specialization with human Peyer's patches: an ultrastructural study of intestinal lymphoid follicles. *Gastroenterology* 66:189, 1974
10. Walker WA, Bloch KJ: Gastrointestinal transport of macromolecules in the pathogenesis of food allergy. *Ann Allergy* 51:240, 1983
11. Saavedra-Delgado A, Metcalfe DD: Gastrointestinal defense mechanisms: their role in the pathogenesis of food allergy. *Immunol Allergy Practice* 5:116, 1983

12. Donaldson RM: Normal bacterial population of the intestine and their relation to intestinal function. *N Engl J Med* 270:994, 1964
13. Campos JVM, Hoenen W, Costa A, Trabulsi L, Pontes JF: Changes in intestinal flora under tetracycline. *Gastroenterology* 34:625, 1958
14. Porter JR, Rettger LF: Influence of diet on distribution of bacteria in stomach, small intestine, and cecum of white rats. *J Infect Dis* 66:104, 1940
15. Reilly RW, Kirsner JB: Blind loop syndrome. *Gastroenterology* 37:491, 1959
16. Goldstein F, Wirtis CW, Josephs L: Bacterial flora of the small intestine. *Gastroenterology* 42:755A, 1962
17. Kraft SC, Rothberg RM, Knauer CM, Svoboda AC, Monroe LS, Farr RS: Gastric output and circulating anti-bovine serum albumin in adults. *Clin Exp Immunol* 2:321, 1967
18. Adinolfi M, Glynn AA, Lindsay M, Milne CM: Serological properties of IgA antibodies to *Escherichia coli* present in human colostrum. *Immunology* 10:517, 1966
19. Dixon JM: Fate of bacteria in the small intestine. *J Path Bact* 79:131, 1960
20. Strombeck DR, Harrold D: Binding of cholera toxin to mucins and inhibition by gastric mucins. *Infect Immun* 10:1266, 1974
21. Lake AM, Bloch KJ, Sinclair KJ, Walker WA: Anaphylactic release of intestinal goblet cell mucus. *Immunology* 39:173, 1980
22. Miller HRP, Nawa Y, Parish CR: Intestinal goblet cell differentiation in *Nippostrongylus*-infected rats after transfer of fractionated thoracic duct lymphocytes. *Int Arch Allergy Appl Immunol* 59:281, 1979
23. Walker WA, Isselbacher KJ: Uptake and transport of macromolecules by the intestine: possible role in clinical disorders. *Gastroenterology* 67:531, 1974
24. Triger DR, Cynamon MH, Wright R: Studies on hepatic uptake of antigen. I. Comparison of inferior vena cava and portal vein routes of immunization. *Immunology* 25:941, 1973
25. Brandtzaeg P: The humoral immune systems of the human gastrointestinal tract. *Monogr Allergy* 17:195, 1981
26. Brandtzaeg P, Baklien K: Immunohistochemical studies of the formation and epithelial transport of immunoglobulins in normal and diseased human intestinal mucosa. *Scand J Gastroenterol* [suppl 11]36:1, 1976
27. Bull DM, Bienenstock J, Tomasi JB: Studies on human intestinal immunoglobulin A. *Gastroenterology* 60:370, 1971
28. Girard JP, De Kalbarmatten A: Antibody activity in human duodenal fluid. *Eur J Clin Invest* 1:188, 1970
29. Haneberg B, Aarskog D: Human faecal immunoglobulins in healthy infants and children and in some with diseases affecting the intestinal tract or the immune system. *Clin Exp Immunol* 22:210, 1975
30. Parrott DMV: The gut as a lymphoid organ. *Clin Gastroenterol* 5:211, 1976
31. Gowans JL, Knight EJ: The route of re-circulation of lymphocytes in the rat. *Proc R Soc Lond* 159:257, 1964
32. Brandtzaeg P: Complex formation between secretory component and human immunoglobulins related to their content of J chain. *Scand J Immunol* 5:411, 1976
33. Williams RC, Gibbons RJ: Inhibition of bacterial adherence by secretory immunoglobulin A: a mechanism of antigen disposal. *Science* 177:697, 1972
34. Ogra PI, Kargon DT: Distribution of poliovirus antibody in serum, nasopharynx, and alimentary tract following segmental immunization of lower alimentary tract with polio vaccine. *J Immunol* 102:1423, 1969
35. Galindo B, Myrvick QN: Migratory response of granulomatous alveolar cells from BCG-sensitized rabbits. *J Immunol* 105:227, 1970
36. Muller-Schoop JW, Good RA: Functional studies of Peyer's patches: evidence for their participation in intestinal immune responses. *J Immunol* 114:1757, 1975
37. Prausnitz C, Küstner H: Studien über die Ueberempfindlichkeit. *Zbl Bkt Orig* 86:160, 1921
38. Ratner B, Gruel HL: Passage of native proteins through the normal gastrointestinal wall. *J Clin Invest* 13:517, 1934
39. Gray I, Harten M, Walzer M: Studies in mucous membrane hypersensitiveness. IV. The allergic reaction in the passively sensitized mucous membranes of the ileum and colon in humans. *Am J Intern Med* 13:2050, 1940
40. Selbekk BH, Aas K, Myren J: In vitro sensitization and mast cell degranulation in human jejunal mucosa. *Scand J Gastroenterol* 13:87, 1978
41. Lindholm S: Mast cells in the wall of the alimentary canal. *Acta Pathol Microbiol Immunol Scand (suppl)* 132:11, 1959
42. Norris HT, Zamcheck N, Gottlieb L: The presence and distribution of mast cells in the human gastrointestinal tract at autopsy. *Gastroenterology* 44:448, 1963
43. Metcalfe DD: Effector cell heterogeneity in immediate hypersensitivity reactions. *Clin Rev Allergy* 1:311, 1983
44. Kriebel CW, Kraft SC, Rothberg RM: Locally produced antibodies in human gastrointestinal secretions. *J Immunol* 103:1268, 1969
45. Shiner M, Ballard J, Smith ME: The small-intestine mucosa in cow's milk allergy. *Lancet* 1:136, 1975
46. Parish WE: Detection of reaginic and short-term sensitizing anaphylactic or anaphylactoid antibodies to milk in sera of allergic and normal persons. *Clin Allergy* 1:369, 1971
47. Ingelfinger FJ, Lowell FC, Franklin W: Gastrointestinal allergy. *N Engl J Med* 241:303, 1949
48. Mathews KP: A current view of urticaria. *Med Clin North Am* 58:185, 1974
49. Champion RH, Roberts SOB, Carpenter RG, Roger JH: Urticaria and angioedema: a review of 554 patients. *Br J Dermatol* 81:588, 1969
50. Sampson H: Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis. *J ALLERGY CLIN IMMUNOL* 71:473, 1983
51. Van Metre TE, Anderson SA, Barnard JH, Bernstein JL, Chaffe FH, Crawford LV, Wittig HJ: A controlled study of the effects on manifestations of chronic asthma of a rigid elimination diet based on Rowe's cereal-free diet 1, 2, 3. *J ALLERGY* 41:195, 1968
52. Golbert TM, Patterson R, Pruzansky JJ: Systemic allergic reactions to ingested antigens. *J ALLERGY* 44:96, 1969
53. Bock SA, May CD: Adverse reactions to food caused by sensitivity. In Middleton E, Reed CE, Ellis EF, editors: *Allergy principles and practice*. St. Louis, 1983, The CV Mosby Co, p 1415
54. Metcalfe DD: Food allergens. *Clin Rev Allergy* (in press)
55. Aas K: Antigens and allergens of fish. *Int Arch Allergy Appl Immunol* 36:152, 1969
56. Elsayed S, Bennich H: The primary structure of allergen M from cod. *Scand J Immunol* 4:203, 1975
57. Hoffman DR, Day ED, Miller JS: The major heat stable allergen of shrimp. *Ann Allergy* 47:17, 1981
58. Sachs MI, Jones RT, Yunginger JW: Isolation and partial characterization of a major peanut allergen. *J ALLERGY CLIN IMMUNOL* 67:27, 1981

