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STATEMENT OF PURPOSE
Dysfunction within the gastrointestinal system manifests in typical digestive diseases such as gastroesophageal reflux disease, irritable bowel syndrome, inflammatory bowel disease, and even colorectal cancer. It can also manifest as imbalanced immunologic function, creating and/or contributing to both atopic illness and autoimmune dysfunction. Dietary approaches provide the most effective means of restoring balance within the gastrointestinal system, but the profound dietary changes undergone by humans over the past 100 years conflict with the nutritional input that our genetic structure evolved to maximize. This discordance creates a complex array of clinical needs that require support for the whole being to regain balance and optimal function.

TARGET AUDIENCE
This activity is designed to meet the educational needs of physicians and other healthcare professionals who diagnose, treat, and manage patients who have or are at risk for gastrointestinal disorders.

OBJECTIVES
After completing this article, participants should be able to:
1. Identify the critical functions of the commensal flora.
2. Symptomatically evaluate patients who have alterations in bowel patterns defined by the Rome II Criteria to determine whether they have irritable bowel syndrome.
3. Describe the characteristics of probiotics, and name the most common probiotic bacteria. (Altern Ther Health Med. 2006;12(5):52-62.)

DISCLOSURE
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The gastrointestinal tract, the tube within a tube, connects us to our environment through a dynamic interface that is larger than a doubles' tennis court. Over the course of our lifetimes, we will ingest many tons of macronutrients.
micronutrients, chemicals, and toxins. (Experts vary on the tonnage, but figures range from 30 to 60 tons of food consumed in the lifetime of the average well-nourished adult.) These materials provide the building blocks for everything human. Imbalances in our functional ability to make the most of these nutrients have ramifications for every aspect of our being. Imbalance in the gastrointestinal system has implications that extend far beyond gastrointestinal symptoms; thus, the clinician must be vigilant to gastrointestinal dysfunction in nearly every clinical interaction.

Classically, the functions of digestion and absorption are considered the principal roles of the gastrointestinal epithelium. The quality of discernment that traditional Chinese medicine (TCM) attributes to the “Small Intestine Official” is manifested through its ability to separate the wheat from the chaff, but also in the embedded relationship of the innate and adaptive immune system within the gastrointestinal system. The impact of diet and nutrients on the balance of commensal flora is considerable. Digestion and absorption provide proper macronutrients and micronutrients, while responses such as appropriate physiologic inflammation, the development of oral tolerance, the production of neurochemicals by the “second brain” (Michael Gershon’s term for the enteric nervous system), and the appropriate excretion of waste must all function effectively and in balance with each other in order to foster health and well-being.

Dysfunction within the gastrointestinal system manifests in typical digestive diseases such as gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), non-alcoholic steatohepatitis (NASH), and even colorectal cancer (CRC). Gastrointestinal dysfunction can also manifest as imbalanced immunologic function, thus creating and/or contributing to both atopic illness (including allergy and asthma) and autoimmune dysfunction (including rheumatoid arthritis, type 1 diabetes, and Hashimoto’s thyroiditis). Other diseases of immune dysregulation and gastrointestinal dysfunction now include the autism spectrum disorders. The evolution of these diseases begins long before the presentation of symptoms and thus the opportunity for prevention and early intervention can have tremendous impact on the burden of suffering and disease.

Dietary approaches provide the most effective means of restoring balance within the gastrointestinal system and there are many opportunities to bring these tools to patients. However, the profound dietary changes experienced by humans over the past 10,000 years—and greatly accelerated over the past 100 years—conflict with the nutritional input that our genetic structure evolved to maximize. This discordance creates a much more complex array of clinical needs that require support for the whole being to regain balance and optimal function.

Functional medicine allows us to intervene along a continuum from illness to wellness, where the approach is of value at each level—addressing treatment of disease, relief of symptomatic imbalance even before pathologic disease has manifested, prevention, and optimal wellness. The determination of appropriate therapeutic approaches is contingent upon the degree of imbalance that is present. Observation of history, signs, and symptoms (including noting the patient’s own antecedents, triggers, and mediators) helps with initial understanding. Diagnostic testing helps to further illuminate and clarify the degree of dysfunction.

