ALLERGIES

DISEASE OR SYSTEM AFFECTED: Gastrointestinal system, immune system, lungs, nose, skin, stomach

SPECIALTIES AND RELATED FIELDS: Dermatology, family practice, immunology, internal medicine, otorhinolaryngology, pediatrics, pharmacology

DEFINITION: Exaggerated immune reactions to materials that are intrinsically harmless; the body’s release of pharmacologically active chemicals during allergic reactions may result in discomfort, tissue damage, or, in severe responses, death.

KEY TERMS:
- allergen: any substance that induces an allergic reaction
- anaphylaxis: an immediate immune reaction, triggered by mediators that cause vasodilation and the contraction of smooth muscle
- basophil: a type of white blood cell which contains mediators associated with allergic reactions; represents 1 percent or less of total white cells
- histamine: a compound released during allergic reactions which causes many of the symptoms of allergies
- IgE: a type of antibody associated with the release of granules from basophils and mast cells
- mast cell: a tissue cell with granules containing vasoactive mediators such as histamine, serotonin, and bradykinin; the tissue equivalent of basophil

CAUSES AND SYMPTOMS

Allergies represent inappropriate immune responses to intrinsically harmless materials, or antigens. Most allergens are common environmental antigens. Approximately one in every six Americans is allergic to material such as dust, molds, dust mites, animal dander, or pollen. The effects range from a mere nuisance, such as the rhinitis associated with hay fever allergies or the itching of poison ivy, to the life-threatening anaphylactic shock that may follow a bee sting. Allergies are most often found in children, but they may affect any age group.

Allergy is one of the hypersensitivity reactions generally classified according to the types of effector molecules that mediate their symptoms and according to the time delay that follows exposure to the allergen. P. G. H. Gell and Robin Coombs defined four types of hypersensitivities. Three of these, Types I through III, follow minutes to hours after the exposure to an allergen. Type IV, or delayed-type hypersensitivity (DTH), may occur anywhere from twenty-four to seventy-two hours after exposure. People are most familiar with two of these forms of allergies: Type I, or immediate hypersensitivity, commonly seen as hay fever or asthma; and Type IV, most often following an encounter with poison ivy or poison oak.

Type I hypersensitivities have much in common with any normal immune response. A foreign material, an allergen, comes in contact with the host’s immune system, and an antibody response is the result. The response differs according to the type of molecule produced. A special class of antibody, IgE, is secreted by the B lymphocytes. IgE, when complexed with the specific allergen, is capable of binding to any of several types of mediator cells, mainly basophils and mast cells.

Mast cells are found throughout the skin and tissue. The mucous membranes of the respiratory and gastrointestinal tract in particular have high concentrations of these cells, as many as ten thousand cells per cubic millimeter. Basophils, the blood cell equivalents of the mast cells, represent 1 percent or less of the total white-cell count. Though the cells are not identical, they do possess features related to the role that they play in an allergic response. Both basophils and mast cells contain large numbers of granules composed of pharmacologically active chemicals. Both also contain surface receptors for IgE molecules. The binding of IgE/allergen complexes to these cells triggers the release of the granules.

A large number of common antigens can be associated with allergies. These include plant pollens (as are found in rye grass or ragweed), foods such as nuts or eggs, bee or wasp venom, mold, or animal dander. A square mile of ragweed may produce as much as 16

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**Information on Allergies**

**CAUSES:** Antigens such as pollen, mold, certain foods (nuts, eggs, seafood), drugs (penicillin), bee or wasp venom, animal dander, dust mites, etc.

**SYMPTOMS:** Sneezing, runny nose, coughing, itching, breathing difficulties, hives, inflammation, vomiting, diarrhea, shock

**DURATION:** Chronic, with acute episodes

**TREATMENTS:** Antihistamines, mast cell stabilizers, steroids (cortisone), desensitization
tons of pollen in a single season. In fact, almost any food or environmental substance could serve as an allergen. The most important defining factor as to whether an individual is allergic to any particular substance is the extent and type of IgE production against that substance.

Type I allergic reactions begin as soon as the sensitized person is exposed to the allergen. In the case of hay fever, this results when the person inhales the pollen particle. The shell of the particle is enzymatically dissolved, and the specific allergens are released in the vicinity of the mucous membranes in the respiratory system. If the person has had prior sensitization to the materials, IgE molecules secreted by localized lymphocytes bind to the allergens, forming an antibody/antigen complex.

