

Toward An Understanding of Allergy and In-Vitro Testing



By Mary James, N.D.



Great Smokies Diagnostic LaboratorySM

Toward An Understanding of Allergy and In-Vitro Testing

By Mary James, N.D.

Learning to recognize and manage food allergies can go a long way in achieving better clinical results with patients.

Food represents the largest antigenic challenge facing the immune system. Assuming complete digestion, an intact intestine, a sturdy constitution, and minimal antigenic exposure such that the immune system is not overwhelmed, all goes well. Weaknesses in one or more of these areas, however, can result in immune attacks upon foods as if they were foreign invaders. A long list of conditions have been associated with food reactions, including fatigue, migraines, irritable bowel syndrome, inflammatory bowel disease, gallbladder disease, arthritis, asthma, rhinitis, Attention Deficit Hyperactivity Disorder (ADHD), enuresis, epilepsy, eczema, psoriasis, aphthous ulcers, and recurrent sinusitis, otitis media and other infections.⁽¹⁾ A patient with numerous and seemingly unrelated symptoms often moves from doctor to doctor in search of a diagnosis. When the inflammatory response to an allergen takes hours or days to develop, the relationship between foods and symptoms is often hard to pin down. Learning to recognize and manage food allergies can go a long way in achieving better clinical results with these patients. The intent of this paper is to provide such an understanding.

In this paper, we will focus on IgE- and IgG-mediated immune reactions. Reasons why some individuals develop allergies while others

don't will be discussed, or why a specific food elicits symptoms in an individual at one point in time, yet appears to be well tolerated at other times. We will examine why an individual sometimes feels better from eating an allergenic food, but feels worse from eating it following a period of elimination. We will look at why an allergy test might be normal in an individual who knows he experiences symptoms when ingesting certain foods, or why an in-vitro test may show elevated antibodies to foods in an asymptomatic person. Finally, we will discuss how to effectively manage allergenic food elimination, reintroduction and rotation. While there are admittedly many useful approaches to the diagnosis and treatment of allergic disorders, the following discussion will be limited primarily to in-vitro assessment and dietary management.

The Immune System

Before embarking on a discussion of allergy, let's start with a few basics of the immune response. The following overview will provide a foundation for our discussion.

The principle cells of the immune system are lymphocytes, plasma cells and macrophages, collectively organized into lymphoid tissue. Lymphocytes can be further divided into B-cells and T-cells. Interestingly, these cell names were based on parts of a chicken, as studies of the thymus (T) and the

bursa of Fabricius (B) (a lymphoid organ near the cloaca) brought about the first understanding of their respective immunological functions. The chief role for B-cells is the provision of humoral immunity. Upon exposure to an antigen, B-cells proliferate and evolve to antibody-synthesizing plasma cells that then produce antigen-specific immunoglobulins of different isotypes, called IgM, IgG, IgE, IgD and IgA. T-cells, on the other hand, provide cell-mediated immunity.

There is considerable interaction among components of the immune system. Subsets of T-cells, function as: helper T-cells, which stimulate B-cell activity; or as suppressor T-cells which suppress both humoral and cell mediated immune responses. Macrophages are released from the bone marrow as monocytes, and develop into macrophages upon entering tissue. Macrophages serve to present antigen to both T- and B-cells, as well as to clear antigen/antibody complexes from the circulation. The efficiency of this function is critical in controlling food-induced hypersensitivity reactions, as we will discuss.

Getting Our Terms Straight

The terms "food intolerance," "allergy" and "hypersensitivity" are often used interchangeably. For clarification, it's useful to differentiate among them...

Intolerance

The term "intolerance" generally applies to non-immune mediated

reactions to foods and other substances. Examples include lactose intolerance, pharmacological responses to alkaloids in foods such as solanine (potato family), salicylate sensitivity, and lectin reactions, in which dietary lectins interact with surface antigens on cells, causing them to agglutinate. Bacteria and bacterial toxins may

Non-immune Mediated Reactions to Foods

- Lactase deficiency (dairy) → bloating, flatulence, diarrhea, abdominal pain
- Spoilage or contamination of food by bacteria (*Proteus*) or heat-stable toxins (tuna, bonito, mackerel) → itching, rash, vomiting, diarrhea
- Gallbladder disease → abdominal pain (RUQ), nausea, flatulence, aggravation by fats
- Vasoactive amines
 - phenylethylamine (chocolate, aged cheese, red wine) → migraine
 - tyramine (cheddar cheese, French cheeses, brewer's yeast, chianti, canned fish) → migraine, erythema, urticaria, hypertensive crises in patients on MAO inhibitors
 - histamine (fermented cheese, fermented foods (e.g. sauerkraut), pork sausage, canned tuna, anchovies, sardines) → erythema, headache, hypotension
 - histamine-releasing agents (shellfish, chocolate, strawberries, tomatoes, peanuts, pork, wine, pineapple) → urticaria, eczema, pruritis
- Food additives (e.g. tartrazine, FD&C Yellow No. 5, sodium benzoate) → hives, rash, asthma
- Sulfites (salad bar lettuce, shrimp, dried fruits and vegetables, wine, beer) → asthma or anaphylaxis, loss of consciousness
- Monosodium glutamate (Chinese and Japanese dishes) → headache, facial tension, sweating, chest pain, dizziness
- "Nightshade" alkaloids (potatoes, tomatoes, eggplant, peppers, tobacco) → joint pain
- Hypoglycemia → Fatigue, palpitations, shakiness, cognitive impairment, mood swings, poor memory, blurred vision, anxiety, dizziness, headache
- Lectin reactions (wide variety of foods) → wide variety of symptoms, depending on blood type compatibility. (Refer to: *Eat Right 4 Your Type*, by Peter D'Adamo, N.D.)

