

Functional Medicine University's Functional Diagnostic Medicine Training Program

INSIDER'S GUIDE

INTERPRETATION OF FOOD ALLERGY, SENSITIVITY AND INTOLERANCE

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What is the Story Behind Allergies?

The battle among educated researchers and health care professionals on the topic of food allergies is one that bears no winners except the sole patient who acknowledges you there here for helping them restore their health.

Food allergy has become quite a problem and is rapidly becoming a great concern of many clinicians. From a conventional stand-point, adverse reactions to foods whose pathogenesis involves an immunological response to food components are appropriately called **food-hypersensitivity reactions**. This term is considered to be synonymous with "food allergy."

It is now estimated that up to 20% of the population have adverse reactions to foods and nearly 4% of Americans have immune mediated allergies.

Why has the incidence of allergy risen so dramatically?

Food products most frequently incriminated in allergic reactions are often hidden as ingredients in commercial foods.

Many modern foods, as well as medicinal drugs such as penicillin, also contain preservatives, stabilizers, artificial colorings, and flavorings. Some scientists believe that increased chemical pollution in our air, water, and food is to blame. Foods can easily become contaminated by the use of insecticides in farming.

The multifactorial causes currently under investigation include: genetic atopic predisposition, allergen exposure and sensitization in early childhood, viral respiratory tract infections in young children, smoking during pregnancy, poor quality diet, reduced breast-feeding, childhood obesity, immunologic predisposition (Th2-prone), environmental pollution, and childhood immunization.

Other possible reasons for increased food hypersensitivity include genetic manipulation of plants, resulting in food components which cross-react with normal tissues; less diversity in the diet, cultural differences and route of exposure. The way in which we process and cook foods along with our individual digestive capacity can also increase food hypersensitivities.

The long standing question

The long standing question that continues to cause an on-going tiff between traditional trained allergist and functionally trained health professionals is

*"Is the well established intradermal, skin prick, RAST test the **ONLY** true "allergy" test or does the literature support other means of testing adverse reactions to foods?"*

This guide has been prepared to help the clinician make sense of all and help provide clinical support for both.

Before we begin, let's review some **nomenclature**:

Food Allergy, Sensitivity or Intolerance

Although there is some disagreement underlying mechanisms, most experts agree that adverse reactions to food should be classified as **food allergy, food sensitivity, or food intolerance**.

The term **allergy** was originally coined by von Pirquet to include both facets of the altered state; the beneficial was termed immunity and the harmful, hypersensitivity. Today, however, the term has become **synonymous with hypersensitivity**. Allergy, or hypersensitivity, may be defined as the **altered reactivity to an antigen**, which can result in pathologic reactions upon subsequent exposure to that particular antigen.

The pathogenic effects of immunologic processes are separated into two hypersensitivity reactions, **immediate and delayed**. These **immunologic reactions** are further classified into Types I, (immediate) II, III, and IV (delayed).

Type I is an IgE antibody-mediated reaction commonly called an **immediate hypersensitivity**. This maladaptive allergic reaction occurs in less than two hours post allergen exposure or ingestion. Most immediate reactions are so fast that individuals can easily identify the cause of their reactions, (i.e., eating strawberries and breaking out with hives). Antigens bind to preformed IgE antibodies already attached to the surface of the mast cell or the basophil and cause the release of chemical mediators such as histamine and eosinophilic chemotactic factor. A variety of allergic symptoms may result, depending on the location of the mast cell: in the nasal passages there may be sinus congestion; in the bronchioles, constriction (asthma); in the skin, hives and eczema; in the synovial cells, arthritis; in the intestinal mucosa, inflammation with resulting intestinal spasm or malabsorption; and in the brain, headaches, loss of memory, and inability to concentrate.