Events commonly associated with allergies to pollen—a runny nose and itchy, watery eyes—result from the formation of such complexes. A sequence of events is set in place when the immune complexes bind to the surface of the mast cell or basophil. The reactions begin with a cross-linking of the IgE receptors on the cell. Such cross-linking is necessary because, in its absence, no granules are released. On the other hand, artificial cross-linking of the receptors in laboratory experiments, even in the absence of IgE, results in the release of vasoactive granules.

Following the activation of the cell surface, a series of biochemical events occurs, the key being an influx of calcium into the cell. Two events rapidly follow: The cell begins production of prostaglandins and leukotrienes, two mediators that play key roles in allergic reactions, and preexisting granules begin moving toward the cell surface. When they reach the cell surface, the granules fuse with the cell membrane, releasing their contents into the tissue.

The contents of the granules mediate the clinical manifestations of allergies. These mediators can be classified as either primary or secondary. Thus, clinical responses are divided into immediate and late-phase reactions. Primary mediators are those found in preexisting granules and that are released initially following the activities at the cell surface. They include substances such as histamine and serotonin, associated with increased vascular permeability and smooth muscle contraction. Histamine itself may constitute 10 percent of...

Microscopic pollens, which are responsible for many allergic reactions. (PhotoDisc)
the weight of the granules in these cells. The result is the runny nose, irritated eyes, and bronchial congestion with which so many are familiar. Secondary mediators, which are released in the late phase, are synthesized following the binding of the immune complexes to the cell surface. These substances include the leukotrienes (also called slow reactive substances of anaphylaxis, or SRS-A) and prostaglandins. Pharmacological effects from these chemicals include vasodilation, increased capillary permeability, contraction of smooth muscles in the bronchioles, and, more important, a group of chemotactic activities that attract many different white cells in the site to magnify the inflammatory reaction. This is why an allergic reaction is divided into two phases and the late reaction may last for days.

Foods to which one is allergic may trigger similar reactions in the gut. Mast cells in the gastrointestinal tract also contain receptors for IgE, and contact with food allergens results in the release of mediators similar to those in the respiratory passages. The result may be vomiting or diarrhea. The allergen may also pass from the gut into the circulatory system or other tissues, triggering asthmatic attacks or urticaria (hives).

In severe allergic reactions, the response may be swift and deadly. The venom released during a bee sting may trigger a systemic response from circulating basophils or mast cells, resulting in the contraction of pulmonary muscles and rapid suffocation, a condition known as anaphylactic shock. The leukotrienes, platelet-activating factor, and prostaglandins play key roles in these reactions.

Delayed-type hypersensitivities, also known as contact dermatitis reactions, are most commonly manifested following the presentation of a topical allergen. These may include the catechol-containing oils of poison oak, the constituents of hair dyes or cosmetics, environmental contaminants such as nickel or turpentine, or any of a wide variety of environmental agents. Rather than being mediated by antibodies, as are the other types of hypersensitivities, DTH is mediated through a specific cellular response. These cells appear to be a special class of T (for thymus-derived) lymphocytes.

DTH reactions are initiated following the exposure to the appropriate antigen. Antigen-presenting cells in the skin bind and “present” the allergen to the specific T lymphocytes. This results in the secretion by these T cells of a variety of chemicals mediating inflammation. These mediators, or cytokines, include gamma interferon, interleukin-2, and tumor necrosis factor. The result, developing over a period of twenty-four to
seventy-two hours, is a significant inflammatory response with subsequent localized damage to tissue.

The other classes of hypersensitivity reactions, Types II and III, are less commonly associated with what most people consider to be allergies. Yet they do have much in common with Type I, immediate hypersensitivity. Type II reactions are mediated by a type of antibody called IgG. Clinical manifestations result from the antibody-mediated destruction of target cells, rather than through the release of mediators. One of the most common forms of reaction is blood transfusion reactions, either against the A or B blood group antigen or as a result of an Rh incompatibility. For example, if a person with type O blood is accidentally transfused with type A, an immune reaction will occur. The eventual result is destruction of the incompatible blood cells. Rh incompatibilities are most commonly associated with a pregnant woman who is lacking the Rh protein in her blood (that is, Rh negative) carrying a child who is Rh positive (a blood type obtained from the father’s genes). The production of IgG directed against the Rh protein in the child’s blood can set in motion events that result in the destruction of the baby’s red blood cells, a condition known as erythroblastosis fetalis.

Type III reactions are known as immune complex diseases. In this case, sensitivity to antigens results in formation of IgG/antigen complexes, which can lodge in the kidney or other sites in the body. The complexes activate what is known as the complement system, a series of proteins which include vasoactive chemicals and lipolytic compounds. The result can be a significant inflammation that can lead to kidney damage. Type III reactions can include autoimmune diseases such as arthritis or lupus, or drug reactions such as penicillin allergies.