Diagnostic considerations include, first and foremost, an extensive health history to gain an understanding of dietary inputs, utilization of antibiotics, laxatives, fiber, herbs, etc. In addition, one must elicit the current pattern of bowel movements, including frequency, history, abdominal pain, gas, bloating, relationship to meals, and duration. It is amazing how many patients consider their altered bowel movements to be normal. Western medicine does not have a defined norm of bowel movement frequency, while other forms of healing such as Ayurveda and traditional Chinese medicine view the regular functioning of the gastrointestinal tract to be a critical barometer of health and well-being, with one well-formed bowel movement per day as the norm. Other diagnostic considerations include the evaluation of stool to gather information on parameters of digestion, absorption, inflammation, infection, and altered gut flora (known as dysbiosis).

Let us look more closely at the specific imbalances faced by clinicians as we examine how they manifest in pathophysiology and how they can be balanced to optimize health.

**GUT FLORA**

Cordain describes the dietary patterns most common today, and compares them with the characteristics of ancestral diets. He notes alterations in glycemic load, fiber content, essential fatty acid composition, pH balance, and macronutrient/micronutrient composition, all of which have tremendous effects on the balance of the commensal flora within the gastrointestinal tract.

The critical functions of the commensal flora are:

- **Metabolic processes:**
  - fermentation,
  - vitamin synthesis,
  - energy production;
- **Trophic stimulation:**
  - epithelial cell differentiation,
  - immunomodulation;
- **Pathogen protection:**
  - competing for nutrients, space, adherence;
  - producing bacteriocidins.

New evidence is evolving that the persistent interactions between host and bacteria that take place in the gut may constantly reshape the immune system. Clinicians see the profound effects of altered commensal flora in the nearly 15% of the population who are affected by the functional GI disorder, IBS. It is also becoming clear that the immune dysregulation of IBD is profoundly influenced by the role of gut flora. Symptomatic evaluation of patients who have alterations in bowel patterns defined by the Rome II Criteria (see Table 1) meet the definition of IBS.
TABLE 1 IBS—Rome II Criteria

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<td>12 or more weeks of continuous or recurrent abdominal pain or discomfort, plus at least 2 of the following:</td>
</tr>
<tr>
<td>1. Relieved by defecation and/or</td>
</tr>
<tr>
<td>2. Associated with change in frequency of stool and/or</td>
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<tr>
<td>3. Associated with a change in form (appearance) of stool and/or</td>
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<td>and an absence of alarm symptoms:</td>
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<tr>
<td>• Anemia</td>
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<tr>
<td>• Fever</td>
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<tr>
<td>• Heme-positive stools</td>
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<tr>
<td>• New or recent onset if &gt; 50 years old</td>
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<tr>
<td>• Nocturnal symptoms</td>
</tr>
<tr>
<td>• Palpable abdominal or rectal mass</td>
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<tr>
<td>• Persistent diarrhea or severe constipation</td>
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<tr>
<td>• Recent antibiotic use</td>
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<td>• Weight loss</td>
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Studies have demonstrated the alteration in commensal flora present in IBS in both colonic biopsy samples and stool analysis. There is considerable research on optimal methodology for evaluating gut flora. Dysbiosis can be measured by stool analysis and culture, but 99% of colonic flora are facultative anaerobes and only ~50% will be picked up by culture methods. Alterations in the distribution of metabolic by-products of bacterial fermentation, including n-butryate, propionate, and acetate, can provide a proxy for the distribution of colonic flora. Decrease or absence of normal Lactobacillus, Bifidobacter, and Escherichia coli species in stool culture is an indicator of imbalance.

Recent studies on the pathogenesis of IBS have evaluated the common association with small bowel bacterial overgrowth (SBBO), also known as bacterial overgrowth of the small intestine (BOSI) and small intestinal bacterial overgrowth (SIBO). SBBO is noted when the coliform and anaerobic bacteria from the large intestine produce deleterious effects within the delicate environment of the small intestine. A simple breath test is performed by measuring hydrogen and methane gas produced after oral administration of lactulose. As gut bacteria ferment the lactulose, the gas production increases. Typically, the gas production will increase when the fermentable substrate has passed into the large intestine, but patients with SBBO have this increase in gas production much earlier. Intestinal dysbiosis has been noted to be present in 78% of IBS patients who tested positive for SBBO. When treated with antibiotic therapy, 48% of patients no longer met the Rome Criteria for IBS. Studies have recently begun to evaluate probiotic therapy to improve the rate of SBBO, but results are not yet available.

