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Food Allergies: The Immune Response

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In popular literature, it has become convenient for all adverse reactions that result from eating to be labeled food allergy. The word allergy is commonly misused, even by health professionals who do not understand the complex mechanisms of an allergic reaction. This article will explain those mechanisms and help dietetic professionals understand how and why the miserable symptoms we call food allergy, food intolerance, food sensitivity, or adverse reactions to foods occur.

The symptoms of an allergic reaction are caused by biologically active chemicals produced by the immune system in its attempt to protect the body from a foreign invader. Our immune system is designed to protect us from anything that may cause disease. Usually, this is a microorganism such as a virus, bacterium, or other pathogen.

However, the immune system of an allergic (atopic) person attempts to "protect" the body from harmless substances such as pollens, animal dander, dust mites, mold spores, and components of certain foods. The question that has always puzzled doctors and scientists is: What causes the immune system of one individual to fight a harmless substance while another's system recognizes the same materials as innocuous?

Although we do not know the entire answer to that question, we know that food itself is incapable of causing any disease in the way that viruses, bacteria, and cancer cells can; there are no "bad foods." Rather, it is the body's response to components of a food that causes symptoms. The explanation for why one person's body responds to food by developing distressing symptoms and another's uses the same food for comfort and nurture lies in the process of recognizing what is safe and what may be harmful to the body. Several factors are involved, including the following:

- the individual's inherited genetic makeup;
- the circumstances under which the food was first encountered;
- the type of microorganisms that live within the digestive tract;
- other diseases present at the same time;
- oral medications; and
- other immunological factors that we are only beginning to understand.

Moreover, food sensitivity is unlike any other disease entity in that it has many different causes since any food is capable of triggering an allergy in a person who has been sensitized to it or who lacks the systems required to process it adequately when it enters the body. The same food may be absolutely safe for others.

Furthermore, food allergy can result in different symptoms in diverse organ systems. For example, one person may develop skin symptoms such as eczema or hives; another may have digestive tract symptoms such as stomachache, diarrhea, nausea, or vomiting; and another may develop symptoms in the lungs such as asthma or in the upper respiratory tract such as a stuffy, runny nose or earache. Sometimes, all body systems are involved (anaphylaxis). And all these varied reactions may come from eating the same food, such as peanuts or shellfish. Each allergic individual differs in the way his or her immune system responds to food and which foods it responds to.

Definition of Terms
For many years, the nomenclature for food allergy and other adverse reactions to food was based on the directives of the American Academy of Allergy, Asthma & Immunology (AAAAI) and the National Institute of Allergy and Infectious Disease (part of the National Institutes of Health [NIH]).1 They define an adverse food reaction as any untoward reaction after the ingestion of a food, which can include food allergy or food intolerance. The difference is that a food allergy is the result of an abnormal immunologic response after ingestion of a food and a food intolerance is the result of nonimmunological mechanisms.

However, as research has progressed, further distinctions have been made. The most recent (2001) definitions from the European Academy of Allergology and Clinical Immunology (EAACI) define allergy as a hypersensitivity reaction initiated by immunologic mechanisms.2 Thus, when immunologic mechanisms have been demonstrated, the appropriate term is food allergy. If the role of immunoglobulin (Ig) E is highlighted, the correct term is IgE-mediated food allergy. All other reactions, previously referred to as food intolerance, should be referred to as nonallergic food hypersensitivity. Any adverse reaction to food should be called food hypersensitivity.

Severe, generalized allergic reactions to food can be classified as anaphylaxis, a severe, life-threatening, generalized, or systemic hypersensitivity reaction. Atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis (hay fever), or eczema/dermatitis.

As a result of—or more likely because of—these seemingly precise but sometimes conflicting academic definitions, authors of research papers and articles on food allergy now frequently define their own use of the terms in any published work so that the reader is quite clear about their meaning in that specific context. This article uses the 1984 definition of the AAAAI/NIH; the terms anaphylaxis and atopy are used as defined by the EAACI. Chart 1 defines the terms used in this article.

The Immunological Process
A food allergy is a response of the immune system to an antigen in a food that it recognizes as "foreign."3 (Note: An antigen is a protein, glycoprotein, or a molecule linked to a protein that elicits a response of the immune system.) Antigens that trigger an allergic reaction are called allergens. When an allergen enters the body of a person at risk for allergy, an extremely complex series of events is set in motion that will result in the release of chemicals (called inflammatory mediators) that act on body tissues to cause the symptoms of allergy. All immunological processes involve white blood cells (leukocytes) and the different types of chemicals they produce.

