# Gastrointestinal Health

## Intestinal Function, Permeability, Specific Food Antigen Response, and Validation for Treatment With Whole Foods

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There is perhaps no organ more important to the long-term health of the human body than the small intestine. This organ possesses its own nervous system, the enteric nervous system, and with a surface area equal to that of a tennis court and more exposure to the external environment than the skin and lungs combined, it is the ultimate arena for the assimilation of food and the exclusion of foreign materials (Figure 1). Gut-associated lymphoid tissue (GALT) accounts for greater than 60% of all immune activity in the body. The dual functions of digestion/absorption and barrier defense against the permeation of macromolecules, microorganisms, and toxic compounds can be disrupted by any number of mechanisms, resulting in localized and systemic disease (Asfaha et al., 2001; Couper, 2001; Hruby et al., 2001; Ramachandran and Balasubramanian, 2001; Catanoso et al., 2001; Juvonen et al., 2000; Hollander, 1999; Stein et al., 1998; Katz and Hollander, 1989; Roberts et al., 1989; Walker, 1986; Sandhu and Fraser, 1983).

Abnormal increased permeability of the intestinal mucosal barrier has been shown to be a causative factor in a large number of clinical disorders, such as allergic disorders, food allergies, inflammatory bowel disease, inflammatory joint disease, skin disorders (psoriasis and eczema), Chrohn's disease, and rheumatoid arthritis (Iwata et al., 2001; Arnott et al., 2000; Dainese et al., 1999; Vaile et al., 1999; Chou et al., 1998; Majamaa and Isolauri, 1997; Sartor, 1997). Decreased permeability has been shown to be a major cause of malnutrition, malabsorption, and the inability to thrive (Aguilera et al., 2000; Ahmed and Fuchs, 1997). The function of the intestine presents a challenge—how to allow enough permeability to absorb properly digested small food particles without allowing toxic or excessively large molecules through.

Allergies, stress, endotoxins and exotoxins, yeast and bacterial overgrowth, parasites, dietary imbalances with consummate nutrient deficiencies, low dietary fiber intake, antibiotic overuse, and inflammation are a few of the factors that often combine to take a high toll on digestion and intestinal function. Metabolic toxins from these agents and dysfunctions can drastically alter digestive and immune function. The removal of these stimuli, in conjunction with nutritional and detoxification support, is often the first step toward recovering normal intestinal function.

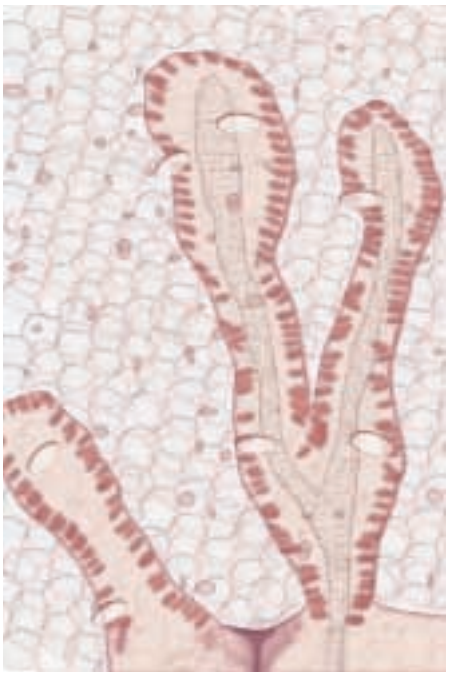

**Figure 1** The normal intestinal mucosa is rich in microvilli, extensions of the epithelial cells that line the intestinal lumen. Microvilli provide a very large surface area for digestion and absorption, while the tight junctions between the cells protect against the permeation of large macromolecules and toxins. Damage to microvilli leads to malabsorption of nutrients and loss of tight junctions reduces the integrity of the barrier and increases vulnerability to foreign antigens that may enter the blood stream via the resulting "leaky gut."

