Introduction

Allergy is one of the most widespread diseases of the modern world. More than 25% of the population in industrialized countries suffers from allergies (Valenta; 2002). According to the Asthma and Allergic Foundation of America (2002), allergies are the sixth leading cause of chronic diseases in the U.S, and the annual cost of dealing with them is estimated at $18 Billion.

Every individual has his or her own immune system; the stronger the immune system, the healthier will be the person. Allergies, also known as hypersensitive reactions, occur when the immune system overreacts to substances that do not affect most people. These substances, also known as allergens, could be pollen, animal dander, chemicals, fungi, dust mites, or foods such as nuts, eggs, shellfish, fish, and milk.

Different people show different symptoms of allergies, which can be mild (runny nose) to severe (anaphylaxis). Symptoms generally depend upon the part of body contacted by the allergen, e.g., pollens from the air enter the respiratory tract via the nose and cause respiratory symptoms such as cough, itchy and runny nose, nasal congestion, sneezing, and wheezing. Food allergy related symptoms include vomiting, nausea, abdominal pain, and diarrhea. Skin allergy symptoms are lesions, rashes, blisters, redness and itchiness, and so on.

The Immunology of Allergies

The immune system protects our body against pathogens and other foreign substances by producing a kind of glycoprotein known as immunoglobulin (Ig) or antibodies from plasma cells or B-cells (a type of lymphocyte). Antibodies are mainly of five types, each one having a different function; the type involved in allergy is immunoglobulin E (IgE).
Immunoglobulin E (IgE) is overproduced during an allergic response. On the very first exposure to an allergen, an allergic person becomes sensitized by producing allergen-specific IgE that binds with IgE receptors on mast cells (in tissues) and basophils (in circulation). If the sensitized person has another exposure to this specific allergen, then this allergen will bind to the antigenic determinant site (Fab) of IgE attached to the mast cells and basophils. Binding of two or more IgE molecules to mast cells (crosslinking) is required to activate the mast cells. These activated cells result in the release of certain chemicals, such as histamine, serotonin, proteoglycans, serine protease, leukotriene C4 and heparin, that will further bind with their receptors present in other cells (e.g., histamine receptors of blood vessels) and lead to inflammation, irritation, redness and other allergic symptoms.

The primary function of our immune system is to defend against infection; however, during an allergic reaction the immune system responds against a substance that is harmless to most people. There are two subpopulations of T helper cells, Th1 and Th2. Th1 cells are helpful in protecting against invading microbes and other particles by producing interferons and some cytokines. Th2 cells are responsible for triggering allergies by the overproduction of IgE, and are also involved in the struggle against parasitic worms. Th2 cells produce cytokines like interleukins (such as IL-5) that enhance the production of specific IgE antibodies by B cells and result in hypersensitivity, eosinophil activation, mucus production and IgE secretion (Drouin et al. 2001).

The Allergic Cascade
National Institute of Allergy and Infectious Diseases (NIAID) (6610 Rockledge Drive, MSC 6612, Bethesda, MD 20892-6612) taken from the version at http://health.howstuffworks.com/allergy2.htm
Reducing the Risk of Developing Allergic Diseases

While the exact cause of allergies is not clear, many scientists believe that genetic factors in the allergic person and environmental factors act together in their development. Numerous studies have reported an association between genes that exert their effects predominantly in combination with environmental factors, e.g., cigarette smoke (Kabesch, 2006) or tobacco smoke (Diaz-Sanchez, 2006), to cause allergies.

At least some early life exposure to common household microbes and unpasteurized milk reduces our later risk of acquiring allergies. Allergic people can avoid triggering allergy symptoms by limiting the exposure to allergens. Healthy eating habits and exercise can further strengthen one’s immune system and avert undesired effects.
Bacterial extracts have been reported as “modulators” of the host immune system. In one study farmer’s children and rural residents were reported to be less likely to develop allergies than their urban counterparts. Perkin and Strachman (2006) proved that unpasteurized milk consumption was associated with significantly lower IgE levels and fewer allergy symptoms. Several studies in human volunteers report that ingestion of probiotic bacteria (Lactobacillus, bifidobacterium, eubacteria) or fermented milk products or exposure to environmental mycobacteria are helpful in preventing allergies (Matricardi et al., 2003; Schrezenmeier and Vresem, 2001; Adlerberth et al. 1991). These different bacteria have a role in modification of Th2 to Th1 immune response and induction of interferons (IFN-γ), interleukins (IL-2, IL-12) and allergen-specific IgG antibodies that antagonize IgE mediated effects. (Matricardi et.al, 2003).