59. Moroz LA, Yang WH: Kunitz soybean trypsin inhibitor. *N Engl J Med* 302:1126, 1979
60. Langeland T, Harbitz O: A clinical and immunological study of allergy to hen's egg white. *Allergy* 38:131, 1983
61. Spector SL, Wangaard CH, Farr RS: Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J ALLERGY CLIN IMMUNOL* 64:500, 1979
62. Stevenson DD, Simon RA: Sensitivity to ingested metabisulfites in asthmatic subjects. *J ALLERGY CLIN IMMUNOL* 68:26, 1981
63. Kenney RA: Placebo-controlled studies of human reaction to oral monosodium L-glutamate. In Filer L Jr, Garattin S, Kare MR, et al, editors: *Glutamic acid: advances in biochemistry and physiology*. New York, 1979, Raven Press, p 363
64. Hughes JM, Merson MH: Fish and shellfish poisoning. *N Engl J Med* 295:1117, 1976
65. May CD, Bock SA: A modern clinical approach to food hypersensitivity. *Allergy* 33:166, 1978
66. Crawford LV: Allergy diets. In Bierman CW, Pearlman DS, editors: *Allergic diseases of infants, childhood, and adolescence*. Philadelphia, 1980, WB Saunders Co, p 394
67. Aas K: The diagnosis of hypersensitivity to ingested foods. *Clin Allergy* 8:39, 1978
68. Chua YY, Bremner K, Lakdawalla N, Llohet JL, Kokubu HL, Orange RP, Collins-Williams C: In vivo and in vitro correlates of food allergy. *J ALLERGY CLIN IMMUNOL* 58:299, 1976
69. Subba Rao PV, McCartney-Francis NL, Metcalfe DD: An avidin-biotin micro ELISA for rapid measurement of total and allergen-specific human IgE. *J Immunol Methods* 57:71, 1983
70. May CB, Alberto R: In vitro responses of leukocytes to food proteins in allergic and normal children: lymphocyte stimulation and histamine release. *Clin Allergy* 2:335, 1972
71. Reisman RE: American Academy of Allergy: position statements—controversial techniques. *J ALLERGY CLIN IMMUNOL* 67:333, 1981
72. Kuitunen P, Visakorpi JK, Savilahti E, Pelkonen P: Malabsorption syndrome with cow's milk intolerance: clinical findings and course in 54 cases. *Arch Dis Child* 50:351, 1975
73. Perkkio M, Savilahti E, Kuitunen P: Morphometric and immunohistochemical study of jejunal biopsies from children with intestinal soy allergy. *Eur J Pediatr* 137:63, 1981
74. Katz AJ, Goldman H, Grand RJ: Gastric mucosal biopsy in eosinophilic (allergic) gastroenteritis. *Gastroenterology* 73:705, 1977
75. Bock SA: The natural history of food sensitivity. *J ALLERGY CLIN IMMUNOL* 69:173, 1982
76. Brostoff J, Carini C, Wraith DG, Paganelli R, Levinski RJ: Immune complexes in atopy. In Pepys J, Edwards AM, editors: *The mast cell: its role in health and diseases. Proceedings of International Symposium, Davos, Switzerland*. London, 1979, Pitman Medical Publishing Co, Ltd, p 380
77. Harries MG, O'Brien IM, Burge PS, Pepys J: Effect of orally administered sodium cromoglycate in asthma and urticaria due to foods. *Clin Allergy* 8:423, 1978
78. Danneus A, Foucard T, Johansson SGO: The effect of orally administered sodium cromoglycate on symptoms of food allergy. *Clin Allergy* 7:109, 1977
79. Buisseret PD, Youtlen LIF, Heingelman DI, Lessof MH: Prostaglandin-synthesis inhibitors in prophylaxis of food intolerance. *Lancet* 1:906, 1978