It is well recognized that several other chronic diseases have a high degree of overlap with IBS, including fibromyalgia, interstitial cystitis, and chronic fatigue syndrome. Studies in patients with fibromyalgia have shown that 100% and 77% of patients also have SBBO. It has been postulated that the immune response to bacterial antigens present in the small intestine provides a framework for understanding the hypersensitivity present in both IBS and fibromyalgia. Thus, we begin to see that alteration in the distribution of gut flora is associated with clinical syndromes outside of the gastrointestinal tract. It is useful and important to modulate the gut flora for improved health by supplementing the diet with prebiotics and probiotics. Assessment of the overall microbiota community with stool culture allows for initial evaluation and the opportunity for evaluating treatment efficacy.

The word probiotic (derived from the Greek and meaning “for life”) was first used in 1965 to describe a function that is opposite to that of antibiotics. It has subsequently been defined as “a preparation of or a product containing viable, defined microorganisms in sufficient numbers, which alter the microflora (by implantation or colonization) in a compartment of the host and by that exert beneficial health effects on the host.” A probiotic must be of human origin, be non-pathogenic in nature, be resistant to destruction by gastric acid and bile, adhere to intestinal epithelial tissue, and be able to colonize the gastrointestinal tract (if only for a short period). Other common desirable properties include being able to produce antimicrobial substances, modulate immune responses, and influence human metabolic activities.

A prebiotic has been defined as “a non-digestible food ingredient which beneficially affects the host by selectively stimulating the growth of and/or activating the metabolism of one or more health-promoting bacteria in the intestinal tract, thus improving the host’s intestinal balance.” Prebiotics induce antimicrobial effects via their selective stimulation of commensal strains that modulate immune function and compete with pathogens for receptors. Specific prebiotics are now being developed to help promote the growth of beneficial bacteria and selected probiotics. Combinations of prebiotics and probiotics are collectively known as symbiotics.

The most common probiotic bacteria are:

- Bifidobacterium—25% of adult colonic bacteria and 95% of a breastfed newborn;
- Lactobacillus—several beneficial strains (GG, NCFM, acidophilus) have been identified;
- Saccharomyces boulardii—a patented yeast product that inhibits growth of pathogens.

Probiotic supplementation has been shown to be beneficial in antibiotic-associated diarrhea, necrotizing enterocolitis (NEC), cancer prevention, health promotion, and H pylori prevention. Recently, researchers have also demonstrated the beneficial effect of probiotics for improving symptoms in IBS and for normalizing imbalances with inflammatory cytokine ratios. Probiotics are moving into the mainstream of treatment options for IBS, as well as IBD. Disease-specific activity and modulation of the immune system are bacterial species- and subspecies-dependent processes. Thus, the overall community of

54 ALTERNATIVE THERAPIES. SEPT/OCT 2006, VOL. 12, NO. 5 Balance of Flora, GALT, and Mucosal Integrity
bacterial flora becomes a critical determining factor for promoting health and preventing/treating disease.

As the human host is highly adaptive to the presence of commensal bacteria, there is a dynamic learning opportunity that continues to unfold as probiotics and prebiotics are utilized therapeutically and preventively. What is the optimal endpoint for treatment? New quantitative molecular techniques with 16S ribosomal RNA probes are now being developed to characterize and quantify the 400+ bacterial families present within the colonic environment. Questions abound regarding what constitutes optimal flora. This is an important limitation for treatment planning and health-promotion efforts. In the future, nutritional interventions may target probiotic strains based upon their specific characteristics to activate an inhibitory mucosal response. Until that time, phenotypic markers of digestion, absorption, inflammation, and dysbiosis will help clarify the patient’s progress.