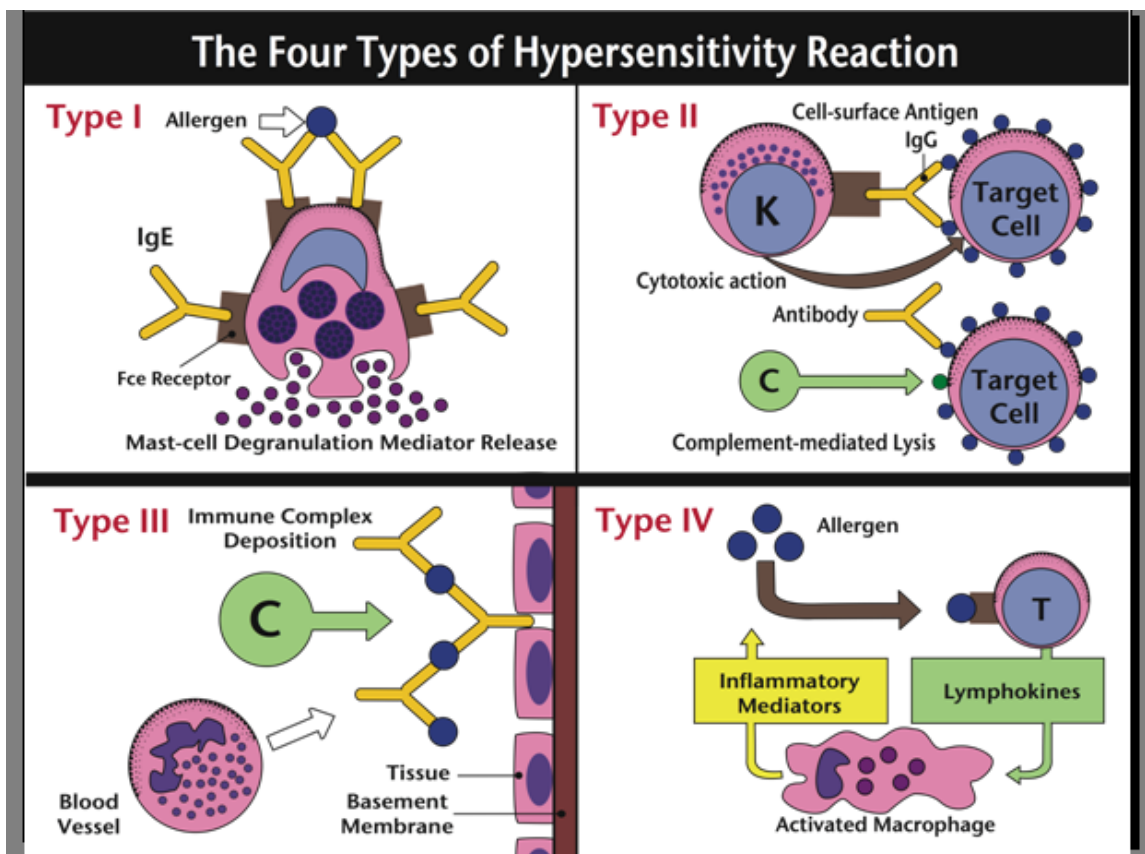
Type II (Cytotoxic Hypersensitivity) is also antibody-mediated (IgG, IgM) and is commonly called **delayed hypersensitivity** because the allergic reaction occurs from two hours to several days post allergen exposure. The immunoglobulin class (isotype) is generally **IgG and IgM**. Type II hypersensitivity occurs when antibodies bind to either self-antigens or foreign antigens, and leads to phagocytosis, killer cell activity or complement-mediated lysis. IgG activates complement leading to formation of the membrane-attack-complex and cell lysis. IgM, while activating complement lasts only for 60-90 days and usually cannot be measured in chronic delayed allergies. These reactions involve the binding of either IgG or IgM antibodies to cell-bound antigen. **Erythrocytes and platelets** are the cells most commonly affected with cytotoxic hypersensitivity.

Type III (Immune complex-mediated reactions) immune complex is also a delayed hypersensitivity, because the allergic reaction occurs **days to weeks post allergen exposure or indigestion**. A Type 3 food allergy (aka - delayed food allergy, food sensitivity) also **involves the immune system**. They occur when your immune system creates an overabundance of antibody Immunoglobulin G (IgG) to a specific food. The IgG antibodies, instead of attaching to Mast cells, like IgE antibodies in Type 1 allergies, bind directly to the food as it enters the bloodstream, forming different sizes of so-called circulating immune complexes (food allergens bound to antibodies circulating in the bloodstream). The allergic symptoms in Type 3 immune reactions are delayed in onset - appearing anywhere from a couple of hours to several days after consuming allergic foods. Type III hypersensitivity develops when immune complexes, **usually IgG**, are formed in large quantities and cannot be cleared adequately by the reticuloendothelial system via the CR1 receptor site. Allergen exposure results in production of IgG, which, in turn, binds to the allergen, forming immune complexes in blood. Immune complexes activate complement, resulting in covalent binding of C3b to IgG forming immune complex-C3b. Immune complexes are deposited at various sites throughout the body. Damage ensues when immune complexes deposit at a site and further

activate the complement, producing inflammatory cytokines. This causes leukocytes to release protease, mast cells and vasoactive amines that damage blood vessels, which escalates the inflammatory process.

They have been shown to involve both IgG and IgE immune complexes

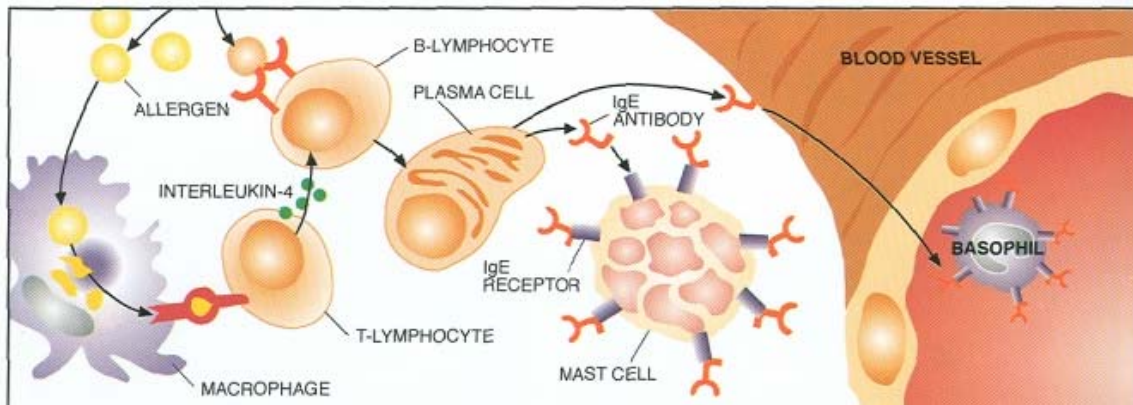
Type IV is the cell mediated form of delayed hypersensitivity. The allergic reaction occurs days to weeks post allergen exposure. The most serious delayed hypersensitivity is granulomatous tissue rejection, which occurs when macrophages ingest but cannot degrade an allergen, resulting in persistent macrophage stimulation. Stimulated macrophages elaborate cytokines that cause the macrophage itself and other cell types to concentrate in the area of injury. T-cells are then stimulated by cytokines, which activate complement and induce immune complex formation.



