Health Condition: Gastrointestinal Disorders

"The surface of the digestive tract is the size of a tennis court, and the immune system is in charge of sorting out the good things and bad things coming from there. We cannot fully understand the immune system without acknowledging that what the immune system is doing most of the time is patrolling the complexity of events going on in the gut."

—Sidney Baker, MD
Author, *Detoxification and Healing*

The Importance of the Gastrointestinal System to Overall Health

Starting with the first moments of life after delivery, the inoculation of our gastrointestinal tract with bacteria is ongoing throughout life. We have a tremendous number of bacterial species and parasitic potential within the GI tract. There are, in fact, 2 ½ to 3 pounds of living organisms residing principally in the large intestine (the colon), but also to some extent in the small bowel. These bacteria represent the second largest organ in the body, second only to the skin. These several hundred species of living organisms have different personalities and different genes. They produce different molecules. They communicate different messages. As such, we are in constant communication with this very complex ecosystem called our bacterial flora.

The gastrointestinal system is one of the premier messaging systems of the body. It transmits messages that originate outside of the body to internal receptors. One might think of the GI mucosal cells as being loaded with antennae or membrane receptors that pick up messages from the internal milieu of the GI tract. These are messenger molecules that come from the ingestion of food, biological organisms, contaminants, and xenobiotics. A large number of infectious agents, allergens, and foreign proteins enter our bodies orally and through the nasal and upper respiratory tracts, intestines, and reproductive tracts. These messages are picked up by the GI mucosal information system and translated through the immune system into regulatory modulators such as cytokines, lymphokines, leukotrienes, and prostanoids. Downstream, these messages ultimately influence the Kupffer cells in the liver (the embedded white blood cells), the circulating white cells, and even the embedded white cells in the brain called the microglia, all of which receive some of their messages from the process that was initiated at the gut level.

The Gut and the Immune System

"The big issue is that in our immune system, the way in which we relate and interface with the world--the way in which we determine self from non-self--70% of that immune system is present in our gut, in our gastrointestinal tract. The way in which it grows, to be able to educate itself (the way in which it learns), is actually through interrelationship with the environment, interrelationship with the food we eat, and also with the 'old friends' that we come in contact with: the normal, commensal bacterial flora, and even parasites (worms, viruses). All of these things are what educate our immune system to be able to say, 'Are you a friend or are you a foe? Am I going to

mount an inflammatory reaction to you, or am I going to say that everything here is okay and I am going to be tolerant of these particular foods or these particular antigens that are presenting themselves?' That entire process is one of being able to set the stage. The most fascinating part in this, to me, is that the way in which you set the stage in the first two years of life has ramifications for what your gut flora will be and what your set point is for the remainder of your life…The immunologic cross talk that is a part of the ongoing education of the gut- associated lymphoid tissue of the immune system is a process where the body is constantly sampling. It is using lymphocytes that are lining the intestinal walls. The intestinal wall, spread out, is as big as a double tennis court. In it, you are putting in antigens--30 to 50 tons of food over a lifetime--and there are bacterial flora that outnumber us ten to one. There are 100 trillion bacteria in our gut and 10 trillion cells in our body. The body is constantly sampling (with the immune system) to say, 'Who's out there?' It samples based upon different kinds of receptors, so called toll-like receptors that are receptors that are set. They are preprogrammed to be able to understand what the appropriate relationship is supposed to be with our environment, and, in the stimulation of that, they either get turned on or they get turned off."

--Patrick Hanaway, MD

December 2006

We think of GI microorganisms as being in three families. There are the symbiotic bacteria that participate in immunological upregulation and have a trophic 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.

The intestinal epithelium (the cell boundary between the external environment and the tissues of the GI tract) protects the host against invasion by alien microbes that in imbalanced or disturbed microflora can become foe rather than friend. What do we know about the function of the gut epithelial barrier? There is a high turnover rate. The goblet cells, the entero-endocrine cells, and the absorptive epithelial cells, which are all derived out of the stem cells in the gut mucosa, are redifferentiated upon the gut mucosal turnover, probably every 7 to 10 days. 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.

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. The immune system is normally 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 effects on the immune system.

With few exceptions, the expression of a barrier function alteration is known to be associated with chronic inflammatory conditions. Does 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. 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.