Although allergens are known to increase symptoms in allergic individuals, early exposure to some of them, e.g., common environmental microbes as fungal spores or bacteria in mattresses, carpets, play grounds, unsanitary places, decreases the chances of developing an allergy. The exposure to bacterial endotoxins and lipopolysaccharides present in unpasteurized milk, yoghurt or fermented milk early in life helps prevent the development of asthma and other related allergies (Douwes et al. 2006; Yufa and Christine, 2006). Similarly, the presence of an animal in the home has been associated with decreased sensitization to animal allergens.

Infections with helminths in early life reduced the risk of developing allergies. Mangan et al. (2006) proved in their animal model studies that infection with parasitic worms like Schistosoma mansoni in mice reduced respiratory allergic disorders by increasing the production of interleukins (IL-4, IL-10 and IL-13) and reduction of IL-5 levels. If a person has little or no exposure to helminth infections in childhood, Th1 cells will not be stimulated to produce the cytokines and interferons that help prevent the overproduction of IgE which results in an increased risk of developing allergies (Bell, 2002). Thus some exposure to microbes, helminths, and unpasteurized milk in early life can reduce the probability of developing allergies.

**Beware of the Common Allergens**

Pollen is one of the major causes of allergies. Some of the most common allergy-inducing pollens are from birch, olive, oak, maple, plantago, rye grass, and ragweed. Major pollen allergens constitute expansins, profilins and calcium-binding proteins. Food plants such as cooked potatoes, apples, beans, tomatoes, onions, cabbage, soy, peanuts, and the wheat proteins omega-5 gliadin and glutein can also cause allergies. A lot of work is going on to identify the various allergens. For example, it’s been found that tomatoes have four enzymes, which act as allergens: polygalacturonase, β-fructofuranosidase, superoxide dismutase and pectin esterase (Kondo et al. 2001). The quantity of these allergens increases as the fruit matures. So in persons allergic to tomatoes, the more ripened tomatoes he will eat, the greater the chances of developing allergy symptoms.
Latex is also a strong trigger for allergic disease, and in patients with spina bifida the chances of a Type 1 hypersensitivity reaction to Hevea brasilienses latex are greatly increased. The major allergen in natural rubber latex are the IgE-binding epitopes known as hevein (Hev b1, Hev b 6.02 and Hev3) and prohevein (Hev b 6.01) (Alenius et al. 1996, Bohle et al. 2000, Drew et al. 2004).

Allergens can be of animal origin. Many people develop seafood related allergies. In most edible fish, parvalbumin has been identified as the major allergen. Fish like cod, salmon, pollack, herring, and Wolffish contain the most potent allergens, whereas halibut, flounder, tuna and mackerel are the least allergenic (Thien van Do et al., 2005). Shellfish causes allergies in some people and the major allergen identified in shrimp is Pen m2. Nematodes Anisakis, parasitic to fish, cause allergic airway hyperreactivity and dermatitis in fish-processing workers exposed to them by air and contact. Allergies to pets have been reported in some people especially to fur. In cats, the allergen has been identified as Fel d 1, a protein found in cat saliva and dander.

Treatments under Development

1. DNA vaccines
Several types of new allergy treatments are under development. Because they are not proteins and can’t translate into proteins to become allergens in allergic persons, DNA vaccines can be used to reduce allergic reactions. DNA vaccines can be developed by one of three approaches: (i) using the naked DNA of allergens (ii) using hypoallergenic derivatives of allergen DNAs by modification of nucleotides; or (iii) fragmenting allergen DNA and fusing with ubiquitin, as fragmenting the antigen destroys its native structure. Based on their Th1-promoting properties, DNA vaccines balance Th2-mediated immune reactions, a quality which renders them a promising alternative for immunotherapy against allergies (Weiss et al. 2003).

