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THE DIAGNOSIS AND TREATMENT OF FOOD ALLERGY[1]

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INTRODUCTION AND DEFINITIONS

In discussing a topic as complex as food sensitivity, a precise definition of terms is necessary to avoid confusion. With this in mind, a glossary of terms as

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defined by the Committee on Adverse Reactions to Foods of the American Academy of Allergy and Immunology (1) is presented in Table 1. It is obvious, upon examination of these definitions, that adverse food reactions may be separated into two distinct categories that are distinguished by whether or not the immune system participates in the development of the reaction. By this criterion, the term "food intolerance" is designated to refer to idiosyncratic, pharmacologic, metabolic, or toxic reactions to foods in which the immune system does not participate. The terms "food allergy" and "food hypersensitivity" are synonomous and refer to adverse reactions to foods in which the immune system plays a prominent role. In the following discussion, a brief review of the histology and host defense mechanisms of the gastrointestinal

Table 1 Definitions relative to adverse reactions to foods

Term	Definition
Adverse reaction to a food	A clinically abnormal response believed due to an ingested food or food additive.
Food sensitivity	A general term implying an adverse reaction to an ingested food or food additive.
Food hypersensitivity	An immunologic hypersensitivity or truly "allergic" reaction resulting from the ingestion of a food or food additive.
Food allergy	A term synonymous with "food hypersensitivity," but frequently overused and applied to any adverse reaction to a food or food additive.
Anaphylactoid reaction to a food	Anaphylaxis-like food reaction as a result of "nonimmune" release of chemical mediators which can mimic the signs and symptoms of food hypersensitivity.
Food idiosyncrasy	A quantitatively abnormal response to a food or food additive; this response differs from its physiologic or pharmacologic effect and resembles a hypersensitivity reaction, but it does not involve an immune mechanism.
Food intolerance	A physiologic response to an ingested food or food additive which is *not* proven to be immunologic in nature. This category includes idiosyncratic, pharmacologic, metabolic, or toxic food reactions.
Food toxicity	A general term implying an adverse reaction following the ingestion of a food or food additive as a result of a direct nonimmune action.
Food poisoning	An adverse reaction following food ingestion which is a result of a natural toxic constituent of the food, or contamination of the food by microorganisms and/or their toxins.
Pharmacologic food reaction	A reaction in the host recipient as a result of chemicals in ingested food including food additives.
Metabolic food reaction	A metabolic response in the host recipient to ingested food or food additives.

tract is provided. In addition, allergic reactions to foods are further categorized into immediate and delayed reactions based upon the timing of the onset of symptoms after ingestion of the offending food. Further characterization of immediate and delayed allergic reactions to foods is presented, including a review of the immune mechanisms involved, the clinical features of these reactions, and the methods used in their diagnosis and treatment.

GASTROINTESTINAL HISTOLOGY AND HOST DEFENSE MECHANISMS

Histology

Since the gastrointestinal tract is the portal of antigen entry in allergic reactions to foods, a brief review of the histology of this organ is in order. Proceeding from the lumen outward on cross-section of the wall of the gastrointestinal tract, the mucosa, submucosa, muscularis externa, and serosa are encountered (Figure 1). The mucosa consists of an epithelial layer, the lamina propria, and the muscularis mucosa. In the small and large intestines, the epithelium consists primarily of columnar epithelial cells, which are capable of absorbing nutrients, and goblet cells, which produce and release mucus. The lamina propria contains many mast cells and may be infiltrated by neutrophils, eosinophils, and macrophages. Plasma cells, capable of producing antibodies, and lymphocytes are also abundant in the lamina propria and appear as aggregates of immunocompetent cells called Peyer's patches. The epithelium overlying

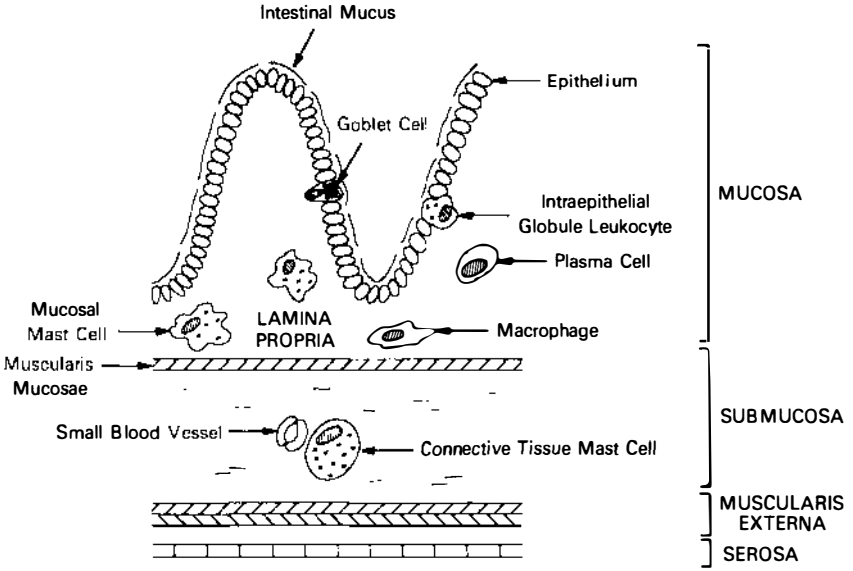

Figure 1 A diagrammatic representation of the histology of the normal gastrointestinal tract.

Peyer's patches contains modified membranous columnar cells called M cells, which sample environmental antigens and present them to the underlying immunocompetent cells (53).

