

FUNCTION OF THE INTESTINAL BARRIER

Proper intestinal barrier function is essential for maintaining optimal health and balance throughout the body. It is the first line of defense against an increasingly toxic environment. The barrier consists of an intrinsic layer, including epithelial cells and tight junctions, and an extrinsic layer, which is comprised of bacteria and a coating of mucus with high concentrations of secretory IgA.

On a daily basis, the intestine is exposed to an unlimited number and variety of antigens derived from ingested food, xenobiotics, bacteria and viruses. Some of these antigens pose no threat to the host, while others are harmful and may lead to disorders effecting the nervous and immune systems. The intestine samples these antigens by allowing some to permeate the epithelium and thus interact with the intestinal and systemic immune systems. These small quantities of intact protein antigens that cross the intestinal barrier are part of a normal physiological process, which for most individuals, does not elicit unhealthy consequences. However, for some people, absorbing even “normal” amounts of antigens can result in systemic immune response.

Interaction between macromolecules and the immune system can lead to immunologically-mediated damage, if compensatory mechanisms do not exist within the host. Research indicates that increased antigen uptake precedes the onset of a number of diseases and conditions that reach beyond the gut. Thus, immune response to particles and large molecules in the circulation may be pathologically significant and can be measured to assess intestinal permeability.

NEUROIMMUNOLOGY OF TESTING PARAMETERS

The gastrointestinal tract is home to aerobic and anaerobic bacteria, and yeasts held in check and balance by its own ecosystem. **Aerobic Bacteria**, *Enterococcus* and *Esherichia coli*, are an integral component of this homeostasis. These microorganisms, through cellular respiration, use oxygen to oxidize substrates, such as sugars and fats, thereby harnessing energy. **Anaerobic Bacteria**, *Clostridium perfringens* and *Bacteroides fragilis*, work in the absence of oxygen to break down food matter. If imbalanced, these bacteria can contribute to enhanced intestinal permeability. In such cases, they may play a role in autoimmunity. Additionally, lipopolysaccharide (LPS), an endotoxin from these gram-negative bacteria, plays a role in progressive neurodegeneration by activating cells in the liver to produce $TNF\alpha$, which enters blood circulation and transfers to the brain through $TNF\alpha$ receptors to produce more $TNF\alpha$ along with additional pro-inflammatory factors. This cycle creates a self-propelling neuroinflammation that induces the loss of DA neurons in the substantia nigra. This neuroinflammation is found in Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, Multiple sclerosis, Amyotrophic lateral sclerosis and some forms of depression.

Candida albicans is the most common and problematic yeast found in normal flora of the intestine, vagina and skin. Under a variety of conditions, *Candida* can over-grow causing

mal-absorption of nutrients, intestinal barrier dysfunction or increased intestinal permeability, fatigue, bloating and inflammation of the gut. Due to *Candida*'s cross-reactive nature to all tissues, susceptibility to autoimmune disorders is elevated. This fungus has a predilection for vascular structures, and thus may cause vasculitis, intraparenchymal hemorrhage, mycotic aneurysms and thrombosis of small vessels with secondary infarction. Kondori and colleagues found antibodies to *Candida* in patients with rectal neoplasms, aneurysm, aortic aneurysm, diabetes mellitus, Non-Hodgkin's lymphoma, and atrial fibrillation. *Candida* organisms can enter the CNS. They tend to cause focal necrosis in the area around the microcirculation, producing microabscesses located mainly in the gray-white matter junction, in the basal ganglia, and in the cerebellum.

Serum immunoglobulins to food antigen macromolecules have been found in patients with IBD and celiac disease indicating that these proteins permeate in increased amounts causing systemic immune responsiveness. **Dietary Proteins**, wheat, corn, soy, egg and milk, are measured for two reasons. First, they are commonly eaten on daily basis; second, they are the most common dietary proteins associated with inflammation of the gastrointestinal tract, which leads to intestinal barrier dysfunction or intestinal permeability. In cases of intestinal permeability, autoimmune and neuroautoimmune disorders, such as diabetes, multiple sclerosis and fibromyalgia, are likely to develop. When exorphins, opioid peptides from undigested food proteins, cross the blood-brain barrier, they bind to opiate receptors in the locus ceruleus and other regions of the brain. By disrupting the neurotransmitters' normal use of opiate receptors, this event can significantly affect behavior, emotions and cognitive ability, as well as, pain threshold.

INTESTINAL BARRIER DYSFUNCTION

Bacterial endotoxins, infections, enzymes, xenobiotics and other environmental factors can induce mucosal immune dysregulation. Pro-inflammatory cytokines TNF- α , and IL-6 induce the production of IL-1 β . This newly formed cytokine then binds to IL-1 receptors near the tight junction complex and activates the NF- κ B inflammatory cascade.

