October 2005 Issue | Kenneth Fine, MD EnteroLab

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Welcome to *Functional Medicine Update* for October 2005. We are already preparing for the 13th International Symposium on Functional Medicine, which will take place on April 19-22, 2006 at the Tampa Marriott Waterside Hotel & Marina, a beautiful five-star resort. The symposium will focus on: Managing Biotransformation: The Metabolic, Genomic and Detoxification Balance Points. There are so many aspects of detoxification that I thought it might be useful to devote several months of FMU to some preliminary information about it. I want to begin with what functional medicine has to do with the barriers of defense. Some of you might think this is a somewhat esoteric topic. How do the barriers of defense relate to detoxification and toxicity? Hopefully, by the end of this issue of FMU, you will see that they play an important role in regulation and defense against potential toxic exposure.

There is probably no one who has described the epithelial barriers better than our own master teacher, Dr. Sidney Baker. In his lectures, writings, and books, he has spoken so eloquently about barriers of defense, the mucosal surfaces, and the fact that we are enfolded, protected, wrapped, and cloaked against exposure to potential toxic substances, both internally and externally, as a consequence of these membranous barriers. As Dr. Baker has pointed out, the gastrointestinal mucosal barrier, when stretched tight so that all the villi are laying flat, would occupy an area almost equivalent to a doubles tennis court. This very large, membranous barrier defends us from the environment and is involved with selective permeability, pulling in the good things and rejecting the bad things. These barriers of defense play very important roles in maintaining health against a hostile environment.

The membranes are not confined to the mucosal surfaces; they also include the enfolding of membranes within every cell. It might be the endoplasmic reticular membrane, or the cellular membrane, or the nuclear envelope membrane, or the membrane that surrounds the mitochondria. We are composed of all these metabolic and physiologic processes that occur on the surfaces of specific topological structures called membranes. These membranes become both the barriers and an active part of our cellular organelle systems.

Both on a gross level (epithelial level), and a cellular level (membranous level), we think the barriers of defense play a very important role as a fundamental principle in functional health. In our Applied Functional Medicine in Clinical Practice training program, we spend quite a bit of time talking about the basic core principles that differentiate a functional medicine approach by viewing a patient through the lens of histopathology, rather than the traditional, differential diagnostic methodology, which looks at the endpoints of a process of loss of function, arriving at some determined or agreed-upon point of pathology. Well before that, however, signs and various biochemical changes occur that reflect changing function. One of the principal, early-stage changes that often occurs is in the barriers of defense, leading to

breakdown or loss of selective or active transport, which influences the function of the cell, tissue, organ, or organ system, until it eventually leads to a pathology.

A discussion of the barriers of defense in physiological systems includes the role they play in protecting against exposure to injurious substances, either endogenously or exogenously produced, as well as the active role of these membranous surfaces to pull in what is necessary from the outside world by active transport, or get rid of things from inside the cells of the body that are not necessary. These would be the excretory processes of membranous surfaces. All of these become a dynamic and important part of understanding functional physiology. It is with that in mind that we are going to focus our attention this month on the epithelial barriers in human health and disease.

Undoubtedly, some of what I am going to be saying will be review and perhaps repetition for many of you who are well inculcated in the functional medicine model. But I believe it is important to set the ground rules for all of us as we move forward to this month's Clinician of the Month interview. I will begin with some basic principles, as I have come to understand them over the years.

First of all, the tissue level barriers have physiological function. They are not like dams. They have dynamic function, and we actually see these epithelial and membranous barriers as being part of our organ systems involved with the homeodynamic processing of environmental information. Barriers not only separate fluids, but they also do very important work by resorbing solutes from different compartments, or secreting substances. In doing so, they establish gradients across themselves. These gradients are maintained as a consequence of energy processes. Whenever there is a high concentration of something on one side and a low concentration on the other, metabolic work requiring energy has to be done in order to maintain that concentration gradient. This energy requires the same cofactors and intermediates from which all other processes in cells derive their energy—the high-energy-containing molecule adenosine triphosphate (ATP), the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH), the reduced form of flavin adenine dinucleotide (FADH2), and the reduced form of nicotinamide adenine dinucleotide (NADH). These are particular high-energy and electron transfer molecules that are formed as a consequence of aerobic metabolism, or mitochondrial oxidative phosphorylation.

There is a connection between biochemical energetics and membrane function that is important to keep in mind. Concentration gradients that are maintained by membranes require an energy process, which is tied to oxidative chemistry and mitochondrial oxidative phosphorylation—glycolysis, aminolysis, lipolysis—the things in intermediary metabolism that we have discussed. These gradients are used to establish other gradients—for instance, the sodium or potassium gradients. All of these concentrations are maintained through proper membranous function and structure.

What constitutes a barrier? An epithelial barrier, or even an endothelial barrier that lines the surface of our vasculature, that one-cell-thick lining, has several elements related to its function. There are luminal secretions, such as mucus or unstirred layers on top of the apical cells, and there are the epithelial or endothelial cells per se, which maintain things like various messenger molecule sensitivity. There are proteins bound or embedded within the epithelial or endothelial barriers, which are receptor sites that pick up messages and transmit them from outside the cell to inside the cell through signal transduction processes.

The point I am trying to emphasize is that we should not think of the epithelial barrier as being static and simply a structure, like collagen. We should think of it as a dynamic, fluid, mosaic model that is aggregating and disaggregating, changing its personality in real time, binding certain messenger molecules and transmitting them to the interior of the cell, and altering the phenotype of cells based upon environmental signals that are picked up on these membrane receptor surfaces.

Epithelial Barrier Function

What do we know about the function of the gut epithelial barrier? There is a high turnover rate. These cells are in a very caustic environment; the pH changes from very acidic to more basic. Microbes proliferate and produce their own irritant chemicals to which the epithelium has to respond. It has to maintain its integrity; if it does not, the epithelial barrier breaks down. Its intracellular junctions (called "tight junctions") can be compromised; a breakdown of the intracellular junction leads to paracellular flux of materials, sometimes called "leaky gut" syndrome, where larger molecular-weight molecules that were previously excluded now become permeable to the gut and have access to the internal compartments across the barrier. There is also transcellular flux, where substances are transported directly across the epithelial cells themselves. This does not require breakdown of the tight junctions, and is different than leaky gut syndrome. Leaky gut syndrome would be defined as a breakdown of the tight junctions and an increase in paracellular flux by osmotic diffusion across the membrane, leading to vasolateral membranous exposure to the substances that were previously excluded.