In addition to the benefit of probiotic therapies in IBS and IBD, additional studies have successfully used probiotics as a preventive strategy for infants at risk for atopic illness. Based upon the immunologic imbalance of T-helper cells offered in the hygiene hypothesis, researchers in Finland gave probiotics to infants with a family history of atopic illness and demonstrated a 50% reduction in incidence. A follow-up study at four years confirmed these findings. Isolauri and her colleagues showed that the anti-allergenic and anti-inflammatory activity of supplemental probiotics was mediated, at least in part, by a decrease in intestinal permeability. These findings have been confirmed in children with moderate to severe atopic dermatitis, with the improvement in intestinal permeability correlating with improvements in the severity of eczema.

The innate immune system discriminates between potential pathogens and commensal bacteria by using a number of pattern-recognition receptors (PRRs). Mammalian cells express a series of toll-like receptors (TLRs) that recognize bacterial and microbial structures, including DNA. When infection or pathogens are present, the inflammatory response can increase intestinal permeability. This allows for increased sampling of gut flora by the immune system—a physiologic process of checks and balances. In the presence of an alteration of the gut flora, immune dysregulation, or a genetic predisposition, there is a sustained chronic inflammation and release of calprotectin from neutrophils. Conversely, the presence of healthy commensal flora and/or probiotics has been shown to have an anti-inflammatory effect on the gastrointestinal epithelium.

**MUCOSAL INTEGRITY**

Significant permeability changes in the gut mucosa can have profound effects on anatomic and immunologic barriers to disease. Intestinal hyperpermeability, also known as leaky gut, can lead to increased inflammatory cytokine production and a propagation of inflammation within the intestine. There is a great deal of evidence linking increased intestinal permeability with multi-organ system failure, systemic disease, and immune dysfunction. Animal models also demonstrate that stress significantly increases intestinal permeability. Studies have focused on animal models and the results are now being brought to bear on cases of trauma and sepsis. Studies on ischemia and reperfusion injury have confirmed a disturbed intestinal barrier and increases in intestinal permeability correlate with multiple organ failure.

The assessment of intestinal permeability is performed with a standardized double sugar test. The client drinks a mixture of lactulose and mannitol. The larger lactulose molecule is only minimally absorbed (in the healthy patient) and the smaller mannitol molecule is absorbed through the microvilli of the duodenum and jejunum. Absorbed sugars are then excreted through the urine and measured individually. The relative ratio of urinary lactulose/mannitol is used as the determinant of increased permeability. Decreased levels of mannitol are indicative of poor absorption and may be an indication of microvilli damage.

While some have questioned the more simplistic model of leaky gut, the gastroenterology literature has validated the value of the double sugar test in studies using histology and electron microscopy. Studies have demonstrated that the bacterial translocation across the gastrointestinal epithelium induces antibodies to bacterial components with antigenic cross-reactivity to HLA antigens. Klebsiella has been associated with ankylosing spondylitis when cross-reactivity occurs with the HLA-B27 antigen. Similarly, Proteus mirabilis has been associated with reactive arthritis and is known to cross-react with the HLA-DR4 antigen. There is currently anecdotal evidence that the modification of gastrointestinal flora with antibiotics can have an effect on these arthritides, although formal studies to confirm or deny this relationship are not currently available.

It has also been observed that a number of inflammatory conditions, such as asthma, eczema, psoriasis, and Crohn’s disease, all affect the epithelial surfaces. Alterations in barrier defense and epithelial permeability are present in each of these diseases. Further clinical studies have demonstrated that there is an increase in intestinal permeability in asthma, suggesting that the entire mucosal immune system is affected. Intervention
trials have not been reported, but anecdotal data from researchers and naturopathic physicians have suggested that there is a sub-set of asthmatic and atopic patients (~10-20%) who improve with treatments to decrease intestinal permeability.

The first approach to decreasing intestinal permeability is to effectively remove any inflammatory stimuli from the mucosal surface of the intestine. This entails an understanding of tools to assess digestive function, as well as the diagnostic tools that can be utilized to identify/quantify the degree of intestinal permeability. Sources of inflammation and increased intestinal permeability include infections and pathogens (including Candida), altered commensal flora (i.e., dysbiosis), celiac disease, lactose intolerance, and food allergies. Once the implicated agent has been effectively removed, clinical symptoms often begin to improve within 3-5 days, the turnover time of the intestinal epithelium.