2. Anti-IgE antibodies
Binding of IgE antibodies to specific high affinity receptors (called Fc epsilon receptors, or FceRI) on basophils and mast cells triggers the release of histamine and other mediators that result in allergy symptoms. Thus developing anti-IgE antibodies against IgE could be a potential therapeutic option for allergy treatment. Various such antibodies have been developed. An anti-IgE monoclonal antibody termed BSW17 peptide has been synthesized that is nonaphylactogenic, predominantly blocks binding of IgE to FceRI,
recognizes IgE already bound to FcεRI, and interferes with the function of IgE-sensitized basophils and mast cells (Rudolf et al. 2000).

Another such humanized monoclonal antibody is Omalizumab, which not only inhibits the binding of IgE to FcεRI but also decreases FcεRI expression on mast cells and basophils. It also reduces the synthesis of IgE by B plasma cells and thereby attenuates hypersensitivity reactions (Schulman; 2001). Leung et al. (2003) also humanized an IgG1 monoclonal antibody for peanut related allergies called TNX-901 that recognizes and masks an epitope in the IgE responsible for binding to the FcεRI on mast cells and basophils. Their results indicate that a dose of 450mg of TNX-901 significantly increases the threshold of sensitivity to peanuts from a level of 178mg (1/2 a peanut) to 2805mg (9 peanuts).

3. Modification of the epitopes
Modification of IgE binding sites, i.e. epitopes of allergens, could be another approach to attenuate hypersensitivity reactions. Epitopes of allergens can be created by modifying allergens and their hypoallergenic derivatives. Singh and Bhalla (2003) have demonstrated that the anaphylactic potential of rye grass pollen can be reduced by introducing a few point mutations in their allergens before using them for immunotherapy. In the shrimp allergen tropomycin, eight IgE epitopes were identified and mutated. These mutations had no effect on their secondary structure (in other words, did not change the basic structure of the IgE) but the allergic response was reduced by 90-98%, so this mutant could be helpful for therapy (Reese et al. 2005).

4. Target mast cells and basophil cells expressing FcεRI
Another possible option to reduce IgE related hypersensitivity reaction is to directly kill the mast cells and basophils expressing high affinity receptors (FcεRI) for IgE. Human originated apoptosis-inducing proteins can be used, as these will be less toxic or less immunogenic than the proteins produced in a different animal or plant. From two human apoptosis-inducing proteins, Bak and Bax, new chimeric proteins termed as Fcε-Bak/Bax have been synthesized that induce apoptosis in FcεRI-expressing mast cells and basophils (Belostotsky & Galski; 2001).

Also, these chimeric proteins do not degranulate mast cells. In birch pollen allergic people, the degranulation of mast cells releases enzymes such as α-chymase and other serine proteases (Mellon et al. 2002). Interestingly, the chymase cleaved IgE-binding epitopes of profilin giving profilin no chance to react with IgE and thus attenuated mast cell activation. Destruction of IgE binding epitopes of profilin with chymase could further limit pollen allergic reaction in sensitized individuals.

5. Immunotherapy
Immunotherapy (biologic therapy) is indicated for people who are extremely allergic to specific allergens. Immunotherapy is done by gradually exposing the patient to lower
doses of allergens to reduce the sensitization. It relies on the progressive production of the blocking antibody IgG and reduction in excessive production of IgE.

Li et al. (2003) developed a new chimeric peanut protein and co-administered it with adjuvant heat-killed *Listeria monocytogenes* (HKLM) to mice that were allergic to peanuts. The researchers found that these mice showed lower histamine release and fewer peanut specific IgE antibodies, and that allergic symptoms were reduced. Thus, their results suggest that immunotherapy with peanut protein and HKML could treat peanut allergic patients.