The term food allergy and/or food sensitivity will be used to designate an **immunologically mediated adverse reactions** mediated by food-triggered basophil or mast cell histamine release. Food allergy and/or food sensitivity causes the immune system to synthesize and release reactive chemical agents, such as histamines, cytokines, lymphokines, and interferons.

These reactions are immediate in nature and can be severe. This is the **Type I allergic reaction**. The IgE-mediated food allergy is the most commonly known reaction where contact with food causes an immediate response. In some cases, this can cause anaphylaxis.

Classical Allergic Reaction



The following are the chain of events which happen in allergic reactions:

1. An allergen must be present in the body. Allergens tend to be **protein molecules**. Interestingly enough, the immune system only detects particles of a certain size as potential troublemakers and protein molecules are just the right size.
2. The allergen is detected by the **B-lymphocyte cells (Plasma cell)**.

Plasma B cells are large B cells that have been exposed to antigen and are producing and secreting large amounts of antibodies, which assist in the destruction of microbes by binding to them and making them easier targets for phagocytes and activation of the complement system. They are sometimes referred to as *antibody factories*.

3. Every B cell produces its own, specific antibody, depending on the type of intruder it needs to respond to and in turn has the capacity to neutralize allergens. It is easy to understand why the body must have a ready pool of millions of antibodies, in order to combat these numerous offenders. There are five main categories of antibodies (**IgG, IgA, IgM, IgD and IgE**) which the body releases under different circumstances. In the case of allergies, the body produces the antibody **immunoglobulin E (IgE)**.
4. Usually, antibodies will bind directly to the appropriate damaging substance and neutralize it. However, IgE deviates from this common path. It first attaches one of its legs to one of the body's numerous **mast cells**. The other leg is used to hold on to the offending allergen. This action signals the mast cells to begin disintegrating, thereby releasing **histamine**.

The hallmark of immediate hypersensitivity reactions is the release of mediators from **basophils or mast cells**.

When two IgE molecules bind to an allergen, basophils and mast cells degranulate releasing histamine, proteoglycans (e.g. heparin and chondroitin), and proteolytic enzymes (e.g. elastase and lysophospholipase). They also secrete lipid mediators like leukotrienes, and several cytokines that contribute to inflammation mediating an allergic reaction manifested as asthma, hay fever, rhinitis, atopic dermatitis, and urticaria.

These chemical mediators released from mast cells or basophils in response to antigen is a function of the final common pathway of **Type I and Type III hypersensitivity**.

Allergic reactions can occur under a variety of circumstances. For instance, inhaling certain substances, such as grass pollen, house dust, etc., may cause an allergic response. **However, the consumption of certain foods may do the same.** Allergies typically bring on complaints very rapidly upon contact with the allergen.

Immediate reaction to foods may involve one or more target systems, including the **skin, respiratory tract, GI mucosal, and cardiovascular system.** In a double-blind challenge, the first signs of a reaction are usually noted within minutes following ingestion of a food known to provoke such a reaction, and almost always within the span of an hour. Careful clinical observation has made it possible to document that the signs and symptoms initially follow a pattern reflecting the sites of initial exposure to the incriminated food. **Thus, oropharyngeal reactions are frequently reported first, followed by gastrointestinal responses, and then involvement of the skin and respiratory tract.**

Therapeutic Pearl

Sodium cromoglycate and the **bioflavonoid quercetin** are both effective agents in blocking mast cell degranulation.

Immediate and Delayed Sensitivities

Food allergies are divided into two major categories: **immediate and delayed.**

When an **immediate food reaction** occurs, sufferers experience symptoms within hours of having ingested the food. Symptom onset is rapid and may include tingling of extremities, wheezing, coughing, tightening of the throat, nausea, abdominal cramps, and diarrhea. Sometimes in cases where nuts, shellfish, fish, and peanuts have been eaten anaphylaxis can occur.

Immediate food reaction is a **fixed food allergy.** The food to which you are allergic will almost always provoke an immune reaction when ingested. In immediate reactions the body over produces what is called Immunoglobulin E antibodies, (IgE).