The first stage of the immunological response involves recognition of the invading antigen. All foods contain numerous antigens. Not all antigens are allergens, but all allergens are antigens.

When an antigen enters the body, white blood cells called lymphocytes are activated to recognize and respond to anything foreign. We can visualize lymphocytes as the sentinels of the immune system. There are two different types of lymphocytes in blood: T cells and B cells. T-cell lymphocytes are the ultimate "gatekeepers" and controllers of the immune system.

Certain types of T cells, called helper T-cells (Th cells), are responsible for identifying foreign materials that enter the body through any route, such as the mouth, nose, and skin. They initiate and direct the subsequent activities of the immune system if the foreign material is deemed a threat. T cells exert their control of the whole immune response by means of a number of different types of "messenger chemicals" called cytokines. The response of T-helper cells in allergic and nonallergic individuals is different. The two types of responses have been designated Th2 and Th1 response, respectively. Different cytokines are released in each response and control the way the body reacts to the foreign material.

When a pathogen (disease-causing microorganism) enters the body, the immune system protects the body by a Th1 response. Cytokines such as interleukin 1 (IL-1), interleukin 2 (IL-2), interferon-gamma (IFN-g), and others are produced. They stimulate the formation of antibodies of the IgG type, which eventually destroy the invading microorganism by means of a complex series of events known as the complement cascade.

The human body produces five different types of antibodies: IgA, IgD, IgE, IgG, and IgM. Each of these antibody types have specific functions within the body. The complement system comprises a group of more than 20 enzymatic proteins in the blood that act together to destroy foreign cells by splitting them apart (lysis). This process is known as the complement cascade, which releases various chemical by-products that act as opsonins, chemotaxins, and anaphylatoxins to help destroy a threat to the body and results in inflammation in various tissues.

Symptoms such as fever, aching muscles, fatigue, and general malaise that are typical of an infection such as the flu are the result of the body's response to cytokines and other inflammatory mediators produced during this battle between the immune system and the foreign invader.

In an allergic reaction, a similar battle is engaged, but this time, it is between the immune system and a nonthreatening invader such as a food. In this case, the Th2 cytokines control the immune response. Instead of the IL-2, IFN-g, and similar cytokines of the Th1 response, an entirely different set of cytokines are produced. Interleukins 4, 5, 6, and 13 (IL-4, IL-5, IL-6, and IL-13) are typical of the Th2 response and result in production of antibodies of the IgE type. Unlike IgG, IgE antibodies do not trigger the complement cascade. Instead, they initiate a series of reactions that result in the release of inflammatory mediators, such as histamine, and other reactive chemicals from specialized cells called mast cells. The inflammatory mediators act on body tissues and produce the itching, swelling, reddening (flushing), and smooth muscle contraction (eg, the bronchospasm of asthma) that are typical of allergies.

Simply stated, the Th1 response protects the body from disease, and IgG are the antibodies responsible for the ultimate destruction of the invader. The Th2 response results in allergies, and IgE antibodies are responsible for the release of inflammatory mediators that cause the symptoms of the allergy.

As well as determining which antibody type is produced, Th1 and Th2 responses interact with each other and with other leukocytes in a complex process of stimulatory and inhibitory regulation. Under certain conditions, cytokines of the Th1 type can down-regulate those involved in the Th2 response and vice versa.4

The Th2 Response
The reaction can be viewed as occurring in two phases: early and late response. The early phase results in the release of inflammatory mediators from mast cells in tissues and circulating basophils in blood. The late phase results in the recruitment of additional granulocytes, which are drawn to the reaction site by chemotactic factors released in the early phase. The newly recruited granulocytes are stimulated to release their own inflammatory mediators, which augment the allergic reaction by increasing the levels of those already present.5

Early Phase
As soon as IgE antibodies are produced by the activated B-cell lymphocytes in the IgE-mediated hypersensitivity reaction, they migrate to the surface of specific white blood cells that have receptors on their surface to couple with the antibody. These receptors are designated FceR1 receptors, indicating that they are compatible with the IgE type of antibody.6

Mast cells in tissues and basophils, which circulate in blood, possess these IgE-compatible receptors. The mast cell is the essential granulocyte in the allergic response. It has been estimated that there may be as many as 500,000 receptors for antibody molecules on the surface of a mast cell.