The submucosa is separated from the lamina propria by the muscularis mucosa and consists primarily of connective tissue, blood vessels, lymphatic vessels, and scattered mast cells near these vessels. The muscularis externa is formed of an inner circular and outer longitudinal muscle layer except in the stomach, where the muscle is irregularly arranged as is typical for saccular organs. Unique glands occur in the mucosa and submucosa at each level of the gastrointestinal tract and are responsible for the secretion of mucus and digestive substances.

While digesting and absorbing ingested nutrients, the gastrointestinal tract is regularly exposed to a number of antigens and potentially toxic substances. As a result, the integrity of the gastrointestinal mucosa, which serves as both a digestive organ and a selective barrier to lumenal materials, must be maintained by a number of nonimmunologic and immunologic host defense mechanisms.

Nonimmunologic Host Defense Mechanisms

Important local nonimmunologic host defense mechanisms in the gastrointestinal tract include the indigenous intestinal flora, gastrointestinal secretions, the "gastric barrier," intestinal motility, and other intralumenal and mucosal processes which may affect antigen degradation or absorption. The indigenous microbial population of the gastrointestinal tract results from the interplay of a number of factors including diet (76) and competitive interactions with other organisms (21). Secretions such as goblet cells mucus that line the epithelial surface of the gastrointestinal tract have been suggested to be protective by inhibiting attachment of bacteria to the intestinal surface and preventing bacterial replication (29). Decreasing the ability of unwanted macromolecules and bacteria to adhere to the epithelial surface of the intestine allows for more efficient clearance of these substances from the intestinal tract by the normal peristaltic activity of this organ. Interruption of intestinal motility leads to extensive bacterial replication and results in the development of the "blind loop syndrome" with steatorrhea and anemia (61).

"Gastric barrier" refers to the acid environment of the stomach and the proteolytic activity of pepsin that limit the access of unwanted materials to the lower digestive tract. The importance of this host defense mechanism is illustrated by the increased incidence of gastrointestinal infections and hypersensitivity reactions to macromolecular antigens found in patients with achlorhydria. More specifically, in regard to limitation of antigen presentation to the small intestine, it has been shown that adults with achlorhydria have an increased incidence of antibovine serum albumin antibodies, which suggests that lack of degradation of bovine serum albumin in the stomach lead to greater

availability of this molecule for absorption in the small intestine (43). Other mucosal processes may also decrease antigen absorption and reduce antigen availability. For example, it has been demonstrated in animals that pancreatic enzymes may enhance the breakdown of antigens complexed with antibody on the surface of intestinal microvilli (78). The constant renewal of the mucosal lining of the gastrointestinal tract is another important defense mechanism which, if interrupted through drug exposure or certain disease states, is associated with diarrhea, malabsorption, and passage of toxins and bacteria into the systemic circulation.

Immunologic Host Defense Mechanisms

Both the humoral and cellular arms of the immune system participate in protecting the gastrointestinal tract. The humoral immune system in the gut centers primarily around the local production IgA and IgM. In adults, IgA-producing cells predominate, followed by IgM-producing cells (6–18%), then IgG-producing cells (3–4%), and finally, IgE and IgD isotypes (less than 1%) (8, 9). IgA levels in adult human secretions have been reported as high as 27.6 ng/100 ml (13). In contrast, newborn exocrine fluids lack IgA and IgM. With exposure of the individual to bacterial and food antigens, the immunoglobulin content of intestinal secretions increases. IgM production in infants appears particularly important as judged from the antibody response to oral vaccination with *E. coli* (30). Measurement of fecal IgG antibodies in bottle-fed healthy infants suggests that the intestinal IgA-producing cell system may reach maturity as early as one to two months (36).

The induction of the humoral response appears to occur primarily in the Peyer's patches. There is considerable evidence that ingested antigenic molecules pass through the epithelium of the gastrointestinal tract by macromolecular transport in absorptive epithelial cells (17) and membranous epithelial or M cells (53). Antigens entering the subepithelial zone interact with lymphocytes leading to lymphocyte sensitization. Primed lymphocytes leave the area through the efferent lymphatics and pass through the mesenteric nodes and thoracic duct to the systemic circulation (55). These cells migrate through the spleen and other organs and return to the lamina propria (33) where B-lymphocytes complete their differentiation into immunoglobulin-producing plasma cells. IgA synthesized by these cells in the mucosa of the gastrointestinal tract is dimeric, and IgM, pentameric, as determined by the incorporation of polypeptide joining, or J, chains (7). When these molecules are released into the interstitial fluid, each molecule is joined to an epithelial glycoprotein referred to as a secretory component or secretory piece. This secretory piece aids in the transport of immunoglobulin and makes it more resistant to proteolysis. The functions of immunoglobulins in the gut include defense against microorganisms and the control of antigen absorption.

Cell-mediated immune responses may also occur in the gastrointestinal tract, where such immunity may be independent of a comparable systemic immunity (26). In a manner similar to the B-lymphocyte migration previously discussed, T-lymphocytes may also travel through the thoracic duct to the bloodstream and thereafter return to the lamina propria as T-effector cells. It is likely that cell-mediated immunity plays a role in protection of the gastrointestinal tract against certain infections.

The liver is another integral part of the immunological defense system of the gastrointestinal tract. Most blood flows through the liver after passing through the gut. Because approximately 30% of the mass of the liver is composed of reticuloendothelial cells, known as Kupffer cells, this organ is specially suited to phagocytose and detoxify noxious substances that reach the portal circulation in spite of other local intestinal defense mechanisms. When liver disease interrupts normal function of the liver, symptoms may result from the escape of toxic substances into the systemic circulation (77). Evidence suggesting that liver cells participate in the immune response is provided by the difference in both humoral and cellular immune responses to antigens injected into the portal circulation versus the responses observed with antigen injection into the inferior vena cava (72).