Delayed food sensitivities can take up to three days to appear. This type of reaction is **IgG and IgA mediated.** Unlike immediate food reaction, delayed food reaction is not a fixed food allergy. It is cyclical in nature. For example, you may be IgG or IgA sensitive to milk.

If you were to increase your intake and/or frequency of milk consumption, it is at this point that symptoms would likely appear. (IgG is primarily produced in response to allergens in the blood while IgA is produced in response to allergens primarily in the GI tract and other mucous membranes. Therefore, it is recommended that you test for both IgG & IgA since you are testing different areas of the body and different aspects of the immune system.)

Diagnosing Immediate Sensitivities

Prick Test

A prick test is often used by allergists when a patient has clear allergy symptoms but is not certain which food is causing those symptoms (or whether the symptoms are caused by a food at all). They are often used when patients have hives, eczema, or hay fever symptoms.

Prick tests (sometimes called scratch tests) are performed on the skin of the forearm or the back. Allergists put a small amount of an extract of a potential allergen into a shallow scratch. Within twenty to thirty minutes, a positive result will show as a hive, or wheal, on the scratch. The size of the hive may correlate with the intensity of the allergic reaction.

In the event of a severe reaction, the allergist will administer a rescue medication such as epinephrine or an antihistamine. Severe reactions to a prick test, however, are uncommon.

Intradermal Test

The intradermal test is more sensitive than the skin prick test but is more often positive in people who do not have symptoms to that allergen (false-positive test results). This type of evaluation involves injecting a very small amount of a suspected allergen underneath the skin (rather than just scratching the surface of the skin as in a scratch test) and observing the skin surface for signs of reactivity. (This method tends to be more accurate than the scratch test, which often does not correlate very well with what we see clinically in the food challenge tests.)

Treatment for Food Allergies Based on Intradermal Testing

Once intradermal testing for allergens has been completed, an antidote for all foods causing allergies can be put together in one formula. Injections of the antidote can be given on an individual schedule, depending on the severity of the allergy. Some people take them every day or even several times a day. Others get injections twice a week.

Elimination Diets (Exclusion Diets)

An exclusion diet, or elimination diet, is a diet in which likely allergens or other foods to which a patient may be sensitive are avoided. Elimination diets are commonly used both to confirm other diagnostic tests, like RAST tests and prick tests, as well as to pinpoint possible food intolerances. In cases where a particular food is suspected to cause an allergic reaction or an intolerance, that food is strictly avoided for a period of time. If avoiding the food causes the symptoms to subside, and ingesting some in a double-blind food challenge causes them to return, that normally indicates allergies.

RAST Test

The radioallergosorbent blood test is used to test for IgE allergies. It was first described by Wide in 1967, and because it had the glamour of immunology and an aura of scientific precision it became in a very short time the accepted standard allergy test.

RAST tests are often used in combination with skin tests, or in situations when other tests are considered risky (e.g., when a patient has experienced a severe allergic reaction after eating a food). Because the test takes place in blood drawn from the patient, and not in the patient's skin or body, there is no risk of adverse reaction as with a prick test or a food challenge.

Clinical Pearl

Specific IgE has a half-life in circulation of one to two days, and a half-life on the mast cell of about 14 days. IgG, on the other hand, appears to have a circulating half-life of 21 days, with a

residual time on the mast cells that can last as long as 2-3 months.

Complications: Antigenic Cross-reactivity

Now that highly sensitive methods for antibody detection are used (radioisotope and enzyme techniques), **antigenic cross reactions are frequently found**. It is no surprise to find that wheat and rye share several antigenic determinants, since these grasses are closely related botanically, and with more sensitive methods some cross reactivity is also demonstrated with (in decreasing order) barley, oats and even to some extent rice and maize".

Similarly, there is considerable cross reactivity between goat's and cow's milk and, indeed, between different species of mite.

Unexpected cross reactions between totally different botanical families also occur. In Scandinavia, where a short but vicious birch pollen season causes considerable allergy, high degrees of sensitization to birch pollen (assessed by RAST and skin prick tests) are strongly correlated with food intolerance, particularly to apple; this clinical cross-sensitivity is reflected in the RAST's

These instances of cross reactivity – and the many others no doubt yet undiscovered – cause an unknown number of false-positive test results.

Food Intolerance

A food intolerance is defined as an adverse physiologic response to a food, or given foods.

There has been much confusion on the term food intolerance. It has been used indiscriminately with food allergies and food sensitivities,

Unlike true food allergies, food intolerances **do not elicit an immunoglobulin response**. In essence there is **no immunological mechanism** of adverse food response.

They can result from factors inherent in a food such as salicylates, lectins, toxic contaminants, or can be due to the pharmacologic properties of the food (eg tyramine in aged cheeses). A food intolerance can also be due to metabolic disorders in the host. An example of this would be a lactose deficiency.

In some patients, food intolerances, rather than food allergies can be the cause of their symptoms.

Conventional medicine can easily diagnose and treat allergies for foods or inhalants. Here, the so-called RAST test plays a very important role, because this test can demonstrate the presence of IgE.

However, demonstrating the presence of intolerance is more difficult. In this situation, similar to the case of classical allergies, the body responds abnormally and, in addition, the immune system **does not produce IgE**. It quite often takes much longer for complaints to come on, thereby masking the possible link between the offensive substance and the complaints themselves.