Mast cells, basophils, and other granulocytes synthesize and store inflammatory mediators in internal granules (hence the name granulocyte). The inflammatory mediators are the chemicals that protect the body in the process of inflammation. When required to defend the body against a potential threat, the mediators are released in a complex sequence of reactions called degranulation. It is the action of these biologically active chemicals on body tissues that causes the symptoms of allergy.7

The process of degranulation is initiated when an allergen cross-links two IgE molecules on adjacent receptors on the surface of a mast cell, forming a bridge between them. The allergenic antigen needs to be a specific size (between 10 and 70 kilodaltons) to effect this bridging. In food allergy, the size of the molecule that passes through the epithelium lining the digestive tract, therefore, is an important determinant in whether the food will trigger an allergic reaction.

When the digestive epithelium is hyperpermeable (a condition that can arise in a number of situations, especially when there is inflammation in the digestive tract), molecules of the critical size to trigger degranulation are more likely to pass through into circulation. At the same time, there must be a sufficient number of IgE molecules on the cell surface to ensure that two are close enough for the allergen to bridge them.

Often, the first exposure to an allergen does not result in a sufficient number of IgE molecules to allow these allergen-antibody bridges to form. So, a single exposure to an allergen rarely results in the release of inflammatory mediators and is usually symptom-free. However, once the allergen-specific T and B cells have been produced, memory cells remain, which respond immediately when the same allergen enters the body on a subsequent occasion. Thus, every exposure after the first will result in the immediate production of antibodies specific to the triggering antigen (or allergen), and the amount of antibodies in circulation will increase with each exposure.

The process in which a person is exposed to an allergen but does not exhibit symptoms is generally referred to as the sensitizing event. On subsequent exposure, when sufficient IgE molecules are present on the surface of the mast cells, degranulation will occur and overt symptoms will be experienced.

Degranulation involves the following series of complex reactions:

- The phosphatidyl-inositol (PI) cycle is activated at the cell surface.

• Extracellular calcium ions enter the cell ("calcium channeling").

• The intracellular granules and their contents are released in a process of exocytosis.6

• Within a short time after allergen exposure (a few minutes to two hours), the preformed inflammatory mediators act on body tissues.

The preformed inflammatory mediators include the following8,9:

• Histamine, which mediates a number of different tissues, including vasodilation (widening of small blood vessels); increase in vascular permeability, allowing exudation of protein and fluid from the vessels; bronchoconstriction (contraction of smooth muscle surrounding the lungs); stimulation of nerves, resulting in itching; and increased secretion of mucus.

• Chemotactic chemicals (chemoattractants), which draw additional granulocytes such as neutrophils and eosinophils to the reaction site. These granulocytes contain their own inflammatory mediators, which are released in phase 2 of the allergic response.

• Enzymes, such as tryptase, kininogenase, and phospholipases, which result in further activation of inflammatory processes. Phospholipase A1 is the key enzyme that leads to de novo synthesis of several different types of powerful inflammatory mediators in a two-step enzymatic reaction.

First, the omega-6 lipid arachidonic acid is released from its position in the membrane of the cell. Arachidonic acid is then metabolized by two pathways to form secondary mediators of inflammation (known as eicosanoids). Two important eiconsanoids are prostaglandins and leukotrienes. The enzyme systems responsible for their production are the cyclo-oxygenase and lipoxygenase pathways.

Prostaglandins are essentially regulatory chemicals. For example, PGF2a stimulates mast cell degranulation while PGE1 and PGE2 tend to inhibit mast cell degranulation. The type of prostaglandin produced is dependent on the pathway that is activated.

Activation of the the cyclo-oxygenase system results in the production of prostanoids of the "2 series" (containing two double bonds in their structure), written as PG2. They include prostaglandins, prostacyclin, and thromboxane. Several prostaglandins are important mediators of atopic symptoms; for example, PGD2, like histamine, causes vasodilation, bronchoconstriction, nerve stimulation, and mucus secretion.

Activation of the lipoxygenase system produces the leukotrienes of the "4 series" (four double bonds in their structure), written as LT4. Some of the leukotrienes are powerful inflammatory chemicals and include LTB4, a vigorous chemoattractant for granulocytes responsible for augmenting the allergic response when the newly recruited granulocytes release their own battery of inflammatory chemicals, and LTC4, LTD4, and LTE4, which cause smooth muscle contraction and are key factors in the bronchospasm of asthma. They also mediate mucus secretion and mucosal edema, which are frequent symptoms of allergies.