Microorganisms in the Gut

The gut environment is home to many different types of microorganisms. Certain disease organisms seem intent on getting into the stromal and/or vascular fluid compartments from the luminal compartment. One of the things that prevents that from happening is the epithelial barrier of defense. The epithelial barriers have immunological function, particularly in the gut, with production of mucus and secretory IgA antibodies that help to defend the gut mucosal barrier against potential injury due to opportunistic infection in the gut.

When we begin to look at this dynamic process, we recognize that GI microorganisms can play an important role in modifying gut mucosal barrier function. We think of microorganisms as being in three families. There are the symbiotic bacteria that participate in immunological upregulation and have a tropic effect on gut immunity. There are commensal microorganisms that find a friendly place and do not harm the host. Last are the parasitic organisms that can result in damage to the GI mucosal environment and the immunological system of the gut, and produce disease, resulting in things like compromised intracellular junctions, paracellular flux, and leaky gut. A leaky gut lets the larger molecular-weight molecules slip through the mucosal barrier and enter into portal circulation. Other parts of the body, principally the immune system, get exposed to these substances. There may be a downstream hepatobiliary effect, and a systemic effect through immune cells, which may be communicated to barriers at a distance, such as the blood-brain barrier (BBB). From that, we begin to see the emergence of clinical conditions like hepatoencephalopathy.

We should call it GI hepatoencephalopathy, because it is the gut connected to the liver connected to the brain. If there is compromised GI function, breakdown of paracellular junctions, and absorption of these potentially toxic molecules, they are taken to the liver. If the liver's system for managing those toxins is compromised or overwhelmed, there is a relay system that sets these activities into systemic circulation through either direct or indirect effects of the immune system on the BBB. This leads to potential putative

neurotransmitters, or neurotoxins being delivered, or an upregulation of the gut's immune system, which leads to an upregulation of the liver's immune system through the Kupffer cells and, ultimately, an alteration of the immune system of the brain—called the microglia—leading to potential of neuronal injury or apoptosis, or accelerated brain cell death as a consequence of exposure to these toxic molecules.

Celiac disease, for example, has long been associated with neurological disorders, including dementia,[1,2] and it is becoming more clear that gluten sensitivity, short of full-blown celiac disease, is probably a factor in many of these conditions. We could hypothesize the connection from intestinal injury to dementia as a result of gluten sensitivity in the following way. The gut mucosa breaks down, activating the immune system and hepatic Kupffer cells; these processes, unchecked (as, for instance, by the continuing ingestion of gluten), eventually cross the blood-brain barrier and begin to create alterations in the brain's immune system (the microglia) that can lead to neuronal injury or apoptosis—accelerated brain death—as a consequence of exposure to these toxic molecules.

Food for one may be the poison of another. Not everybody gets dementia from eating wheat, but those individuals who may have a unique connection between a gut messenging system and, ultimately, a brain neuronal activation through glial cell upregulation, may be at risk.

When we look at this story from a functional medicine perspective, we have to look at it as a web. We cannot look at each of the compartments in isolation. We cannot just ask what the gastroenterologist, hepatologist, immunologist, or neurologist would say. It is part of a system of understanding how these agents are connected through these mechanisms. It begins with alterations in function through immunological and defensive barrier changes, leading to the greater absorption of some of the potential immunological or toxic-activating molecules.

Diarrhea

One of the clinical manifestations of microbial dysfunction in the gut is diarrhea. Diarrhea illustrates how epithelial barrier dysfunction leads to disease pathology. Diarrhea can occur for many reasons. Diarrhea from inflammation relates to cell death and ultimately leads to blood in the stool. Non-inflammatory diarrhea can be due to secretory and osmotic effects. Secretory diarrhea generally occurs when the small intestine and, to a lesser extent, the large intestine, secrete large amounts of electrolytes and water in excess of their resorptive capacity. This is generally a consequence of what is called "dilution as the solution to pollution." If there are toxic bacteria present, such as *Shigella*, that are producing "funny" metabolites, the body has the ability to try and dilute the concentration by pulling water from the cells into the GI contents, which results in diarrhea. Unfortunately, electrolytes come with the water and a serious case of a *Shigella* toxin can eventually lead to electrolyte imbalances and dehydration. In developing countries in the world, this can lead to infant death. Even in a healthy person, a severe case can be very compromising. Those of us who have experienced traveler's diarrhea know how uncomfortable that is. Secretory diarrhea is caused by bacterial toxins and enterogenic viruses.

Osmotic diarrhea is very similar and occurs when solutes that are water soluble and unabsorbable remain in the bowel and retain water, such as lactulose. It is often used to treat hepatic encephalopathy. A non-absorbable sugar is given, which produces a hyper-osmolar condition in the gut and it pulls a lot of water from the cells and creates diarrhea. It overloads their absorption capacity. Diarrhea can be produced in almost anyone if he or she drinks enough salt or eats enough high-solute-containing materials that are not easily absorbed. It will cause osmolar shock that causes dilution that results in diarrhea.

H0157 E. Coli

The toxic forms of diarrhea related to the release of various toxins from certain parasitic bacteria include the serious cases of enterotoxic E. coli that produced the "hamburger crisis" from the fast-food chains some years ago—the H0157 E. coli. This is a very serious toxin that may lead to a breakdown of gut mucosal function. It stresses the liver and ultimately has a toxic effect on the kidneys. The cause of death was often renal failure in the children that had a fatal outcome from exposure to this bacterium. That is the outside edge of toxicity.

Well before that, however, there are many bacteria that produce less serious conditions that result in more chronic problems—things like the *Clostridium perfringens* enterotoxin, which causes increases in gut permeability and is physically associated with the production of a variety of inflammatory proteins from the gut mucosa. *Clostridium difficile* is another bacterium, an anaerobe that causes antibiotic-associated diarrhea and colitis. Many people who are on long-term antibiotic therapy end up getting an overpopulation of this parasitic organism, which is associated with many toxic effects leading to GI mucosal breakdown, absorption of other molecular-weight molecules from the gut, and hepatic- and immune-related stress from a functional medicine perspective.

In infants, these conditions can also be caused by viral infections, such as rotaviruses, which cause severe secretory diarrhea. The virus infects columnar epithelial cells and inhibits the absorptive capacity of these cells, causing a net secretion of water and salts, giving rise to watery diarrhea. Since that we are always exposed to these potential pathogens out there in the world in which we live, how do we maintain a healthy gut? The gut mucosal lymphoid tissue helps to protect us.