Therapeutic agents include probiotics—to utilize their anti-inflammatory nature—along with the cultivation of appropriate metabolic substrates to assist in the differentiation of the epithelial lining. After removing the source of initial injury and inflammation, glutamine is one of the most powerful agents used to supply energy to enterocytes and colonocytes. L-glutamine is a very useful clinical tool, but it is also a substrate for lymphocytes and macrophages, in addition to being a precursor of nitric oxide. Thus, it is necessary to ensure that inflammation is resolved before treating with this powerful trophic factor. Glutamine has also been noted to be a substrate for Candida synthesis, so this should be evaluated before initiating therapy.

MUCOSAL IMMUNE SYSTEM

As has been noted, the intestine is the primary immune organ in the body, containing nearly 70% of the immune cells—more than 10^10 lymphocytes/g of tissue. The gut-associated lymphoid tissue (GALT) represents the largest mass of immunocompetent cells within the human body. The regulatory function occurs in several areas—e.g., the more organized Peyer’s patches and the diffusely distributed intra-epithelial lymphocytes (IELs). These critical components of the innate immune system sample the luminal contents of the gastrointestinal tract, coordinate host responses, and synthesize inflammatory mediators as they differentiate between potential pathogens and commensal bacteria. Much of this process is mediated by the recently discovered toll-like receptors (TLRs), a sub-set of pattern recognition receptors that recognize different bacterial components and quickly respond with differential stimulation of the adaptive immune response.

The dialogue between host and bacteria at the mucosal interface plays an important part in the development of a competent immune system. Microbial colonization of the gastrointestinal tract affects the composition of the GALT. Many diverse interactions between microbes, epithelium, and gut-associated lymphoid tissue are involved in creating the memory of the immune system. For instance, commensal flora are intimately involved in the development of oral tolerance, part of the body’s acceptance of something as self. The ability to recognize food particles and commensal bacteria is critical for educating the adaptive immune system properly.

Immunologic Cross-Talk

Inflammatory bowel disease (IBD) is an important example we can use to understand how to evaluate imbalance within the mucosal immune system. Three factors are required for abnormal physiology to evolve into inflammatory bowel disease: altered intestinal permeability, access of gut contents to immunologic cells within the GALT and the MALT (mucosa-associated lymphoid tissue), and an abnormal immune response. Alterations in mucosal integrity that do not include an abnormal immune response will also tend to cause dysfunction within the system, though in a much more subtle manner. Luminal contents that can have a stimulatory effect on the immune system include bacteria, bacterial antigens, food antigens, and toxins. Translocation of bacteria can stimulate a physiologically normal inflammatory response when function is healthy and balanced. When a significant number of pathogenic bacteria translocate across the epithelial lining, there is an overt inflammatory response from the gut-associated lymphoid tissue. The upregulation of inflammatory cytokines provides the body with a rapid response to invasion. Multiple mechanisms of cross-talk between the bacteria and epithelia that differentiate between the process of recognition and oral tolerance vs effectively responding to pathogenic bacteria have been described.

Oral Tolerance

Oral tolerance has been defined as the immunologic hyporesponsiveness to an antigen encountered through the enteric route, usually through oral administration. The mucosal immune system is able to tolerate an abundance of dietary antigens and commensal bacteria, while still effectively repelling pathogens. Desensitization methods have been used to deal with allergic reactions, including food allergies, since the 1960s. Studies have been done in humans that apply the principles of oral tolerance to autoimmune and allergic diseases. In at least one such study, ~80% of patients with food allergies were desensitized to increasing doses over time; however, treatments for autoimmune diseases such as IDDM, multiple sclerosis, and Reiter’s syndrome have been less effective. Several trials with rheumatoid arthritis were effective, with therapeutic responses to oral collagen challenge. The reason for this therapeutic effect is not clear, though it has been postulated that the source of initial antigen exposure may also be oral. Animal studies also seem to indicate that the relationship of maternal fatty acid ingestion during pregnancy may influence the induction of neonatal immunological tolerance. This means that mothers who had increased n-6/n-3 fatty acid ratios while pregnant had offspring with an increased prevalence of allergy. Different bacteria induce different immunologic responses. Nonpathogenic bacteria also elicit different cytokine responses from epithelial cells, inducing differential effects on the GALT and the adaptive immune system. We can see from this
dynamic interplay between the gut flora and the GALT that the immunologic response system can be modified, based upon dietary changes (in the form of prebiotics) and beneficial bacteria (in the form of probiotics).