The increased uptake of macromolecules that occurs when the cells of the small intestine exhibit abnormal or excessive permeability results in an inflammatory response that can further inflame and injure intestinal cells. If injury and inflammation continue, the mechanical barrier formed by the tight junctions is compromised, allowing the uptake of bacterial and dietary antigens, potentially pathogenic bacteria (sepsis), and other inflammatory molecules, all of which are normally excluded from absorption into the bloodstream. The resultant flood of metabolic and microbial toxins into the bloodstream compromises the detoxification systems in the liver, over-stimulates the immune system, and overwhelms the lymphatic system. This systemic overload and challenge results in the breakdown of organ function and produces disease states. To summarize:

- The small intestine functions in a dual capacity of digestion/absorption and immune barrier to the uptake of macromolecules and toxins
- Abnormal or increased permeability in the small intestine has been clearly associated with both localized and systemic disease
- Allergies, nutritional deficiencies, and metabolic toxins from these and other agents alter digestive and immune function
- Nutritional and detoxification support can help in the recovery of normal function

## Measurement of permeability

Testing for normal and abnormal intestinal permeability is carried out using the Intestinal Permeability Test, which measures the ability of two non-metabolized sugar molecules, mannitol and lactulose, to permeate the intestinal mucosa. To perform the test, patients drink a challenge mixture of premeasured amounts of lactulose and mannitol. The amount of lactulose and mannitol recovered from a 6-hour urine sample is measured. Small molecules like mannitol readily penetrate cells and passively diffuse through them. Thus, if intestinal transcellular uptake is normal, the mannitol should clear in the urine quite quickly. Larger molecules like lactulose are normally excluded from uptake by intestinal cells, and if the intestinal permeability is normal, uptake of this sugar will be very minimal. If lactulose is taken up, it indicates increased absorption of large molecules due to increased paracellular uptake (between the cells) and a lack of tight junctions. Thus, lactulose uptake serves as a marker for lack of intestinal mucosal integrity (Figure 2).

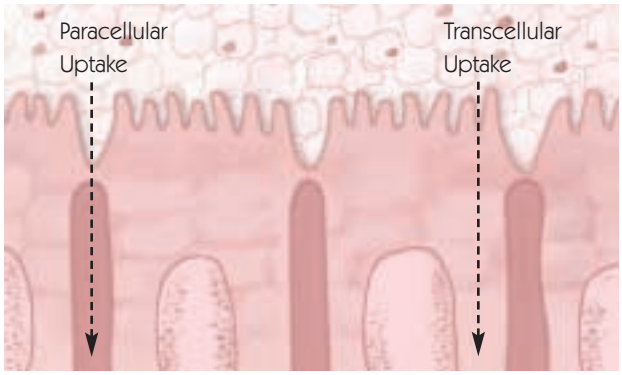


**Figure 2** Transcellular vs. Paracellular Transport in the Intestinal Epithelium: Transcellular uptake occurs via passive diffusion of molecules through the epithelial cells of the intestinal lumen. Paracellular uptake occurs in the spaces between epithelial cells when tight junctions are damaged or destroyed. Typically, small molecules pass through the epithelium via transcellular uptake, while large molecules pass via paracellular uptake. Either mechanism can be pathological.

There are numerous studies connecting the increased permeability of intestinal cells and the increased porosity of the normally tight junctions between cells with susceptibility to food allergies (Dainese et al., 1999; Laudat et al., 1994; Cantani, 1992; Butkus and Mahan, 1986), celiac and small bowel disease (Uil et al., 1997; Vogelsang et al., 1996; Cummins et al., 2001), and autoimmune conditions such as rheumatoid arthritis, spondylitis, and pancreatitis (Juvonen et al., 2000; Guillou, 1999; De Keyser et al., 1998; Chou et al., 1998; Sartor, 1997; George et al., 1996; Meddings et al., 1999; Stevens et al., 1992). Increased permeability to small molecules through the intestinal epithelium may also result in the passage of small antigens across the mucosal barrier triggering immune responses (Caradonna et al., 2000; Hamzaoui and Pringault, 1998; Urao et al., 1997).

## Causes of abnormal permeability

Proper permeability of the intestine occurs as a result of many factors, nutritional sufficiency being the most important. Optimal function is dependent on the adequate intake of a wide variety of quality nutrients, including essential fatty acids, electrolytes, zinc, vitamin A, and folate. Nutritional insufficiencies of these factors or imbalances caused by excessive intake of poor quality food nutrients compromise the body's ability to function with integrity.

Perhaps the greatest cause of altered permeability contributing to systemic disease is food allergy (Dupont and Heyman, 2000). Food represents the greatest and most frequent antigenic exposure and challenge our

immune systems face. Intact intestinal permeability with proper digestion and limited exposure to food antigens results in a healthy immune response. But if any of these functions become altered and weakened, food fragments essentially enter the bloodstream and the immune system initiates an attack on the food particles as if they were foreign invaders (inflammation).