Someone once asked me why more than 50 percent of the immune system of the body is clustered around the intestinal tract. I never received a direct pipeline of divination on understanding that, but the logic most people use teleologically is that the gut mucosa is so rich in immune function because, over the course of living, we will be exposed to nearly 20 tons of foreign molecules in what we eat, which have to be converted into friendly molecules by a process of adjustment and by immune tagging so that they look like friends. The immune system defends us against foreign molecules and foreign "critters." The second largest organ (in mass) in the body is the GI enteric bacteria; something like 2 kg of bacteria live in the human GI tract. These organisms produce the results of their own metabolism and waste products and exhibit their own personalities. Our gut mucosal immune system has a responsibility for managing all of that, and it is quite a task. That probably explains why so much of the immune system is clustered around the gut through the gut-associated lymphoid tissue (GALT) and the mucosa-associated lymphoid tissue (MALT). These are present to help protect against injury to gut mucosal barrier function.

Barrier Function and Allergens

When we think about this barrier function, we also have to recognize that not only microorganisms, but molecules can induce injury to the mucosa. Some of these would be called allergens, which are known to affect barrier function. The immune system is normally in a luminal compartment (a fluid compartment opposite the lumen in nearly all cases for epithelial tissues). Environmental allergens contact the organism through its luminal compartments; for instance, nasal airways or bronchi in GI mucosal lumens. Allergens will not cause an inflammatory response (the source of their bad reputation) unless they gain access to the interstitial compartment on the other side of the barrier. There has to be some type of breakdown of the mucosal epithelium of the nasal airway, bronchi, or the GI mucosa, for a significant allergy response to result. We think of exposure to something as triggering an allergy, but it is exposure

leading to mucosal breakdown that leads to the effects on the immune system.

In instances of chronic allergic rhinitis, nasal mucosa has exhibited not only desquamation of the epithelium, but also increased permeability of epithelial junctions. Dust-mite allergens have been found to possess several proteolytic enzymes capable of causing progressive breakdown in the mucosal barriers. They have a stealth system to break down our defense, allowing entry of antigens into the immune system. These proteases are both cysteine- and serine-specific and they lead to well-known cleavage sites in the mucosa and open the portals of entry to gaining access to the immune system.

The Immune System and Inflammation
The immune system, once activated, may lead to inflammation. When one thinks about the immune system from a compartmental or barrier point of view, it is striking that it is often an endothelial or an epithelial barrier away from the action source itself. Downstream, ultimately, the inflammation occurs from the upstream breakdown of the mucosal barrier. Microorganisms normally first enter the body by colonizing luminal compartments, simply because these compartments have the most contact with the environment. If there is a dysfunctional relationship between the bacteria on the mucosal surface, it "engages the enemy," and ultimately can lead to the breakdown of the mucosal surface, exposing the immune system to the debris or secondary metabolites that activate the immune system. Although the changes may be seen locally with rubor, calor, or dolor, the redness, heat, and pain of inflammation, they can have systemic effects because the immune system is in a state of alarm and these processes are not isolated in one tissue. They can travel through the blood stream by the activation of things like tumor necrosis factor alpha (TNF- α), interferon gamma (IFN- γ;), interleukin-1 (IL-1), or interleukin-2 (IL-2), the proinflammatory cytokines, which can lead to an activation of the immune system and potential systemic effects.

It is important to recognize that breakdown in barrier function and activation of the immune system can be associated with a state of chronic inflammation, which produces effects on all sorts of different tissues. With few exceptions, the expression of a barrier function alteration is known to be associated with chronic inflammatory conditions. You might ask if inflammation causes a barrier function breakdown, or does a barrier function breakdown cause inflammation? The answer is, both. It is a cycle. One can approach it from either perspective. An inflammatory process can trigger a breakdown or a breakdown can trigger inflammation due to immune upregulation.

Barrier Function and Coronary Artery Disease, Inflammatory Bowel Disease, and Colon Cancer
Diseases previously not considered as being associated with breakdown of barrier function are now being seen as possibly having an early etiological connection to this breakdown. In coronary artery disease (CAD), there is arterial endothelial cell dysfunction and loss of barrier function on the endothelium, initiating aspects of the pathophysiology that leads to atherogenesis. We think of inflammatory bowel disease (IBD), such as Crohn's disease. We also think about relative risk of certain types of colon cancer associated with gut mucosal barrier dysfunction and inflammation that leads to alteration in gene expression patterns, oncogene mutagenesis, and ultimately, cancer. A wide variety of different conditions may result from breakdown of barrier function across different diagnostic profiles and different medical specialties.[3]

There is no organ left behind.

"The function of the gut mucosa is dependent on its cellular constituents, as well as on its assembly into a cohesive unit. The developing gut faces unique challenges as one of the longest and largest organs in the body and also because it is constantly interfacing with external factors through the diet."[4]

As I mentioned, we will eat nearly 20 tons of foreign molecules over the course of our lifetime. Our gut mucosa has to differentiate the friend from foe. It has to extract the nutrients and reject all the toxins over the course of living. The location of the GI mucosa deep within the body has, until recently, hampered investigation, but now the patterning of the gut along its longitudinal and radial axes is one of the most fascinating issues that pertain to the development, function, and homeostasis of the GI organ. Gastroenterology is undergoing a tremendous revolution in thinking because it is now being seen that the GI system is a messenger system to the rest of the body through not only the barrier function, but through the gut immune system and all the various tropic effects and mediators that are produced by the gut, even things that trigger functions in the brain leading to satiety, or things that trigger functions to other members of the endocrine system that cause secretion downstream. The gut may be a very important translator of external stimuli into systemic functional changes.

This was beautifully described in a series of articles that appeared in *Science* magazine titled, "The Inner Tube of Life, that describe gut function very well. These articles appeared in the March 25, 2005 issue.[4,5,6] I think you will find these articles quite informative, because they paint a picture of the gut as a dynamic functional organ that is more than just a tube; it is a very important part of the signaling system and the immune regulation of the body that has effects on distant sites (or, for other medical specialties, so to speak).

What about self-renewal of the gut mucosa? The intestinal epithelium represents an exquisite model for the study of stem cell biology because the gut mucosa constantly has to regenerate itself. It is likely the simplest mammalian study model for tissue self-renewal, yet it features multi-potent stem cells, transit-amplifying compartments, and several binary lineage decisions that require cells to create daughter cells that are of the same integrity as the parent cells. The function of the mammalian intestinal epithelium poses formidable challenges by being able to maintain integrity after exposure to toxins in the environment, either the skin as epithelium, or the gut mucosa being exposed to its contents.