In summary, a number of interacting host defense mechanisms participate in enabling the gastrointestinal tract to maintain a barrier to toxic substances while simultaneously performing the vital function of nutrient digestion and absorption. Although generally of great benefit to the host, occasionally adverse systemic reactions occur as a direct result of the immune response to antigens encountered through the gastrointestinal tract.

IMMEDIATE ALLERGIC REACTIONS TO FOODS

Definition

One practical way that allergic reactions to foods can be characterized is based on the timing of the onset of symptoms following ingestion of the offending food. Using this categorization, reactions occurring within minutes to hours of food ingestion are referred to as immediate allergic reactions to foods, and reactions beginning several hours to days after food exposure are considered delayed allergic reactions to foods. The etiology, pathogenesis, diagnosis, and treatment of immediate reactions to foods is discussed first.

Etiology and Pathogenesis

In 1963, Gell & Coombs described four basic immune mechanisms capable of producing tissue damage. Most immediate allergic reactions to foods are the result of Gell & Coombs type I reactions, also referred to as "anaphylactic," "IgE-mediated" or "immediate hypersensitivity" reactions. The exact inci-

dence of IgE-mediated hypersensitivity to foods is unknown; however, estimates in the pediatric population, in which these reactions are thought to be more prevalent, range from 0.5–7% (1, 11, 24). The basic components of such reactions include an antigen to which the host has been sensitized through previous exposure, immunoglobin of the IgE class directed specifically against the sensitizing antigen, and a mast cell or its blood-borne counterpart, the basophil. A brief discussion of each of these components of IgE-mediated reactions follows, with attention to information relevant to their participation in immediate allergic reactions to foods.

Much remains to be discovered about the antigenic substances in foods. Only a limited number of specific food antigens responsible for IgE-mediated reactions have been isolated and characterized. These include allergens from codfish (22), shrimp (39), peanut (63), and soybean (52). Protein fractions from cows' milk and egg have also been examined for antigenicity. Of the more than 20 different proteins found in cows' milk, only five are thought to be of particular significance in provoking allergic reactions. Of these, casein and beta lactoglobulin are heat-stable, while bovine serum albumin and bovine gamma globulin are heat-labile. Alpha lactalbumin is only partially heat-labile. Beta lactoglobulin is the principal protein in the whey protein fraction, and appears to be the most allergenic of the milk proteins. It has a molecular weight of 36,100, consisting of two identical 18,000-dalton polypeptide chains, and is relatively protease-resistant. Individuals allergic to egg are usually sensitive to proteins in egg white. Ovalbumin, which is heat-sensitive, is the primary protein of egg white; lysozyme and ovomucoid, which account for 11 and 4% of egg white protein respectively, are more allergenic. Ovomucoid, the most allergenic of the two, is heat-stable and heterogenous by electrophoretic studies and may be contaminated by a protease inhibitor, ovoinhibitor. Another protein in egg white, ovotransferrin, is also allergenic (46).

The mast cell, first discovered over 100 years ago by Paul Ehrlich, is a metachromatically staining cell located primarily in the connective tissue, often near blood vessels, nerves, glandular ducts, and in association with lymphoid tissues. Unique to these cells are numerous cytoplasmic granules composed of a negatively charged heparin core to which a number of biologically active molecules such as histamine, chemotactic factors, and enzymes are bound. The gastrointestinal mucosa is particularly rich in mast cells. For example, human duodenal mucosa contains approximately 20,000 mast cells per mm^3, amounting to almost three times the number contained in human skin (7000 mm^3), another organ rich in mast cells. The mucosa of the stomach, duodenum, and ileum contain more mast cells than the esophagus, colon, and rectum. 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 (47).

The remaining fundamental component of immediate hypersensitivity reactions to be discussed is immunoglobulin E (IgE). This heat-labile immunoglobulin with a molecular weight of 196,000 has a serum half-life of only 2.3 days. Plasma cells capable of forming IgE have been found in the mucosa of secretory surfaces in the body including the gastrointestinal, pulmonary, and urinary tracts. A genetic predisposition to form antigen-specific IgE following antigen exposure is noted in allergic individuals. Once formed and released by plasma cells, antigen-specific IgE binds by its Fc fragment with high affinity to specific receptors on the surface of mast cells and basophils. Binding of the antigen-specific Fab portions of two adjacent IgE molecules on the surface of a mast cell or basophil by the appropriate antigen results in perturbation of the cell membrane resulting in the extrusion of the cytoplasmic mediator-containing granules. Although IgE is the principal immunoglobulin capable of sensitizing mast cells and basophils to food antigens, an IgG antibody termed "heat-stable, short-term sensitizing antibody" has been reported in sera from children developing symptoms after milk ingestion (54). These IgG antibodies reportedly sensitize monkey skin at two to four hours, have agglutinating activity, and do not compete with IgE reagins for cell receptors. The clinical significance of such observations has not been determined fully.

There is indirect evidence that gastrointestinal mast cells degranulate not only to IgE-mediated stimuli, but upon exposure to the complement-derived anaphylatoxins, C3a and C5a, as well. It is known that IgA, IgG, and IgM 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 cows' milk sensitivity (67). Such complement activation and the concomitant generation of anaphylatoxins could lead to mast cell degranulation. In addition, it should be remembered that mast cells also degranulate when exposed to certain pharmacologic agents such as codeine.

