Many people think of allergies exclusively in terms of airborne allergens such as pollen, dust, and molds. However, immune reactions also can result from reactions to foods. The immune system is made up of two functional components: the adaptive and the innate immune systems. The innate immune system prevents penetration and spread of foreign invaders. The sites of the innate immune system include the skin or mucosa while lysosomes, complement, and phagocytosis are used to prevent the spread of foreign invaders. The adaptive immune system responds after an initial sighting and develops a specific immunological memory aimed at inactivation or removal of an infectious agent. While the innate immune system is thought to be genetically predetermined, the adaptive immune system responds to its environment. When an antigen enters the body, specialized helper T-cells (Th cells) that are responsible for responding to foreign material, respond. There are two types of Th responses: Th2 and Th1. Each respond in different ways (see Figure 1). Th1 and Th2 determine which antibody type is produced, and thus the type of reaction. IgE is associated with Th2 and IgG is associated with Th1.

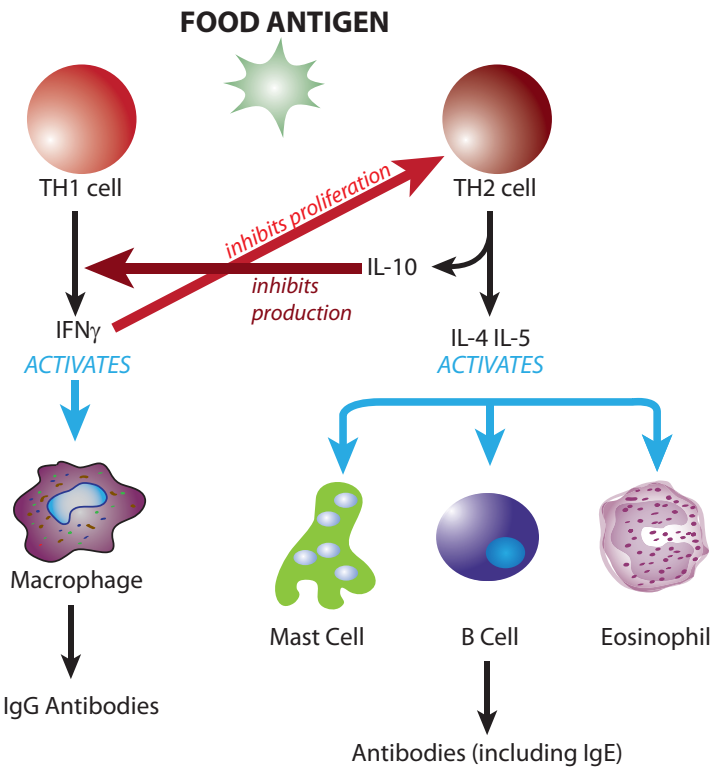

Figure 1: Activation of Th1 or Th2 cells results in IgG or IgE antibody production. Both react to antigens.

Reactions to food are classified into two major categories: IgE mediated (allergic) and non-IgE mediated food reactions. The IgE food reactions are primarily Th2 mediated and generally occur immediately after exposure. The symptoms include itching, swelling, reddening (flushing), and smooth muscle contraction, resulting in edema, asthma, GI symptoms, atopic dermatitis, and life-threatening anaphylaxis reaction. These clinical symptoms of IgE reactions are due to inflammatory Th2 cytokines.[1] IgE antibodies also initiate a series of reactions that result in the release of inflammatory mediators, such as histamine, and other reactive chemicals from specialized cells called mast cells. IgE does not initiate complement.

