August 2009 Issue | Nathalie Delzenne, PhD Associate Professor

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Welcome to August 2009 *Functional Medicine Update*. If you have been listening the last two months, you know we've been exploring a topic that really is evolving very rapidly and has significant clinical implications. Certainly all the questions aren't yet resolved, but we are starting to see the landscape of this concept of a food that is considered "good" to now become-in the minds of some (and in their physiologies)-a "poison." The food of one is the poison for some. I'm talking about gluten and its relationship to grain-based protein products.

You might ask the question: What's really going on with gluten? Why is something that has been in our diets for some period of time (since the rise of the agricultural revolution in the golden triangle of the world-in civilization-some 40,000 years ago) now emerging, ultimately, to be a contributor to chronic-related illnesses? This is about far more than just celiac disease. As you have listened to the last two issues of *Functional Medicine Update*, you certainly have heard our extraordinary clinicians and resource experts talk about the rising tide of chronic age-related diseases that are associated with the activation of the immune system by the exposure to what would be considered a natural part of grain-based proteins, the gluten family of molecules.

Last month, in our July issue, we took another step forward in understanding that maybe there are things occurring as a consequence of genetic hybridization (or epigenomic modulation) through altered environmental situations that impact the regulation of protein synthesis within grains that are post-translationally modifying the gluten molecules to make them more epitopically reactive, to make them more immunologically seen as a foreigner. This concept of post-translational modification, or epigenetic modification, which has been a major theme for functional medicine in the last year (including two webinars that we have done on nutritional epigenomics), is truly a revolutionary concept that is emerging at the frontier of knowledge in the area of functional and nutritional medicine. I would say it is helping us to better understand not only the rising tide of certain types of chronic age-related diseases, but also how they may have heritable impacts on future generations in ways that we previously never fully understood. This concept may help us understand how things like autism are increasing in prevalence at a much faster rate than we would expect by normal, Darwinian, natural-selection-types of processes. There may be factors that tie to certain environmental alterations that have epigenetically tagged the genome in such a way as to create an outcome that we call autistic spectrum disorders.

This theme is much broader than just celiac disease. Certainly celiac disease is part of the story, but it isn't the whole story. The environment is connected to the individual through the digestive system (through the gut recognition system--the mucosal-associated lymphoid tissue and the gastrointestinal-associated lymphoid tissue, or the MALT and the GALT), and that communicates information to the immunological

recognition system of the body through the Kupffer cells of the liver to the circulating white cells, and ultimately even into the neurological system through the microglia (or the brain's immune system). This interconnectedness that I'm describing can alter the functional state of the organism to express itself as disorders of immunological alarm across many diagnostic categories, not just that of a digestive disorder with inflammatory bowel disease (Crohn's disease or celiac disease). These disorders can connect to type 1 diabetes, rheumatoid arthritis, multiple sclerosis, or maybe even pre-senile dementia. These more complicated connections are now starting to be seen through the lens of this web of physiological immune-neuroendocrine interaction. So the broad theme becomes this term that connects together multiple organs: neuro-immuno-endocrinology (depending on how you put the order of the words together). This term means something that connects the nervous system to the immune system to the endocrine system that ultimately leads to the translation of outside messages to inside alarm reactions within the body.

The Microbiota Community: Symbionts, Commensals, and Parasitic Bacteria

Part of this story involves the translation between the outside environment (let's say our food) and the inside communication system (our immune, nervous, and endocrine systems) through an intermediary. That intermediary is our gut enteric flora. I think we often neglect being mindful of the fact that in our intestinal tract we have a very vast community of microbiota, which can participate in our function at three different levels. One level is that which we call symbionts, which help us to function. Symbionts can digest things way down in this plumbing called our digestive tract and produce secondary trophic factors that are immunologically sensitizing and help balance our immune system and make our immune system more capable of properly regulating function. They can synthesize vitamins. They can transform certain things like lignans in food into various bioactive materials like equol, which then can augment endocrine function and immune function. Symbionts can have a variety of very favorable effects on modulating function of the body.

The second class of microbiota that live in our intestinal tract are called commensals. The commensals take up space and create their own personalities in our digestive tract, but they don't seem to really produce many substances that are necessarily beneficial for the host, nor do they produce substances that are detrimental to the host. They just kind of reside in the gut and take up some space and are friendly neighbors, but they don't necessarily do a lot to build new cities, so to speak. We would call these commensals.

The third family most often gets our concern. These are organisms that produce secondary byproducts from their metabolism that may be potentially harmful to the host. They may be nitrogen-based molecules or derivatives of these compounds that become toxic, both directly to the gastrointestinal mucosa (in other words, they may be in situ carcinogens that are being produced), or they may be absorbed through enteropathic circulation and ultimately influence, at a distance, function by sending out putative messages of neurotransmission, or by being molecular mimicry substances that modulate the way that our body is signaling to itself. These organisms play a role in causing our immune system and our nervous system to be on guard and ready to do battle. We call this the parasitic family of gut enteric bacteria.

The Gut Microbiota Are Constantly Dynamic

It turns out that these class distinctions that I've just made among symbionts, commensals, and parasites are somewhat arbitrary because under certain conditions, in the immune system of our gut, what was once a friendly bacterium can come to be seen as a not-so-friendly bacterium. We could have something that was a commensal , that under a different immunological distress of our gut now suddenly becomes

parasitic and releases into circulation cell wall debris from that bacterium that are called lipopolysaccharides (or LPS). In a leaky gut or a permeable gut situation, LPS can induce systemic inflammatory response and be a contributor, therefore, to overall systemic immune activation.

I think we need to be a little cautious when differentiating symbionts from commensals from parasites, and make sure we recognize that they are in constant equilibrium balance and dynamic interaction with the environment of the gastrointestinal tract. They can change their personalities to some degree, based upon the state of the environment. However, with that said, I would say that there are certain bacteria (*Clostridia* and rotaviruses and things) that are more likely to be known as gut parasites (or gut-offending bacteria, or viruses) that create dysfunction rather than create function. By doing cultures, we would be able to determine a prevalence of those particular species that are more likely to be associated with an alarm reaction of the body rather than a quieting or a balancing of the immune system. Generally we use things like stool cultures or erectile swabs to try to identify organisms that have toxic/parasitic-related functions.