6. Harvesting nature

Aqueous extract of the plant bugleweed (*Lycopus lucidus*) decreases allergic response by reducing histamine, TNFα and interleukin (IL-6) release from mast cells (Kim et al. 2005). The same effect was reported by using hop, *Humulus lupulus*, extracts on rat mast cells of rats and human basophilic cells (Kamei et al. 2006).

7. Reducing the allergenicity of food crops

Scientists are trying to develop methods to reduce plant allergenicity. Generally it is believed that environmental stress to plants due to pollution, fertilizers, pesticides, heavy metals, etc., reduces their vitality and makes them produce various defense molecules (Thi and De Blic, 2005); these defense molecules could be active allergens (Uguz et al. 2005). Malkov et al. (2006) have reported that soil treatment with silicate breaking bacteria (*Bacillus oligonitrophilus* KU-1) in apples and strawberry plants can attenuate plant allergenic potency. The bioavailability of silicon produced by *B. oligonitrophilus* KU-1 increases the vitality of plants and reduces the production of allergens. So soil treatment with *B. oligonitrophilus* is a simple and inexpensive method for reducing the allergenic capacity of food crops.

**Treatments**

Over the counter medicines such as antihistamines, corticosteroids or decongestants are helpful in only treating the symptoms of allergic disease, not preventing the onset of allergies.

*Allergen immunotherapy (allergy shots)* is the process by which increasing doses of an allergen are injected subcutaneously (under the skin) over time as a treatment to prevent allergic symptoms. Immunotherapy involves a series of injections (shots) containing a mixture of allergens to which a person is sensitive, regularly for several months or even years. The first shots start with very tiny amounts of the allergens and eventually dosages increase over time. This process is also called desensitization or allergen immunotherapy. Medications help in reducing symptoms but immunotherapy is the only available treatment for reducing sensitivity to allergens.
Rush immunotherapy (RIT), also known as accelerated immunotherapy, is done very quickly, with shots given every few hours, instead of every few days or weeks, to increase the tolerance to an allergen (Nelson, 1995). Rush immunotherapy can be done quickly if someone gets a life-threatening allergy, for instance caused by a bee sting or other insect venom. Recently it was found that patients receiving both Omalizumab (monoclonal antibody) and RIT had fewer adverse symptoms than those receiving either treatment alone. Pretreatment of Omalizumab enhances both the efficacy and the safety of Rush immunotherapy (Casale et al. 2006).

Homeopathic remedies: Homeopathic remedies and natural products such as Lycopodium, Pulsatilla and sulfur can be useful in reducing allergic response (Colin, 2006). Intestinal commensal bacterial flora or eating the right kind of yoghurt (probiotic bacteria) can also be used for inhibiting the development of allergic responses to food related allergens (Bashir et al., 2004). Studies in mice have shown that induction of allergen-specific IgE and symptoms is associated with functional TLR4 receptors of lipopolysaccharides (toll like receptors-4). Strains of mice treated with TLR4 showed reduced symptoms than untreated strains. Mice lacking TLR-4 produce higher amounts of IgE and histamine levels. Mice react to TLR-4 by producing liposaccharides and show increased levels of IL-13 and allergy specific IFNy and thus allergy reduction.

Avoiding exposure: Because prevention is better than cure, personal hygiene may be the best alternative for reducing allergies. Persons prone to respiratory symptoms should avoid exposure to allergens; they should cover their noses or wear pollen/dust masks while going outside or exercising during pollen season. Air filters in furnaces and air conditioners should be changed monthly. Air purifiers and cleaning of air vents and ducts can help in cleansing the air. Wooden or cement floors are preferable to carpets, while frequent washing of bed sheets, covers, and other linens also reduces allergens. Avoid exposure to stored clothes in boxes or wardrobes for months after removal from storage and wash them before wearing. The simple way to avoid pet related allergy is to avoid the pets; pet lovers can keep a hypoallergenic pet. Researchers have developed a cat which lacks the allergen (Fel D 1) so that people allergic to cats can own a hypoallergenic pet (http://www.allerca.com/)

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References