These are only a few of the reasons why food intolerance is considered a fairly controversial concept in conventional medicine. Intolerance can be responsible for a wide variety of complaints which, at first glance, seem to lack a plausible explanation. Intolerance can manifest themselves as the following:

- gastrointestinal complaints: stomach ache, irritable bowel, Crohns disease, ulcerative colitis
- Skin complaints: itching, eczema, hives, acne (in adults)
- Joint and muscle complaints: ranging from atypical pains to rheumatoid arthritis
- Headache and migraine
- Chronic fatigue
- Asthma, chronic rhinitis or sinusitis
- Pre-menstrual syndrome
- Hypoglycemia
- Depression, anxiety
- Sleeping disorders

Diagnosing Intolerance

It is impossible to accurately demonstrate intolerance through conventional testing methods, however, such **non-immunological tests** as cytotoxic, computerized cytotoxic, applied kinesiology, vega tests, and others have tried but each of these tests share the same critical disadvantage - they are frequently inconsistent in providing reliable results.

Body Part	Symptoms That May Be Caused by Delayed Allergy Reactions
Head/Brain	Migraine ("allergic") and multiple sclerosis
Eyes	Blurring of vision due to retinitis
Ears	Ringing in the ears and earaches due to autoimmune meniere's syndrome
Nose	Rhinitis from chronic sinusitis
Throat	Cold and flu symptoms (recurrent due to weak/burdened immune system)
Heart rate	Palpitations, arrhythmia, and increased heart rate due to autoimmune myocarditis
Lungs	Asthma due to hypersensitivity
Intestines	Nausea, vomiting, diarrhea, and constipation due to inflammatory bowel conditions
Skin	Eczema and psoriasis
Muscle/Joint	Chronic muscle/joint aches and swelling, rheumatoid arthritis, and fibromyalgia
Bladder/Kidney	Unexplained salt/water retention due to immune complex activity

How delayed food sensitivities develop

One major theory as to how delayed food sensitivities develop revolves around the concept of a "leaky gut."

Ordinarily the digestive tract will efficiently break down and absorb consumed food as small molecules, amino acids, simple carbohydrates, etc., which are, in general, non-antigenic.

If, for various reasons not uncommon today, digestion becomes less efficient and/or the intestinal lining becomes more permeable to large molecules, the conditions are set for the development of an IgG response to eaten food. It is assumed that this "leaky gut" condition

allows macro-molecular food fragments into the circulation, where they can stimulate a typical immune response where IgG is the primary antibody produced to defend the body against perceived non-self-invaders.

Inadequate digestion of food products due to hypochlorhydria and/or pancreatic enzyme deficiency is also thought to be a significant cause of food allergies.

Insufficient brush border enzymes such as lactase and sucrase also affect the body's ability to breakdown food to an elemental form.

When proteins are not digested to amino acids, dipeptides, or short chain polypeptides, they retain their antigenic properties. These antigenic molecules may then be absorbed through a damaged mucosal barrier or "leaky gut" and exposed to the immune system.

This in turn can create a state of chronic immune hypersensitivity and inflammation. In general, foods with a higher protein content (>20%) are more likely to be allergenic.

The Need for Laboratory Tests for Delayed Food Sensitivity

If all food allergy/sensitivity syndromes were typical and occurred within a few minutes of ingestion every time the food were taken, there would be no need for laboratory tests.

Unfortunately, the onset of some food allergy/sensitivity syndromes is delayed for several hours or days (perhaps longer) after taking the food making it impossible to depend on traditional allergy testing such as the RAST tests.

Though considered controversial among traditional medical allergists, yet with outstanding utility values, the introduction of innovative immunological allergy testing has afforded many people the opportunity to get well.

The validation of laboratory tests

The futility of accurate diagnosis vs. the utility value

In an ideal world laboratory tests should be positive in all patients who have a food sensitivity and negative in all people who do not. But if we cannot be certain of making the correct clinical diagnosis we have no yardstick against which measure the reliability of our tests. **We can only try to get as close as possible to accuracy.**

With that be said, let us not throw out the baby with the bathwater of academic niceties.

Instead it is wise to consider that accurate diagnosis is only a means to that end, and not the only means. For some of the tests we will review accuracy calculations are non-existent, but the tests still enable a good number of ill people to get better, and that is arguably the more important datum as long as it is honestly acknowledged.

Some respected physicians have named this the **'utility value' of the test.**

What to Look for in a Reputable Lab

- Is the laboratory properly licensed?
- Are high quality reagents used?

- Are potent or standardized antigens used?
- Are there positive and negative controls used on each run and/or for each antigen? Are the results in true quantitative terms and is the reference curve calibrated against an international standard, preferably the World Health Organization (WHO) standard for IgE?
- Is the laboratory monitored by a program, such as that of the College of American Pathologists? If these points are known, then it is reasonable to place confidence in that laboratory.