The Relationship Between the Bacterial Flora and the Foods We Eat

With all of that in mind, here is the logical question I think you would ask: Is there a connection between the species and the activity of this bacterial flora that resides in our gut and the way that we respond to certain food-related information molecules? When we eat, we are not just eating calories, or bulk, or vitamins and minerals and essential fatty acids and essential amino acids. We are also eating information molecules, and those information molecules can elicit a response by binding to receptors that trigger certain kinds of ligand receptor interactions that then alters intercellular signal transduction processes, and ultimately signals, at a distance, certain information content to the body. It could be friendly information or it could be information about a foreigner onboard (or, "we need to call out the guard and do battle").

Is there a correlation between the way the information molecules eaten in the diet are received and translated into transmissible information in the body based upon the gut microbiota or gut flora? That is the question I am raising. It's a very interesting question. We could then go right back and look at something like gluten, and say, "Do different gut flora have different impacts upon the way a person would respond to gluten in their diet, or is it gluten is gluten is gluten, regardless of what is present in the digestive system or in the gut microbiota?"

That question connects the last two months of *Functional Medicine Update* on gluten and its relationship to neuro-endocrine-immune alteration and function to that of this month's issue. We are going to have the privilege of talking to two of the most remarkable researchers in the field of gut flora and the relationship it has to function. I think the connection between the June and July issues of *Functional Medicine Update* and this month is exemplified by an interesting paper that was published recently in the *British Journal of Nutrition* called "Effects of a Gluten-Free Diet on Gut Microbiota and Immune Function in Healthy Adult Human Subjects."[1] Here is where we connect the concept of gluten together with gut microflora, and how those together, then, impact immune function. The authors of this paper point out that it is well known that diet influences the composition of gut microbiota, and therefore has an impact on host health. It is kind of a new emerging understanding for us that when we are talking about the relationship of food to health, we have to interpose our discussion with the topic of the gut flora because the food response may be different in an individual depending upon the status of their gut community/ecology. This is particularly seen in patients suffering from food-related dysfunctions, where they have what they call adverse reactions to food.

In this discussion, I want to differentiate between strict food allergy and atypical reactions to specific foods because, as we know, there may be things like histamine reactions or response to phenylethylamine or other kinds of constituents within food that produce a toxic-like reaction that resembles a food allergy but is not actually a true allergy; you would not pick this up as an IgE- or an IgG-mediated response. In the last two months we have talked a lot about celiac disease as a permanent intolerance to cereal gluten proteins. The therapy of choice in patients with celiac disease and gluten intolerance is to adhere to this lifelong gluten-free diet, which becomes the standard of identity for that person.

The Effects of a Gluten-Free Diet on the Gut Microbiota

This study in the *British Journal of Nutrition* contrasts with ideas about a gluten-free diet that we have been developing over the last two months in *Functional Medicine Update*. This study, examined the effects of a gluten-free diet on the composition and immune function of the gut microbiota in healthy human subjects over one month, and the fecal microbiota was found to modify itself significantly on a gluten-free diet. When the authors of the study looked at the *Bifidobacteria*, *Clostridium*, and other types of fecal microflora, they found very interesting differences after being on the gluten-free diet (and this is in people without gluten intolerance, I might add-these are "normal" individuals). "Normal" really is in the eye of the beholder. I think that term tends to be one that we overuse in medicine. I think "people who didn't have demonstrable gluten sensitivity" would probably be a better way of saying it.

In this study, alteration in various gut microflora was quite significant when individuals were put on the gluten-free diet. The study authors looked at things like various cytokines, such as TNF alpha, interferon gamma, interleukin-10, and interleukin-8 production by blood mononuclear cells. They found there was a very significant difference in immune reaction in these healthy individuals after they were put on the gluten-free diet and their gut microflora changed. The results suggested that the gluten-free diet constitutes an environmental variable that influences gut health, even in individuals without gluten sensitivity, by modulating gut microbiota and the influence they have (secondary effects they have) on gut-immune function and ultimately on systemic immune function.

This is a complex web of interaction. We can't just say it is only a consequence of looking at a reactive molecule (gluten) that then hits a target receptor in the gut to initiate, in genetically susceptible individuals, an immune activation that we call celiac disease. There are many different levels, or shades, of this in different individuals that have to do with the complex shifting of the microbiological community that is in our gut, how that influences or interacts with the gut-immune system of that individual, how that diet then plays a role in modulating that function, and ultimately altering or affecting immune function activity.

That leads us to the question: Can you modulate the immune system through food? That is a very interesting question that looks beyond just gluten sensitivity. Many papers have now been published that would tend to support the idea that it appears as if food can be used as a systemic immune-modulating component, both for the betterment of the immune resiliency and plasticity, and also because some foods can activate the immune system and put that person in a constant state of vigilance (their immune system in a constant state of alarm). One of the things that would certainly initiate increased vigilance (and you are going to hear more about from our wonderful researchers this month), is a high-fat/high-sugar diet, which, when consumed on a repetitive basis, is known to constantly keep the immune system of the gut in a hyper-vigilant state, and it can modify gut enteric bacteria. You have a different species-a different community-of gut flora when you eat a high-fat/high-sugar diet than you would on a diet that is lower in

saturated animal fat and lower in simple carbohydrate in the form of sugars. That, then, has influence not just regionally on gut-immune function, but systemically on overall immune vigilance.

I'm quoting from a 2009 article that characterizes the kind of theme that I'm discussing, titled "Immunomodulation by Food: A Promising Concept for Mitigating Allergic Disease?"[2] In this particular paper the author advanced the thought that if you have a person that has a problem with food sensitivities and allergies, you ought to go back and re-evaluate the whole of the diet, not just for the allergic-producing substances in that diet, but for how the diet, as a whole that they have been consuming, may contribute to alteration of gut enteric flora and ultimately to activation of the immune system in the absence of a true food allergy. There may be diets that would be considered inflammatory-prone diets that initiate gut inflammatory processes that create systemic immune activation, rather than just regional conditions that we see as Crohn's disease, or colitis, or inflammatory bowel disease.

I think these are very interesting topics that are starting to develop that have deep clinical implications because we often don't think of the diet at large as being a variable that could be very important clinically for modifying a patient's overall neuro-endocrine-immune function in the absence of allergic response. Clinically we do things like make sure we screen various foods for their allergic potential in that individual by IgE or IgG testing.If a person comes up negative on a screen then we often make the assumption that their diet must not be a major contributor to their immune dysfunction because we didn't pick up a lot of food-related allergies. But lower than that (or below that) is the question of how their diet, notwithstanding the allergic component, may be influencing gut enteric flora and gastrointestinal-associated immune function that then has a spreading effect to the whole of the body with regard to neuro-endocrine-immune function and/or dysfunction.