The measurement aspects of intestinal permeability can be summarized as follows:

- It is measured as a percentage of recovery of two non-metabolized sugars, mannitol and lactulose
- Small molecules like mannitol should pass easily via transcellular, passive diffusion
- Large molecules like lactulose should not move through the intestinal barrier easily and if they do, it indicates increased paracellular uptake and increased permeability
- Food allergy greatly alters intestinal integrity and permeability

Although there are numerous factors that should be considered as potential causes of abnormal intestinal permeability, as suggested above, the focus of this article is on the Specific Food Antigen Response as it relates to intestinal permeability.

## Food Allergy and Antigen Response

Occurrences of allergies have been recorded as far back as ancient Greece when Hippocrates, a Greek physician, observed that the ingestion of milk could cause gastric upset and hives. When a Viennese doctor, Baron Clemens von Pirquet, first coined the term "allergy" in 1906, it meant adverse reactions to any substance in ways that didn't bother most people. These reactions provided immunity to infections and also caused marked reactions to certain foods, insect stings, and pollen, but he intended this new word to refer to any altered response to the environment, whether to food, water, the air we breathe or all things that come in contact with our skin. He also introduced the word "allergen" describing the substances that created these reactions (Brostoff and Gamlin, 2000).

In the 1960s, it was discovered that an antigen-specific immunoglobulin (IgE) was involved in many allergic reactions and it was identified as the main player in so-called classical allergic responses. Conventional medicine then defined allergy as any IgE-mediated response and traditional allergists still strictly adhere to this definition. These responses include Type I reactions, typified by the binding of IgE molecules on the surface of mast cells to specific antigens (chemical targets found on invading microbes). Mast cells, in turn, release chemical messengers like histamine upon exposure to allergens, causing the symptomatology of allergies (a runny nose in hay fever is caused by the release of histamines and other immunological compounds from nasal mast cells). In these cases, the link between a specific allergen and associated symptoms can usually be identified easily because these reactions occur almost immediately following exposure. Examples include hives, hay fever, and anaphylactic responses. IgE-mediated food reactions are often fixed, meaning that eating or exposure to any amount of a specific allergen (the focus being food) will cause a reaction and symptoms even after months or years of avoiding the triggering substance. The half-life of IgE in the blood stream, if not re-exposed to the same antigen, is about two days. However, the immune B-cells that produce IgE remain in an activated state indefinitely and will begin production of new IgE on re-exposure to the antigen.

In recent years, research has discovered that other specific immunoglobulins, particularly immunoglobulin G (IgG), form immune complexes that also are involved in the onset of food allergy symptoms. These are known as Type III reactions.[1] The gradual nature of IgG complex formation may delay the onset of symptoms related to exposure or ingestion by hours and even days. These symptoms are not defined as "true allergies" by traditional allergists but they still indicate acquired hypersensitivities to antigens that result in harmful immunological reactions. The delay in the onset of symptoms can make it very difficult to identify offending foods that may have been eaten hours before. Immune complexes thus formed initiate inflammatory responses that can damage the cells lining the small intestine (Savilahti, 2000). The cells that are compromised from repeated assaults of this nature develop excessively permeable membranes that allow direct movement of molecules into the bloodstream, further inciting an overly charged immune response. The end result is excessive intestinal permeability or "leaky gut syndrome." On the bright side, IgG-mediated food reactions are not fixed, and if problem foods are avoided for a given period of time (the half-life of the IgG response is about 25-30 days), the body's production of these antibodies and the associated

[1] There are also Type II and Type IV reactions, but they are rarer and their mechanisms of action are beyond the scope of this review.

symptoms are reduced. Problem foods can usually be re-introduced without producing symptoms if they are eaten in moderate amounts and only infrequently. This gives us two main immune responses to food allergens:

- Type I: IgE-mediated "true" allergy; immediate responses
- Type III: IgG-mediated; delayed responses

## Identifying the Specific Antigen Response

Diagnosis of specific food allergies should be a clinical consideration whenever there is a suspicious symptom picture that the clinician feels may be caused by an immediate or delayed food hypersensitivity response. These symptoms include, but are not limited to, hives, migraine headaches, diarrhea, myalgias and arthralgias of unknown etiology, rheumatoid arthritis, heart palpitations, red, itchy, or watery eyes, edema, ulcerative colitis, and fatigue. Even though testing may reveal no specific antigen associated with the symptoms, it is valuable for eliminating the possibility of a food cause for the symptomatology. Any food that causes an adverse reaction should be eliminated regardless of the mechanism because there are many non-immunologic responses to food substances, including those from vasoactive amines, food additives, sulfites, alkaloids, and monosodium glutamate (MSG), as well as problems associated with lactose intolerance and food spoilage or contamination by bacteria.