Immunological Allergy Testing

IgG Testing

IgG is the most abundant immunoglobulin comprising about 75% of all circulating antibodies. IgG antibodies are the potential indicator of delayed food allergies or food sensitivities. The delayed IgG antibody response often appears 1 to 3 days after exposure to the trigger food. In contrast to the IgE antibody reactions, tiny amounts do not set off symptoms, only excess amounts – overloads.

Symptoms are more generalized than IgE mediated food allergies, and the delayed onset makes the cause and effect diagnosis more difficult. These symptoms range from headache, muscle ache, tension and fatigue, to exacerbation of allergic IgE rhinitis and asthma. A clinical history geared to detection of food sensitivity is most useful in assisting the diagnosis of food sensitivities.

Those foods that are eaten frequently would be the foods suspect in causing symptomatology.

High IgG levels would indicate a frequent exposure to a particular food. Individuals with inflammatory gastrointestinal disorders and dermatitis frequently have high levels of food specific IgG antibodies.

IgG food sensitivity testing is also valuable as a preventative tool for people who are not overtly experiencing symptoms. It can identify unsuspected food sensitivities, which if ignored may result in stress on the immune system, catalyzing the development of additional illness.

IgG(4) antibody test

0075 IgG4 Food Antibodies (90 Antigens)

Methodology: ELISA

Results ng/mL	Response	Class	Results ng/mL	Response	Class	Results ng/mL	Response	Class												
Dairy/Meat/Poultry			Strawberry	< 10		Walnut	46	Mild +1												
Beef	< 10		Watermelon	< 10		Vegetables														
Casein	233	Mod +3	Grains			Avocado	10													
Chicken	13		Barley	14		Broccoli	70	Mild +1												
Egg, White	17		Corn	10		Cabbage	14													
Egg, Yolk	38		Oat	< 10		Carrot	< 10													
Lamb	11		Rice	10		Celery	18													
Milk	384	Mod +3	Rye	29		Cauliflower	27													
Pork	< 10		Wheat	< 10		Cucumber	13													
Turkey	< 10		Legumes			Asparagus	15													
Fish/Shellfish			Pea, Green	< 10		Garlic	< 10													
Clam	22		Lentil	24		Lettuce	< 10													
Codfish	55	Mild +1	Lima Bean	< 10		Mushroom	< 10													
Crab	< 10		Navy Bean	26		Mustard	42	Mild +1												
Flounder	16		Peanut	302	Mod +3	Olive	< 10													
Halibut	10		Pinto Bean	21		Onion	24													
Lobster	< 10		Soybean	17		Pepper, Green	< 10													
Mackerel	< 10		Bean, String	23		Spinach	15													
Oyster	12		Miscellaneous			Sweet Potato	< 10													
Trout	< 10		Aspergillus	21		Potato	< 10													
Salmon	11		Black Pepper	< 10		Tomato	< 10													
Shrimp	< 10		Chocolate	20		Zucchini	11													
Tuna	< 10		Cinnamon	10		<table border="1"> <thead> <tr> <th colspan="2">Class Definitions:</th> </tr> </thead> <tbody> <tr> <td>Class</td> <td>Cutoffs</td> </tr> <tr> <td>Negative</td> <td>0-40</td> </tr> <tr> <td>Mild (+1/+2)</td> <td>80/150</td> </tr> <tr> <td>Moderate (+3/+4)</td> <td>500/900</td> </tr> <tr> <td>Severe (+5)</td> <td>> 900</td> </tr> </tbody> </table>			Class Definitions:		Class	Cutoffs	Negative	0-40	Mild (+1/+2)	80/150	Moderate (+3/+4)	500/900	Severe (+5)	> 900
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Severe (+5)	> 900																			
Fruits			Coffee	51	Mild +1															
Apple	< 10		Ginger	15																
Banana	14		Malt	15																
Blueberry	42	Mild +1	Tea	< 10																
Cantaloupe	14		Vanilla	< 10																
Cranberry	10		Yeast, Baker's	< 10																
Apricot	16		Yeast, Brewer's	17																

IgG4 antibodies are associated with delayed hypersensitivity reactions, which are the most common—yet most difficult to detect—type of food reaction. These delayed or “hidden” food reactions can cause a variety of chronic symptoms. These antibodies are the slowly occurring variety, which do not appear in the blood until 24 to 48 hours after exposure to an offending food or substance. The reliability of this test varies between 80 and 90%.

Upon continued exposure to the antigen, IgG1 antibody production will **"class switch" to IgG4.**

Interestingly, IgG4 antigen complex does **not activate the complement cascade.**

While IgG subclasses are divalent and monospecific, IgG4 subclasses are monovalent (can only bind to one epitope of an antigen at a time) and can be bi-specific.

IgG1 antibodies tend to be **more "sticky" and can bind more non-selectively to antigens, leading to a greater chance of cross-reactivity and false-positives** whereby IgG4 antibodies are less sticky and less likely to produce false-positives on in vitro tests.

The IgG4 antibody is, therefore, a more clinically relevant marker of chronic food-immune reactions and possible intestinal permeability:

Measuring both IgG1 and IgG4 together can cause many unnecessary food eliminations.