Anatomy of the Small Intestinal Epithelium
If we think about structure and function as being tied together, the anatomy of the small intestinal epithelium demonstrates the tremendous evolutionary adaptation through natural selection to, functionally, be able to maintain the balance between being a barrier protective function and being a dynamic organ. The microvilli with their cells embedded, the crypt-villus junction, allows the cells to have personalities of both defense and transport. The goblet cells, the entero-endocrine cells, and the absorptive epithelial cells, which are all derived out of stem cells in the gut mucosa, are redifferentiated upon the gut mucosal turnover, probably every 7 to 10 days. There is a constant shedding and reformation of the gut mucosa, just as there is on our skin, but perhaps more dynamically in the gut mucosa.

Malnutrition and Stress and Rapid Tissue Turnover
In the case of malnutrition or high stress, these rapid turnover tissues (that have high tissue specificity and embryological development), may also be most rapidly affected by temporal undernutrition, malnutrition, or stress. That is often what happens. We often notice that the first signs in people under stress or who are not eating right often happen in the mouth—canker sores, changes in tongue texture, chapped lips, or

chylosis at the corner of the mouth. The rapid turnover tissues start to be reflective of the stress in life, or undernutrition. In a nutritional assessment, we often ask the person to stick his or her tongue out to see if they have geographic tongue, hairy tongue, dark tongue, or poor tongue color. We look at their lips and gums for gingivitis. We look at the mucosa in the oral cavity. All of these signs are indicative of what is going on. This is the lining of the surface. We can't look at the pulmonary epithelium or the GI mucosal epithelium as easily as we can look in the mouth, so we often use that as our indirect, or surrogate assessment tool for evaluating barrier function.

B Vitamins

Certain vitamins play a big role in helping to prevent injury to the mucosa in the tongue and the epithelium in the mouth. B vitamins are very important in the energy-processing systems of the body. Recall what I said in the introduction. When our energy processing systems, our mitochondrial oxidative phosphorylation, and our Krebs cycle activities are compromised, barrier function rapid turnover cells cannot get the proper energy necessary for regeneration. This is the underpinning of what leads to bleeding gums in scurvy (vitamin C deficiency), or the various things we see with thiamine deficiency, with beri beri in the oral cavity. When we discuss how molecular metabolic function connects to whole-organism observations, one of the signs and symptoms we see is related to breakdown in epithelial function.

What about host-bacterial mutualism in the human intestine? Starting with the first moments of life after delivery, the inoculation of our GI tract with bacteria is ongoing throughout life. The distal human intestine represents an anaerobic bioreactor and it is producing secondary metabolites from the fecal bacteria that live in the southern hemisphere portion of our GI tract, principally in the colon, but they can find their way up into the rest of the small intestine, even as far up as the esophagus and into the oral cavity.[6] In people who have very deranged GI mucosal function or immune function, such as individuals on immunosuppressive drugs or those who have been taking very strong chemotherapy, we will often find disturbed bacterial dysregulation, which leads to proliferation into what is called small bowel proliferation, even into the esophagus.

The bacteria do not necessarily have one place in which to stay. If there is a change in the GI pH, a change in the peristaltic action, a change in electrolytes, and a change in immune function within the gut, these bacteria can travel up through various junctions and be seen throughout the whole of the GI tract. Now, there is a risk of bacterial overgrowth, breakdown of barrier function, and what we call leaky gut that can be in the small intestine. The distal human intestine, however, is where most of this microbiological activity occurs. It is anerobic in nature. These organisms are fermenting various substrates. We call them bioreactors. They are producing their own secondary metabolites, and they have an enormous effect on the immune activity of the gut. If there is a lot of gram-negative bacterial overgrowth and death, things like lipopolysaccharides are released. These lipopolysaccharides are very powerful immune-activating agents that, in severe cases, can produce things like septic shock, activation of immune system nitric oxide (NO) output with vasorelaxation, low blood pressure, and hypotensive death. That is the extreme case. In the milder cases of chronic imbalances, there are symptoms that are more diffuse and hard to understand-"feeling crummy," as Dr. Robert Sapolsky has described it.

There are many organisms in the gut that play important roles in helping to defend against parasitic organisms. There is now evidence that even those organisms that we might have thought were parasitic may be mutually beneficial at low levels, such as H. pylori. Due in part to the work of Barry Marshall and

his colleagues, H. pylori has been tagged with the reputation of being a toxic organism leading to peptic ulcer disease. But there is now strong evidence to indicate that some level of H. pylori may be considered desirable as a commensal, or perhaps even symbiotic organism, because it helps to defend against esophageal cancer, and esophageal inflammatory injury and breakdown. There is a wonderful review paper that appeared in the February 2005 issue of Scientific American, titled An Endangered Species in the Stomach.[7] In this article, the author points out that colonization of H. pylori may increase the risk of stomach disease, but it protects against esophageal disorders. There is some kind of balance between the two that is very important. If H. pylori is completely eradicated, the risk of peptic ulcer disease and stomach cancer might be lowered, but there may be increased the risk of Barretts esophagus, adenocarcinoma of the esophagus, and acid reflux disease, which appears to be more prevalent in the absence of H. pylori rather than its presence. I am suggesting that we should be mindful not to tag a bacterium too quickly as always being bad. It is balance and looking at the personality in concert with other bacteria. Eradicating one type of bacterium in the gut may not always produce the most favorable outcome.

How is proper function of healthy flora in the gut established? One clinical way of doing so is with the use of pre- and probiotics. This is an important part of functional medicine therapy for GI-related disorders. There is an interesting review that appeared in the *Journal of Nutrition*describing the important role of probiotics in modifying both GI and systemic disease risk[8]The authors discuss probiotics, which are the live bacterial cultures we consume that are documented to survive through the GI mucosal digestive process, and ultimately can have anti-inflammatory or anti-diarrheal, and anti-allergic effects in infants, children, and adults, and help to balance thymus dependent-1 (Th1) and thymus dependent-2 (Th2) immunological function.