It should be kept in mind, however, that none of these reactions is inherently abnormal. Under normal circumstances, these same reactions mediate an inflammatory defense against foreign pathogens. For example, the normal role of IgE appears to be associated with the destruction of parasites such as are found in helminthic infections (such as parasitic worms). The release of mediators under these conditions is important as a defensive reaction leading to the expulsion or destruction of worms. It is only when these same mediators are released inappropriately that one observes the symptoms of allergies.

Most individuals are familiar with immediate hypersensitivities as reactions involving a localized area. The most common form of allergy is rhinitis, known as hay fever, which affects approximately 10 percent of the population. When a person inhales an environmental allergen such as ragweed pollen, the result is a release of pharmacologically active mediators from mast cells located in the upper respiratory tract. If the release occurs in the lower respiratory tract, the condition is known as asthma. In both instances, the eyes and nose are subject to inflammation and the release of secretions. In milder cases, the person suffers from watery discharges, coughing, and sneezing. In more severe asthma attacks, the bronchioles may become constricted and obstruct the air passages.

**TREATMENT AND THERAPY**

Three methods for dealing with allergies exist: avoidance of the allergen, palliative treatments, and desensitization. Ideally, one can attempt to avoid the allergen. For example, cow’s milk, a common allergen, should not be given to a child at too young an age, and one can stay away from patches of poison ivy or avoid eating strawberries if one is allergic to them.

Yet avoidance is not always possible or desirable, as the problem may be the fur from the family cat. In any event, it is sometimes difficult to identify the specific substance causing the symptoms. This is particularly true when dealing with foods. Various procedures exist to identify the irritating substance, skin testing being the most common. In this procedure, the patient’s skin is exposed to small amounts of suspected allergens. A positive test is indicated by formation of hives or reddening within about twenty to thirty minutes. If the person is hypersensitive to a suspected allergen and finds a skin test too risky, then a blood test (RAST) may be substituted. In addition to running a battery of tests, a patient’s allergy history (including family history, since allergies are in part genetic) or environment may give clues as to the identity of the culprit.

The most commonly used method of dealing with allergies is a palliative treatment—that is, treatment of the symptoms. Antihistamines act by binding to histamine receptors on target cells, interfering with the binding of histamine. Two types of histamine receptors exist: H-1 and H-2. Histamine binding to H-1 receptors results in contractions of smooth muscles and increased mucus secretion. Binding to H-2 receptors results in increased vasopermeability and swelling. Antihistamines that act at the level of the H-1 receptor include alkylamines and ethanolamines and are effective in treating symptoms of acute allergies such as hay fe-
ver. Histamine II blockers such as cimetidine are effective in the symptomatic treatment of duodenal ulcers through the control of gastric secretions.

Many antihistamines can be obtained without a prescription. If they are not used properly, however, the side effects can be serious. Overuse may result in toxicity, particularly in children; overdoses in children can be fatal. Because antihistamines can depress the central nervous system, side effects include drowsiness, nausea, constipation, and drying of the throat or respiratory passage. This is particularly true of histamine I blockers. A new generation of H-1 antihistamines is available on the market. They are long-acting and are free of the sedative effect of other antihistamines.

Other symptomatic treatments include the use of cromolyn sodium, which blocks the influx of calcium into the mast cell, and thus is called a mast cell stabilizer. It acts to block steps leading to degranulation and the release of mediators. In more severe cases, the administration of steroids (cortisone) may prove useful in limiting symptoms of allergies.

Anaphylaxis is the most severe form of immediate hypersensitivity, and unless treated promptly, it may be fatal. It is often triggered in susceptible persons by common environmental substances: bee or wasp venom, drugs such as penicillin, foods such as peanuts and seafood, or latex protein in rubber. Symptoms include labored breathing, rapid loss of blood pressure, itching, hives, and/or loss of bladder control. The symptoms are triggered by a sudden and massive release of mast cell or basophil mediators such as histamine, leukotrienes, or prostaglandin derivatives. Treatment consists of an immediate injection of epinephrine and the maintenance of an open air passage into the lungs. If cardiac arrest occurs, cardiopulmonary resuscitation must be undertaken. Persons in known danger of anaphylaxis should carry with them an emergency kit containing epinephrine and antihistamines.