cause gastrointestinal and systemic reactions, such as in scombroid poisoning from the ingestion of contaminated tuna. Vasoactive amines (epinephrine, norepinephrine, tyramine, dopamine, histamine and 5-hydroxytryptamine) are found in bananas, tomatoes, avocados, cheeses, pineapples and

Any food eliciting an adverse reaction should ideally be avoided, no matter what the mechanisms, and careful investigation aimed toward the causative factors.

wines, and can contribute to symptoms such as migraine headache. Sulfite, used as a preservative in foods such as lettuce, shrimp, dried fruit and wine, can cause asthma and urticaria.⁽²⁾ Some compounds, such as alcohol, may even induce histamine responses, although the reaction is not immune mediated.

Because of the conspicuous relationship between ingestion of the food and the onset of symptoms, such reactions are frequently mistaken for allergy, yet an allergy test may be negative for that food. Any food eliciting an adverse reaction should ideally be avoided, no matter what the mechanism, and careful investigation aimed toward the causative factors.

Hypersensitivity

Although the use of the term "hypersensitivity" is sometimes reserved only for Gell and Coombs' classification of Type III, IgG-mediated reactions, traditionally the term is applied to all four types of tissue injury. Types I through IV all depend upon the interaction of antigen with humoral antibody, and result from an excessive immune reaction to antigen, leading to gross tissue changes and symptoms.

•**Type I** reactions are mediated by IgE antibodies, and are characterized by the release of histamine and other chemical mediators upon exposure to an allergen. Type I reactions are responsible for "immediate-onset" allergies, such as hay fever or anaphylaxis. They will be discussed in more detail below.

•**Type II** immune reactions involve antibody-mediated destruction of tissue following adherence of foreign material. This reaction is often referred to as a "cytotoxic reaction." Examples of Type II reactions include penicillin reactions and those resulting in red cell or platelet destruction.

•**Type III** reactions are mediated by mixed immunoglobulins, but primarily IgG. Complexes composed of antigen and antibody activate complement and cytokines in the body, resulting in an inflammatory response. Type III reactions constitute the basis of "delayed-onset" food allergies. Symptoms are delayed because of the time required for the formation of complexes. These reactions will also be discussed in more detail.

•**Type IV** refers to cell-mediated immune reactions, where T-cells act as the primary players. T-cells become cytotoxic cells when activated by antigen, capable of killing viruses, bacteria, tumor cells or other target cells. Type IV reactions play a significant role in tuberculosis, mycotic and viral infections, contact dermatitis and allograft rejection. These reactions may also be involved in some food allergies, such as protein-losing enteropathies and celiac disease.

Allergy

The definition of the term "allergy" is much debated. Although many traditional allergists strictly reserve the use of the term for Type I IgE-mediated reactions such as hay fever, a more general definition of "allergy" refers to any acquired hypersensitivity to an antigen that results in harmful immunologic

consequences. For our purposes, we will apply this broader definition to both Type I and Type III immune reactions.

Immediate-Onset IgE Reactions

When an antigen attaches to IgE antibodies already stationed on a mast cell or basophil, pre-formed bundles of histamine are released. Inhalation of antigens usually leads to the symptoms we commonly associate with "allergy" such as sneezing, itching of the palate or ears, runny nose, itching and tearing in the eyes, and fatigue. Ingestion of an antigen may lead to symptoms such as asthma, an itchy rash, angioedema or gastrointestinal symptoms such as abdominal cramps and diarrhea.

Chronic IgE allergies may manifest as sinusitis, recurrent ear or upper respiratory infections, mouth breathing and post-nasal drip. "Allergic shiners" under the eyes and a white line across the nose, from repeated upward wipes of the nose with one's hand, are common signs of IgE-mediated allergies in children, although these signs have also been observed in individuals with IgG allergies. Severe Type I reactions may include anaphylaxis. The allergic reaction occurs immediately upon exposure to the antigen (usually less than two hours); consequently, the person experiencing the reaction usually easily recognizes the link between allergen and symptom.

Specific IgE-mediated allergies are not inherited, although Type I allergic diseases in general tend to run in families, and end-organ sensitivities associated with nasal,

bronchial and cutaneous allergies show a familial tendency. This is particularly true for asthma, hay fever, recurrent rhinitis and bronchitis, and eczema; when present in a parent, there is an increased prevalence of the same disorder in the child.⁽³⁾ If neither parent is allergic, a patient's symptoms are less likely to reflect an IgE-mediated reaction. IgE allergies are in place for life. Antibody levels may drop with avoidance of exposure, but re-exposure will quickly result in the mobilization of IgE antibodies and the subsequent release of histamine.