I think it raises the bar higher. It spreads the clinical importance for doing the appropriate evaluation, and there are certain diets that even in the absence of allergens can induce immunological dysregulation of activation. As I've said (and as you will hear more about today), diets that are very high in saturated fat and sugars have a greater possibility of doing this. What about diets that contain all sorts of funny molecules, like trans fatty acids from partial hydrogenation? Or what about diets that contain a rich array of chemicals like preservatives, emulsifiers, texturants, or synthetic antioxidants? Are we sure this complex chemical soup that we have been feeding individuals doesn't have some immunological effect upon gut flora and ultimately gut-immune function that is unique to that individual? That a "clean" diet (a diet that is minimally processed, organic, and rich in things that are close to the soil) doesn't have a salutary effect on immune function, regardless of whether there is an allergy or a non-allergy component that is part of the process?

I think these are really important emerging parts of the story, and certainly this immunomodulation-by-food concept that appeared in *Analytical Chemistry and Bioanalytical Chemistry* is a very interesting part. The author states, "The importance of a properly functioning and well-balanced immune system for maintaining health has become strikingly evident. Roughly, since World War II, there has been an apparent decrease in the prevalence of 'traditional' infectious diseases, with a concomitant increase in immune-related disorders." Certainly part of this is the increasing presence of allergies. A relationship with changes in lifestyle factors such as the increasing use of various types of antibiotics seems a part of changing this whole gut flora-immune relationship, but also (as the author points out), diet can affect the functioning of immune parameters, and maybe we ought to apply this concept of diet and its relationship to immune function at the gut level in attempts to prevent or mitigate allergic reactions, versus the

development of targeted diets and targeted food products that really are immune modulating using the gut receptor system as a way of signaling friendly balanced immune function to the rest of the body. The article goes on to talk about the fact that there may be both pro- and prebiotics that influence this in a favorable way, and that these types of materials then may help to balance the Th1/Th2 types of immunological balance that we have spoken so much about in previous issues of *Functional Medicine Update*, and ultimately lead to immunoregulation or immunomodulation

We are really talking about interposing the gut microbiome between diet and immune function in our clinical thought process. The microbiome is emerging to be a very important part of expressing its personality in terms of how the immune function operates. There was a very nice paper recently published in the *Journal of Gastroenterology*. It's a review paper titled "Targeting the Gut Microbiome with Probiotics and Prebiotics," and the subtitle is "Gastroenterology enters the Metagenomics era," which I think this is a very interesting concept.[3] What the authors of this article talk about is that the "metagenomics" (meaning not the genome of the host, but the genome of species that are interrelated and living with the host-- the gut microbiome) can influence the function of the individual. It is this kind of metagenomic connection to the human microbiome that expands our knowledge of the composition of microbial communities and how they influence human function.

This article really does a nice job of helping to increase understanding of how microbial variation and differences in the genes of bugs in our gut can then alter the information that is translated to our gut-associated immune system that then remodels (or tailors) our human-associated gut-immune function. Physiological features such as the development of innate and adaptive immunity, relative susceptibilities to infection, immune tolerance, bioavailability of nutrients, and (obviously) also intestinal barrier function or gut mucosal integrity are all modified by changing the composition of these microbial communities, or the gut microbiome. As the field of gastroenterology is evolving, it is starting to recognize that GI system function is profoundly affected by the gastrointestinal microbiota. Now that that is understood, ways to rationally modify the actual gut environment to then improve functional status of the immune system is becoming "a new frontier" of gastroenterology.

The article authors talk about first kind of sterilizing the bowel of unfriendly organisms using antibiotics (this sounds a little bit like our 4R Program of Remove, Replace, Reinoculate, Repair). The first step is remove the unwanted critters that are actually inducing immunological dysfunction, and then add back (as we suggest in our 4R Program with the replace, reinoculate, and repair phases) the appropriate environmental agents, which would be done by giving prebiotics and probiotics and nutrients such as pantothenic acids, glutamine, and arginine that help to stabilize gut mucosal integrity. The prebiotic/probiotic supplementation can enhance a proliferation of beneficial microbes that then stabilize immune system function. The human microbiome then can be manipulated by smart strategies to prevent and treat not only localized gastrointestinal disorders, such as acute gastroenteritis, antibiotic-associated diarrhea, colitis, inflammatory bowel disease, irritable bowel syndrome, and necrotizing enterocolitis, but also a variety of other systemic disorders, including even far-reaching disorders we have talked about in previous issues of *Functional Medicine Update*, such as cardiovascular disease risk as it pertains to endothelial dysfunction that is associated with immunological dysregulation that may have started in the gut with a permeable mucosa. There is a web of interacting variables that we would call a functional medicine connection: the connection of gut-immune function to endothelial function in the vasculature in cardiovascular disease. I think this *Gastroenterology* article/review paper from 2009 really does a nice job of laying out the concept (the landscape) of how diet can specifically be tailored to deliver functional

characteristics that improve the gut microbiota, which then ultimately modulates immune function, which then has systemic implications. These implications, clinically, are quite far reaching. Let me give you some thoughts about this in preparation for the discussion we are going to have with our researchers/clinicians on this topic.

What about using probiotics to improve outcomes after gastric bariatric surgery (the Roux-en-Y gastric bypass surgery)? A very nice paper was published in the *Journal of Gastrointestinal Surgery* in 2009 looking at improved outcome in patients at six months who had been supplemented with probiotics after completing Roux-en-Y gastric bypass surgery for morbid obesity.[4] It's a very interesting study showing that probiotic administration not only reduced bacterial overgrowth of the resident intestine, but it also improved vitamin B12 bioavailability, which is one of the concerns that you often have post-surgery because by reducing the intestinal mucosal surface area for absorption, often these patients end up with nutrient malabsorption syndrome. So it improved vitamin B12 bioavailability and weight loss and reduced inflammation post-surgery, providing evidence that the GI microbiota is very, very important for maintaining proper immune function, but also in helping to stimulate greater weight loss when the bacterial microbiota have the right speciation and number. According to these findings, the success after Roux-en-Y surgery is in part related to re-establishing proper gut microflora because GI microbiota-if they are of the right families-can help influence appropriate weight loss, post-surgical intervention.