Testing for Type I allergies is routinely done with a skin prick test. A small amount of an extract of the food to be tested is injected under the skin and the clinician measures any skin inflammation at the site following injection. There are some disadvantages to this method, including the potential for discomfort during the testing process. In addition, antihistamine use can inhibit the responsiveness of the test and there is a very real risk of anaphylaxis due to IgE-mediated reactions. Because of the short duration of skin prick testing, it cannot indicate Type III IgG delayed hypersensitivity reactions, and thus positive results may not correlate with the wide range of symptoms presenting in the hours and days after the test.

Type I- and Type III-mediated reactions can be measured by taking a sample of serum from a patient and testing it for antigen-specific antibodies to foods *in vitro*. The most commonly used testing methods for IgE antibodies are MAST (multiple antigen simultaneous test) and RAST (radio allergosorbent test).

ELISA (enzyme-linked immunosorbent assay) testing is used to detect both IgE and IgG antibodies. While serum collection for the testing procedure can be seen as a disadvantage, there is no danger of anaphylaxis due to direct exposure to allergens and no interference from antihistamines. Because they are highly reproducible, these tests offer excellent screening for foods that elicit a specific antigen response. If testing shows a greater global IgG response, this suggests there is impaired intestinal permeability and the immune response may be due to a large number of intestinally absorbed food-derived molecules.

## Efficacy of testing

As long ago as 1928, experiments clearly showed that ingested food antigens can penetrate the gastrointestinal barrier and can be transported to mast cells in the skin (Brunner and Walzer, 1928). Current and past research clearly indicates a relationship between food allergies and commonly observed disease states such as atopic dermatitis (Caffarelli et al., 2001; Ogura et al., 2001; Kanny et al., 2001; Sampson, 1991; Burks et al., 1991), asthma (Aba-Alkhail and El-Gamal, 2000; Thaminy et al., 2000; Karakaya et al., 1999; Yazicioglu et al., 1999; Businco et al., 1995; Rowe and Young, 1959), and migraine headaches (Monro et al., 1980; Sinclair, 1999; Meggs, 1995; Finn, 1992; Mylek, 1992). Adverse reactions to foods and food products are now being reported in nearly 25% of young children (Kjellman, 1991).

It is believed that increased air, water, and food pollution, insecticide contamination, allergenic ingredients in commercial foods, preservatives, flavorings, artificial colorings, stabilizers in foods and drugs, genetic manipulation of plant foods, and a decrease in the diversity of the average diet (resulting in repeated exposure to the same antigens) have all contributed to a dramatic rise in food allergies (Wuthrich, 1999; Boris and Mandel, 1994; Andre et al., 1994; Kanny et al., 1994).

A connection between food allergy, inflammatory states, diseases, and an increase in intestinal permeability have also been found repeatedly (Dupont and Heyman, 2000; Pena and Crusius, 1998; Kohout et al., 1991; Majamaa and Isolauri, 1997; Hamilton et al., 1985; Andre et al., 1987). Intestinal permeability testing has become widely accepted as a valuable tool in assessing food allergy and disease (Johnston et al., 2001; Hollander, 1999; De Keyser et al., 1998). Clearly

solutions are needed for therapeutic intervention and healing. The most common therapeutic tools used today are:

- dietary avoidance of suspected allergens
- rotation diets
- medicinal drug therapies
- whole food therapeutics

# Treatment and validation

## Avoidance and Elimination

Undesirable reactions to foods are common. Symptoms may arise from the IgE or IgG antibody reactions or non-immunological reactions to foods for which it may be nearly impossible to test. In either case, however, the elimination of the specific offending food(s) often produces quite favorable results. There are many studies showing improvement in excessive intestinal permeability following a period of allergen avoidance (Dupont et al., 2001; Andre, 1986; Barau and Dupont, 1990) and specific IgE and IgG antigen testing with avoidance of reactive foods often results in a dramatic improvement in symptoms that can help identify non-immune reactions as well. The major disadvantage in using avoidance and rotational food plans is poor patient compliance. Foods being what they are, it is often difficult to identify the hidden sources of specific allergens and many patients find it difficult to follow the rotational regimen. However, when the regimens are followed, they generally do work.