The possible pathophysiologic consequences of mast cell degranulation with exposure of surrounding gastrointestinal tissue to mast cell–derived mediators include local changes in vasopermeability, stimulation of mucous production, increased muscle contraction, stimulation of pain fibers, and recruitment of inflammatory cells. Local intestinal anaphylaxis has been shown to facilitate the passage of macromolecules through the gastrointestinal barrier (14). Thus, food antigen may enter the body and be distributed to other target organs, initiating degranulation of mast cells at those sites.

There is abundant clinical evidence to confirm that IgE that reacts with food antigens is present on mast cell surfaces. Immediate wheal and erythema reactions in the skin following local injection of minute amounts of food antigen have been demonstrated (5). Such reactions have been passively transferred by the intracutaneous injection of serum from an allergic individual

into the skin of a normal recipient followed by the local injection 24 hours later of the food antigen to which the donor is sensitive (57). Similar local reactions have been reported when the food antigen was administered orally 24 hours after injection of serum into the skin (59). Local reactions similar to those that followed mast cell degranulation in human skin have been reported in vivo after passive sensitization of human ileum and colonic mucosa (34). Local reactions after passive sensitization could be induced by ingestion or direct application of the antigen.

Clinical Features

Because immediate allergic reactions to foods are generally the result of immediate hypersensitivity reactions to foods, the spectrum of clinical signs and symptoms encountered in IgE-mediated reactions is reviewed here. Such reactions range in severity from innocuous to life-threatening, depending upon a number of factors including the age and general health of the patient, the quality and quantity of the food ingested, and the method of treatment used. Symptomatology may be confined to the gastrointestinal tract alone, may affect only sites distant to this organ, or may involve the gastrointestinal tract and distant organs as well.

Often the sites of initial exposure to food antigen, the oropharynx and gastrointestinal tract, are the first to develop symptoms. Edema and pruritis of the lips, oral mucosa, and pharynx are generally transient and are not always followed by other symptoms. As the offending food passes through the remainder of the gastrointestinal tract, nausea, cramping, abdominal distention, vomiting, flatulence, and diarrhea may develop. Hyperactive bowel sounds and an increase in abdominal girth may be observed (15).

Symptomatology may involve the skin, which is a common target organ in food allergy. Pruritis, exacerbations of eczema, angioedema, acute urticaria (31), and much less frequently chronic urticaria are noted (48). Asthma attacks and allergic rhinitis due to food allergy appear to be more common in children (5) than adults (74). Whether neurological problems, including behavioral disturbances and depression, are manifestations of central nervous system involvement in food allergy remains to be demonstrated conclusively.

Systemic anaphylaxis, a potentially life-threatening reaction, involves numerous target organs simultaneously. Symptoms include those mentioned to occur in gastrointestinal reactions as well as laryngeal edema, dyspnea, chest pain, flushing, pruritus, angioedema, urticaria, hypotension, and shock. Commonly, the reaction begins within minutes following ingestion of the offending food, although occasionally hours elapse before the onset of the reaction (32). The first anaphylactic episode may occur unexpectedly or may be preceded by minor symptoms such as mild abdominal discomfort or urticaria on previous exposure to the food.

Diagnosis

In the diagnosis of immediate food allergy, as in the diagnosis of any allergic disease, three criteria must be fulfilled: identification of the antigen, demonstration of a relationship between exposure to the antigen and occurrence of the reaction, and discovery of the immunologic mechanism involved. No single test is available to confirm or deny the presence of food allergy, so the accurate diagnosis of this disorder is obtained by ruling out the presence of other causes of real or apparent adverse reactions to foods and supporting the diagnosis of food allergy with information obtained from testing procedures available. Thus, the diagnosis of food allergy begins with a careful medical history and physical examination directed at distinguishing food hypersensitivity from other causes of adverse reactions to foods. Examples of substances contained in foods that could cause adverse reactions are listed in Table 2. Other available procedures include skin testing with food antigens, in vitro testing for the measurement of antigen-specific IgE, basophil histamine release, elimination diets, and when required and judged safe, oral challenge with the suspected food to determine the reproducibility of the presenting complaints.

HISTORY A complete description of the previous reactions, including their severity and the circumstances surrounding the episodes, is first obtained. Suspected foods are identified by their ingestion on several occasions in some

Table 2 Substances in foods capable of causing food intolerance

I.	Contaminants
	A. Bacterial toxins
	Botulism
	B. Endogenous toxins
	Certain mushrooms
	Shellfish poisoning
	C. Insect parts
	D. Molds and mold products
	E. Antibiotics
II.	Additives
	A. Dyes
	Tartrazine
	B. Flavorings and preservatives
	Nitrites and nitrates
	Monosodium glutamate
	Metabisulfites
III.	Pharmacologic Agents
	A. Caffeine
	B. Tyramine
	C. Phenylethylamine
	D. Alcohol
	E. Histamine

proximity to the reaction. Foods commonly implicated by food challenge in children include peanuts, nuts, egg, milk, soy, fish, shellfish, banana, and chicken (6). Although these foods appear to be common provocations, other foods may also be allergenic.

In selected instances a suspected food may fail to lead consistently to an allergic reaction. Reasons for this inconsistency include the amount consumed, the presence of simultaneously ingested foods, the manner of preparation of the food, and the possibility that concomitant medications such as antihistamines have masked the reaction. Allergenic food proteins, although generally heat- and enzyme-resistant, may be altered in some instances by food preparation. Thus, whether the food was served raw, cooked, or otherwise processed is important. Food antigens capable of provoking allergic reactions may be limited to only part of the food or may be present only at a certain stage of ripeness. Cross-contamination of one food by another may take place at any time during food processing or preparation, occasionally leading to incrimination of the wrong food. In certain individuals, exercise after ingestion of the food may play a role; cases have been reported of allergic reactions to foods occurring only when ingestion was followed by strenuous exercise (49).