Contact dermatitis is a form of delayed-type hypersensitivity, developing several days after exposure to the sensitizing allergen. Rather than resulting from the presence of IgE antibody, the symptoms of contact dermatitis result from a series of chemicals released by sensitized T lymphocytes in the area of the skin on which the allergen (often poison ivy or poison oak) is found. Treatments generally involve the application of topical corticosteroids and soothing or drying agents. In more severe cases, systemic use of corticosteroids may be necessary.

In some persons, the relief of allergy symptoms may be achieved through desensitization. This form of immunotherapy involves the repeated subcutaneous injection of increasing doses of the allergen. In a significant number of persons, such therapy leads to a decrease in symptoms. The idea behind such therapy is that repeated injections of the allergen may lead to production of another class of antibody, the more systemic IgG. These molecules can serve as blocking antibodies, competing with IgE in binding to the allergen. Because IgG/allergen complexes can be phagocytosed (destroyed by phagocytes) and do not bind receptors on mast cells or basophils, they should not trigger the symptoms of allergies. Unfortunately, for reasons that remain unclear, not all persons or all allergies respond to such therapy.

The Type I immediate hypersensitivity reactions commonly run in families. This is not so surprising if one realizes that the regulation of IgE production is genetically determined. Thus, if both parents have allergies, there is little chance that their offspring will escape the problem. On the other hand, if one or both parents are allergy-free, the odds are at least even that the offspring will also be free from such reactions.

**Perspective and Prospects**

Though allergies in humans have probably existed since humans first evolved from ancestral primates, it was only in the nineteenth century that an understanding of the process began to develop. Type I hypersensitivity reaction was first described in 1839 through experiments in which dogs were repeatedly injected with egg albumin and developed an immediate fatal shock. The term “anaphylaxis” was coined for this phenomenon in 1902, when Paul Portier and Charles Richet observed that dogs repeatedly immunized with extracts of sea anemone tentacles suffered a similar fate. Richet was awarded the 1913 Nobel Prize in Physiology or Medicine for his work on anaphylaxis.

In the 1920’s, Sir Henry Dale established that at least some of the phenomena associated with immediate hypersensitivity were caused by the chemical histamine. Dale sensitized guinea pigs against various antigens. He then observed that, when the muscles from the uterus were removed and exposed to the same antigen, histamine was released and the muscles underwent contraction (known as the Schultz-Dale reaction). The existence of a component in human serum which mediates hypersensitive reactions was demonstrated by Otto Prausnitz, a Polish bacteriologist, and...
Heinz Kustner, a Polish gynecologist, in 1921. Kustner had a strong allergy to fish. Prausnitz removed a sample of serum from his colleague and injected it under his own skin. The next day, Prausnitz injected fish extract in that same region. Hives immediately appeared, indicating that the serum contained components that mediated the allergy. For some time, the Prausnitz-Kustner test, or P-K test, remained a means of testing for allergens under circumstances in which a person could be tested for sensitivity. (It is no longer in use because of safety concerns.) In this test, a serum sample from the test subject was injected under the skin of a surrogate (usually a relative) and later followed with test allergens. The presence of a wheal and flare reaction (hives) indicated sensitivity to the allergen. The serum component responsible for this sensitivity was later identified as the antibody IgE by K. and T. Ishizaka and S. G. O. Johansson in 1967. The target cells to which the IgE bound were later identified as mast cells and basophils.

The discovery of IgE allowed scientists to develop a blood test called a radioallergosorbent test (RAST) that could measure a specific IgE antibody to an allergic substance. RAST is fully as sensitive as a skin test and thus can be a substitute in some clinical circumstances. Furthermore, discoveries of numerous mediators from mast cells and other white cells such as cytokines, chemokines, interleukins, growth factors, and interferon have helped scientists understand the pathology of allergy at the molecular level. It helps clinically to divide the allergic reaction into immediate reaction (onset within a few minutes after exposure to allergens) and delayed or late-phase reaction (onset hours after exposure to antigens and a reaction that may last for days). The definition of allergy has now expanded from the traditional, immediate allergic reaction to the inclusion of chronic inflammatory processes in the tissues. With a better understanding of how allergies develop, better treatments can be offered to patients who suffer from this disorder.

The eventual goal of the research was to understand the molecular defects that result in allergies and ultimately to find a means to eliminate the problem, rather than to test for sensitivity. In the News: Peanut Allergies

In the United States alone, fifty to one hundred people die each year from serious allergic reactions to peanuts. One and a half million Americans have a demonstrated allergic sensitivity that puts them at risk for life-threatening reactions to peanut protein exposure. Reactions can be so severe to minute amounts of airborne peanut protein that some schoolchildren must eat lunch in peanut-free rooms, and many airlines have stopped serving peanuts to passengers. Because peanuts and peanut oil can be ingredients in a diverse range of food items such as chili, potato chips, and egg rolls, peanut allergy sufferers live under a constant threat of having an adverse reaction despite their best efforts to avoid the allergen.