Since IgG4 reactions occur several hours or even days later, there may be no obvious association between consuming a food and an adverse reaction. Food IgG4 levels increase in response to the presence of the food antigens that penetrate a weakened intestinal barrier and enter the bloodstream, particularly with commonly eaten foods (e.g., corn, wheat, dairy, and egg). IgG4 antibodies combine with specific food antigens to form food immune complexes, which cause the problems associated with delayed allergic responses. The complexes can cause inflammatory reactions at various sites in the body, including the small and large intestines, skin, kidneys, ears, sinuses, head, lungs, and joints.

Because they are distinct from IgE-mediated allergies, IgG4 provides the clinician and patient with useful data to design appropriate diets that exclude the offending foods.

Understanding the Results

Many IgG4 Reactions: If multiple foods have strong elevations of IgG4, **an intestinal permeability problem is indicated.**

This "leaky gut" phenomenon causes numerous food antigens to permeate into the bloodstream and present to the immune system's lymphocytes, which then respond by generating **IgG4 antibodies.**

In general, consuming these foods puts the patient under stress. Avoiding the reactive foods may not completely solve the health problem since the leaky gut problem will still exist, and the person will simply make new antibodies to the new foods leaking into the blood from the gut. A better approach is to have the patient eliminate the 3 to 6 most reactive foods and rotate consumption of the others on a 4-day rotation plan; that is, don't eat a food any more frequently than once every 4 days.

By avoiding the most offending foods, the diminished IgG response can provide an interval of relative calm from inflammatory propagation of the gut pathology.

Nutrients that support the development of intestinal integrity include 5 to 10 g daily of **glutamine**, 1 to 3 g of **pantothenic acid daily**, and 25 to 50 mg of **zinc daily**.

The tall columnar epithelial cells of the small intestine derive most of their energy from oxidation of glutamine and the pantothenic acid and zinc provide assurance of support for increased cell mass.

It should not be necessary to maintain this level of support for more than 60 days.

The amount of glutamine required may be reduced to 1.5 g doses by adding 10 mg of pyridoxine and 10 mg of a-ketoglutaric acid with each dose. This combination appears to aid the efficiency of epithelial cell utilization of glutamine.

Various botanical substances, such as aloe, chamomile, slippery elm, deglycyrrhizinated licorice (DGL), okra and marshmallow, have a long traditional history of use for improving gastrointestinal health, and they generally possess mucilaginous properties that allow for a protective coating of the mucosal lining, reducing irritation and facilitating the healing process.

Other herbs and plant bioflavonoids may contribute to intestinal healing by providing an antioxidant and/or anti-inflammatory effect (e.g., ginger, curcumin, boswellia, quercetin, rutin, hesperidin, etc.).

Moderate Number of IgG4 Reactions: IgG elevations to less than half of the foods routinely consumed may indicate a less severe intestinal permeability problem, and steps should be

taken as indicated above. in many cases, total elimination of all of the reacting foods for **1 month coupled with nutritional support will ameliorate this condition**

Food rotation can also be beneficial as symptoms improve. If symptoms return after a resumption of normal eating patterns, the rotation diet and nutritional support should be continued.

Few IgG4 Reactions: If there are only a few IgG reactions to foods, these should again be eliminated from the diet to test for involvement in patient symptoms. In many cases, there will be significant improvement. Other etiological factors may also be involved in patient health problems.

No IgG4 Reactions: The absence of reactions in this test may be due to several possibilities. First, the gut may be intact and there is no intestinal permeability.

Second, non-steroidal anti-inflammatory drugs are known to suppress the immune response and IgG4 production.

Clinical Pearl

Certain foods even with low or negative levels of IgG4. The test results are still valuable since they may guide your clinician to look for **non-immunological causes**.

IgG and IgA-mediated food allergy

Unlike the immediate effects of IgE-mediated allergy, the **IgG and IgA-mediated food allergy reactions may take several days to appear**.

Levels of IgG and IgA antibodies in the blood against different food antigens have been used to demonstrate delayed food allergy reactions. Therefore, raised serum or plasma IgG and IgA levels of food-specific antibodies are often associated with food allergies. **However, the measurement of IgG or IgA in the blood may miss abnormal immune reaction to many food antigens.**

It is known that oral or intragastric administration of dietary soluble proteins, such as bovine gammaglobulin (BGG) and ovalbumin or egg albumin, results in **salivary IgA production, but not in any antibody production in serum**. For these reasons, saliva has been selected, not only because of its relevance in oral disease, but mainly because it is an accessible fluid, easy to collect, and is thought to exhibit representative responses in secretions after enteric or intragastric immunization.

Manifestation of antibodies

The deposition of antigens in the gut has been shown to lead to the production of IgA antibodies in secretion at sites distant from the gut, such as colostrums, human lacrimal and salivary secretions, and salivary secretions from rhesus monkeys and rats.

A general conclusion, therefore, is that the secretory immune system can be stimulated centrally and that precursors of IgA-producing cells migrate from the gut-associated lymphoid tissue to several **secretory sites in addition to the lamina propria of the gut itself**.