Contamination of foods with a variety of substances has lead to reactions that may be confused with food allergy. Mold and mold products may appear in fermented foods such as dried fruits, cheeses, yogurts, and wines. Other contaminants include bacteria, bacterial toxins, and drugs. Scromboid poisoning, resulting from ingestion of spoiled tuna and related fish containing high levels of histamine and saurine, is confirmed by the detection of high histamine levels in the implicated fish (27).

Dyes and other additives may cause reactions that mimic allergic diseases in sensitive individuals. Some individuals with aspirin sensitivity are also sensitive to tartrazine dye (68). Sulfiting agents are used to reduce the spoilage of certain foods such as lettuce, to sanitize food containers, to prevent the oxidative discoloration of foods such as dried apples, and to inhibit the growth of undesirable microorganisms during fermentation, e.g. in wine making. These agents have been shown to induce episodes resembling allergic reactions. In one report, several asthmatics developed severe wheezing and associated anaphylactoid reactions following challenge with potassium metabisulfite (69). Monosodium glutamate is known to cause the "Chinese restaurant syndrome", which consists of a burning sensation, facial flushing, and chest pain associated with a pulsatile headache approximately 20 min after the ingestion of a large enough dose by a susceptible individual (65).

Certain foods may cause symptoms resembling food allergy because they contain pharmacologically active substances. Amines such as tyramine and phenylethylamine, nitrates and nitrites, and alcohol may cause headaches in suspectible individuals. Methylxanthines (caffeine, theobromine, and theo-

phyline) are found in coffee, tea, cola, and chocolate. In large amounts, these substances cause nervousness, tremor, and tachycardia (25). Vasoactive amines (epinephrine, norepinephrine, tyramine, dopamine, histamine, and 5-hydroxytryptamine) are found in bananas (particularly the peel), tomatoes, avocados, cheeses, pineapples, and wines (25). Wines may also contain histamine. Chocolate contains phenylethylamine.

A number of primary gastrointestinal diseases are associated with acute symptomatology after food ingestion. Examples are hiatal hernia, gastric and duodenal ulcers, cholelithiasis, gastric malignancy, diverticulosis, and vascular insufficiency. In infants, gastroesophageal reflux may cause bronchial irritation, chronic cough, and wheezing. Collagen vascular diseases such as scleroderma and systemic lupus erythematosis can have associated gastrointestinal manifestations. Enzyme deficiencies, including lactase and glucose-6-phosphate dehydrogenase deficiency, may be confused with food allergy. Intolerance to foods may also result from fixation on food allergy based on psychoneurosis and functional gastrointestinal reactions (51).

TECHNIQUES USING FOOD EXTRACTS A number of in vivo and in vitro procedures use food extracts in the diagnosis of food allergy. The techniques include skin testing, the radioallergosorbent test (RAST), the enzyme-linked immunosorbent assay (ELISA), and basophil histamine release.

Skin testing is performed by the application of dilute water-soluble extracts of foods using scratch or puncture techniques. Intradermal testing is generally avoided because of a greater danger of systemic reactions. Nonspecific irritant reactions may also be more frequent with intradermal testing. Because of the risk of anaphylaxis, skin testing with food extracts should only be performed by a physician experienced in this procedure. Pediatric studies have shown that food extracts in a concentration of 1:20 (weight: volume) applied by the puncture technique give wheals 3 mm larger in diameter than reactions at negative control sites in subjects having allergic reactions to foods verified by oral food challenge (4). However, certain individuals with skin tests that are positive to a particular food may be able to eat that food without experiencing an adverse reaction. Thus, skin testing is used to support a clinical impression that one or more foods are capable of causing immediate hypersensitivity reactions in a given individual.

The RAST and ELISA are in vitro tests used to demonstrate the presence of antigen-specific IgE. The RAST is the most commonly used in vitro diagnostic test. In this procedure, the patient's serum is incubated with a solid phase support, such as paper discs, to which the food antigen is attached. If present in the serum, antigen-specific IgE attaches to the antigen bound on the support. After it has been washed to remove nonspecific IgE, the antigen-coated support

to which the patient's antigen-specific IgE is bound is incubated with radiolabeled anti-IgE. Measurement of the radioactive anti-IgE attached to the patient's antigen-specific IgE bound to the antigen coated on the support provides a means of quantifying antigen-specific IgE. This RAST procedure is a useful research tool in identifying antigens in foods to which patients may react, and it is being used in the standardization of allergenic extracts. Clinically, the RAST is used when skin testing with extracts might pose a risk, for example on patients suspected of exquisite sensitivity who have histories of previous anaphylactic reactions. It may also be employed with patients who have extensive skin disease that precludes skin testing or in cases where any manipulation of the skin might result in a response that would be clinically indistinguishable from a true positive reaction. The RAST is, however, less sensitive and more expensive than direct skin testing (16).

The ELISA, developed after the RAST, is also used to measure antigen-specific IgE (23). In the ELISA, an enzyme such as alkaline phosphatase or horseradish peroxidase is attached to the anti-IgE rather than a radioisotope. The amount of anti-IgE bound to antigen-specific IgE is then proportional to the bound enzyme activity. The sensitivities of the ELISA and RAST are increased by the sequential use of multiple antibodies, with each directed to the prior antibody, to amplify the original interaction between antigen and antigen-specific IgE. The ELISA has the same potential as the RAST in the identification of food antigen-specific IgE (70).