The concept that somehow friendly bacteria can influence weight loss may apply beyond that of just the bariatric surgery patient. Could it be that our obesity epidemic is in part related to a diet which is altering our gut microflora in such a way as to reduce its favorable effect on signaling that is associated with proper insulin and hormone balance and ultimately fat metabolism, or fat deposition in adipocytes? In other words, can altered gut flora cause obesity? That's an interesting question, and one that you are going to hear more about from the principal investigators belonging to one of the first groups to discover this relationship

Is there a connection that is emerging to between altered gut flora and systemic toxicity or inflammation? The answer is yes. Papers are now being published virtually every month on this rapidly advancing field of understanding I am going to cite one that appeared recently in *Cancer Research* titled "Intestinal Mucosal Inflammation Leads to Systemic Genotoxicity in Mice."[5]

In this particular paper, the authors were looking to ask whether a condition with altered gut mucosal integrity with inflammation and its relationship to altered gut flora could have an influence systemically on altered oxidative stress and free radical injury ultimately measured by changes in patency of DNA in circulating white cells in the animal. In other words, is genomic instability induced by a localized gut inflammatory response and altered gut flora? In 2008 we had an extraordinary discussion with Dr. Michael Fenech, a principal research investigator at the CSIRO in Adelaide, Australia. He told us that one of the best biomarkers for the effect that diet has on oxidative-related dysfunction and injury at the cellular level is to look at genomic instability using the micronucleus assay, which looks for damage to DNA and the genome as a consequence of oxidative stress. This is very reproducible technology that could be used for assessing relative injury to the "book of life," the most precious thing that we own and want to protect within not only our germ cells, but our somatic cells.

This study from *Cancer Research* in 2009 that I am describing showed that regional inflammatory responses in the gut, through activation of the gut-associated immune system and altered gut flora that

contribute to that, produces a systemic oxidative load (or reactive oxygen species) that then induces systemic genotoxicity as seen by altered genomic stability (reduced genomic stability) through increased micronucleus formation. Here, again, is a very important kind of closing-the-loop concept that ties together what is going on in the gut with its immune system, to what is happening systemically and how that translates over to a precipitating trigger to inflammatory response (in this case, circulating immune cells in which the DNA in those cells are actually seen by micronucleus assay to be injured in their nucleosome integrity and their genomic stability to be adversely influenced). These topics that we have been describing within *Functional Medicine Update* for the last couple of years on epigenetics and genomic stability, environmental influences on the epigenome and on gut function and gluten sensitivity, and now on gut enteric flora-all are interconnected and may be part of our better understanding of the prevalence of various types of diseases that we are seeing that range from obesity through atherosclerosis, neurological dysfunctions and diseases, and ultimately into even chronic fatigue syndrome and fibromyalgia. These are very complex immunological disorders associated with immune disturbances.

What about pain syndrome? Certainly the gut flora also has a very interesting influence on pain, both regional pain and systemic pain. I cited a paper a few years ago that appeared in *Nature Medicine* that kind of addresses our thinking in this area; it was titled " *Lactobacillus acidolpholus* Modulates Intestinal Pain and Induces Opioid and Cannabinoid Receptors."[6]This was a very interesting study that looked at the influence that various probiotic organisms have (these are favorable symbionts) when supplemented, and how they influence the receptor activation of pain receptors in the gut, not only reducing the activation of pain receptors in individuals that may have gut pain, but also transmission of that pain through gut mechanisms (the systemic pain-related dysfunction).

I want to emphasize that this particular study I'm citing was a study done under control conditions with rodents, but it was able to demonstrate (under controlled conditions) that there is a very significant advantage to favorable symbiotic organisms modulating intestinal pain and through modulation of the opioid and cannabinoid receptor activities that have to do with pain transmission and activation. By the way, this work was done by Professor Desreumaux and his colleagues in Belgium. This month we will be actually talking to investigators that are in the same field, at the same university, in the same country. There is a lot of activity going on in Belgium and in France pertaining to the probiotic connection to immune function and inflammatory function. I think this *Nature Medicine* paper is another very important part of our advancing understanding as to how proper gut flora may influence pain reception and pain transmission (starting from the gut, but having systemic influences).

Lastly, I want to talk about this whole concept of does metabolism really change? Does whole-organism metabolism change as a consequence of the differing types of enteric microflora or microbiota that are present? There are many papers that are now being published in this area. I mentioned one about the Roux-en-Y gastric bypass surgery and the influence that probiotics have on weight loss, suggesting that there is a systemic effect from gut flora on thermogenesis and storage of calories. We are starting to see ever increasing reports of the metabolic activity of gut microbiota contributing to the pathogenesis of obesity and also hepatic steatosis, which we call nonalcoholic fatty liver disease, or we call nonalcoholic steatohepatits in the more extreme cases. In past issues of *Functional Medicine Update* we've correlated these liver conditions with metabolic syndrome and hyperinsulinemia, and in this issue, we are correlating metabolic syndrome and hyperinsulinemia with alterations in enteric microbiota. In other words, change in the microbiome. I'm now quoting from a paper that just appeared in the *American Journal ofClinical Nutrition* that showed that by changing gut enteric microbiota we can actually influence fatty acid

composition within the liver in animal studies (this is both in rodents and in pigs) and change adipose tissue deposition (in other words, cause weight loss).[7] This is an extraordinary new emerging concept--that this interposition of gut microflora (the microbiome) between our environment, our gut, and our immune system may be a modulator of function that signals distantly to the body through various types of neuro-endocrine-immune-modulating systems to alter function. I hope I've set the stage and teed you up for what I believe to be one of the most exciting interviews you'll hear. We are going to be talking with fundamental researchers that are making these discoveries every day in their laboratories.

INTERVIEW TRANSCRIPT

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Here we are once again at that section of Functional Medicine Update that is really, I think, the heart of our issue every month. This month we are very fortunate to have a double-hitter (a homerun, so to speak) because we not only have a clinician and a researcher, but we have two very, very well-respected scientific celebrities in the field. You are going to learn more about some things that are presently in the news-things that I think are at the forefront of functional and nutritional medicine.

Let me introduce our two guests today. Dr. Nathalie Delzenne is a Professor at the Université catholique de Louvain in Belgium. You are aware of her work whether you are familiar with her name or not. She has been at the forefront of research into prebiotics, probiotics, and symbiotics for some period of time and is very actively involved (with her research group) in this whole relationship between the microbiome (gut enteric bacteria) and its relationship to general metabolism. I think you are going to learn some extraordinary things from Dr. Delzenne.