The Individual Uniqueness of Gut Ecology

No two people are identical in the susceptibility of their gut mucosa to imbalances. The composition of the gut microflora (e.g., its “personality”) can change based upon what it is fed and the environment that is provided. An interaction of both genes and microbial factors results in chronic diseases. Sinusitis and rhinitis may occur in one person from eating peanut butter, but in another person, it may result from eating something containing wheat protein.

One can have defective mucosal defense due to altered bacteria in the gut that can change the gut immunological defense. Altered mucous formation and increased intestinal permeability (the so-called “leaky gut syndrome”) may cause cellular starvation, impaired resuscitation, and lead to defective bacterial clearance. The contribution of both persistent infection and defective mucosal defense may result in dysbiosis, where protective bacterial counts are decreased and aggressive and harmful bacteria counts are increased, leading to a dysregulated immune response with loss of tolerance, aggressive cellular activation, and defective apoptosis of the gut mucosal cells.

A number of laboratory techniques can be used to evaluate the functional integrity of gastrointestinal lumen, the gut-associated lymphoid tissue (GALT), mucosal integrity, colonic bacterial flora activity, and various aspects of digestion and absorption. These functional gastrointestinal tests are designed to look not at gastrointestinal pathology, but at the functional aspects of GI activity that may precede the onset of pathology.

The Gut-Brain Connection

"A simple nervous system is an oxymoron…

Serotonin plays an important role, first of all, as a sensing cell in the epithelium of the gut. The enterochromaffin cell, which is where most of the serotonin of the body is, is a detector cell. In some parts of the gut, it functions as a glucose receptor. In most parts, it's a pressure receptor, so it detects those changes in the lumen of the gut. In the duodenum, it's also an acid receptor. Serotonin is released in response to increases in pressure, glucose or acid. That serotonin goes primarily into the wall of the gut and stimulates the intrinsic primary afferent neurons, the sensory neurons of the gut, initiates intrinsic reflexes within the gut, and also sends signals back to the central nervous system (CNS).

None of those signals going back to the CNS mediated by serotonin coming from the enterochromaffin cells is pleasant. I like to say that the gut is not an organ from which you wish to receive frequent progress reports—pain, bloating, nausea, and so on.

There's a very famous transporter for serotonin called SERT. This serotonin transporter is best known as the target of Prozac and the other SSRIs. When you inhibit the serotonin transporter, you potentiate serotonin by interfering with its inactivation. That accounts for the GI side effects of the SSRIs and other antidepressants. They are not side effects; they are direct effects. They lead to nausea, diarrhea, and ultimately to constipations, all coming from direct effects on serotonin."

--Michael Gershon, MD

Author of *The Second Brain: A Groundbreaking New Understanding of Nervous Disorders of the Stomach and Intestine*

March 2002

We know that the gut is a brain and the brain is a gut. That may sound like taking the brain down from its pedestal or putting the gut on a pedestal it doesn't deserve. The enteric nervous system is interrelated with brain via neurotransmitters that act on gut receptors. The gut releases neurotransmitters that are brain hormones; the nervous and digestive systems communicate in this way.

The gut has a tremendous propensity and capability to generate neuroactive molecules. The brain produces about one-third of the body's serotonin and is influenced by the gut, which produces two-thirds of the body's serotonin. We have a second brain, that which is associated with gut physiology.

Some call the gut the second brain because it shares so many of the putative messaging compounds that the brain produces as neuroregulators. In terms of the blood-brain barrier (as a kind of

compartmentalization that the brain itself has), the gut doesn't really have the barrier. Is it possible that some of the things that we think are neuroactive are really operating through gut-signaling phenomena?

To what degree is the gut the seat of emotion? When a portion of the gut messaging system is removed, the connection between the gut hormones and the brain hormones is modified. By disconnecting the signaling of the gut, some of what is called emotion-based (or reward-based) eating habits are disconnected. People often talk about eating as being totally controlled by the lateral nucleus of the hypothalamus, meaning centrally-mediated. It seems more likely, if we are to learn something from gastric bypass surgery, that there is also change happening at the gastric-hormonal-neuroendocrine level. From a functional medicine perspective, it reminds us of the web of interaction of the gut hormones with the beta cells of the endocrine pancreas, with the effects of adipocyte signaling, adipocytokines, central mediation, muscle cell physiology, and the important metabolic role the liver plays in managing calories or energy economy through lipids and sugars.