As mentioned above, IgE-mediated food allergies are usually easy to spot because of the immediate appearance of symptoms. Common culprits include peanuts and shellfish. Sensitivity to these substances is so extreme in some cases that anaphylaxis may result from the mere inhalation of vapors from food or contact with the skin. Needless to say, management of these allergies requires strict avoidance of the offending substance. IgE reactions triggered by inhalants often show a seasonal pattern, with reactions to tree pollens typically occurring in the spring, grass pollens in late spring and early summer, and weed pollens in late summer and early fall. Reactions to dust mites often appear in the winter, with the onset of home heating. Allergy testing during a symptomatic period can help to identify the responsible antigens. Allergies to pet dander can occur at any time, upon exposure.

Mold and Fungi Reactions

Mold allergies tend to coincide with wet months that feature above-freezing temperatures, e.g.

IgE antibody levels may drop with avoidance of exposure, but re-exposure will quickly result in the mobilization of antibodies and the subsequent release of histamine.

A food allergy test can be most clinically useful for measuring IgG antibodies involved in delayed-onset Type III reactions.

December through March in California, summer in the mid-west, or year-round in Florida. Very dry states, such as Arizona or Nevada, are unfortunately not exempt from inhalant mold allergies, as the moisture in air conditioning units invites the growth of mold which then becomes disseminated throughout the living space. Avoidance of allergen, in the case of molds and fungi, can be extremely challenging since these substances are so ubiquitous in the environment. Common food sources include fermented cheese, wine, beer and bread. Other common, but less suspected sources include tea, processed foods, dough conditioner, commercial fruit juices, citric acid, malt flavorings, chocolate, soy sauce, tomato products (crushed and left to sit for better flavor), Lactaid and B vitamins. Fungal colonization of the skin or mucous membranes represents a third source of exposure which may serve to amplify reactions to other fungi in the environment. Since different fungi from different sources share common surface proteins, the immune response to fungi may cross-react. As a result, correcting conditions such as dandruff, athlete's foot and *Candida* overgrowth often helps to lessen reactions to the other sources.

Such reactions are all primarily IgE-mediated and feature the symptoms commonly associated with histamine, such as sneezing, runny nose and asthma. More severe illness may result when an individual is exposed to a much larger number of fungal particles, such as in occupational exposures. Due to the massive amount of antigen exposure, these reactions

typically are Type III and IV and involve IgG antibodies. Symptoms may include flu-like illness with fatigue, rash, muscle and joint pain, headache, fever and nightsweats. Fungal colonization may be life-threatening in immunocompromised individuals.

Delayed-Onset IgG Reactions

Type III reactions involve the formation and deposition of antigen/antibody (Ag/Ab) complexes, mostly involving IgG. In contrast to the immediate IgE histamine-mediated reactions, these reactions are delayed, since they involve the gradual formation of immune complexes. Because these reactions are delayed by hours or even days following the exposure, the relationship between food and symptoms is much more difficult to spot. It is these reactions for which a food allergy test measuring IgG antibodies can be most clinically useful.

IgG-mediated reactions typically result from exposure to an excess of antigen over an extended period of time. In the case of food allergy, increased intestinal permeability coupled with repetitious ingestion of particular foods causes excessive antigen to be presented to the immune system. Formation of insoluble antigen/antibody complexes results in the activation of complement and the subsequent respiratory burst in neutrophils, the release of proteolytic enzymes, mast cell mediators and vasoactive peptides, and the aggregation of platelets. Although complement stimulates inflammation, it also functions to prevent the progression from small complexes to

larger ones, a factor that helps minimize the severity of symptoms. Macrophage activity triggers the release of inflammatory mediators such as interleukin-1, tumor necrosis factor, reactive oxygen species and nitric oxide.

Symptoms are typically delayed in onset, by hours or days, and vary, not only according to the specific nature of the immune complex, but also according to the tissue in which the complexes are deposited. Headache, vasculitis or hypertension may result from deposition in the vascular space; asthma, alveolitis or recurrent infection may result from deposition in respiratory tissue, dermatologic changes from deposition in the skin, and joint pain from deposition of complexes in the joint space. Symptoms such as rhinitis or angioedema may also occur, since two elements in the complement cascade (C3 and C5) are capable of inducing histamine release. Any system may be affected and any symptom is possible, depending on an individual's susceptibilities. Reactions may last for days.

Immune Competency and "Total Load"

Although an immune interaction between antibody and antigen occurs every time an individual is exposed to an allergenic food, the presence and the degree of symptomatology depends upon the solubility of complexes and the reticuloendothelial system's ability to clear them. Macrophages pick up Ag/Ab complexes immediately, but have a finite capacity. With an efficient immune response, the half-life of a complex may only be a few minutes, and exposure to allergens

may NOT elicit symptoms, despite the fact that an immune reaction is occurring. An overload of antigen, however, will saturate the macrophages' capacity, resulting in the circulation of complexes and their deposition in tissue. Immune compromise may lead to the same end, resulting in symptoms. (This process is quite different from the "loaded gun" IgE response which is elicited with every exposure.) This "overload" phenomenon may help explain why reducing exposure to one allergen may result in an individual being better able to tolerate other allergens. Unlike Ag/Ab interactions, macrophage clearance is NON-specific. This means that ANY reduction in demand on macrophages (including non-allergic conditions such as infection or xenobiotic exposure) may serve to reduce symptoms and allow other reactive foods to be eaten.