Some of the greatest, simple therapeutics in GI medicine are the pro- and prebiotics. Prebiotics are the selective foods to feed the friendly gut bacteria, such as the *lactobacillus acidophilus* or the bifidobacteria. They are things like arabinogalactans, orfructans, or fructooligosaccharides. These are specific substrates upon which the friendly bacteria can ferment and proliferate, producing butyrate as a secondary byproduct in the colon. Butyrate enhances the defense of the GI immune system. Its production *in situ* is an important part of immune defense in the gut and can be improved through the consumption of pre- and probiotics, helping to maintain proper gut mucosal integrity and metabolism. This was discussed in a paper that appeared in *Carcinogenesis.*[9]

The 4R Program

Pre- and probiotics are important therapeutic tools and become part of what in functional medicine is called the 4R Program. Some of you know that the four Rs stand for remove, replace, reinoculate (where the pre- and probiotics occur), and repair. Repair is the use of things like pantothenic acid, L-arginine, L-glutamine, and zinc in a non-irritating form to improve mucosal integrity.

Let us now move to the interview with our Clinician/Researcher of the Month.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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JB: It's time for our Clinician/Researcher of the month. This month, we are fortunate to have a gastroenterologist who represents both of those categories—Dr. Dr. Kenneth Fine. Dr. Fine pursued his medical education at the University of Missouri, Kansas City, School of Medicine, and his post-graduate training in gastroenterology and internal medicine at Baylor University. He was later on the faculty at Baylor and was actively involved in functional gastroenterological research from both the clinical and experimental sides. He is now the medical director and director of operations for EnteroLab, a reference laboratory in the area of GI assessment that we will be talking about. Dr. Fine brings a rich background of experience in the area I would call the "sweet spot" in functional medicine—the role the gut has in modifying or modulating function systemically, and the interrelationship between GI function and liver function and how that can influence other inflammatory functions throughout the body. It is a great privilege to have you with us, Dr. Fine and we welcome you to FMU.

I would like to ask what led you to study diarrheal disorders and moving from there into so many areas relating to functional gastroenterology?

KF: First of all, I would like to thank you for having me on FMU today. It's a great honor to tell you stories about my past research and where I think it's going. My original interest started early in medical school, when I became intrigued with nutrition. Obviously, the intestine is the conduit for all of the nutrients in the body, for the most part. It was my desire to be at the best institution and work with the best researcher that I was aware of at the time—Dr. John Fordtran. That led me to Baylor University Medical Center to do my medicine residency, and I did a three-year fellowship with Dr. Fordtran. He has been a pioneer and the world's expert in both diarrheal diseases and intestinal physiology for decades, and he is still active there. It was my association at that institution, which is sometimes called a "quaternary referral center," that led to my present focus. When the tertiary referral centers can't come up with diagnoses for chronic diarrheal disorders and very complicated inflammatory disorders of the bowel, they would be referred to Baylor from all over the world. I was fortunate enough to come under Dr. Fordtran's mentoring to the point where I eventually had my own research program in the microscopic form of colitis, as well as in celiac disease and gluten sensitivity. While I worked with Dr. Fordtran, my research was generally morein the area of diarrheal disease. I was the director of the specialized laboratory for functional and diagnostic testing. We called it the GI physiology laboratory. My experience at Baylor and working with a great researcher, Dr. Fordtran, led me to all of my present positions today.

JB: That's a tremendous background. I'm sure you have everyone's attention now because when an expert speaks, people listen. Let's go from there into an area you have published highly on, that of chronic diarrhea and its various causes and diagnoses. Perhaps you would give us a summary of how one differentiates the causes of acute versus chronic diarrhea.

Differentiating Acute from Chronic Diarrhea
KF: Differentiating acute diarrhea from chronic diarrhea is very important because most of the causes of acute diarrhea are usually infectious contact—short-lived exposure to a medication, or a supplement that might be new. Once diarrhea progresses beyond four to six weeks, we usually differentiate it as being chronic. Then, there are some very simple things that should be done. They are usually diagnostic tests to differentiate the causes and possibly the different routes of diagnostic evaluation to take. In my field, we always say, "the proof is in the pudding." Therefore, fecal analysis is of paramount importance in the

assessment of not only diarrheal disease, but probably all GI disease, whether there are inflammatory cells or derivatives of inflammatory cells, such as lactoferrin, which is the stool test we have pioneered, looking at causes of inflammation. We can use a very simple analysis of fecal sodium and potassium to determine if osmotic diarrhea is present. That is always caused by ingestion of some osmotically active agent that dilutes the sodium and potassium concentrations to a point where it's mainly the presence of some other osmotic factor. Magnesium is one that we've published on. We found that 4 percent of people referred to our quaternary referral center were either having chronic diarrhea from magnesium supplements or antacids or, every now and then, it will even be what we call "surreptitious laxative abuse,"where a patient is taking laxatives. It is kind of a psychiatric disorder.

Fecal Fat Analysis

There is also fecal fat analysis. If someone is experiencing malabsorption, that puts it into a totally different category of disease, separate from others in which a different approach would be taken. That's how we settled into the area of fecal analysis, which is the best service we can give to clinical practitioners, referral laboratories, and the public—that there is so much to be learned from some simple analyses. Of course, we have since found how frequent food sensitivity, particularly gluten sensitivity, can be, even in something like chronic diarrhea.

JB: In at least a couple of your publications, one in the journal Gastroenterology in 1999,10 and the other in Gastrointestinal Endoscopy in 2000,11 you talk about how one might look at the major etiological agents associated with chronic diarrhea. From your clinical experience, if you were to evaluate those, how would they rank as 1, 2, and 3 in terms of precipitating triggers for chronic diarrhea? You mentioned magnesium being in the 4 percent range. How would you rate those precipitating causes?

Causes of Chronic Diarrhea

KF: It depends most on the clinical setting. The more refractory and/or the more difficult in diagnosing a problem, the more the list changes. We have found that microscopic colitis accounts for as much as 50 percent of chronic diarrhea at the tertiary referral stage, although now, it's better known and biopsies have become a standard part of colonoscopic evaluation. Before we knew about that, the diagnosis would be missed because the mucosa looked normal. It comes down to what setting you're in. The main causes of chronic diarrhea are inflammatory bowel disease (IBD), ingestion of some agent, or food sensitivity, such as we talked about. Our understanding of the magnitude of the problem is growing, with 50 percent of people with irritable bowel syndrome (IBS) being found to be gluten sensitive, if you actually look inside the intestine, either with jejunal aspiration or with our fecal testing. In terms of functional causes, for the most part, it comes down to food and flora. It's now well known that almost all chronic inflammatory disorders of the gut are directed at either the food or the flora in the gut. With many animal models of chronic IBD, simply introducing a greater number of bacteroiodes species, rather than lactobacillus species, or a chemical insult, will lead to attack of the normal flora that now becomes immunogenic, with loss of immune tolerance. Suddenly, you have colitis rather than no reaction to all those bacteria.