Inflammatory Bowel Disease: Ulcerative Colitis & Crohn's Disease

Inflammatory bowel disease is a collective term encompassing both ulcerative colitis and Crohn's disease. These significant health problems affect between 0.1 and 0.2 percent of the population in developed countries. These disabling conditions are characterized by diarrhea, pain, bleeding, and other intestinal symptoms, and by lifelong relapses. Ulcerative colitis is confined to the mucosal layer of the large bowel, whereas Crohn's disease can affect any portion of the intestinal tract. The pathogenesis of inflammatory bowel disease is complex, but it appears to involve interaction among three essential components: host genotype (functional genomics), intestinal bacteria and the environment of the intestinal tract, and the gut mucosal immune response.

How amplified or balanced is that response? Once we understand these things, we can deal with the problem. We can't change the patient's genes, but we can deal with the other two factors—the host GI environment, bacteria, and the mucosal immune response, i.e., NFκB-mediated TNFα -related functional oxidative stress reactions.

The immune response in the intestinal mucosa is conditioned by the indigenous bacterial microflora, which affects the regulatory network within the GALT. In susceptible individuals, inflammatory bowel disease arises when the immune system misperceives danger within the normal gut microflora and interprets the harmless enteric bacteria as pathogenic invaders. This leads to a breakdown in normal regulatory constraints and mucosal immune function, enhances NFκB and TNFα function, and activates oxidative stress inflammatory damage.

Celiac Disease and Gluten Intolerance

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. 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? 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?

In 2009, a paper was published in the *British Medical Journal* titled "Effects of a Gluten-Free Diet on Gut Microbiota and Immune Function in Healthy Adult Human Subjects."[1] The authors of this paper point out that it is well known that diet influences the composition of gut microbiota, and therefore it has an impact on host health. 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.

This study examined the effects of a gluten-free diet on the composition and immune function of the gut microbiota in healthy human subjects who were not sensitive to gluten 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. 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. The results suggest 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 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.

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 a 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 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 has influence not just regionally on gut-immune function, but systemically on overall immune vigilance.

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. It is not just a search for the allergic-producing substances in that diet, but rather for how the diet, as a whole, 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. This raises the bar higher. It underscores the clinical importance for doing the appropriate evaluation, because there are certain diets that even in the absence of allergens can induce immunological dysregulation of activation.

Please see the “Autoimmune Disorders” page for additional information about celiac disease and gluten intolerance.

Therapeutic Approaches

When we go back to the original discussion about the connections among the brain, the gut, and the diet, we begin to piece together a mechanism that explains this complex interrelationship. Our genetic inheritance, the food we select, and our dietary habits influence the floral ecology of our gut, the bacteria that live in our gut mucosa. That ecology relates to digestion, pancreatic function, and how well we can break down food proteins to their nonimmunogenic amino acids. It also relates, in turn, to our absorptive functions and the immunological effects, both in the mucosa of the gut and the liver itself with its embedded Kupffer cells, which are lymphocytes with immunological function in the liver.

A 5-part nutritional support program for improved gastrointestinal function has been used successfully in clinical settings. Such a program involves first removing offending parasites, microbes, and yeasts from the gut using herbal anti-microbials or pharmaceutical agents to rid the body of foreign invaders. Additionally, the idea of "removal" includes removing not just these offending organisms already present in the gut, but eliminating allergenic foods from one's eating. In the second phase of this program, missing digestive enzymes or acid is replaced as needed. If the person is hypochlorhydric or achlorhydric, he or she could have a problem regarding ablation of the parietal cells in the stomach, resulting in lower stomach acid and intrinsic factor secretion. In such cases, acid with can be replaced with something like a supplement containing betaine hydrochloride. Digestive enzymes, protease, amylase, and lipase enzymes are replaced when needed for pancreatic enzyme support. The next step is to reintroduce friendly prebiotic and probiotic organisms. A prebiotic is the food-friendly bacteria consumed for their proliferation. Probiotics are the actual organisms themselves, such as certain adherent forms of acidophilus and bifidobacteria, which bind to the gut mucosal membranes and proliferate in the presence of prebiotics to push away the unfriendly parasitic bacteria by competitive inhibition.