So-called "rare food" diets have been used to achieve clinical improvement in symptoms. In such diets, patients begin by eating only foods that were usually eaten less than once per week for two weeks. Gradually, other foods are re-introduced, perhaps one every four days following the initial two weeks. 60%-95% reductions in symptoms relating to cholesterol and triglyceride levels, depression, anxiety, poor concentration, insomnia, migraine headaches, and arthralgias and myalgias have been achieved with this approach in clinical studies (Borok et al., 1995; Crook et al., 1961; Hall, 1976). The most common offending foods were found to be cow's milk, eggs, and chocolate.

## Medicinal Drug Therapies

Clearly, the use of medications does not cure the problem, but the palliative care can make a quality of life improvement for patients who are suffering. Medications often help in acute bouts of asthma, sneezing, and/or hives. They are primarily used for inhalation-related allergies and are largely limited to antihistamines, decongestants, and steroidal medications.

## Whole Food Therapeutics

Whole food therapeutics is largely based on providing nutrients in food form to eradicate established nutrient deficiencies. There is substantial evidence that providing some of these required nutrients, even at the beginning of life via breastfeeding, has substantial benefits. In infants, breast milk feedings have been shown to encourage helpful intestinal bacterial colonization, assist in the development of the intestinal mucosal barrier, and deliver immunologic properties directly to the intestinal mucosa, all of which contribute to the prevention of allergies (Yellis, 1995). Additional research has investigated essential fatty acids, vitamin A, digestive enzymes, selenium and other trace minerals, the proper balance of intestinal bacteria (via prebiotics and probiotics), and the amino acid glutamine on intestinal permeability and allergic responses.

## Essential Fatty Acids

Research has shown clear associations between essential fatty acid metabolism, specific essential fatty acid (EFA) deficiencies, and atopic eczema (Horrobin, 2000; Biagi et al., 1988). Patients supplemented with essential fatty acids showed dramatic improvement in their clinical condition after only four weeks. Intestinal permeability challenge tests showed significant improvement following the supplementation protocol. These studies have suggested that EFA deficiency and/or disturbed EFA metabolism are major contributors to allergic responses and intestinal integrity problems (Horrobin's study suggested a reduced conversion of linoleic acid to gamma-linolenic acid in patients with eczema). The Standard American Diet (SAD) shows major EFA deficiencies, especially of omega-3 fatty acids (Fallon and Enig, 1999; Kidd, 1998), in favor of saturated fats, the consumption of which can contribute to inflammatory responses. Increased intake of EFA's and a reduction in the intake of saturated fats may contribute to the integrity of the intestinal barrier.

## Vitamin A

The role of vitamin A in the support and maintenance of epithelial cell integrity is well known (Kurpakus-Wheater et al., 2001; Lampen et al., 2000; Swartz-Basile et al., 2000). In a recent study in England, vitamin A and $\beta$-carotene supplementation decreased gastrointestinal morbidity and decreased intestinal permeability in infants of HIV-infected South African women (Filteau et al., 2001). This suggests that an increased consumption of the full vitamin A complex found in whole foods, like liver, carrots, fish oils, winter squash, kale, parsley, and beet greens, can contribute to intestinal integrity and epithelial repair. As the lack of integrity of the intestinal barrier is directly associated with allergic responses, regular consumption of these foods is likely therapeutic.

## Prebiotics/Probiotics

A healthy balance of intestinal bacteria is of paramount importance to health. Clearly, not all bacteria are beneficial. *Lactobacillus* and *Bifidobacterium* are two "beneficial" bacterial species of the intestinal tract, called probiotics, that require specific carbohydrates for proper growth. These carbohydrates are called prebiotics, and they include inulin, fructooligosaccharides, and galactooligosaccharides. Prebiotics are found in many common foods consumed by humans for centuries, like Jerusalem artichokes, onions, asparagus, garlic, leeks, and chicory root, to name just a few. As prebiotic fuel is provided for these intestinal bacteria, they produce beneficial short-chain fatty acids (SCFAs), like butyrate, via fermentation. SCFAs supply nearly 70% of the fuel used by intestinal cells. Studies clearly show the benefit of butyrate in the promotion and healing of intestinal cells, via a reduction in paracellular permeability and increased mucosal repair (Mariadason et al., 1997).