Non-Steroidal Antiinflammatory Drugs (NSAIDs) and GI Disorders

I want to mention the widespread use of NSAIDs, which obviously impair the mucosal barrier, the permeability barrier of the gut. Those drugs are a pretty common cause of GI problems, whether it be ulcers at the top or inflammation at the bottom.

JB: I want to follow up on one of the comments you made. Is there any evidence that certain types of IBS

are precursors of IBD and/or microscopic colitis, or are these two separate disorders that don't have an interrelationship?

IBD versus IBS

KF: They sound more similar when you use the acronyms than they probably are. IBD, inflammatory bowel disease, is typically Crohn's disease, ulcerative colitis, and now, microscopic colitis. Those are inflammatory disorders directed at flora that has changed in such a way that there's not enough protective "good bacteria" to keep the genes that are probably hypersensitive to gut stimulation from reacting. It should be mentioned that the diagnostic test for Crohn's disease has now been found to be a serum test against dietary yeast, Saccharomyces cerevisiae. That, in itself, may play a large role in causing these inflammatory disorders.

IBS, irritable bowel syndrome, is a separate disorder that, to some extent, has a different epidemiology and is more of what we call functional bowel disease, but what that's really boiling down to mean is that to a large extent, the neurologic function is abnormal. Either the motility is slow and therefore causes more bloating symptoms, allowing bacterial overgrowth to occur as a secondary phenomenon, or there's also hypersensitivity of the neuroafferent stimuli so that they respond and sense greater pain at smaller stimuli, such as a smaller pressure and size of distension of the intestine.

I would look at those separately. I would say there is a common denominator, because in both disorders, food sensitivity plays a role, and it's always been known that people with IBD have a pretty high (more than double, almost triple), frequency of serum antibodies to gliadin and, to some extent, the milk proteins, than normal people do. It's always been either cast off as a false negative, or maybe something secondary to the abnormal permeability. When you think about the function of mucosal protection and permeability, attention should definitely be paid to exposure to food antigens and bacterial antigens leading to the inflammatory response. That's how I would boil those down.

JB: That's very helpful. Let's move from there into the other topic you alluded to—assessment. You have been actively involved in looking at and developing different assessment tools. In one of your articles in the American Journal of Gastroenterology in 1998, you mentioned the neutrophil protein, lactoferrin for assessing inflammatory causes of chronic diarrhea.12 You also mentioned other stool tests. How would clinicians approach this diagnostically in working up the patient to do an evaluation?

GI Diagnostic Tests

KD: I was hired as the director of the GI Physiology Laboratory at Baylor University Medical Center to improve the service and the methodology. I saw most of these tests as being of yesteryear. To an extent, some of the tests in GI analysis are still decades old—intestinal biopsies for celiac sprue or 72-hour fecal fat studies. These are things that came out of the 1950s for biopsies and the 1940s for 72-hour fecal fat, and it's interesting as a historic note, that that test was originally a test of intestinal function in celiac patients. It was developed by the biochemists who worked with William Dickey, the pediatrician who discovered the link between gluten and celiac disease. It was my goal to see what could be done to make diagnostic testing easier on the patient, easier on the clinician, and easier on the laboratory. If you've ever seen a laboratory filled with buckets of stool, you'd appreciate the fact that anything that could be done to reduce the volume and numbers of 72-hour collections is favorable to everybody.

We applied an existing test for inflammation (fecal white cells were the standard for inflammation).

These tests have been done less frequently than in the past. Laboratory technicians, because they are operator-dependent, became less and less skilled. In addition, the test itself has its own variability because of trying to find white cells floating in the fecal water. We applied a test developed by a company, primarily to detect acute diarrhea, and tried to differentiate acute bacterial infectious causes of diarrhea from mostly viral and other causes of acute diarrhea by the presence of fecal white cells. We applied that to the chronic diarrheal states and found that, for the most part, in chronic diarrhea, if there is evidence of fecal neutrophils, which, in the case of our test is a lactoferrin, then that almost always is either Crohn's disease or ulcerative colitis. Because the test offers a semi-quantitative analysis of the severity of the inflammation—if it's 2+ or 3+ rather than 1+—then it's always one of those two disorders. Microscopic colitis is a T cell infiltrative disease with rare neutrophils. Most cases are going to be negative, but sometimes there are enough neutrophils to be positive; however, they will always be of the 1+ lower quantitative assessment of the amount of information. Then, if there's no inflammation, it pretty much rules out active colitis, either Crohn's disease, ulcerative colitis, or any cause of mucosal disruption. Microscopic colitis is different because the integrity of the mucosa remains intact. We're still looking at other potential fecal tests to hopefully be able to diagnose that without having to go to biopsy.

The next test of paramount importance is the fecal fat test. You have to get a way outside of these quaternary and possibly tertiary referral centers. You've got to get away from 72-hour collections because they're somewhat intractable; they're so dependent on collection, because the output is calculated from the measured fat concentration, multiplied by the total collection, somewhat like a 24-hour urine collection. If there are any collection misses at all, the analysis is going to be falsely negative. We were able to improve upon the old, qualitative microscopic fecal fat analysis by Sudan stain testing, and we developed a quantitative analysis that perfectly linearly correlated with 72-hour collections. This was published in the American Journal of Clinical Pathology in 2000, showing that one stool with this quantitative fat analysis could determine, with a numeric expression, whether someone had malabsorption or not, and that could be followed over treatment to see if there was improvement.13 Those are two tests that must be applied.

Magnesium and Diarrhea

What we call a fecal osmotic gap, which requires a fecal sodium and potassium, can easily differentiate osmotic diarrhea from some ingested agent. Truthfully, if it's going to be magnesium (and we've found that's the most common ingested osmotic agent in causing diarrhea), a lot of times just asking the patient if he or she is taking antacids or vitamin and/or mineral supplements. I was a magnesium researcher, not only of diarrhea, but also of magnesium absorption, so a lot of times, I'll look at supplements containing magnesium. The dosing of magnesium in most supplements is excessive, to the point where more than half of the magnesium will be absorbed. If taken more than once a day, there may be enough to cause chronic diarrhea. So, those are the three initial tests.