The effects of a nutritional support program can be measured by stool analysis before and after therapy. Post-therapy, there may be reductions in the stool of enzymes like beta-glucuronidase, which is a detoxifying, deconjugating enzyme. When it is elevated, beta-glucuronidase can be associated with increased in situ carcinogenesis. Second, there may be a reduction in the stool of branched organic acids like valerate and isobutyrate, which are a result of putrefaction of protein. High levels of isobutyrate and valerate in the stool indicate increased protein putrefaction, so lowering them is beneficial. A third effect is increased levels in the stool of the linear short-chain fatty acids acetate, propionate, and butyrate, which are gut fuels associated with improved colonic cell health.

The fourth phase of a nutritional support program is to make sure there is an adequate level of the nutrients necessary for nourishment and repair of the GI mucosa. These nutrients include inulin and fructooligosaccharides, which help produce butyrate, and resistant starch, another important contributor to enhancing short-chain fatty acid production. Other repair nutrients are the amino acid L-glutamine, zinc, and pantothenic acid or calcium pantothenate. All of these nutrients have been shown to help improve gut mucosal healing. A nutritional support program can be a useful for individuals with GI distress, functional gastrointestinal disturbances, gut inflammation, or altered gut mucosal membrane barrier protection with increased leakage of middle molecular weight molecules across the lumen, which impacts the cellular immune system. Using fish oils along with the fructooligosaccharides and antioxidants appear to have a favorable effect on colonic phospholipids composition and anti-inflammation.

Finally, the last phase calls for establishing a sense of relaxation and rebalance in one's life to overcome the effects of stress on one's gut. Indeed, it is well-known that that stress has a number of deleterious influences on the gut, including increasing the presence of unwanted organisms, reducing essential digestive secretions, and altering the microflora. Stress may not be able to be controlled, but there are effective ways to manage it better in one's life, thereby eliminating or at least decreasing some of its effects on the gut. There are personalized ways to cope with stress better, as it affects everyone differently, including exercise, eating specific foods and supplementing with nutrients to help the body blunt the impact of stress, and even journaling, to name a few.

Probiotics & Prebiotics

The concept of therapeutically manipulating enteric microflora by feeding nonpathogenic bacteria has been a fundamental tenet within functional gastroenterology and functional medicine. Manipulation of the microbial flora includes the use of nonpathogenic bacteria (probiotics) and the companion prebiotics that selectively feed the beneficial bacteria. Prebiotics include oligosaccharides of a specific chain length and molecular weight distribution. They selectively feed the friendly rather than the unfriendly bacteria.

Pro- and prebiotics together represent a fundamental treatment in the effort to restore proper GI immune function related to pediatric atopic disorders, infant diarrheal disorders, and asthma-related disorders. These are systemic inflammatory conditions associated with altered immune function. Pro- and prebiotics can also be beneficial in localized digestive disorders like irritable bowel disease (IBD), Crohn's disease, or certain forms of irritable bowel syndrome (IBS).

Mary Ellen Sanders, PhD, is an internationally recognized expert in probiotic microbiology. In an interview with Dr. Jeffrey Bland, she explained the history and rationale behind the application of probiotics for gut health:

"The concept of probiotics probably originated with Elie Metchnikoff, a Russian Nobel Prize-winning scientist at the Institute Pasteur in Paris. At the turn of the last century, he published a book titled *The Prolongation of Life*. In it, he presented a theory that the reason people in certain cultures in Russian society lived such long and healthy lives was because they consumed quite a few live *Lactobacilli* in the fermented milk common in their diet. Dr. Metchnikoff was a strong proponent of supplementing the diet with these types of bacteria. The concept of probiotics was really born at that time, although the term probiotics was not coined until about the mid 1970s. Now, it refers to the fact that live microorganisms, when consumed in adequate amounts, can confer a health benefit on the host.

Through studies by a variety of microbiologists and clinicians, we have found that certain microorganisms, especially the *Lactobacillus* and *Bifidobacterium*, appear to be associated with healthy intestinal tracts. The results of those studies, and the observations of Metchnikoff highlighting the value of *Lactobacillus*, turned the probiotics industry in the direction of that particular genre—*Bifidobacterium* and *Lactobacillus*. Having said that, the type of

research we have seen going on in recent decades has focused specifically on the advantages of particular strains of those groups of bacteria.