Another in vitro test occasionally used to support the diagnosis of IgE-mediated sensitivity to foods is the basophil histamine release assay. In this test peripheral blood basophils from individuals with suspected food allergies can be examined in vitro to determine whether they degranulate upon exposure to dilute concentrations of food antigens. Degranulation requires the presence of IgE on the basophil specific to the suspected food and is monitored by the measurement of histamine released into the supernatant fluid. Basophil degranulation testing procedures correlate with skin tests; however, they do not establish a diagnosis of food allergy, are time consuming and expensive, and have no advantage over skin testing (38, 50). A high spontaneous in vitro release of histamine from basophils taken from subjects allergic to foods has been reported (50), but the clinical significance of this observation is unclear.

Cytotoxic testing, provocative subcutaneous testing, and provocative sublingual testing involve the use of food extracts in attempts to diagnose food allergy. Cytotoxicity testing is based on the claim that specific allergen added in vitro to whole blood or to serum leukocyte suspensions results in reduction in white cell count or death of the leukocytes. Provocative subcutaneous and sublingual testing involve subcutaneous injection or sublingual administration of sufficient antigen to elicit symptoms corresponding to the patient's com-

plaints. A position statement issued by the American Academy of Allergy reported all three techniques to be unproven and held that their use should be limited to well-constructed diagnostic trials (62).

ORAL FOOD CHALLENGE Oral food challenge is occasionally used in the diagnosis of food allergy if the correlation between specific foods and symptoms remains unclear. It is not used if the medical history and physical examination, skin testing, and dietary studies have resulted in a diagnosis. The use of oral challenge to reproduce symptoms is always avoided in cases that have histories of previous severe anaphylactic reactions to a suspected food. Such procedures must be performed only under the supervision of a physician and in a setting where severe adverse reactions can be properly treated.

Food challenge is performed in an open, single-blind, or double-blind manner. In an open food challenge, both the 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 given. In a double-blind food challenge, the patient is unaware of whether a specific food or a placebo is being given and a neutral observer such as physician or nurse is also unaware of what is being administered. Results are scored by the patient and the medical observer. Although double-blind challenge has the advantage of objectivity, open oral food challenge is reliable when the resulting symptoms can be objectively observed, such as with urticaria, angioedema, rhinitis, diarrhea, or asthma. During challenge procedures, the subject remains on a limited diet using foods known not to cause symptoms. The food being tested is prepared in the same manner 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 suspected sensitivity. The patient is observed for a period of time exceeding the time determined in the history between food ingestion and appearance of symptoms. If no symptoms are reproduced by the test dose, the challenge is repeated and the dose is increased until the amount of food ingested exceeds the amount that caused previous reactions.

When double-blind food challenge is performed, neither the patient nor the neutral observer should be able to detect whether the suspected food or a placebo is being administered. The two methods used to hinder detection of the challenge food are administration of the food in a dried state in capsules and masking of the challenge food within other foods. Any food or capsule used to hide material being administered must itself be shown not to cause symptoms.

The presence of objectively observable symptoms such as urticaria, angioedema, laryngeal edema, or asthma after double-blind challenge provides the link between ingestion of a particular food and the development of an adverse reaction. In cases of subjective complaints, a number of tests positive to a suspected food and negative placebo tests are necessary to substantiate the

diagnosis. However, 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 may omit the possibility of reactions in the mouth, pharynx, and esophagus and may decrease early digestion of the food by salivary enzymes. Small amounts of foods may be regurgitated or eructated and identified by taste and smell. 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.

SPECIALIZED DIETS FOR DIAGNOSIS Elimination diets followed by return of suspect foods to the diet are applied only in situations where symptoms are not life-threatening, e.g. in cases with chronic hives or rhinitis. Removal of the offending food from the diet must lead to resolution of the patient's symptoms. In practice, the likelihood of establishing a diagnosis using elimination diets is greater when few foods are responsible for the symptoms. Changing the type and amount of foods may also alter symptoms of other diseases such as disaccharidase deficiency, gluten-sensitive enteropathy, and cystic fibrosis. Before any diet is initiated, it is useful for the subject to remain on his usual diet for approximately 10–14 days. During this time, the subject keeps a diet diary and records the types and amounts of foods ingested and the occurrence and character of adverse reactions. This record is useful in searching for suspect foods and establishing baseline symptoms against which the success or failure of elimination diets can be measured. If symptoms fail to occur within this period, their occurrence may be too infrequent to be affected by the change of frequency during the period of an elimination diet. If only a few foods are suspected as the cause of symptoms, the initial elimination diet consists simply of removing these foods. Such an approach is more likely to be of benefit in pediatrics, as allergy to such foods as milk, egg, or soy is common in early life. Care is taken that suspected foods are not hidden in other foods and inadvertently consumed. Further, biologic cross-reactivity between foods in the same food group may occur.

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 due to foods such as is the case in chronic urticaria, initiation of a severely limited diet under a physician's care may be warranted. Severe elimination diets, especially for children, are used for only short periods of time. Extensive elimination diets include, for infants under three months of age, breast milk or milk substitute alone; for infants from three to six months, breast milk or milk substitute and rice cereal; for children from six months to two years, milk substitute with vitamin supplement, rice cereal, applesauce, pears, carrots, squash, and lamb (18); and for older children, lamb and rice

(Table 3). Caution is always taken to instruct the individual to take nothing by mouth but the foods on the diet and water. Both oral and topical medications are avoided when possible. Continuation of symptoms while the patient is on the restricted diet indicates that symptoms are not caused by foods. The unlikely possibility that individual foods on the restricted diet cause symptoms is eliminated by substituting other foods 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 the symptoms. Such cycling must reproducibly eliminate or provoke symptoms in order to allow the conclusion that symptoms are secondary to foods. If a relationship to a diet is established, foods representing food groups eaten by the patient during the control period are individually returned to the diet in normal amounts at intervals of three to four days. Foods

Table 3 Lamb and rice diet

Foods allowed
Brown rice—natural, long grain, short grain; par boiled
White rice—enriched, converted; cook without added fat
Brown or white rice flour
Brown rice cakes—containing *only* brown rice and salt (if desired)
Puffed Rice Cereal—containing only brown rice
Lamb
Water
Salt

All food must be prepared without added fat. Rice, lamb, salt, and water are the only allowable foods. No food containing any other ingredients is to be eaten. Check labels. Salt or baking soda should be used to brush the teeth.