IgE-mediated Allergy: Late Phase
During the late phase of the allergic response, granulocytes such as neutrophils, eosinophils, monocytes, and basophils are attracted to the reaction site by chemoattractants. The presence of eosinophils in particular is usually considered to be an indication that symptoms are due to a hypersensitivity reaction.7
When the granulocytes release their intracellular inflammatory mediators, the allergic reaction is powerfully augmented. This can be experienced in the late phase reaction of asthma or anaphylaxis when an initial reaction seems to be resolving but then suddenly becomes extremely acute and puts the patient in serious danger. It is often the second phase of an anaphylactic reaction that has been presumed resolved that proves fatal. The second phase may occur several hours after the initial response but usually is exhibited within a maximum of four to six hours after the first.10

In a forthcoming article, we will look at other types of allergic reactions and the foods that cause them.

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Chart 1
Definition of Terms

• Adverse food reaction and food sensitivity are generic terms referring to any troublesome reaction after the

ingestion of a food.

- Adverse food reactions can be food allergy or food intolerance.

- A food allergy is the result of an abnormal immunologic response after ingestion of a food.

• Immunological hypersensitivity is the same as allergy.

• A food intolerance is the result of nonimmunological mechanisms.

• Anaphylaxis is a severe, life-threatening, generalized (systemic) allergy or hypersensitivity reaction.

• Atopy is a term used to indicate IgE-mediated allergy.

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Examination

1. The Th1 response of T-helper cells results in:
a. IgE-mediated allergy.
b. release of inflammatory mediators from mast cells.
c. IgG-mediated immune protection.
d. blocking o histamine receptors.
e. all of the above.

2. When individuals are allergic to the same food, they have the same symptoms.
a. True
b. False

3. _____ is responsible for the allergic reaction.
a. Production of the antibody IgG
b. Stimulation of Th1 cytokines IL-1, IL-2, and IFN-g
c. Depression of the Th1 response
d. Stimulation of Th2 cytokines IL-4, IL-5, IL-6, and IL-13
e. Augmentation of the complement cascade

4. IgE antibodies, produced during an allergic reaction, are responsible for:
a. protecting the body from foreign invaders and disease.
b. triggering the complement cascade.

c. releasing inflammatory mediators and the symptoms of allergy.
d. preventing the body from reacting to nonthreatening food allergens.
e. all of the above

5. Once IgE is produced, it binds to receptors on which of the following cells:
a. mast cells and basophils
b. B lympocytes and neutrophils
c. T lymphocytes and neutrophils
d. B lymphocytes and mast cells

6. Degranulation, part of the early phase of an allergic reaction, is best described as:
a. the production of IgE from B lymphocytes in response to an allergen.
b. the production of cytokines, particularly IL-1, IL-2, and IFN-g, in response to stimulation of the immune system.
c. the Th1 response of the immune system to the threat posed by the allergen.
d. the release of inflammatory mediators from mast cells, basophils, and granulocytes in response to a threat.

7. Degranulation can not occur until _____
a. there is a sufficient quantity of cytokines to stimulate the release of mediators.
b. the cross linking of two IgE molecules on adjacent receptors occurs.
c. a sufficiently large quantity of food has been consumed.
d. there is sufficient production of prostaglandins, particularly LTC4.

8. The first exposure of an individual to a food allergen is the sensitizing event and is usually characterized by:
a. an overwhelming number of symptoms throughout the body.
b. a slight reaction to the allergen, with minimal symptoms.
c. only symptoms in the gastrointestinal tract are activated.
d. no symptoms.

9. The secondary mediators of inflammation, produced after degranulation, include:
a. leukotrienes and antibodies.
b. cytokines and prostaglandins.
c. prostaglandins and leukotrienes.
d. cytokines and antibodies.

10. The late phase of the Type 1 hypersensitivity reaction is characterized by:
a. the reaction slowly ebbing as the immune cells die off.
b. attraction of more granulocytes, which release inflammatory mediators that augment the allergic response.
c. the production of specific symptoms, such as mucous buildup and trouble breathing.
d. the body stopping production of IgE and inflammatory mediators, so the allergic symptoms begin to resolve.