One of the factors noted in the degree of immune response is the adhesion capacity of antigens to epithelial cells.28 Strong adhesion of antigens to the epithelial cells is seen with increased immune response. Now it is seen that IBD patients are not tolerant of their own gut flora29 but, interestingly, the administration of fecal flora derived from healthy controls has been shown to be effective.70 A continuum of symptoms from IBS to IBD has been proposed71 that includes alterations in gut flora, immune dysregulation and inflammation, altered mucosal permeability, and stress-induced symptoms. Epidemiologic evidence seems to bear out that some of the rapid increase in IBD may be due to large numbers of IBS patients, and the continuously increased risk of IBD detection in IBS patients favors a true association between the two.72

Food Allergies

These data indicate that commensal flora may play a paradoxical role in immune regulation, depending upon the antigen, intestinal permeability, degree of inflammation, and maturation of the GALT. This phenomenon is particularly important in early infancy. The intestinal barrier is more permeable with a physiologic inflammation present, as noted by elevated fecal calprotectin levels over the first six to 12 months of life. The cytokine profile is polarized toward humoral immunity (antibody production) and away from cell-mediated immunity.

This immunologic imbalance sets up the situation in which the immature gut is much more sensitive to oral antigens and food allergy. It is clear that allergic reactions to food are much more common in the first few years of life.73 It has been postulated that the increased prevalence of formula feeding and subsequent loss of the critical immunologic factors present in breast milk have contributed to the increase in the incidence of immune-based disorders, such as allergy and asthma.74 The studies by Isolauri et al discussed earlier strongly support this hypothesis, as the prebiotic effect of breast milk encourages the growth of bifidobacteria and leads to significant differences in gastrointestinal flora at six months of age.75

The environmental setting of low-grade inflammation and increased mucosal permeability induces changes in antigen handling that lead to sensitization. This implies that allergic response to dietary antigens is caused by a failure of the GALT to maintain oral tolerance to these antigens.76 It would follow that the role of probiotics in the treatment of food allergies in adults would be of benefit.77 In general, the clinical approach to working with food allergies is to evaluate the client with an elimination/challenge diet. The removal of an antigen that is recognized as foreign for 21 to 28 days should improve symptoms, but it is necessary that all offending antigens be removed. Thus, a modified elimination diet may not have the requisite restrictions to be effective.

After removal of potentially offending food antigens for three to four weeks (the time period may be increased up to several months if needed), the patient carefully adds back a new food once every few days; frequency recommendations vary, but 2-4 days between foods is a common range for the reintroduction process. This time frame allows for recognition of delayed hypersensitivity responses. This methodical process is usually limited to the most common food allergens, including cow's milk, wheat, egg, corn, soy, and tree nuts; however, it can be adapted to eliminate and challenge any suspicious foods. This elimination/challenge process is the gold standard of allergy testing. No commercially available allergy tests, regardless of methodology, are as accurate. Patients are strongly encouraged to follow through with the elimination/challenge diet, but it is imperative that the clinician help the patient to embrace the process with adequate preparation and a positive attitude.

Considering the diversity of immunologic pathways, it is clear that using a single entity (such as serum IgG levels) to measure food allergies would be incomplete.79 Functional assays to measure lymphocyte stimulation have not demonstrated good reproducibility. A recent study did demonstrate clinical utility in the utilization of IgG levels as a diagnostic tool to determine a modified elimination diet in patients with IBS. In comparison with a group receiving a sham diet, the patients whose diet was based upon eliminating foods with IgG reactivity were 30% improved.76 In her commentary on this study, Isolauri notes the profound impact of low-grade inflammation and altered mucosal integrity on antigen transfer and the development of allergies: "A healthy gut microbiota is thus an indispensable component of gut barrier function."80