This concept of "total load" cannot be overemphasized. It was not until the middle of the last century and the growth of the industrial revolution that the diseases which we now call atopic allergic diseases, were recognized as entities. ⁽⁴⁾ Hypersensitivities involving bronchial symptoms and asthma nearly doubled during the 1980s and early 1990s. ⁽⁵⁾ Air pollution, including the contribution by diesel exhaust particle emissions, has been shown to enhance both nasal IgE production and the expression of Th2 cytokines ⁽⁶⁾, and may serve as a carrier for pollen and other compounds.

Food allergies can develop at any point in one's life, but an individual may also be born with them. Such allergies are usually to foods that the mother consumed fre-

*Antigen "overload"
may help explain why
reducing exposure to one
allergen may result in an
individual being better able
to tolerate other allergens.*

An allergy test should always be assessed in conjunction with a patient's clinical picture.

quently during her pregnancy, although the antibodies are the baby's own. Since maternal dietary proteins are capable of reaching amniotic fluid, and since the fetus is capable of mounting antibody and other immune responses as early as the tenth week of gestation, it is possible that fetal sensitization to these proteins begins as early as the first trimester of pregnancy.⁽⁷⁾ Maternal IgG antibodies traverse the placenta during pregnancy, but levels of these in the infant are typically down by 3-6 months after birth.⁽⁸⁾ Dietary proteins from the mother's diet are also transferred to breast milk. While a certain amount of antigen passage into the breast milk is probably important for the development of the infant's tolerance to foods, excessive exposure can result in hypersensitivity. Breast-fed infants whose mothers take dietary precautions during lactation are observed to have a markedly reduced incidence of atopic eczema.⁽⁷⁾

Unlike IgE allergies, those mediated by IgG may be cured, following a period of avoidance and attention to underlying contributing factors. Although a food may be tolerated at some point on a limited basis, the immune system "holds a grudge," in a sense. Because the hypersensitivity is recorded in the body's "memory cells" (antigen-stimulated lymphocytes), the response may be reactivated if exposure again becomes excessive or too frequent.

DIAGNOSIS

An allergy test should always be assessed in conjunction with a patient's clinical picture. If an individual's immune clearance mechanisms are effective in averting

symptoms, yet allergies exist, a test can help to identify those foods which to some degree are stressing the immune system. If a person is allergic to numerous foods, the test can also help provide a starting place, in terms of elimination.

In-Vivo Skin Testing

Type I allergies are often diagnosed with skin prick testing, or with intradermal testing, often employed as a follow-up to a negative skin prick test. Advantages of skin testing include rapid results, good sensitivity, and the ability to test any antigen. Disadvantages include the discomfort inherent in the procedure, possible danger of anaphylaxis,⁽⁹⁾ the contraindicating effects of medications such as anti-histamines, decongestants, beta blockers, bronchodilators and theophylline, and occasional interference from skin disease. Since skin testing only reflects IgE-mediated reactions, it also cannot inform clinicians as to the potential for the delayed hypersensitivity reactions responsible for such a wide range of symptoms seen clinically.⁽¹⁰⁾

In-vitro Antibody Measurement

The measurement of antigen-specific antibodies is a useful tool for assessment of allergies, particularly to foods. One study of young children found that 62.5% of children with symptoms had specific IgG antibodies and 22.9% had specific IgE antibodies, while the children without symptoms of food allergy had neither.⁽¹¹⁾

Three widely used methods for measuring specific antibodies include ELISA, MAST and

RAST/RASP. ELISA (enzyme-linked immunosorbent assay) can detect either IgG or IgE antibodies. MAST and RAST (radioallergosorbent procedure) measure IgE antibodies, although MAST testing for IgG antibodies is currently being developed. Some laboratories measure only IgG4 for foods; however, measurement of total IgG is recommended.

Although all IgG subclasses are involved in the immune response, IgG1 is thought to be the main instigator of inflammation. The role of IgG4 in food allergy has been debated. IgG4 is unable to activate complement, so does not contribute to a true inflammatory reaction. It is, however, able to precipitate the release of histamine from basophils⁽¹²⁾, which might partially explain the elevated levels observed in atopic individuals and amelioration of symptoms upon removal of the "positive" foods from the diet.⁽¹³⁾ At the same time, it has been suggested that IgG4 may function as a "blocking" antibody to allergic reactions, particularly since levels tend to increase dramatically following successful immunotherapy for IgE-mediated pollen allergies.⁽¹⁴⁾ Although IgG4 can induce histamine release, its release appears to be more delayed and the reaction less acute than in the Type I IgE reactions.

In-vitro tests offer the advantages of convenience, safety (no danger of anaphylaxis), lack of interference by antihistamines or skin condition, and good reproducibility. In -vitro also allows the use of parallel controls with each run. A positive reaction on an in-vitro test signifies allergy in that individual. For the "global reactor," in-vitro test-

ing can provide a starting place for trial elimination programs. As a screen for an asymptomatic individual, in-vitro testing may reveal food allergies which are currently being effectively managed by the immune system (hence, no symptoms), but which could manifest symptomatically in the future, in the event of increased immune burden.