Therefore, if antigens are injected into the submucosal tissues, they are likely to induce serum IgG antibodies, as well as **secretory IgA antibodies in saliva**. However, if it is applied topically to the skin or to the intraepithelial tissue, secretory IgA is the main product detected in saliva.

The role of topically applied antigen in the localization and persistence of IgA responses has been demonstrated in several secretory sites, including the respiratory tract, oral cavity, the gut and vagina.

The evidence that cells migrate from the gut to various secretory tissues, and that immunization in the gut leads to antibodies at various secretory sites has led to the concept of a common mucosal system. However, this concept may be an oversimplification since, although immunization in the lungs may lead to antibodies in distant secretory sites, such as salivary glands, immunization in the lacrimal glands has also been shown to lead to the production of antibodies in saliva. Thus, with firm evidence that antigen deposition in the gut may lead to antibodies not only in the gut but also in saliva, lungs lacrimal secretions, and in the genitourinary tract, it is probably more correct to designate the system as an enteromucosal system.

Saliva is a source of body fluid for the detection of an immune response to bacterial, food, and other kinds of antigens present in the oral cavity and GI tract.

For a better diagnosis of food allergy, we first recommend the measurement of saliva IgA antibodies and then the measurement of serum IgG antibodies.

IgA is produced upon initial exposure to dietary peptides and has a short half-life. As a result, IgA may be indicative of new or active immune reactions. IgG is produced upon repeated exposure to offending dietary peptides and has a longer half-life than IgA. Therefore, IgG may be more indicative of on-going food sensitivities. The assessment of both IgA and IgG offers the most complete picture.

Antigen Leukocyte Cellular Antibody Test (ALCAT)

The ALCAT Test differs from other food allergy or intolerance tests as it accurately and objectively measures leukocyte cellular reactivity in whole blood, which is a final common pathway of all mechanisms. The test utilizes electronic, state of the art, hematological instrumentation. Standard allergy tests, such as skin testing or RAST are not accurate for delayed type reactions to foods and chemicals. They measure only a single mechanism, such as the effect of mast cell release of histamine or the presence of allergen specific IgE molecules. Delayed reactions to foods and chemicals are NOT IgE mediated.

The ALCAT Test also differs from standard IgG tests in that they rely exclusively on one immune pathway, serum levels of immunoglobulin G (IgG). In fact, high food specific IgG titers are indicative only of exposure, not necessarily intolerance.

The ALCAT Test reproducibly measures the final common pathway of all pathogenic mechanism; whether immune, non-immune, or toxic. It is the only test shown to correlate with clinical symptoms by double blind oral challenges, the gold standard.

The Sage ELISA Delayed Food Allergy Test

The Sage Delayed Food Allergy Test is based on an Enzyme Linked Immunosorbant Assay (ELISA) which measures the presence of both IgG and **immune complexes** against a wide variety of foods, food additives and dye antigens in a patient's serum. Unlike other ELISA tests which measure only IgG, this test employs a unique process (patents pending) to measure both **IgG and immune complex**. Simultaneously measuring **Type II and III reactions**, the test

provides physicians with a more complete picture of the allergic process than measuring IgG alone.

Immune Complex

Immune complex is the key. Blood contaminated with partially digested food coming from the gastro-intestinal tract travels through the liver where most immune complexes are removed. If circulating immune complexes pass the liver filter, they may cause disturbances in many of the body's organs. The other path of malabsorption of food particles from the gastro-intestinal tract is through lymphatic drainage. The lymph channels in the gut wall converge to form the thoracic duct which drains its contents into the subclavian vein. The combination of antibody with complement in the blood stream is a **circulating immune complex.** Immune complexes attach to CR1 receptors of red and white blood cells. Individuals have varying numbers of CR1 receptors. In most cases, circulating immune complexes are simply removed from circulation by macrophages in the liver and spleen prior to triggering a cascade of events which may cause multiple symptoms and possible tissue damage.

Sage is far more comprehensive test for delayed food reactions. This does not mean that IgE or IgG4 tests are bad, they are just limited in the number of pathways of immunological responses. When delayed food reactions are missed by other methods, the patient's chronic conditions will not improve.

Final Thoughts

Review of the current literature as well as having obtained detailed information on allergy testing from Genova, Metametrix, SAGE, Alletess, ImmunoLabs, NeuroSciences and Alcat has caused me to have more questions than answers.

Each of the above labs claim to have “best” means of testing for delayed immunological food sensitivities.

As I reviewed each of above lab tests, I have to conclude that there is no one test that represents the total solution for identifying delayed immunological food sensitivities. However, that is not to say that any of the above tests are useless. Far from it!

It is our opinion that a clinician **MUST** first have a patient complete a detailed food diary and **STUDY** it for possible common food culprits that may be contributing to the patient's symptom complex.

It is also imperative to rule out or in intestinal hyperpermeability (leaky gut) which is likely to give a significant number of false positives.

The main value of ordering a delayed immunological food sensitivity test then rests on the issue of **lightening the total load** of allergic foods on the already compromised immune system.

It is **NOT** recommended to order a delayed immunological food sensitivity test without first **THINKING**. Basically, do not place all your faith on “**the**” test as having all the answers. Use it as a complement to a good dietary history.