Eliminate
All foods not listed above, especially coffee, tea, soft drinks, juices, chewing gum, toothpaste, vitamins, aspirin, and any medication not ordered by a doctor must be eliminated.

Possible Menu

Breakfast	*Lunch*	*Dinner*	*Snack*
Rice mush	Rice patties	Rice and lamb sauté Pan-fried lamb chops	Rice cakes

Instructions
Stay on basic diet for _____ days.
Then, on _____ add _____ all by itself, first thing in A.M.
Then, on _____ add _____ all by itself, first thing in A.M.
Then, on _____ add _____ all by itself, first thing in A.M.
Next, on _____ add _____ all by itself, first thing in A.M.
Next, on _____ add _____ all by itself, first thing in A.M.

Continue food additions one at a time at _____ day intervals until most or all other foods in the diet have been tested. Keep a diet diary as indicated. Add foods in large amounts, and eat them several times a day during addition period.

returned to the diet without induction of symptoms may remain in the diet. Foods provoking symptoms are removed.

THERAPY The management of immediate allergic reactions to foods consists of dietary avoidance of offending foods and pharmacologic management of reactions resulting from inadvertent exposure. At present there is no evidence to support desensitization either by oral or parenteral routes. Avoidance of the offending food is accomplished by aiding the patient in the construction of an elimination diet and educating him on hidden sources of the food. In designing an elimination diet for long-term use, optimal nutrition and palatability are important considerations. Instructing the patient in regard to the botanic families and the classification of foods from animal sources may be necessary because of the occasional cross-reactivity of foods in the same groups. When treatment is first instituted, strict avoidance of all sources of the offending foods is necessary. If the initial diagnosis is correct and compliance is maintained, the patient's condition should improve. Eventually, in the absence of anaphylactic sensitivity, small amounts of the offending food may be tolerated upon cautious reintroduction into the diet. Through experimentation, most people learn the volume and method of preparation of a particular food that they may ingest without inducing symptoms.

Each patient should be instructed in the appropriate manner of approaching inadvertent exposure to the offending food. A patient with a history of anaphylactic reactions and exquisite sensitivity should be taught how to self-administer adrenalin and should have antihistamine and a syringe containing epinephrine available at all times. Identification tags stating the patient's sensitivity are also advised. In a patient with less dramatic reactions, the appropriate treatment depends upon the organ system involved. For example, the treatment of food-induced urticaria is the same as the treatment of idiopathic urticaria, and the treatment of asthma resulting from food ingestion is no different from asthma provoked by exposure to other allergens. Gastrointestinal symptoms following inadvertent exposure are usually treated with antihistamines.

Clinical studies using cromolyn sodium to treat food allergy appear inconclusive (19). Bronchospasm following 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 (10, 37). In the first study, administration of cromolyn prior to food challenge was also reported to reduce entry of antigen and the formation of immune complexes (10). In a double-blind trial evaluating cromolyn in preventing food allergy, cromolyn administered orally was more effective than placebo. However, mean symptoms scores for placebo and cromolyn were not significantly different (19). Oral cromolyn sodium has not yet been approved for the treatment of food allergy by the Food

and Drug Administration. Although the prophylactic use of nonsteroidal anti-inflammatory agents has been reported to prevent food-induced acute allergic symptoms (12), this report must be considered preliminary.

PREVENTION Efforts to prevent the development of IgE-mediated food allergy are directed toward the newborn and young infant. The basic thrust of such efforts includes the early identification of infants at a high risk for the development of allergic disease and the implementation of measures directed at minimizing exposure to potentially sensitizing foods (Table 4). A significant body of research exists to suggest that such measures may be beneficial. Several reports in humans involving the study of mothers and their normal offspring (3), twins (2), and families (28) suggest the heritability of serum IgE levels. Thus, allergic parents, who are in turn more likely to have allergic offspring, can be identified by the use of medical history, physical examination, determination of the serum IgE level, and, in certain cases, the use of selected skin tests. Other studies have supported the use of an elevated total serum IgE level during infancy and childhood to identify individuals with an increased risk of developing allergic disease (41, 42). Therefore, identification of a high-risk group appears possible.

In the high-risk infant, measures to reduce exposure both before and after birth are recommended. Maternal IgE does not cross the placenta; however, the ability of the fetus to produce IgE upon antigen exposure in utero is suggested by both animal (60) and human (40, 58) studies. For this reason, diets have been developed to reduce the maternal intake of certain foods such as milk, egg, peanut, soy, fish, and citrus, particularly during the last trimester (64). Studies showing that small amounts of antigens in foods ingested by a lactating