I also published a study showing that in the assessment of chronic diarrhea, if there is going to be an endoscopic procedure, it does not have to be a full colonoscopy. The shorter and less invasive test, not requiring sedation, is the 60 centimeter flexible sigmoidoscopy with biopsies which is adequate. If that's normal, you can essentially rule out microscopic colitis and, as long as the fecal lactoferrin is negative, you've also ruled out Crohn's, colitis, and ulcerative colitis. Those are probably the simple things. Of course, I cannot speak on the subject without mentioning the importance of the fecal antigliadin antibody to test for gluten sensitivity, which turns out in the most exclusive patient populations. Those for whom all of the other disorders tend to be diagnosed, may account for as much as 50 percent of chronic diarrhea.

JB: That's a wonderful segue. That's exactly where I hoped we were going next. I was very impressed with your paper in the American Journal of Gastroenterology in 2001, looking at celiac sprue and its association with autoimmune liver disease,14 as well as your paper in the American Journal of Gastroenterology in 2000 on the high prevalence of celiac sprue in people with certain HLA-DQ gene polymorphisms.15 You looked at things like anti-endomysial antibodies and tissue anti-transglutaminase antibodies, andcorrelating that with dietary gluten and small intestinal pathology. It seems to me that there is an emerging recognition of something that has been rejected by traditional gastroenterology for some time—that the concept of gluten immune sensitization is more prevalent than we previously thought. It sounds like that's where your work is taking us.

Celiac Sprue-Like HLA-DQ Genes

KF: The paper on celiac-like genes and the one on the small intestinal pathology in patients with microscopic colitis, really kicked the door wide open on this whole field. It was so important to me that I felt obligated to bring this researchand fruits of these diagnostic tests directly to the public. That's how I ended up in a career of public service, rather than in a traditional academic medical career.

Microscopic colitis is a chronic inflammatory disease with a T helper cell-mediated chronic inflammatory response. When we looked at the HLA genetics, we saw that 64 percent of the population had the HLA-DQ2 gene that is normally highly associated with celiac disease. Ninety to 95 percent of American celiacs have an HLA-DQ2 gene. We always tend to think of it as the celiac gene, and the product of that gene does, indeed, bind gliadin and present it to the immune system as an antigen. If you have that gene, you are binding gliadin in your gut and presenting it to your gut-associated mucosal system as an antigen. Whatever reaction you get from there is under further genetic control, environmental control, and a lot of other factors, both intraluminal to the gut, as well as possible external environmental factors.

Under the microscope, microscopic colitis looks like a total villus atrophic lesion of the small intestine. There are no villi in the colon like there are in the small intestine, but when you have celiac disease, all those villi go away (in the worst cases, there is total villous atrophy). What you are left with is a chronically inflamed, flat mucosa with an abnormal surface epithelium infiltrated with T cells, which we call inter-epithelial lymphocytes, as well as lymphocytes in the lamina propria. There is a histologic lesion that smells like celiac disease. There is a genetic propensity of the celiac genes in this disorder, and yet, if you look at serologic assessment of anti-gliadin, anti-endomysial, or tissue transglutaminase antibodies, you do not see any greater expression of those in the serum of those patients than you do in a normal population. It should be mentioned that even in a normal population, 10-12 percent of people will have antigliadin antibody in their serus. Already, we know that 10 percent of "the normal American population" is walking around with an antibody to gliadin in their blood.

There were three lines of past research that led me to my search for an antibody in the stool. The first were studies in gluten-sensitive patients who did not have villous atrophy. The first study was published in 1980, titled "Gluten-sensitive diarrhea without evidence of celiac disease."16 The researchers had eight patients with chronic diarrhea. Everything else seemed normal. They did a very detailed analysis of small intestinal pathology. Although there was no villous atrophy and no significant chronic inflammation, they did some sophisticated counting techniques and found that there were more plasma cells than not, and that the patients responded to a gluten-free diet. These patients were diagnosed in a celiac center, so they obviously had a focus on that potential.

There were subsequent studies in 1996 and 2001, one of which looked at IBS patients where they did a small intestinal aspiration and found anti-gliadin and even anti-casein, the milk protein antibody, inside the intestine, along with the DQ2 gene. Those patients also got better on a gluten-free diet. There was a third study, and I take my hat off to this group because they are still following this line of research. We are following similar lines of research where I'm doing fecal testing. In their initial study, they took intestinal biopsies and put them with gluten in vitro. They found that suddenly, the otherwise normal-appearing mucosal biopsies would start to express more of the HLA antigens, as well as produce anti-endomysial antibody in the fluid of the Petrie dish. We now know that you do not have to have villous atrophy for your intestine to react to gliadin and that you can get better on a gluten-free diet. That's what all of the studies showed. There was even a fourth study out of Finland in 2001. That was one line of research.

The other line of research was the fact that serologic tests were not finding all of the people with celiac disease, especially if they had anything less than total villous atrophy. There were a couple of studies on that. One was out of England; the other was out of the Netherlands. They found that only 31 percent of celiacs that had partial villous atrophy (not total villous atrophy), had serologic positivity of either anti-gliadin or anti-endomysial antibodies. I took that piece of information back to my microscopic colitis population. None of them had total villous atrophy, and almost all of them had minimally expressed inflammation of the small intestine. I began to think that perhaps they were like celiacs who don't get villous atrophy and don't get serologic positivity.

There was a third line of research done over a 30-year period by Dr. Anne Ferguson in England. She did an intestinal lavage procedure where they would wash out the gut contents and measure the effluent for anti-gliadin, IgA, and IgM. She always called it a "celiac-like pattern of anti-gliadin antibody." You could have more anti-gliadin antibody in your intestine than normal, much like a celiac, which is why they use the term "celiac-like," and we also used it in our research, but you did not have villous atrophy. They always thought those people were latent celiacs, meaning that at some future point, they would become celiacs.

We extended on her research, but obviously, doing an intestinal lavage on everybody to be assessed for gluten sensitivity is not practical. Why no one did it in the stool before we did, I can't say. I have to think that maybe it's because laboratories and personnel tend to be a little phobic about stool. Because my upbringing was in that field, it certainly was no issue for us. Lo and behold, we found that about 75 percent of patients with microscopic colitis, 50 percent of people with chronic diarrhea, and 100 percent of people in the control group with untreated celiac sprue, had these antibodies in their stool. In celiac disease overall, there's only about a 75 percent positivity of these antibodies in the blood. We haven't turned back from that fact because not only are there a large number of people with diseases, but about 2 1/2 times the number of people with anti-gliadin antibody in their serum can be found to have this in their intestine, which is the precursor of getting some expression, either eventually as a disease or as a serologic antibody.