Once again, probiotics may have a therapeutic role in the case of food allergies. Bacteria produce a number of enzymes and products to assist with the metabolism of food. For example, Lactobacillus rhamnosus GG was able to hydrolyze casein and reduce the production of IL-4 in atopic infants with cow's milk allergy.81 Probiotics modify the structure of potentially harmful antigens and lower their potential for harm. Current studies are now underway to evaluate the feasibility of creating a group of probiotic bacteria with the capacity to break down gluten in such a manner that people diagnosed with celiac disease will still be able to eat wheat products.82

Commensal bacteria have effects that extend across a range of immunologic imbalance. We have discussed the importance of commensal flora on stabilizing gut flora, promoting the integrity of the intestinal barrier, supporting host resistance to pathogenic bacteria, and modulating immune response. All of these qualities extend to the therapeutic use of probiotics. The anti-inflammatory and immunomodulatory effects of probiotics provide the basis for therapeutic intervention. Beneficial effects have been demonstrated in IBD,83 IBS,84 atopic illness,85 and food allergies.86

Stool Analysis

Evaluating the effectiveness of probiotics in normalizing the gut flora may not be as simple as measuring the change in bacterial counts in stool culture at the species level, although these are the best clinical tools that we have right now. Microbial analysis
of stool samples provides clinical insight into the flora population of the distal colon. Quantitative growth on the agar plate reflects the levels of bacteria in the distal colon. Results obtained from fecal samples demonstrate that 50-80% of total microscopic composition is recovered by fecal culture. There is good agreement on the degree of biodiversity when fecal culture is compared with 16S rDNA sequence analysis.87

The predominant beneficial bacteria in the large intestine are *Bifidobacteria*, strict anaerobes that constitute as much as 25% of the overall colonic flora in healthy adults. In the colon, obligate anaerobes such as *Bifidobacteria* predominate over facultative anaerobes such as *Lactobacilli* by 1,000:1. Recovery of these organisms in stool culture should therefore ideally be in the 3+ or 4+ ranges. *Lactobacilli*, facultative anaerobes, have culture growth at 1+ or 2+ in healthy adults. Non-pathogenic *E coli* populate the distal colon, although they are usually found in reduced quantities, comparable to levels of *Lactobacilli*. A growth of non-pathogenic *E coli* from 1+ to 2+ is therefore considered normal.88

To date, it has been assumed (though not confirmed) that probiotics adhere to the gastrointestinal mucosa.89 Only in vitro studies have been able to detect the presence of adhesive substances from probiotics and demonstrate adherence to tissue cells.90 It is clear that probiotics exert a number of beneficial effects; however, effects from supplementation may occur from transient passage through the GI tract rather than actual colonization. Studies have shown that 3-14 days after exogenous supplementation ceases probiotics are no longer recovered from the stool.91 It is therefore doubtful in the absence of supplementation that beneficial bacteria will be recovered unless they are of indigenous origin.92 One can assess levels of beneficial bacteria when taking probiotics to ensure that they are delivered to the colon and thus are able to exert their beneficial effects on the host. Alternatively, one can re-evaluate the stool microbiology on a patient who has been treated for dysbiosis to ensure that the imbalance in stool flora has been corrected.

**Probiotic Treatment**

Probiotic dosage will vary based upon the indication for treatment (and/or prevention) and the age of the patient. Strain-specific effects are just beginning to be published and efficacy data on one sub-species or strain may not be applicable to another, even within the same species. Current data suggest that the intestinal flora in IBD is not normal, even as we strive to better understand the exact nature of the term “normal flora.”93 Epidemiologic data support the idea that insufficient protective commensal flora may impair immune system homeostasis.94 Intervention studies are beginning to prove this therapeutic approach. Studies have demonstrated efficacy for maintenance treatment of pouchitis using 450 billion colony-forming units (cfu) per day.95 Much higher doses are currently being studied for treatment of IBD.96 Additional trials have demonstrated efficacy as adjunctive97 and primary therapy98 for ulcerative colitis, using doses of 10-75 billion cfu/day.