There are also other reactions to foods that can occur hours or days later. These reactions are predominately IgG reactions.[2] IgG reactions often cause different kinds of symptoms from IgE reactions, and can include: bloating or sluggishness soon after eating, GI symptoms, dark circles under the eyes, chronic post nasal drip or sinus congestion. IgG reactions are primarily a Th1 response, which includes increased production of interferon-gamma (INF-gamma), tumor necrosis factor-alpha (TNF-alpha), and other pro-inflammatory cytokines whose reactions are associated with delayed response to foods.[1, 3] IgG consists of four subclasses, each with different roles: IgG_1, IgG_2, IgG_3, and IgG_4. Among allergic individuals there is an abundance of IgG_1 and IgG_4. IgG_4 is found in the gut. Repeated exposure to a food antigen may lead to marked IgG_4 antibody response. IgG_4 reactions have been postulated as blocking agents of the more severe IgE reactions.[4] Allergen immunotherapy (IT), known as allergy shots, is known to reduce symptoms of allergic rhinitis and asthma. IT has been shown to result in increases in IgG (2- to 10-fold) and IgG_4 (10- to 100-fold), along with a gradual decline in anti-allergen IgE antibodies.[5] IT is also associated with increases in IgA antibody.[5,4] This IgG_4 blocking action is not without side effects. Research has found that some subjects experience an elevation of IgG_4 with no rise in IgE, but still have symptoms when specific foods are consumed.[6-8] These symptoms may be due to IgG_4 forming antigen complexes that the body reacts to. Avoidance or rotation diets have been shown to decrease the response and clinical symptoms. It thus holds to reason that long-term stimulation of IgG_4 reactions may account for some chronic health conditions, especially those related

to immune system activation and have not responded to conventional treatments. Infants with IgE-mediated cow's milk allergy can tolerate soy but among those with IgG_4 reactions to cow's milk allergy, almost half react to soy and require a hydrolyzed formula.[9, 10] Testing both IgE and IgG_4 can help to tailor treatments to each individual patient.[11]

A significant contributing factor to the level of immune reaction is the strength of the mucosal barrier. In the best scenario, the enterocytes in the gut have tight junctions that function to keep out large molecules or other allergens. However, in a condition called "leaky gut" or increased intestinal permeability, the enterocytes sustain damage and "loosen" the tight junctions and allow antigens and bacteria to cross the intestinal membrane entering circulation where the immune system launches an attack. In the leaky gut hypothesis, poor intestinal barrier function can be the result of stressors such as NSAIDS, alcohol, or pronounced chronic immune reactions to foods that can result in permeation of the intestinal mucosa. This increase in membrane permeability can lead to an increase in immune reactions leading to an elevation in the number and severity of immune reactions to foods. An increase in IgG_4 antibodies to foods has been associated with this increased barrier permeability.[12-14] IgG_4 and IgE food testing can aid the clinician in developing a patient specific exclusion diet which has been shown to improve symptoms and is thought to decrease the level of inflammatory gut reactions. Elimination of foods for which patients have elevated serum IgG_4 antibodies has relieved symptoms of irritable bowel syndrome,[15] autism,[14] and chronic urticaria.[13]

Recent research studies have also linked both IgG and IgE with obesity. In a study of 60 children, those who were obese had significantly higher IgG food antibodies than normal-weight children. Anti-food IgG antibodies were also associated with low grade systemic inflammation, identified by elevated hsCRP, and intima media thickness of the common carotid arteries. The findings raise the possibility that anti-food IgG are involved in the pathophysiology of obesity and atherosclerosis.[16] In a larger study of over 4,000 children, researchers looked at total and allergen-specific IgE or antibody levels to a large panel of indoor, outdoor, and food allergens, body weight, and responses to a questionnaire about diagnoses of hay fever, eczema, and allergies. Total IgE levels were higher among obese and overweight children than among normal-weight children. The odds ratio (OR) for atopy (any positive specific IgE measurement) was increased in the obese children compared with that seen in those of normal weight; this association was driven largely by allergic sensitization to foods. C-reactive protein levels were associated with total IgE levels, atopy, and food sensitization.[17] Thus, IgG and IgE immune reactions to foods should be evaluated in obese patients and/or those with increased systemic inflammation. Clinical experience and research have consistently shown that testing IgE and IgG_4 together gives a fuller picture of which foods the patient is reacting most strongly to, helping to identify an individualized treatment more quickly.