Dr. Delzenne graduated in pharmacy in 1986 and obtained her PhD in 1991 from the School of Pharmacy at Université catholique de Louvain. She followed human nutrition and did studies at Université de Lausanne in Switzerland. She has been a NATO grant recipient, and she spent years in France at INSERM, where she was involved in studies on nutritional modulation of gene expression. She is a member of the European Academy of Nutritional Science and is a member of the staff at the Division of Biochemical Toxicology at the Université catholique de Louvain.

Professor Delzenne's colleague is Patrice Cani. Dr. Cani is a doctoral fellow who also graduated from the Université catholique de Louvain, and is now working as a research associate in collaboration with Dr.

Delzenne. Their productivity and creativity-innovation-in this area is really remarkable. The number of publications that have come out of their group over the last few years is truly impressive.

Professor Delzenne and Dr. Cani, welcome to Functional Medicine Update. Tell us a little bit about the concept of prebiotics, probiotics, and symbiotics, just so we can establish the context of how they relate to the metabolism of enteric flora and systemic immune function.

Belgium Has Been an Active Site for Research on Probiotics and Prebiotics
ND: Thanks very much and thank you also for the kind introduction. I think we are lucky to be in Belgium because this concept of probiotics was born in the lab where we are now, but with another person-maybe you know his name-Marcel Roberfroid. In our lab, we have been working for years on the concept of the nutritional modulation of the gut microbiota. This concept is not so new. It has been known for a long time that some bacteria could have beneficial effects on physiology in human bodies. These bacteria tend to be given orally and they are considered probiotics. They remain viable within the gastrointestinal tract and can exert beneficial effect on the host. This concept of probiotics (in the diet or given as a supplement) having beneficial effect has been known for a long time.

What has been known for a less significant period of time (since 1995, to be precise) is the concept of prebiotics. Prebiotics are compounds which are not digested in the upper part of the gastrointestinal tract. They are fermented by specific types of bacteria in the gut, and therefore, they modulate the endogenous population of the gut microbiota and exert (also) interesting effects on the physiology of the body. Both concepts are similar but different; when you have a probiotic you give a bacteria, and when you have a prebiotic you give a substrate for endogenous bacteria. The rationale is that when you do that you improve some functions of the body. For the symbiotics concept it means that you have a mix of probiotics and prebiotics given together to exert interesting functions. I should say the concept of prebiotics was born with the help of Glenn Gibson in the UK, and John Cummings, and Marcel Roberfroid here in Belgium. Maybe we are the sons and daughters of Marcel in that concept.

JB: I think you are very good daughters and sons. I have had the pleasure of knowing Professor Roberfroid for the last few years. I would say he is kind of the founding father of this field. You are coming from a very good lineage and you are keeping the spirit alive and well. Your work is stunning.

Let me take this concept to the next level. One of the things that has so intrigued the world scientific community about your work is the recognition that these enteric flora not only influence regionally gastrointestinal immune function through the gastrointestinal-associated lymphoid tissue, but also seem to have influence on systemic immune function and systemic metabolic function. I'm thinking of one of your papers that appeared in the journal Diabetes in 2007 that talks about metabolic endotoxemia, obesity, and insulin resistance, which seems like a very interesting combination of topics.8 How does toxemia result? What does the gut enteric bacteria have to do with this and how does that influence obesity and insulin resistance? These are very interesting concepts that maybe people would have never put together. Can you tell us a little bit about that?

Metabolic Endotoxemia: An Explanation of the Term and the Research
ND: I propose that I give you the first rationale of this idea that we could have modulation of systemic inflammation due to probiotics intake, and after that I will give the phone to Patrice Cani, so you have his view of these new results related to metabolic endotoxemia and the modulation of that by the gut

microbiota.

We were working for years on the fact that when you give some prebiotics you may have systemic effects. For example, you may modulate the liver metabolism, thereby decreasing lipogenesis and triglycerides. With research, we have discovered that some immune cells which were present in the liver tissue, namely the Kupffer cells, may be activated through the intake of prebiotics and it may be protective, at least in animals (because these were experimental studies). It may protect the animals against endotoxemia due to really high dose of lipopolysaccharides. So we had in hand, a few years ago, the fact that (for reasons we didn't know yet) we could modulate the systemic function (immune function) of the body, thereby improving health in animals after an acute infection.

I will give the phone now to Patrice Cani. He went further with this story, looking at not only acute endotoxemia, but more metabolic endotoxemia and how the modulation of the gut microbiota may play a role in this field.

PC: Hello.

JB: Hello, Dr. Cani. It's very nice to hear your voice and thank you for being a participant with us.

PC: Thank you. Thank you for the invitation. I will give you some information concerning metabolic endotoxemia. Several years ago, we knew that obesity was related to low-grade inflammation and type 2 diabetes, as well as insulin resistance. The mechanisms linking the development of obesity, insulin resistance, and inflammation were poorly understood. While looking in the literature for some proinflammatory compounds, we found that LPS is a very important proinflammatory molecule. In looking at the context of a high-fat diet feeding, we always found that the high-fat diet feeding induced obesity, insulin resistance, and inflammation only when the gut microbiota was present. Germ-free mice resist the high-fat-diet-induced obesity and metabolic disorders.

Following these two concepts, we measured the LPS in the plasma in mice fed high-fat diets throughout the day, and we found that plasma LPS was first detectable in the plasma, but also always remained higher in the high-fat-diet-fed mice as compared to the normal-chow fed mice. When we looked at the gut microbiota composition, we were first concerned by the fact that the Gram-negative bacteria (the one giving the LPS) were it is not modulated by the high-fat diet. The Gram-positive bacteria were decreased, and more specifically Bifidobacteria were decreased, following the high-fat-diet feeding. At this point, we were able to hypothesize that LPS was involved in the development of insulin resistance and metabolic endotoxemia.