Treatment of IBS with probiotics has also been shown to be efficacious in six of eight trials, with response depending upon dosage and strain of probiotic used.99 Several studies of IBS treatment with probiotics have utilized doses of 25-75 billion cfu/day of *Lactobacillus* and *Bifidobacterium*, demonstrating decrease in flatus and improvement in quality-of-life symptom scores.100-102 Post-antibiotic therapies have been recommended at 20-25 billion cfu/day to help normalize commensal flora.103 Treatment is usually for 3-4 weeks and can begin during antibiotic treatment, as long as it is not taken concomitantly. Benefit in reducing antibiotic-associated diarrhea has also been demonstrated.104

In addition to studies on strain-specific effects, studies are needed to evaluate the appropriate dosages for various conditions. It has been assumed empirically that higher dosages may be effective for treatment of disease, and lower dosages are useful for health promotion and disease prevention. A meta-analysis of the utility of *Lactobacillus* in childhood diarrhea demonstrated its efficacy in reducing diarrhea an average of 0.7 days, with a reduction of bowel movements by 1.6/day on Day 2. A further evaluation of dose response was performed, demonstrating that the reduction in diarrheal days was directly correlated with dosages above 10 billion (10^9) cfu and up to 150 billion (10^11) cfu per day.105 Symbiotics (the combination of prebiotics and probiotics) seem to be effective at lower dosages.106

A recent review summarizes the evidence that the immunostimulatory effect of probiotics extends far beyond the gastrointestinal tract to distant mucosal surfaces, including the respiratory and genito-urinary systems.107 Further research has shown that probiotics enhance cell-mediated immunity in elderly patients, particularly in people whose immune systems showed poor response before treatment.108

Probiotics are extremely safe, even at high doses.109 No pathogenic or virulence properties have been identified for *Lactobacillus* or *Bifidobacteria*.110 To date, there are no documented cases of septicemia associated with *Bifidobacteria*. While *Lactobacillus* has been associated with bacteremia, it has only been documented in severely immunocompromised patients, with prolonged hospitalization and after surgery.111 Data from Finland do not demonstrate any increase in bacteremia over the past 10 years of rapidly increasing probiotic consumption.112

**Prebiotic Treatment**

Fructooligosaccharides (FOS) may act as a fermentative substrate. Because they particularly favor the *Bifidobacteria* population in the gut, regular ingestion can help these organisms become predominant. A dose of 4 g/day appears sufficient to have this effect in vivo.113 Even at a dose five times higher (ie, 20 g/d), there is a negligible amount of intact FOS found in the stool, indicating that FOS have been nearly completely fermented in the colon.114

**SUMMARY**

It is clear that there is a dynamic relationship involving the gastrointestinal flora, environmental inputs (food and other nutrients), and the health of the immune system. Recent
research has taught us a great deal about the role of diet and commensal bacteria in promoting health. It appears that Nobel Laureate Eli Metchnikov may have been correct in his assertion that live bacterial cultures are “the elixir of life.” We are unlocking a number of secrets about immune system functioning, but we keep coming back to a simple intervention that has an ever-expanding opus of research to support it, and an extremely low toxicity ratio.

Future studies will help us to clarify the best strains and the best dosages for individual patients and specific conditions. Assessment of commensal flora and a genomic scan for markers of immunologic dysregulation will be more accurate and more widely available. It appears, however, that the diagnostic and therapeutic tools we have to work with today can make a tremendous difference in reducing the burden of suffering for our patients. If “form follows function,” as Buckminster Fuller was fond of saying, then the form of our immune system may be following the precise functions that our commensal flora is dictating.

We have the opportunity to encourage breastfeeding, decrease unnecessary antibiotic and antimicrobial usage (especially in the first two years of life), improve oral tolerance with a healthy n-6/n-3 fatty acid ratio, and support the development of a healthy commensal flora. These actions on behalf of our immune systems will pay dividends for years to come.

Acknowledgment
This educational material was made possible by an unrestricted educational grant from Essential Formulas, Inc. 1012 McCoy Drive, Irving, TX 75062; Toll-free: (500) 430-6180; Fax: (972) 255-6648; E-Mail: info@essentialformulas.com; Web: www.essentialformulas.com.