The down stream degradation of I κ B results in the translocation of NF- κ B into the nucleus. NF- κ B's key role is the regulation of immune response to bacterial or viral antigens. The activation of this transcription factor indicates down-stream interplay among HPA and sympathetic nerve terminal. Once in the nucleus, NF- κ B activates myosin L-chain (MLC) kinase synthesis, which in turn, degrades the cytoskeletal network and tight junction proteins. With the opening of the tight junctions, bacterial toxins, xenobiotics and food antigens may enter circulation and bring about additional inflammation.

This heightened activation of inflammatory cascades results in further production of proinflammatory cytokines TNF- α , IL-6 and IL-1 β . Such inflammatory conditions promote the opening of the blood-brain barrier, and subsequently, initiate

neuroinflammation in the brain and the production of pathogenic antibodies. This presents a link between gut and brain inflammations.

A number of conditions are known to increase the permeability of the intestinal barrier:

Food sensitivity	Extensive burns
Celiac disease	Septicemia shock
Acute Gastroenteritis	Hypovolumetric shock
Chronic intestinal infections	Neurotransmitter imbalance
Inflammatory bowel disease	Malnutrition
Surgery	Secretory IgA deficiency
Exercise	Anti-inflammatory drugs
Psychosocial stress	Viral infection
Excessive radiation	

Singly, or in combination, these factors can contribute to the dysfunction of the intestinal barrier. The recently enlightened role of intestinal barrier permeability in the pathogenesis of autoimmunity and neuroautoimmunity, can provide sufferers with new hope. Therapies targeted at correcting open tight junctions of the intestinal barrier, can modulate or even reverse the progression of these disorders by disrupting the interaction of the environment with the patient's genetic makeup and immune system response.

INTESTINAL BARRIER FUNCTION PROFILE

A new generation of testing for intestinal permeability or "leaky gut" is now available. This scientifically advanced assessment takes into consideration the individual patient's immune system response to proteins and peptides (macromolecules) which, upon entry into the blood stream, can challenge the immune system resulting in IgG, IgA and IgM antibody production against them. In healthy, normal intestinal immune conditions, antigens are passed through the lumen into circulation, and for many people this common event does not evoke an overreaction in the systemic response. However, for susceptible persons even this passage of antigens can erupt into the beginning of a neuroautoimmune disorder.

The old generation of urine analysis failed many patients because it did not measure the person's immune response. By administering oral molecules with relatively low molecular weights, such as lactulose manitol, to a patient and then measuring the discharged molecules is neither conducive of intestinal permeability, as stated above, nor does it reflect the transfer of food proteins into circulation and thereby initiating a systemic immune reaction. In 1988, researchers were questioning whether or not, this probe used to measure intestinal permeability reflects permeability to intact proteins, and called for a test that would.

The patented Intestinal Barrier Function profiles not only provide a proper immune response assessment in regards to intestinal permeability, they also include evaluations of

factors important to the overall health of the intestinal tract. GI imbalance cannot be understood fully, in its diagnostic and therapeutic implications, without the coordination of the intestinal flora, their toxins (LPS) and dietary proteins. Use of the Intestinal Barrier Function Screen gives clinicians etiologically based analysis of intestinal integrity and its accurate ELISA methodology provides quantitative results which can be used in case management of intestinal-related health problems.

REFERENCES

Brostoff J and Challacombe S (eds). Food allergy and intolerance, 2nd edition, New York; *Saunders*. 2002.

Fasano A and Shea-Donohue T. Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases. *Nat Clin Prac*, 2005; 2(9):416-422.

Gardner MLG. Gastrointestinal absorption of intact proteins. *Ann Rev Nutr*, 1988; 8:329-350.

Jakobsson I *et al*. Human α -lactalbumin as a marker of macromolecular absorption. *Gut*, 1986; 27:1029-1034.

Kondori N *et al*. Circulating β (1-3) glucan and immunoglobulin G subclass antibodies to *Candida albicans* cells wall antigens in patients with systemic candidiasis. *Clin Diagnostic Lab Immunol*, 2004; 11(2):344-350.

Lai P-H *et al*. Disseminated military cerebral candidiasis. *AJNR*, 1997;18:1303-1306.

Maes M *et al*. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. *Neuroendocrinol Lett*, 2008; 29(1):117-124.

Qin L *et al*. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *GLIA*, 2007; 55:453-462.

Walker WA and Sanderson IR. Epithelial barrier function to antigens: an overview. *Ann NY Acad Sci*. 1987; :10-17.

Zioudrou C *et al*. Opioid peptides derived from food proteins. *J Biological Chem*, 1979;254(7):2446-2449.