Occasionally, a test will exhibit "across-the-board" low-level IgG reactivities for an individual. Clinical observation has suggested the possibility of a chronically "leaky gut" in such situations, and the concomitant immune reaction to a large number of absorbed antigens.

Disadvantages of in-vitro testing include the requirement of serum collection, the sometimes lengthy incubation and the possibility of some false negatives for IgE, which may result from a number of factors. Antibodies that are directed toward altered forms of antigen not used in the test, e.g. cooked, spoiled or processed foods, might go undetected. False negatives may also follow immunotherapy, a result of IgG "blocking" antibody production. (This is one of the mechanisms behind immunotherapy's effectiveness for IgE-mediated allergies; antigen now preferentially binds to IgG, rather than IgE, so that the immediate and acute histamine reaction is prevented.) Finally, with the possible exception of anaphylaxis-inducing allergens, specific immunoglobulins tend to gradually diminish in response to antigen elimination. Although the half-life of IgE antibodies is only 3 days and the half-life of IgG 23 days, absorbed antigens which have been sequestered by the liver may, in some cases, be slowly released over several months, resulting in

In-vitro allergy tests offer the advantages of convenience, safety (no danger of anaphylaxis), lack of interference by medications or skin condition, and good reproducibility.

some persistent antibody production. The levels, however, will still decline over time, barring any new exposure. Because foods such as wheat, dairy and corn are widely used as additives in processed foods or cosmetics, IgG levels are more likely to persist in an individual who mistakenly presumes that he has completely eliminated the foods. IgE antibodies to seasonal allergens may be undetectable if measured during an asymptomatic period.

Interpreting the In-Vitro Test

It should be noted that in-vitro antibody tests are semi-quantitative. All procedures involve the binding of specific anti-food antibodies to an antigen that is already bound to a solid phase, e.g. a plate or test tube. Each procedure includes a tag, or signal, which is quantitated. The tag used in the RAST is a radioactive isotope, while MAST uses a luminescent signal. In the ELISA test, the tag is an enzyme that induces a color change which is then read photometrically as "optical densities." The more intense the color change, the higher the concentration of specific antibodies. Because of inherent imprecision in the multi-step processes used in these procedures, there will always be some natural "drift" in the quantification. It is for this reason that reporting of broad categories for reactivity, e.g. 0-3+, has become an industry standard.

Literal reliance upon the larger optical density numbers (in the case of ELISA) can be misleading, as a follow-up test featuring higher or lower optical densities for a par-

ticular food may not, in fact, correlate with improvement in, or aggravation of, an individual's level of reactivity. Even the broad categories of 0-3+ should be evaluated against the patient's clinical picture. A 3+ IgG reaction will generally imply a stronger immune reaction (or a more severe allergy) than a 1+ reaction. However, that 3+ reaction may never manifest as symptoms in a person whose system is effectively neutralizing immune complexes, while a 1+ reaction may result in debilitating symptoms in a person whose reticuloendothelial system is overwhelmed. In other words, the best use of the test is to identify reactive substances which can then be avoided or rotated in a clinical trial.

Elimination Diets

Elimination and reintroduction of foods is an invaluable means of establishing a relationship between a symptom and a particular food. The typical protocol involves the elimination of all possibly allergenic foods (commonly the routine foods in one's diet) for 1-2 weeks and, assuming any clinical improvement during this time, the gradual reintroduction of one food every 2-3 days. If a food in one meal fails to produce symptoms, then a larger amount is eaten in the next couple of meals. If symptoms reappear within the 2-3 days of repeated ingestion of a food, that food is regarded as allergenic, and eliminated from the diet. If no symptoms are induced, the food is now included in the hypoallergenic diet, and the next food is tested in the same manner.

Needless to say, this process may

In-vitro antibody tests are semi-quantitative.

The best use of the in-vitro allergy test is to identify reactive substances which can then be avoided or rotated in a clinical trial.

take several weeks to complete, depending upon the number of foods tested, and it requires more than a modicum of self-discipline. The results, however, prove invaluable. The patient is not only able to ascertain which foods produce which symptoms, but the clinical experience of improvement on the elimination diet and the aggravation upon ingestion of a food, often serves to provide the needed incentive for the subsequent long-term elimination or rotation of offending foods. The process assists in revealing the NON-immune mediated reactions as well. As discussed earlier, a relationship between food and symptom does not automatically mean "allergy."

There are a few disadvantages to relying solely on the elimination diet for diagnosis. The length of time and discipline required are mentioned above. Sub-clinical hypersensitivities will not be detected. Finally, the possibility exists that some of the foods consumed as components of the "hypoallergenic" diet are antigenic for a given individual. In this case, amelioration of symptoms on the diet does not occur, and the false conclusion is reached that foods play no part in the patient's illness. Combining a preliminary in-vitro test with an elimination diet represents the most efficient approach of all, and improves patient compliance.

TREATMENT

Following is a brief discussion of a few of the most popular methods for managing allergies.