We used LPS at low dose in mice by using osmotic minipumps to mimic the metabolic endotoxemia we observed following the high-fat-diet feeding. We observed that by giving a normal-chow diet and giving low-dose LPS, we were able to increase visceral adipose tissue and mice developed some metabolic disorders related to insulin resistance (hepatic insulin resistance and inflammation). Finally, we decided to restore the Bifidobacteria content in high-fat-diet-fed mice by using prebiotics. We found that by feeding mice prebiotics we completely restored the metabolic disorders. High-fat mice fed with prebiotics resist the development of inflammation induced by the high-fat diet. At that time, we found a nice correlation between prebiotics and blood endotoxin levels. After, we found that since LPS could be increased by the elimination of gut microbiota and that gut permeability could be one of the major points

involved in the development of higher endotoxemia in our model, we studied metabolic gut permeability following high-fat-diet feeding and found that high-fat-diet feeding, per se, increases gut permeability in mice fed the high-fat diet, and gut permeability was also increased in genetically obese mice (ob/ob mice).

JB: This work that you are describing to me is absolutely revolutionary. It really reflects what we have been talking about now for 20 years in functional medicine because you can only understand this relationship (as you've described it) if you look at physiology in an ecological perspective (look at it as a systems-wide situation). You can't understand this if you look at it in a compartmentalized, organ-specific perspective. I'm just really amazed at the innovation and the design of your experiments-how you have been able to start unraveling this very complex web of interaction. I applaud you both (or your whole group) for this.

If I can just kind of make sure that our listeners understand the significance of what you have said-because I think it's really one of those "threshold" new concepts. You related to us the fact that this observation that gnobiotic mice (or mice that have sterilized digestive tracts-they don't have bacteria when they are fed a high-fat diet) don't get this insulin resistance and metabolic syndrome, which normal mice with gut enteric bacteria get when fed the same diet. And then what you found is that the bacteria that seemed to be most associated with this response to a high-fat diet that led to what we call insulin resistance or metabolic syndrome appeared to be those of specific families (when you broke them down into Gram-negative or Gram-positive bacteria) associated with a deficiency of the Gram-positive Bifidobacteria that made these animals more responsive, in terms of hyperinsulinemia, to the diet. Have I summarized what you've said correctly or are there modifications to what I have said?

PC: Exactly. It is exactly that.

ND: Maybe I can add something. We always look at what we already know. In the context of the gut microbiota it is true that the modulation of the Bifidobacteria plays a role in view of what we have shown, but I'm pretty sure that there are also a lot of other strains of bacteria that could play a role and that could be modulated by the prebiotics, probiotics, and whatever approach touches the gut microbiota. I really think we are just at the beginning of the discovery of some types of bacteria or some types of bacterial metabolic activity that could be implicated in this process. In the view of today, we work on Bifidobacteria because we know them, but there are (I am pretty sure) a lot of bacteria prone to have positive effects on gut biofunction, gut immunity, and systemic immunity.

JB: Very, very interesting. A term that you have used is kind of new to gastroenterology, and that is "metabolic endotoxemia." For most students in the medical sciences, when they hear "endotoxemia" they think of sepsis; they think of acute infection as it relates to a very significant (or maybe even catastrophic) breakdown of gut mucosal defense and a very high load (systemically) of bacteria, and the person ends up with septicemia. I think is very important to differentiate metabolic endotoxemia. It can occur in people who are "apparently healthy," meaning they are not acutely ill, but they have a stress on their immune system as it relates to this kind of chronic leakage of bacterial LPS and the effect that it has on their immune system. Am I describing this term correctly, "metabolic endotoxemia?"

ND: I can say that this term, metabolic endotoxemia, is used by some scientists and not by others. Some people also talk about low-tone inflammation or low-tone endotoxemia, in order to make a clear

difference between the two concepts of high endotoxemia and low endotoxemia levels. I can give the phone to Patrice, who participated in the studies with humans.

PC: The term "metabolic endotoxemia" was used, as you described, to differentiate from the high levels of LPS known in sepsis. Metabolic endotoxemia means that we can observe LPS (or plasma endotoxemia) levels of variation in healthy subjects, as well as in obese patients. We know LPS can be modulated in healthy subjects by simply feeding a high-fat diet; it has been demonstrated that a fat meal increases LPS levels. This increase is really low compared to sepsis (an increase of 50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}--a two-fold increase--following the diet). It is really important to make the difference between the terms "LPS" and "proinflammatory properties of LPS." In healthy subjects, we found and observed this LPS variation, so the term "metabolic endotoxemia," as Nathalie explained before, could sometimes be confusing for people and should perhaps be defined as "low endotoxemia levels," or should be revised because "metabolic" is sometimes a term which cannot be used in all conditions. In our research, "metabolic endotoxemia," was used to describe high-fat-diet-fed mice in an obese context, but we can also observe the very small variation of endotoxemia in healthy subjects following a normal high-fat meal.

JB: That's very helpful. In the United States there is a nonscientific term that has been coined to describe what you are saying much more scientifically. This term is "leaky gut syndrome," which describes this partial breakdown of gut mucosal barrier function as a consequence of regional immune activation in the gut-associated lymphoid tissue, which then allows for the leakage of middle molecular weight molecules across the GI barrier. This leakage then has access to systemic circulation, influencing downstream (as you said earlier) the Kupffer cells in the liver, and the circulating white cells, and maybe even the immune system of the brain-the microglia-so that you get this more systemic relationship to the load of inflammatory activating substances. We've coined this term "leaky gut syndrome." Do you think that is a little bit too loose in the language or do you think that kind of describes what we are talking about?

Difference Between Metabolic Endotoxemia and Leaky Gut

ND: We can say that sometimes a leaky gut is observed in the pathological situations we are talking about. For example, the high-fat diet may also induce some leaky gut, but we are not aware of all the mechanisms that create systemic inflammation from the gut. It is true that leaky gut may be one way to proceed, but also some physiological functions may be related (for example, the absorption of the lipopolysaccharides to the normal lipid absorption may play a role, and maybe other mechanisms could start in the gut). In gut inflammation certain cytokines may drive some immune response outside the gut and into the systemic circulation and systemic organs. I don't think we can say there is one first event (leaky gut) leading to all other events. I think there are several mechanisms by which you can have a translation of inflammation coming from the gut into the systemic body. We are far away from having one sole mechanism and one sole result. Leaky gut is only part of the story.