Table 4 Prevention of the development of food allergy in infants

I. Identification of infants at risk
   A. Prenatal identification:
      Identification of allergic disease in expectant parents by history and documentation by determination of serum IgE levels and selected skin tests.
   B. Postnatal identification:
      Measurement of serum IgE levels in cord blood or serum.
II. Avoidance of potentially allergenic foods
   A. Prenatal avoidance:
      Structure maternal diet during the last trimester to avoid ingestion of highly allergenic foods.
   B. Postnatal avoidance:
      1. Breast feeding for at least 6 months.
      2. Maternal avoidance of the ingestion of highly allergenic foods during lactation.
      3. Supplemental feedings, if necessary, only with hypoallergenic formulas (no cows' milk or soy formulas).
      4. Gradual addition of foods with low potential allergenicity after 6 months.

mother may be found in breast milk (20, 66) and may cause symptoms in her infant (71) suggest that lactating mothers should remain on such a diet. Breast-feeding during at least the first six months is highly recommended as a means of decreasing exposure to sensitizing antigens and because of the postulated effect of breast milk on intestinal antigen absorption (73, 75) and protection against disease (35, 64, 79). If supplemental feeding is necessary through this period, a hypoallergenic formula (such as Nutramigen) in which the protein source consists of generally low-molecular-weight peptides obtained by the enzymatic digestion of casein may be used. The use of cows' milk and soy formulas is generally avoided because they contain potentially allergenic proteins. After six months, foods with little allergenic potential are gradually added to the diet. Studies to determine the impact of such preventive measures should prove extremely interesting.

DELAYED ALLERGIC REACTIONS TO FOODS

In delayed allergic reactions to foods, the onset of symptoms occurs several hours to days after ingestion of the offending food. Discovery of the precise immunologic mechanism(s) involved in these reactions is extremely difficult because delayed hypersensitivity, antigen-antibody complex formation with complement activation, and immediate hypersensitivity may participate in their development. To illustrate the nature of the disorders included in this category of allergic reactions to foods, three examples (gluten-induced enteropathy, food protein-induced gastroenteropathy, and hypereosinophilic gastroenteritis) will be discussed briefly.

Gluten-induced enteropathy (celiac or nontropical sprue) is a disorder characterized by intolerance to gluten, a mixture of proteins found in wheat, oats, rye, and barley. The ingestion of foods containing gluten by susceptible individuals leads to development of malabsorption characterized by diarrhea, steatorrhea, bloating, and weight loss. Biopsy of the gastrointestinal mucosa of susceptable individuals while they are ingesting foods containing gluten reveals flattening of the mucosal surface and infiltration of the epithelial layer and lamina propria with inflammatory cells. The pathophysiology of the disease is unclear, although it appears that both a direct toxic effect of gluten on the mucosa and the activation of immunologic mechanisms capable of producing tissue damage are involved. The diagnosis of this disease is established by demonstration of the characteristic mucosal lesions while the subject is on a diet containing gluten and improvement after institution of a gluten-free diet.

In most cases, food protein–induced gastroenteropathy is a chronic gastrointestinal disease of infants and children who are sensitive to milk or soy protein (45, 56). The clinical manifestation of this disorder is malabsorption with diarrhea and weight loss. Mucosal biopsies of the gastrointestinal tract of

patients with this disorder may vary from showing minor inflammatory changes to showing villous atrophy. Some evidence suggests that immediate hypersensitivity reactions participate in this disorder, although the exact underlying immunologic mechanisms are not clear. Identification of the offending protein and its removal from the diet lead to improvement in infants and children with the disease. Exacerbation of symptoms is noted upon reintroduction of the offending protein into the diet. In contrast to gluten-induced enteropathy, this disorder often resolves as the patient ages, and many of these children are able to tolerate milk or soy protein in later life.

Eosinophilic gastroenteritis is a disorder characterized by peripheral blood eosinophilia and eosinophilic infiltration of the gastrointestinal wall without evidence of vasculitis. Some patients with this disease complain of abdominal cramping, nausea, and diarrhea after the ingestion of specific foods. These patients frequently have elevated serum IgE levels and positive skin tests to multiple foods, suggesting that immediate hypersensitivity mechanisms may be involved. The diagnosis of this disorder is primarily made by mucosal biopsy with demonstration of eosinophilic infiltration. Additional findings may include gastric outlet obstruction and hypertrophic gastric rugae. Severe elimination diets seldom help even patients in whom sensitivity to certain foods is expected.

A number of individuals relate a multitude of somatic complaints such as vague abdominal pain, headache, tension, fatigue, and depression to the ingestion of certain foods. Multiple foods are often suggested as the cause for any or all of the above complaints, which occur hours to days after food ingestion. At present such associations remain unproven and should be viewed with skepticism. Several centers are currently investigating this association, using double-blind food challenge to determine whether there is a cause-and-effect relationship.

In summary, patients with delayed allergic reactions to foods tend primarily to have complaints related to the gastrointestinal tract, with malabsorption and weight loss as prominent features. The diagnosis is reached through a high index of suspicion and the use of elimination diets and laboratory tests to rule out other disorders. Mucosal biopsy of the gastrointestinal tract may provide a clue to the diagnosis. The treatment consists of avoidance of the offending food. In severe cases of eosinophilic gastroenteritis and food-induced gastroenteropathy, the use of steroids may be indicated.

CONCLUSION

This article reviews the pathogenesis, clinical presentation, diagnosis, and treatment of immunologically mediated adverse reactions to foods. The most difficult problem in assessment of reactions to foods is the exclusion of

nonimmunologic reactions to foods. There is no test for food hypersensitivity that in fact makes the diagnosis. Each individual that experiences an adverse reaction associated with eating must be approached as unique case, and the conclusion as to what the etiologic agent is must be based on all available data. There is sufficient information known about adverse reactions to foods to allow reasonable judgments to be made in many cases; however, it is clear that a greater understanding of the pathogenesis of such reactions, the development of new diagnostic tests, and the exploration of new approaches to therapy must continue.

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