Immunotherapy (Hyposensitization)

Inhalant allergies are most often treated with a combination of avoidance, where possible, and immunotherapy, which consists of injections of serially increasing concentrations of antigen. As antigen is introduced into a patient's system, the immune system gradually develops a mixed IgG response to it, although never enough to cause tissue damage. The IgG antibodies are thought to block the more severe IgE reaction, and symptoms usually abate within a few weeks. Standard immunotherapy is not used for the desensitization to foods and molds because the large amount of antigen exposure from natural sources is usually already so high that severe reactions are likely to be induced. It should be noted that, although IgE antibodies to a substance remain in the system, an IgE blood test may fail to pick them up following treatment, due to the competitive inhibition by IgG. This significant decline, however, appears to occur only after about two years of hyposensitization.⁽¹⁵⁾

Enzyme-potentiated desensitization

Enzyme-potentiated desensitization (EPD) also utilizes the periodic injection of antigen into the patient's skin, but the amount of antigen compared to standard immunotherapy is exceedingly small. Furthermore, the antigen is accompanied by the enzyme beta-glucuronidase which helps to activate T-suppressor (CD8) cells. Unlike immunotherapy, IgG levels do NOT rise in response to the treatment, although tolerance develops. Injections are administered every two months and in most cases can eventually be

Combining a preliminary in-vitro test with an elimination diet represents the most efficient approach of all, and improves patient compliance.

spaced further apart, assuming improvement. EPD is used for food and mold allergy and is preferred by many physicians for treatment of inhaled allergens, as well.

Medications

Other standard treatments for inhalant allergies include the use of anti-histamines, decongestants, glucocorticosteroids, and sodium cromoglycate. This last one serves to block mast cell degranulation, eosinophil and neutrophil chemotaxis and mediator release; however, it is poorly absorbed orally, so must be taken frequently in order to maintain adequate mucosal concentrations. Quercetin is a natural bioflavonoid with similar activity.⁽¹⁶⁾ All of these medications are merely palliative, but of course can make a world of difference in a patient who is experiencing paroxysmal sneezing or a frightening bout with asthma.

Allergen Elimination

The most important component of any allergy program is the reduction of exposure to the offending agent. As long as exposure is maintained, antibodies will continue to be produced and the immune system "primed" to react. IgE-mediated allergies tend to be "fixed," thus avoidance is usually life-long. In contrast, the IgG-mediated allergies may be reversed over time. Reactive foods are ideally eliminated from the diet for a minimum of three months, particularly those that evoke the most severe symptomatology or the highest scores on an in-vitro test. Ideally exposure to foods within the same food family of a reactive food should be reduced as well. A sensitivity to clam, for example, may indicate a

greater likelihood that sensitivities to oyster, scallop and squid (other members of the "mollusk" family) might be present. At the same time, such cross-reactions have been observed to be relatively infrequent, and patient compliance is always a consideration. Care must also be taken that suspected foods are not inadvertently consumed while hidden in other foods, e.g. eggs contained in mayonnaise.

Eliminating the antigenic food provides the immune system a rest. Levels of antibodies gradually decline, immune complexes are cleared, and symptoms improve. Lesser reactive foods are often tolerated in the beginning if eaten no more often than every four days or so; however, this tolerance varies between individuals, and in the more symptomatic patient even foods with 1+ reactivities may have to be temporarily removed from the diet in order to improve clinical outcome.

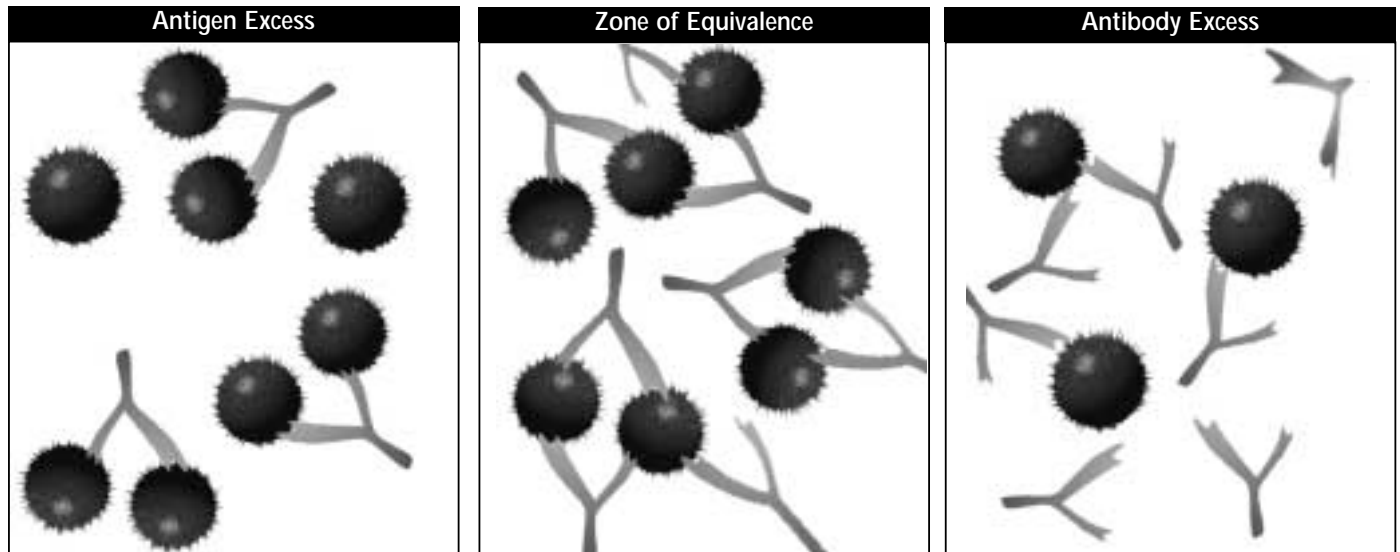
Antigen/Antibody Equilibrium

One of the most important determinants of the pathogenicity of the Ag/Ab complex and the clinical course of the patient is the equilibrium between antigen and antibody. At equivalent concentrations (also called the "zone of equivalence"), complexes can grow to enormous size. The larger and more numerous the complexes, the more likely they are to overwhelm the reticuloendothelial system and deposit in bodily tissues. Individuals with IgG allergies often have the paradoxical experience of feeling immediately better, rather than worse, after consuming an allergenic food. What is happening