JB: Thank you. That is very helpful. We have been speaking about a number of your papers. One that I was very impressed with appeared in Diabetologia in 2007 on the effect of Bifidobacteria in response to high-fat meals and its relationship to endotoxemia.9 You have another very interesting paper that appeared in Current Opinion in Clinical Nutrition and Metabolic Care that talks about the metabolic contribution and the energy homeostasis contribution that gut flora have.10 Could you tell us a little bit about it? I think often people forget about the fact that we have over a kilogram of living organisms in our intestinal tract and these have their own personalities and energy metabolism, which has an influence on

metabolism in general. Maybe you can comment on your understanding and help us to see how these relationships between bacteria and systemic metabolism can relate?
ND: There are a lot of teams working on this in the world. I think the team of Jeff Gordon was one of the first to show that gut bacteria provide energy because they are able (sometimes) to use energy that escaped our own digestion process. But it is rather a simplistic view just only to say that the gut bacteria are able to use the substrate that escaped our digestion, therefore providing energy by the production of the fatty acids, for example. It is one way to have energy, but in view of our diet, we may say that this process of sparing energy through fermentation is not big enough to explain changes in the whole body. I think the team of Jeff Gordon has really shown that beside the fact that you may have some energy sparing coming from the gut fermentation, you may also have the modulation of some metabolic processes that can help the body to spare energy, for example, lipoprotein lipase activity and adipose tissue function and so on.

What is very strange is that when studies are done it is mostly to say the whole gut microbiota have a role in sparing energy in different ways. But what we can say in view of our results and others, is that specific qualitative modulation of the gut microbiota may lead to the inverse process. Just because you have a lot of bacteria, it doesn't mean you are able to spare energy. No. The composition-the qualitative composition of the gut microbiota-may modulate this process and sometimes (as we have observed in rats but it has not been shown in humans) it can decrease the energy harvest as compared to a diet that does not improve this gut microbiota. Once again it is a complex story. I It is completely true that the gut microbiota play a role in energy harvesting. But sometimes qualitative modulation of the gut microbiota may lead to changes in the physiological function that may lead to a decrease in fat mass development or a decrease in food intake and so on. So it depends, really, on what is observed and how it works.

JB: That's beautifully said. You and Dr. Cani have a very nice paper that has just been published in the journal Gut in 2009 describing changes in gut microbiota and their influence on mucosal permeability and signaling through GLP-2.11 Could you tell us a little bit about that? That is a very interesting part of the story-that there may be these receptors on the GI mucosa that signal systemically through incretins or other messaging molecules. I think this another fascinating part of your discovery.

Influence of Gut Microbiota on Mucosal Permeability and Signaling
PC: We had previously demonstrated that the proglucagon-related peptides (I mean glucagon-like peptide 1 [GLP-1] and GLP-2) were modulated by the gut microbiota. We had previously demonstrated that changing gut microbiota by using prebiotics improved insulin resistance, glucose tolerance, and deceases energy intake. We had observed that this phenomenon was always associated with an increase in GLP-1 production. GLP-1 is a peptide involved in insulin secretion and insulin sensitivity (it increases insulin secretion and insulin sensitivity), and it increases satiety also. But GLP-1 is produced by a proglucagon, and a proglucagon is also able to produce (at the same time) glucagon-like peptide 2 (GLP-2). GLP-2 has been demonstrated to be involved in intestinal homeostasis. It increases epithelial cell proliferation and it is now used in clinical drug trials in Phase 2 and Phase 3 to improve gut permeability and nutrient absorption in short bowel syndrome, for instance.

Knowing that prebiotics were involved in changes in GLP-2 and knowing that in ob/ob mice obesity is associated with an increase in gut permeability, we decided to change the gut microbiota by using the prebiotics to see if we were able to change gut permeability in that context. When we changed gut microbiota by using the prebiotics, we improved gut permeability in obese mice and we observed that the

GLP-2 prediction was also increased, as well as the GLP-1. We found nice correlation between the plasma GLP-2 levels and endotoxemia levels (in both plasma and endotoxemia levels). We hypothesized that GLP-2 could be involved in the increase in gut barrier function.

To demonstrate that GLP-2 was involved in this effect, we treated obese mice concomitantly with prebiotics. We changed the gut microbiota by using prebiotics and we blocked the activation of the receptor by GLP-2 antagonists. Using this protocol, we demonstrated that blocking the GLP-2 receptor while we changed gut microbiotacompletely blocked the positive impact of the gut microbiota. Blocking the GLP-2 receptor and at the same time changing gut microbiota cannot change gut permeability; gut permeability remains higher in the prebiotics-treated mice even if the gut microbiota was changed. This phenomenon would maybe have an impact in a feasible condition. I mean that GLP-2 could be involved in the maintenance of the gut barrier function. This hypothesis remains to be demonstrated now in healthy conditions, but this experiment put forward one of the new mechanisms by which changes in gut microbiota can change gut permeability and help demonstrate the new molecular mechanism by which gut microbiota improved the gut barrier function.

JB: That is just stunning work. Again, I want to compliment you both and your group. This is very pioneering and important work that really relates to this whole signaling revolution that we are seeing emerge today in a systems biology approach to medicine, which is really the foundation of what we have been calling functional medicine for 20 years. Thank you both.

In the short few minutes remaining, let me get to the bottom line, which I'm sure a lot of the clinicians that are listening are wondering about. Given all of these extraordinary benefits that pre- and probiotics have (or the symbiotics have) in modulating gut immune function and systemic immune function, how does a clinician start to apply this information? We have talked about Bifidobacteria and we've talked about specific prebiotics that may serve as selective substrates for these symbiotic bacteria. Can you give us some thoughts as to how you see this translating over into clinical management?

Clinical Implications of Research on the Gut Microbiota

ND: What I can say is that fortunately there are now more and more clinical intervention studies that appear concerning the influence of probiotics and probiotics in new context, I should say, (so context that shares obesity and so on). There are not so many papers at the moment, Clinicians now starting to be convinced about a method of modulation of the gut microbiota performed by a non-drug approach. It is not clearly a pharmacological approach, but it touches functions that are related to the normal physiology and improvement of physiology in humans. Obesity has not been considered a disease for very long, and there has been a place for compounds like prebiotics or probiotics to improve the functions associated with the fat mass development. But now obesity basically has become a disease because of the severity of the associated disorders it may lead to. Therefore, it is now also in the heads of the clinicians to think about compounds that could be given in the context of the pathophysiological relevance in obesity now. They have, really, in my view, a good future. They are just at the frontier between nutrition and drugs, but I think that they are more than that. We will also have, maybe, a more common view with people who are commercializing some compounds related to the improvement of physiological function, and the people who are working in nutrition, purely. We know those compounds (at least the prebiotics, for example) are present in the normal diet, which may be helpful in convincing clinicians that those products may be helpful for people. You don't have to necessary to kill bacteria with a drug to obtain efficient effect in some contexts. We can work with a more physiological approach, and I am pretty sure that now the

physicians will be convinced of the relevance of this effect.