Though IgG and IgE reactions are distinct, there are many conditions for which it would be beneficial to assess both IgE and IgG_4. Clinical studies have shown that food elimination can improve skin symptoms in atopic dermatitis (AD).[18] IgE and IgG_4 levels were more elevated in the serum of subjects with AD, compared to non-atopic patients.[19] Although AD has been associated with IgE responses, its production is strongly dependent on T cells who promote the synthesis of IgE antibodies, as well a $sIgG_1$ and IgG_4 antibodies.[18] Patients with AD, along with other allergic conditions such as hay fever, asthma, and conjunctivitis, have been found to have a greater number of IgE elevations. More than 70% of patients with AD have a past history of either asthma or allergic rhinitis and show many of the features of atopy. Research has also demonstrated the level of IgG_4 antibodies to be higher in subjects with AD and associated allergic symptoms.[20] Allergen-specific IgE/IgG_4 ratio has been proposed as one of the clues to understanding the mechanism of food allergy in AD.[18] Ultimately, assessing both IgG and IgE immune responses is important in inflammatory conditions such as AD.

It is also important to remember the immune system is not static and is dependent on other physiologic functions and overall health. Though some clinicians rely on prick tests and food challenges to identify offending foods, these tests are cumbersome to administer and the results can be misleading without concurrent laboratory information. Clinical experience has consistently shown that testing both IgE and IgG_4 reactions to foods gives a fuller picture of which foods the patient is reacting most strongly to and helps to identify a patient's individualized treatment more quickly.

Case Study Example

A 41 year-old woman came to the doctor with AD. She had red and peeling skin covering the majority of her body. She was under significant stress and presented with elevated cortisol levels, an elevated BMI, and Hashimoto's thyroiditis. She ate a standard American diet. The doctor ran both an IgE and IgG_4 food panel along with erythrocyte fatty acids and vitamin D tests.

The table below (Table 1) lists those foods with the greatest IgG_4 reactions and their corresponding IgE reaction. It shows that the foods with +5 IgG_4 reactions appear to be blocking the IgE reactions. The patient gave up foods she had a +4 and +5 IgG_4 reaction to for 3 weeks, then she began a rotation diet. The specific foods are listed in Table 1. The patient had many (>15) +1 and +2 IgG_4 reactions, leading the clinician to suspect a leaky gut. The patient also had low vitamin D (24 ng) and low eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) levels. The physician recommended she take probiotics, glutamine, 2,000 IUs of vitamin D, and 2 grams of fish oil per day, along with her changes in diet. Upon her follow-up visit, she reported significant improvement in her skin and feeling better overall. She had been diligent in following her diet.

Table 1

FOOD	IgG_4 Reaction	IgE Reaction
Casein	+5 Severe	-
Milk	+5 Severe	+1
Egg, White	+5 Severe	+1
Egg, Yolk	+5 Severe	+1
Garlic	+5 Severe	+1
Peanut	+5 Severe	+1
Mustard	+4 Moderate	+1

There are also other areas to consider in immune reactions to foods, such as overall immune status, environment, probiotics, and micro- and macronutrients. One example is an increased response to food antigens that has been associated with a lack of commensal flora. Commensal bacteria, which can be augmented by prebiotics and probiotics, have been shown to decrease the gut inflammation that can develop when mucosal immune response is dysregulated. Probiotics have been explored as a therapeutic option for the treatment of AD. The rationale for their use is that bacterial products may induce an immune response of the Th1 series instead of Th2 and could therefore inhibit the development of allergic IgE antibody production. In children with cow's milk allergy and AD, concurrent administration of probiotics with a hypoallergenic formula had statistically significant improvements in AD symptoms over a hypoallergenic formula alone. Overall nutrition is a major contributor to a healthy gut and a properly functioning mucosal barrier, both helping to avoid an elevated immune response and resulting symptoms. While significant information can be gained by doing an IgG or IgE test alone, the synergistic effect of understanding how the body is reacting in both situations gives the clinician a significant advantage in understanding how the patient is responding overall.