Eliminating the antigenic food provides the immune system a rest. Levels of antibodies gradually decline, immune complexes are cleared, and symptoms improve.

here is a shift into the zone of "antigen excess."⁽¹⁷⁾ In this zone, complexes become more soluble and symptoms may diminish, that is, until more antibody is produced and the "zone of equivalence" is

Plasma cells retain a memory of that sensitivity, and new antibodies could be produced with any exposure. Only a trial reintroduction will answer that question. If no symptoms are elicited when the



again reached, producing more symptoms. Eating more of the food once again brings relief, perpetuating a vicious cycle of addiction that is difficult to break. Following 7-10 days of strict elimination of a reactive food, an individual moves into a zone of "antibody excess." With less antigen on board, complexes reduce in size and number, and symptoms diminish. During this period, he or she is extremely sensitive (hence the conspicuous and diagnostic aggravation from reintroductions of offending foods at this point), and should stay with the elimination diet for three or more months, while antibody levels drop.

After this point, a follow-up in-vitro test might well show lower reactivities for those foods that have been avoided. This fact does not guarantee that the food will be tolerated when reintroduced.

food is reintroduced, the food can usually be replaced into the diet, but ideally on a rotational basis. Repetitive exposure to a food usually contributes to the development of hypersensitivity in the first place, thus a return to the same frequency of exposure often brings with it an eventual return of symptoms.

Other Considerations

In the case of reactivity to molds, yeast or fungi, it is often useful to treat any existing infections. Examples include ringworm, athlete's foot or jock itch, as well as vaginal or intestinal yeast overgrowth. Doing so may help to eliminate cross-reactivity reactions and lower the overall burden on the immune system.

Because IgG allergies can be established as a result of the translocation of food antigens

One of the most important determinants of the pathogenicity of the clinical course of the patient is the equilibrium between antigen and antibody.

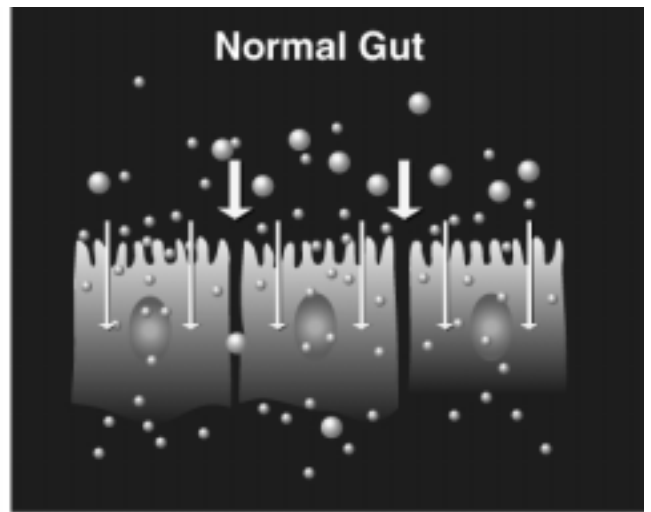
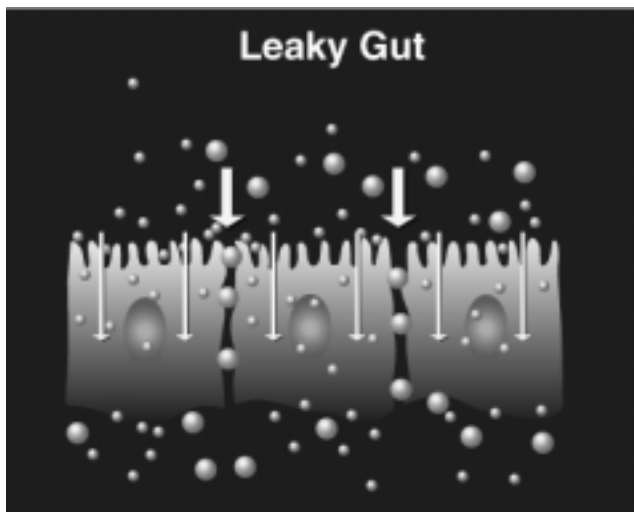
Correcting imbalances in the gastrointestinal flora and providing nutritional support for the immune system can greatly help reduce immune sensitivity.

across a permeable gut wall (18), attention to gut repair is a prerequisite for preventing further problems. It is not uncommon for a person who is eating soy foods, e.g. as a substitute for foods such as cow's milk and wheat, to suddenly find herself now unable to tolerate soy after a few months. Evaluation of intestinal permeability as well as a comprehensive stool analysis can serve to establish the presence of "leaky gut" and contributing factors such as maldigestion, malabsorption, imbalances in flora, secretory IgA deficiency and mucosal injury due to infection or agents such as non-steroidal anti-inflammatories. Correcting any

imbalances will greatly help to reduce the likelihood of developing additional allergies.