In the March 13, 2003, issue of the *New England Journal of Medicine* Dr. Hugh A. Sampson and his colleagues of Mount Sinai School of Medicine in New York reported the results of a study that shows the first successful preventive treatment for peanut allergy. In a double-blind study, eighty-four volunteers with peanut allergy were given either placebo shots or injections of various doses of the experimental drug TNX-901 once a month over a four-month period. At the end of the study, participants were given capsules of peanut flour in increasing amounts until they exhibited an allergic reaction. The results showed that those given placebos reacted when given the equivalent of half a peanut. People who received low doses of the drug could ingest a bit more before reacting. Those receiving the highest doses could ingest, on average, the equivalent of nine peanuts (and for some, twenty-four peanuts) before developing an allergic response.

TNX-901 is a genetically engineered antibody that prevents allergic response by binding to potentially harmful immune cells that are produced in response to allergen exposure. Binding these immune cells interrupts the series of events that lead to an allergic reaction.

While TNX-901 is not a cure for peanut allergy, its preventive potential makes the required monthly shot appealing to those afflicted with the disorder. Since accidental exposure to peanut protein is estimated to be equivalent to one or two peanuts, TNX-901 could provide sufferers with confidence that accidental peanut exposure would not lead to a life-threatening reaction. The drug is still in development, and it will be several years before it is available to the general public.

—Karen E. Kalumuck, Ph.D.
than simply offer palliative measures. For example, it is now known that interleukin-4 (one of the mediators of T cells) raises IgE production, while interferon (another mediator of T cells) lowers IgE production. By understanding the regulation of IgE production, it may become possible to inhibit IgE production in allergic persons selectively, without affecting the desired functions of the immune response.

—Richard Adler, Ph.D.; updated by Shih-Wen Huang, M.D.

See also Antihistamines; Asthma; Autoimmune disorders; Bites and stings; Celiac sprue; Decongestants; Dermatitis; Dermatology; Diaper rash; Food poisoning; Gastroenterology; Gastroenterology, pediatric; Gastrointestinal disorders; Gastrointestinal system; Hay fever; Hives; Host-defense mechanisms; Immune system; Immunization and vaccination; Immunology; Lungs; Mold and mildew; Multiple chemical sensitivity syndrome; Poisonous plants; Pulmonary medicine; Pulmonary medicine, pediatric; Rashes; Shock; Skin; Skin disorders; Sneezing.

For Further Information:


Cutler, Ellen W. Winning the War Against Asthma and Allergies. Albany, N.Y.: Delmar, 1998. This clearly written book provides practical information on all aspects of allergies—what they are, their causes, testing, diagnosis, and treatment, including nontraditional therapies. Preventive measures are covered, as are scenarios for various allergy elimination therapies.


The authors provide extensive discussion of allergies and the roles played by the immune system. They describe the means by which one can learn to cope with allergies and discuss various testing methods for the identification of allergens.

Kuby, Janis. Immunology. 4th ed. New York: W. H. Freeman, 2000. The section on hypersensitivity in this immunology textbook is well written and includes a mixture of detail and overview of the subject. Particularly useful are discussions of the various types of hypersensitivity reactions. Some knowledge of biology is useful.

Life, Death, and the Immune System. New York: W. H. Freeman, 1994. This comprehensive collection of articles from Scientific American provides basic information and research directions on AIDS, autoimmune disorders, and allergies as well as an excellent discussion of the immune system in general.

Roitt, Ivan. Roitt’s Essential Immunology. 10th ed. Boston: Blackwell Scientific, 2001. Written by a leading author in the field, the text provides a fine description of immunology. The section on hypersensitivity is clearly presented and profusely illustrated. Though too detailed in places, most of the material can be understood by individuals who have taken high school biology.

Walsh, William. The Food Allergy Book. New York: J. Wiley, 2000. In this excellent guide to one highly prevalent form of allergy, the author presents useful background information on food allergies and a pragmatic guide to identifying and eliminating food allergens from one’s diet.

Young, Stuart, Bruce Dobozin, and Margaret Miner. Allergies. Rev. ed. New York: Plume, 1999. In addition to discussing the diagnosis and treatment of allergies, the authors evaluate the various remedies on the market at the time of publication. Also useful are lists of organizations to contact for further information.