Research over the past 10 or 15 years has grown by leaps and bounds compared to that done in the 1980s or early 1990s. One big step forward was the advent of the double-blind, randomized, placebo-controlled trial now being more and more commonly used to determine the health effects of these organisms. There is also better definition of the products being used as interventions in these studies. You might see a paper that was published back in 1985 in which the investigators said they used yogurt to try and observe its effects. There was almost no microbiological characterization of the yogurt, and no identification of the particular species or particular strains that were used. Therefore, it was very difficult to know exactly what was being tested in those studies. Today, very defined strains of probiotic bacteria are used in studies. They are defined based on standard microbiological and physiological traits, such as their enzymatic capabilities, their carbohydrate fermentation capabilities, and different physiological structures of the cell. They are also defined using modern DNA-based techniques that allow for patterns: for example, through an electrophoretic gel that shows specific fragments characteristic of a particular strain. We can get DNA-based patterns or reactions to DNA-based probes that will very specifically identify strains.

Additionally, strains are often deposited in international culture collections so that work can be repeated in different labs. We have come a long way with research in this area and have applied modern, molecular techniques to identify what strains are being used and what is being documented for those particular strains.

Some of the most exciting research that's been done in the past ten years has been in the area of immune interactions. A variety of probiotic bacteria have been shown to upregulate immune response, enhance macrophage activity, or enhance certain cytokine or tumor cell killing activities that help a person to better resist infections, either by bacteria or viruses or improvement in their ability to decrease proliferation of certain types of tumor cells. That type of upregulation has been studied for a while and has been shown in different strains of probiotics.

In the past five or six years, probiotics have also been shown to downregulate certain immune functions, including allergic and inflammatory responses involved in varied diseases that are on the rise, such as IBD diseases such as Crohn's disease, and different types of other allergic responses. Certain probiotic bacteria appear to have the ability to either upregulate or downregulate negative responses so as to achieve more optimal or normal functioning of the immune system.

Another large area of research has to do with the ability of probiotics to decrease the incidence or duration of certain diarrheal illnesses.[2,3] The most extensive studies have been done on anti-viral effects and the ability of probiotics to decrease diarrhea in infants, especially in the realm of rotavirus diarrhea. There have also been studies on probiotics and antibiotic-associated diarrhea. Not all of those studies have been positive, however. It depends on what organisms are being examined and at what dose they're administered.

Another area of research is investigating the ability of certain probiotic organisms to deliver lactose to the small intestine, thereby helping its digestion in people who are lactose-intolerant.[4] Dairy products can be better tolerated by people who are consuming certain live microorganisms, either as part of yogurt or a prebiotic supplement. That can be important from a nutritional point of view. There are some interesting studies, many of them done in animal models, on the ability of probiotics to decrease pathogen colonization, such as *Helicobacter pylori* in the stomach and certain intestinal pathogens in the small and large intestines.[5] There have been some very interesting areas of research on the horizon, one in the area of IBD. There have only been a few publications, but some of them have show some positive effects with probiotic bacteria.

There have only been one or two published papers on probiotics and dental caries. Other areas include control of halitosis and control of kidney stone formation. There are a variety of very interesting areas of research being documented right now. What they have in common is that they are all physiological situations contributed to by normal flora. It's the modulation of the flora to some extent than can help control many of the different problems.

If you're considering taking these products for specific therapeutic benefit, you want to make sure that the product has been tested for that benefit, and that there is a basis on which to expect an effect. One wouldn't want to throw any probiotic at someone with Crohn's disease. One would want to look for a probiotic that has been documented to show a downregulation of inflammatory effect. With someone with an immune-suppressed condition, one would want to choose a probiotic that has been shown to have the ability to enhance immune function. If you're looking at probiotics that are just coming through in the food supply, such as yogurt products, they are being targeted for a more healthy population and I don't think we have to be too concerned about an effect going too far in one direction or the other."

In 2009, Dr. Jeffrey Bland interviewed Professor Nathalie Delzenne, and her research colleague, Dr. Patrice Cani, both of the Université Catholique de Louvain in Belgium. They are doing hands-on research on nutritional modulation of the gut microbiota and its role in immune function. Professor Delzenne explained the differences between pro- and prebiotics and the research taking place in Belgium:

"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."

How Gut Ecology May Relate to Obesity: The Role of Metabolic Endotoxemia

Professor Delzenne and Dr. Cani explain their current research and how it connects to systemic inflammation and even obesity.

Professor Delzenne:

“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 lipopolysaccharide (LPS). 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.”[6]

Dr. Cani:

“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).[7]

Professor Delzenne explains the potential clinical ramifications of their work in Belgium:

“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 (so context that shares obesity and so on). Clinicians are 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."

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