The ability of probiotics like *Lactobacillus* and *Bifidobacteria* to enhance the nutritional content and bioavailability of nutrients has been shown. Particularly evident is their usefulness in alleviating the symptoms of lactose intolerance and preventing milk-based allergic symptoms (Goldin, 1998). In a recent study, *Lactobacillus*, which transiently colonizes the human intestine, was found useful in treating several gastrointestinal conditions characterized by increased gut permeability, specifically mild to moderate Crohn's disease in children. Researchers found there was a significant improvement in clinical symptoms one week after starting them on *Lactobacillus*. The effect was sustained throughout the study period. Median pediatric Crohn's disease activity index scores at four weeks were 73% lower than the starting baseline. Intestinal permeability improved in an almost parallel fashion (Gupta, 2000). The common overuse of antibiotics combined with a reduction in dietary intake of traditional fermented foods rich in beneficial bacteria and a general reduction of raw carbohydrate intake results in poor probiotic status, leaving the body and intestine susceptible to diseases. Thus, probiotic supplementation has a clear role in maintaining health and particularly preventing allergic responses.

## Trace Minerals

In Poland, researchers have found a correlation between selenium deficiency and food allergies in children (Kalita et al., 2001). Selenium deficiency was also connected to small intestinal villus atrophy and increased epithelial permeability in the children with allergy. As selenium has both antioxidant and immunomodulatory actions, the authors suggest that this trace element could be used as an adjunct treatment for food allergies and digestive tract diseases. Trace mineral deficiencies in modern society are common (Combs, 2000; Salmenpera, 1997; Mertz, 1981), but these minerals play an important role in the production of enzymes and other metabolic processes. Adequate dietary intake of foods rich in these trace elements can contribute greatly to the healing process.

## Glutamine

Glutamine, the most abundant amino acid in the blood stream, is the main metabolic fuel for enterocytes of the small intestine, lymphocytes, macrophages, and fibroblasts and plays a major role in the first line of defense in the intestine (Newsholme, 2001; Hall et al., 1996). The small intestine is the greatest user of glutamine in the body and intestinal cells are dependent on glutamine supplied either in the diet or from the blood. If glutamine is lacking in the diet, or if a person is being fed parenterally, intestinal cells will take glutamine from the blood eventually depleting the body's stores (Karinch et al., 2001; Rogero and Tirapeugi, 2000). As levels of glutamine drop, intestinal epithelial cells and lymphocytes begin to lose function and this compromises cellular integrity, leaving the intestine vulnerable to microbial translocation and increased intestinal permeability (Castell, et al., 1994; Burke et al., 1989).

Gut-associated lymphoid tissue (GALT), comprised of the Peyer's patches and lymphoid follicles scattered throughout the intestinal mucosa, requires glutamine for optimal function (Kudsk et al., 2000; Li et al., 1997). It is in this tissue that immune B- and T-cells are primed against intestinal antigens and form a front line of defense against toxins and microorganisms. Oral glutamine supplementation has been shown to increase intestinal glutathione synthetase activity (Cao et al., 1998), improving the antioxidant capacity of the gut and increasing the mitogenic response to immune threats (Wu et al., 1994).

Glutamine is found in high protein foods, such as fish, meats, legumes, and dairy products. It is particularly high in the vegetable sources of raw cabbage and beets (Mack, 1998; Ochs et al., 1999). Glutamine is heat labile, so cooking destroys it. The uncooked forms of these foods are required to obtain the desired health effects. Given the complex nature of nutrients in foods, it is doubtful that any single nutrient is totally responsible for the impact that a food such as cabbage has on the optimization of immune responses. However, the synergistic effect between nutrients may amplify the health benefits of any single nutrient in these foods.

## Final Thoughts

Tracing the cause of food allergies and the reasons for increased intestinal permeability can be a daunting task. The effects of environmental toxins, stress, and dietary deficiencies take their toll on the optimal function of the human body. It is clear that supplying proper nutrients in the diet and increasing intestinal function go hand-in-hand. Whole, real, unaltered foods in the diet are perhaps the most important "therapeutic" tool the modern practitioner has in the fight against disease.

### Future Studies

In a separate article appearing in this issue of the journal (See **Intestinal Permeability, Food Antibodies, and the Effects of Specific, Glutamine-Rich Food Complexes**), I report on a small pilot study exploring the role of intestinal permeability, specific food antigen responses, and the use of a glutamine-rich experimental whole food complex for intestinal permeability repair. The results are suggestive that treatment with glutamine can restore intestinal function and illustrates the fact that further clinical research is needed in this area.

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