JB: That's really important information. I was reminded of a paper that appeared in the March issue of the Journal of Gastroenterological Surgery in which they were talking about patients that have morbid obesity and undergo gastric bypass surgery (the Roux-en-Y gastric bypass procedure) and they find that when patients are supplemented with pre- and probiotics post-surgery they have a much better outcome. They have better nutritional status. They have better vitamin B12 status. They don't gain weight back as quickly. And their overall health and immune function is improved. I think the story that you are talking about, Professor Delzenne, relates to so many applications of this concept in clinical practice is really starting to be seen.

I want to thank you both. We really appreciate you being available to share with the listeners of this series. We have been doing this for 27 years and I have had the fortune of interviewing some remarkable contributors to the emergence of the new medicine. I'd have to say this discussion/interview about your work would stand head-to-shoulders with the most interesting and clinically relevant of those topics that we have had the pleasure of discussing. Thank you for making yourself available, and thank you for all of us in the medical community on your pioneering work and the diligence you are bringing to your research.

ND: Thanks very much. We really hope this will help us have a lot of contacts in the future with many people in America. We are really proud of the way that you presented us, also. Good luck, also.

JB: Thank you so much. Dr. Cani, thank you as well. We will be in touch and following your work very closely.

I hope you came away from listening to that interview with the kind of goosebump-experience that I had. That was an extraordinary journey we took with Professor Delzenne and Dr. Cani, unfolding the story of the important role that the gut microbiome plays in modulating function throughout the whole of the body-the systemic signaling.

Let me remind you of a few of the papers this group of investigators has been responsible for publishing that I think demonstrates the rapid change in this field. These are all 2008 – 2009 contributions to the literature. The first one is titled "Gut Microflora as a Target for Energy and Metabolic Homestasis." This topic is exactly in the sweet spot of looking at how friendly bacteria (or the proper gut microbiome) can favorably influence homeostasis of energetics(in other words, maintenance of proper body composition). When the immune system is responding to what it considers to be a foreign gut microflora, dysfunction can induce inflammation processes that are associated with altered adipocyte function, insulin signaling, and the relationship to energy storage.

You might say, "Why is does the body do this? Why does it store energy under alarm?" Maybe this is a very longstanding evolutionary benefit. If you think of the most significant stresses to human survival throughout time, it would be things like starvation and infection. It may be that the body evolved a particular protective mechanism to store energy for a continued battle against what might be considered deprivation and insult, and to shut down functions it doesn't need as importantly as it needs to defend itself against the apparent insult. It might be that this regulation against inflammation of energy storage is part of this protective system of maintenance of energy to mount immune response, and cell repair, and so

forth. This paper that appeared in Current Opinion in Clinical Nutrition and Metabolic Care, authored by Dr. Cani and Dr. Delzenne, I think is a very important contribution to our understanding of how gut microflora can be an important part of our therapeutic target for improving energy metabolism and weight management.

Another paper that appeared during the last year is titled "A Place for Dietary Fibre in the Management of the Metabolic Syndrome, "12 In this paper they are talking about dietary fiber, and not just in terms of slowing the release of glucose across the GI tract, which is the traditional way we have thought of it (as being an influence on digestion and assimilation of simple carbohydrate, which then lowers the load on the insulin regulating mechanisms). They are also talking about certain types of dietary fiber being fermented in the gut by friendly bacteria (or symbionts) to induce not only regional protection upon GI mucosal integrity, but on functional aspects of the GI immune system, which then has favorable effects on systemic immunity, lowering inflammation and having a trophic effect on immune balance. Again, this was another paper that appeared in Current Opinion in Clinical Nutrition and Metabolic Care, showing that things like large arabinogalactans, beta glucans, and other types of what we call prebiotics have a favorable effect in stimulating the metabolic relay and allowing specific agents to regulate things like appetite, and inflammation, and even bioenergetics.

A more recent paper appeared in the journal Gut, which I think is a very important journal. This significant article is titled "Changes in Gut Microbiota Control Inflammation in Obese Mice Through a Mechanism Involving GLP-2-Driven Improvement of gut permeability." In previous issues of Functional Medicine Update over the last several years we have discussed the glucagon-like peptide-1 and the glucagon-peptide-2 (or GLP-1 and GLP-2)-related neuroendocrine functions that then alter things like insulin signaling and immune function, systemically. What this paper that appeared in the journal Gut talks about is that by modulating gut microflora, inflammatory processes in the gut are altered, which then changes this glucagon-like, peptide-driven, neurochemical message and improves gut mucosal integrity and lowers systemic inflammation.

This work has also has indicated (and Dr. Delzenne and Dr. Cani have published papers) showing that appropriate bacteria (enteric bacteria-part of the microbiome) will lower gut inflammation and improve GLP-1 signaling through the adipocyte, which then regulates insulin through these incretin types of signaling mechanisms. Those of you who are familiar with diabetic drugs know that Byetta is a drug that is a GLP-1 agonist. It blocks the enzyme that breaks down glucagon-like peptide and enhances insulin activity as an agonist of incretin activity. Here's a case where you are getting increased activity of GLP-1 directly at the gut mucosal level by friendly bacteria (gut mucosal activity). The connection of gut to insulin signaling through gut microflora (the microbiota) is another very, very interesting emerging topic that this group is advancing.

Lastly, the research coming from this group has shown that selective increases in friendly bacteria (like Bifidobacteria in the gut microbiome) improves the tolerance people have to high-fat-induced diabetes, which reduces mucosal integrity, lowers inflammation of the gut, and reduces the concern of absorption of bacterial LPS and activation, systemically, of inflammation (i.e. this would be called reduction of the risk to chronic endotoxemia). That is another paper that they published in their series. This work was published in Diabetologica, and demonstrates (once again) that appropriate probiotic and prebiotic supplementation can modulate the risk to endotoxemia.

I hope you are starting to see that this theme that we are developing-connecting food as a signaling mechanism to the gut microbiome, and to the gut immune system, and to systemic response--is an extraordinary new chapter that is emerging in functional medicine. Thanks for being with us. We'll look forward to sharing more in September.

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