References

1. Dupont C, Heyman M. Food protein-induced enterocolitis syndrome: laboratory perspectives. *J Pediatr Gastroenterol Nutr.* 2000;30 Suppl:S50-57.
2. Jyonouchi H. Non-IgE mediated food allergy. *Inflamm Allergy Drug Targets*. Sep 2008;7(3):173-180.
3. Kapel N, Matarazzo P, Haouchine D, et al. Fecal tumor necrosis factor alpha, eosinophil cationic protein and IgE levels in infants with cow's milk allergy and gastrointestinal manifestations. *Clin Chem Lab Med.* Jan 1999;37(1):29-32.
4. Bullock RJ, Barnett D, Howden ME. Immunologic and clinical responses to parenteral immunotherapy in peanut anaphylaxis--a study using IgE and IgG_4 immunoblot monitoring. *Allergol Immunopathol (Madr)*. Sep-Oct 2005;33(5):250-256.
5. Greenberger PA. Immunotherapy update: mechanisms of action. *Allergy Asthma Proc*. Nov-Dec 2002;23(6):373-376.
6. Dannaeus A, Inganas M, Johansson SG, Foucard T. Intestinal uptake of ovalbumin in malabsorption and food allergy in relation to serum IgG antibody and orally administered sodium cromoglycate. *Clin Allergy*. May 1979;9(3):263-270.
7. Halpern GM, Scott JR. Non-IgE antibody mediated mechanisms in food allergy. *Ann Allergy*. Jan 1987;58(1):14-27.
8. Paganelli R, Pallone F, Montano S, et al. Isotypic analysis of antibody response to a food antigen in inflammatory bowel disease. *Int Arch Allergy Appl Immunol*. 1985;78(1):81-85.
9. Sicherer SH, Noone SA, Koerner CB, Christie L, Burks AW, Sampson HA. Hypoallergenicity and efficacy of an amino acid-based formula in children with cow's milk and multiple food hypersensitivities. *J Pediatr*. May 2001;138(5):688-693.
10. Maloney J, Nowak-Wegrzyn A. Educational clinical case series for pediatric allergy and immunology: allergic proctocolitis, food protein-induced enterocolitis syndrome and allergic eosinophilic gastroenteritis with protein-losing gastroenteropathy as manifestations of non-IgE-mediated cow's milk allergy. *Pediatr Allergy Immunol.* Jun 2007;18(4):360-367.
11. Zar S, Mincher L, Benson MJ, Kumar D. Food-specific IgG_4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. *Scand J Gastroenterol*. Jul 2005;40(7):800-807.
12. Kemeny DM, Urbanek R, Amlot PL, Ciclitira PJ, Richards D, Lessof MH. Sub-class of IgG in allergic disease. I. IgG sub-class antibodies in immediate and non-immediate food allergy. *Clin Allergy*. Nov 1986;16(6):571-581.
13. Paganelli R, Fagiolo U, Cancian M, Scala E. Intestinal permeability in patients with chronic urticaria-angioedema with and without arthralgia. *Ann Allergy.* Feb 1991;66(2):181-184.
14. White JF. Intestinal pathophysiology in autism. *Exp Biol Med* (Maywood). Jun 2003;228(6):639-649.
15. Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut*. Oct 2004;53(10):1459-1464.
16. Wilders-Truschnig M, Mangge H, Lieners C, Gruber H, Mayer C, Marz W. IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles. *Exp Clin Endocrinol Diabetes*. Apr 2008;116(4):241-245.
17. Visness CM, London SJ, Daniels JL, et al. Association of obesity with IgE levels and allergy symptoms in children and adolescents: Results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol*. Feb 20 2009.
18. Noh G, Ahn HS, Cho NY, Lee S, Oh JW. The clinical significance of food specific IgE/IgG_4 in food specific atopic dermatitis. *Pediatr Allergy Immunol*. Feb 2007;18(1):63-70.
19. Shakib F, McLaughlan P, Stanworth DR, Smith E, Fairburn E. Elevated serum IgE and IgG_4 in patients with atopic dermatitis. *Br J Dermato*l. Jul 1977;97(1):59-63.
20. Wuthrich B, Benz A, Skvaril F. IgE and IgG_4 levels in children with atopic dermatitis. *Dermatologica*. 1983;166(5):229-235.