JB: I want to compliment you. That is a very technically complicated story and you've done a marvelous job of condensing it down into understandable components. I hope our listeners will go back and rerun this discussion several times, because there are so many positive things buried in what you just discussed. Serology may not be the sine qua non for picking up gluten sensitivity relationships. There is a functional continuum of sensitivity, all the way from what we would consider traditional sprue, to the sprue-like

conditions. That marries itself to the whole functional medicine concept. Also, to look at the various parameters in the stool that interrelate various sensitivities in the diet to functional diarrheal disorders. You have painted a magnificent picture. I can see why you have taken your discoveries to the general public. For our listeners, more information about what Dr. Fine is talking about and the tests that he developed can be found on his website at www.enterolab.com. There is also a good discussion about the history and the diagnostic usefulness of the tests on the website.

I want to thank you, Dr. Fine. I wish we had more time. This has been extraordinarily interesting for me. We're going to add a bibliography of your papers in the reference section on the summary cards for this issue of FMU. I'm sure people will be checking in with you for further discussion. You have opened our eyes to another whole chapter on functional gastroenterology.

KF: Thank you very much. People can contact my staff or myself, or go to our website. I also have my own not-for-profit institute called the Intestinal Health Institute (www.intestinalhealth.org). We are devoted to improving intestinal and overall health and, ultimately, better health, hope, and happiness for the entire public health system. We are very supportive, not only of the clinicians, but the patients themselves. I like to help people before they become patients. If they're already ailing, we can be of service to them directly. There are lectures for physicians on our website. The research to date is also listed there. There's a long essay on the whole story, basically the transcript of a talk I have given. We answer all questions by email from any doctors or patrons that have interest. We are there to be of service in the name of healthy intestinal and overall health.

JB: Thanks for spending time with us today, and we'll be checking back with you in the future.

Immunity, Inflammation, and Allergy in the Gut

What we have learned is that the gut mucosa, as an epithelial barrier of defense, is exposed to allergens, toxins, and parasites, all of which can activate the immune system, leading to inflammation or allergy. That can create barrier function breakdown, leaky membrane through transcellular or paracellular transport, and ultimately result in systemic effects. The gut immune system has the challenge of responding to these pathogens while remaining relatively unresponsive to other food materials that lead to what is sometimes called tolerance.[17] When proper immune function in the gut starts early in life, we have tolerance to certain molecules and intolerance to other exposures. One of the reasons you do not want to expose an infant to potentially antigenic substances too early is that you may lose the tolerance effect and produce a memory in certain T cells that sets the child up to become allergic to those materials throughout much of his or her life. You do not want to give them cow's milk too early, or feed them a lot of wheat-based products too early, before the immune system of the gut is fully developed, so they can develop the proper tolerance.

Bacteria in the gut play an important role in maintaining the epithelial immune balance. Inappropriate bacteria or organisms can upset that balance and alter Th1 and Th2 activity. The use of pre- and probiotics is important for restoring proper immunological function in a compromised gut. Removing antigens, allergens, toxins, and parasitic organisms may be very important. There may be times when antibiotic therapy is necessary to sterilize the bowel so it can reinoculated with friendly bacteria to reduce the load of potential antigenic substances.

The Gut and Omega-3 Fatty Acids

Another therapeutic tool that is very important for GI health is omega-3 fatty acid supplementation. This is another in the long list of potential applications of omega-3 fatty acids. In the *Journal of Parenteral and Enteral Nutrition*, an article appeared which is very useful in understanding the connection between omega-3 fatty acids and gut mucosal integrity.[18] The authors looked at the relationship between omega-3 fatty acids and liver, gut mucosa, and tumor tissue inflammatory functions. This was an intervention trial with patients who were supplemented with therapeutic diets pre-operatively They were given supplements with fish oil containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). They were given about 3.7 grams a day of mixtures of these polyunsaturated fatty acids as fish oil. The phospholipid fractions in plasma were examined on the day of surgery. They looked at the various effects the fish oil supplements had on liver function and gut mucosal function and found that preoperative administration of omega-3 fatty acids has an impact on the EPA and DHA levels in liver, gut, and tumor cell membranes. That suggests to me that post-operative inflammatory response after major abdominal surgeries may be lowered by pre-operative administration of these fatty acids.

The omega-3 fatty acids modulate Th1 and Th2 balance toward lowering inflammation (the Th1-dominant type), into a more Th2-balanced activity. This was demonstrated in a recent study published in the *Journal of Nutrition.*[19] In a controlled series of studies in animals, fish oil increased the percentage of Th2-polarized cells because it suppressed Th1 cell frequency, lowering the proinflammatory mediators produced through Th1 activity.

Dietary Supplementation of Omega-3 Fatty Acids

Dietary supplementation of omega-3 fatty acids with folic acid, vitamin B6, and vitamin E has been shown to improve function in individuals with peripheral vascular disease, with improved walking distance, decreased pain, and lowered risk factors, such as the inflammatory markers like intercellular adhesion molecule-1 and high-sensitivity C-reactive protein, after supplementation with a combination of omega-3 fatty acids, folic acid, and vitamins B6 and E. This clinical study was published in the *Journal of Nutrition.*[20] Sixty patients were randomly allocated to two groups. One group received the EPA/DHA supplement, which was about 1 gram a day of a combination of EPA/DHA, and also B6, E, and folic acid at what we would consider normal nutritional therapeutic levels, not mega-nutritional levels.

The improvements seen in this group after intervention illustrate very clearly that enhanced intake of those nutrients was very helpful.

Because all of these things are connected in the web of functional outcome, when we improve GI mucosal integrity and function through omega-3 fatty acids, we establish better endothelial function, hepatobiliary function, membranous function of the BBB, and reduction of cardiovascular disease and cancer risks, because all of these things are interrelated through the web of life, the homeodynamic balance seen through barrier function and the dynamic activity of membranes. This is discussed in the *Journal of Medicinal Food*.[21]

I hope you now have a sense of the important role that barrier function plays in defending against toxins, and how it is seen as part of the detoxification/biotransformation cycle.

We will be exploring these topics in greater detail as we move toward the 13th International Symposium on Functional Medicine.

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