INSTRUCTIONS FOR EARNING SELF-ASSESSMENT CATEGORY I CREDIT

Certification. As an organization accredited for continuing medical education, The American Academy of Allergy and Immunology certifies that when the self-assessment program is used as directed, it meets the criteria for 2 hours of credit in Category I of the Physician's Recognition Award of the American Medical Association.

Instructions. Category I credit can be earned by:

1. Reading the lead CME article in each alternate issue of the Journal
2. Recording the answers on the perforated answer sheet as directed
3. Returning the answer sheet (by the 15th of the month following the Journal's publication month) to:

The American Academy of Allergy and Immunology
Continuing Medical Education Coordinator
611 East Wells St.
Milwaukee, WI 53202

To process the answer sheets correctly, the following precautions must be taken:

1. A No. 2 or soft lead pencil must be used.
2. Corrections can be made, but must be erased com-

pletely to prevent computer reading errors. (CAUTION: Do not erase black computer lines over the responses).

3. A medical education number (ME#) found on your AMA membership card or your direct-dial telephone number (1 + area code + telephone number) can be used as your identification number.
4. Be sure to include the quiz identification number provided at the beginning of each quiz.

The above precautions are necessary to process cumulative results and group statistics.

To ensure anonymity, after group statistics have been developed, individual answer sheets will be destroyed. No records of individual performance will be maintained.

Those who send in answer sheets will be sent a continuing medical education certificate for maintaining credit records upon the completion of 12 tests.

If you wish to maintain a record of your answers for future review, record them on the printed examination questions. Answers to each quiz will be published in the following issue of the JOURNAL.