Finally, it's worth noting that adjunctive nutritional support for the immune system, as well as selective botanicals, homeopathic remedies or acupuncture, may contribute significantly to the reduction in immune sensitivity and the inflammatory response.

Acknowledgements: Special thanks to Vincent Marinkovich, M.D., (Diplomat, American Board of Allergy and Clinical Immunology) for his generous contribution of information on the subject.



REFERENCES

- 1) Gaby AR. The role of hidden food allergy/intolerance in chronic disease. *Alt Med Review* 1998;3(2):90-100.
- 2) Buckley RH, Metcalfe D. Food allergy. *JAMA* 1982;248:2627-31.
- 3) Gerrard JW, Ko CG, Vickers P. The familial incidence of allergic disease. *Ann All* 1976;36:10.
- 4) Mygind N. History of Allergy. In: *Essential Allergy—An Illustrated Text for Students and Specialists*. Boston: Blackwell Scientific Publications, 1986:1-9.
- 5) Chandra RK. Food allergy and food intolerance: lessons from the past and hopes for the 21st century. In: Somoyogi JC, Muller HR, Ockhuizen T, editors. *Food allergy and food intolerance. Nutritional aspects and developments. Bibl Nutr Dieta* 1991;48:149-156.
- 6) Casillas AM, Nel AE. An update on the immunopathogenesis of asthma as an inflammatory disease enhanced by environmental pollutants. *Allergy Asthma Proc* 1997 Jul-Aug;18(4):227-33.
- 7) Chandra RK. Food allergy and food intolerance: lessons from the past and hopes for the 21st century. In: Somoyogi JC, Muller HR, Ockhuizen T, editors. *Food allergy and food intolerance. Nutritional aspects and developments. Bibl Nutr Dieta* 1991;48:149-156.
- 8) Host A, Husby S, Gjesing B, Larsen JN, Lowenstein H. Prospective estimation of IgG, IgG subclass and IgE antibodies to dietary proteins in infants with cow milk allergy. Levels of antibodies to whole milk protein, BLG and ovalbumin in relation to repeated milk challenge and clinical course of cow milk allergy. *Allergy* 1992 Jun;47(3):218-29.
- 9) Sampson HA, Metcalfe DD. Food allergies. *JAMA* 1992;268(20):2840-2844.
- 10) El Rafei A, Peters SM, Harris N, Bellanti JA. Diagnostic value of IgG4 measurement in patients with food allergy. *Ann Allergy* 1989;62:94-99.
- 11) Hofman T. IgE and IgG antibodies in children with food allergy. *Rocz Akad Med Bialmyst* 1995;40(3):468-473.
- 12) Vijay HM, Perelmutter L. Inhibition of reagin-mediated PCA reactions in monkeys and histamine release from human leukocytes by human IgG4 subclass. *Int Arch Allergy Appl Immunol* 1977;53:78-87.
- 13) Gwynn CM, Ingram J. Bronchial provocation tests in atopic patients with allergen specific IgG4 antibodies. *Lancet* 1982;1:254-256.
- 14) Van der Giessen M, Homan WL, van Kernebeek G, et al. Subclass typing of IgG antibodies formed by grass pollen allergic patients during immunotherapy. *Int Arch Allergy Applied Immunol* 1976;50:625-639.
- 15) Szymanski W, Chrek-Borowska S, Obrzut D. IgG, IgA, IgM and IgE serum levels in asthmatic patients sensitive to house dust and mite allergens after two-year specific immunotherapy. *Arch Immunol Ther Exp (Warsz)* 1984;32(4):381-7.
- 16) Middleton E Jr, Drzewiecki G. Flavonoid inhibition of human basophil histamine release stimulated by various agents. *Biochem Pharmacol* 1984 Nov 1;33(21):3333-8.
- 17) Randolph TG. Specific adaptation. *Ann Allergy* 1978;40:333-345.
- 18) Andre C, Françoise A, Colin L. Effect of allergen ingestion challenge with and without cromoglycate cover on intestinal permeability in atopic dermatitis, urticaria and other symptoms of food allergy. *Allergy* 1989;44(9):47-51.



Great Smokies Diagnostic LaboratorySM

63 Zillicoa St., Asheville, NC 28801-1074 • 800-522-4762 • E-mail: cs@gSDL.com • www.greatsmokies-lab.com

Published and distributed by Great Smokies Diagnostic Laboratory in accordance with permissions granted by author Mary James, N.D., owner of the copyright to material contained herein, this monograph may not be reproduced in any form without the express permission of Great Smokies Diagnostic Laboratory or Mary James, N.D.

This information is for the sole use of a licensed health care practitioner and is for educational purposes only. It is not meant for use as diagnostic information. All claims submitted to Medicare/Medicaid for GSDL laboratory services must be for tests that are medically necessary. "Medically necessary" is defined as a test or procedure that is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. Consequently, tests performed for screening purposes will not be reimbursed by the Medicare program. Physicians may deem it medically necessary to order a single test or a portion of a profile.