December 2004 Issue | Mary Ellen Sanders, PhD Consultant

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Welcome to *Functional Medicine Update* for December 2004. It is hard to believe we have arrived at the last month of this year. It seems that 2004 was beginning only last month. That is an indication of the time warp, the compression, the pico-second society in which we live, where time is our most precious commodity. More than anything else, time seems to be the most compressed thing in the world in which we live. That certainly is the case with developments in the field of functional medicine. It has been quite a year. We are beginning to understand the connection between type 2 diabetes, insulin resistance, hyperinsulinemia, cardiovascular disease, and other inflammation-related disorders. The circle draws tighter. Functionality becomes more important in understanding the mechanisms, rather than simply naming diseases. This is the future of medicine.

The Need for Clinical Education in Managing Chronic Disease
In October of this year, I saw a wonderful editorial in the *Journal of the American Medical Association*,written by Dr. Halsted Holman from Stanford University, School of Medicine in Palo Alto, California. He made the following comment in somewhat apologetic tones:

"It is axiomatic that medical education should prepare students well for the clinical problems they will face in their future practice. However, that is not happening for the most prevalent problem in health care today: chronic disease."[1]

Dr. Holman's apologetic tone stems from the fact that chronic illness, which requires a different management strategy than acute illness, represents the most dominant health problem. "Chronic disease is now the principal cause of disability and use of health services and consumes 78{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of health expenditures."

As pointed out by Dr. Holman, we do not have a chronic illness management system today, and it is a tremendous waste of dollars to use an acute care management system to manage chronic illness. Chronic illness management requires a different strategy, a different implementation, a different set of tools, and a different level of communication with the patient than an acute illness from which, presumably, with proper treatment, the patient gets well. In an age-related chronic illness, the patient may have a chronic susceptibility or impairment in functionality througho

Let us look at the concept of chronic illness, what tissues are involved, and whether it is initiated or potentiated. It is related to imbalance in the immunological system. In this issue of FMU, I thought it would be appropriate, perhaps even propitious, to talk about the center of the immune system and how it

regulates, or at least influences, the broad array of dysfunctions associated with chronic illness. I am talking specifically about the gastrointestinal immune (GI) system.

There are extraordinary messages sent out through the GALT and the MALT that are received systemically as well as regionally. They influence, at a distant site, how a tissue or organ responds to its environment and can potentiate or modulate inflammatory response. This understanding, the roots of which go back to the turn of the last century at the Pasteur Institute and the work of Elie Metchnikoff, has taken on a new meaning and implication pertaining to the management of chronic illness.

A functional medicine provider who does not understand the role of the GALT in modulating immunological function may be missing one of the most important things in his or her tool kit for being more successful in the management of chronic illness. This will be the focus of the December 2004 FMU. And, as we talk to our Clinician/Researcher of the Month, we will learn a lot about how to modulate GALT relationships through pre- and probiotic intervention.

Role of the GALT in Immunological Status

First, let us discuss the role of the GALT in overall immunological status and in the balance of inflammation. The GALT is responsible for secreting about three-quarters of the body's antibodies through the B cells. It is also involved with the secretion of various types of lymphokines and cytokines. It is actively involved in phagocytosis mucous secretion, and secretory IgA, the immunoglobulin that coats the interior lining of the gastrointestinal mucosa. The GALT plays an active role in translating friend to foe, or foe to friend at the GI barrier level. One might think of the GI mucosal cells as being loaded with antennae or membrane receptors on their external membranes which pick up messages from the internal milieu of the GI tract. These are messenger molecules that come from the digestion of food, biological organisms, contaminants, and xenobiotics. 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.

Foreign Molecules in the Diet

The gut mucosal tissue represents over 50 percent of the overall immune tissue of the body clustered around the gut. Over the course of life, a person eats at least 50 tons of food. Because those foods are partly composed of molecules foreign to the body, they need to be translated into friendly molecules. That is partially accomplished by digestion, during which they are changed into small nondescript nutrients like amino acids, monosaccharides, and free fatty acids. There are also some residual information molecules present in the diet that have to be further identified as friends or foes, and this is done through the agency of the gut immune system. There are antigen-presenting cells, dendritic cell activity, mucus secretion, and IgAs, all there to defend the body from foreign information coming from the diet. Some people have food allergies due to a breakdown in the translation process of what is food/friend and what is a foe/toxin. Classic examples of food constituents that produce adverse immunological responses are peanuts, cod, and wheat, each of which can produce fairly severe anaphylactic or life-threatening responses based upon activation of the immune system during an alarm reaction.

Not only is the gut/immune system inhabited by many interesting immune cells, but almost a kilogram of

foreign cells resides in the colons of most people. These are called the commensal bacteria. We hope they are commensal and symbiotic, and not parasitic. On a simple arithmetic basis, in any gram of stool, there are hundreds of species of bacteria. The gut is a highly populated area, and the GI bacteria turn over very rapidly. Rather than turning over in a matter of weeks, months, or years, they turn over in a matter of hours. The composition of the gut microflora (e.g., its "personality") can change based upon what it is fed and the environment that is provided for the 10^{11} to 10^{13} bacteria found within it. Witness the rapid onset of gastroenteritis that occurs in many people after exposure to something pleasant, such as stress.

We are starting to understand that there is a dynamic interrelationship between commensal bacteria in the gut, their metabolic activity, and how that influences the GALT, which subsequently influences the immunological system of the host at large and sets up a balance or imbalance of regulatory mediators. This is an important part of the overall story of how the dynamic interplay occurs between the body's external environment and internal immunological signaling, as translated through the GALT.

Etiological Role of Commensal Bacteria

I want to talk about the role of commensal bacteria in a variety of conditions. Balfour Sartor is one of the very knowledgeable researchers in investigating such issues.[2],[3],[4] Let us focus for a moment on inflammatory bowel disease (IBD). This is an interesting model from which we can understand the more general principle about how regulation of gut immune function can influence systemic health through various environmental agents.

Gastrointestinal Bacteria in Normal Humans

The stomach has a fairly small number of microorganisms, which may include *Lactobacillus*, *Candida*, *Streptococcus*,and *Helicobacter pylori*. The duodenum has more bacteria, primarily *Lactobacillus* and *Streptococcus*. The jejunum also has *Streptococcus* and *Lactobacillus*. In the distal ileum, there are many more bacterium, including *Clostridium*, *Bacteroides*, and coliforms. In the colon, there are 10^{11} of various strains of *Bacteroides, Bifidobacterium*, and various strains of *Clostridium*. This is where most of the bacteria reside. It is important to point out that the distal ileum also has quite a few bacteria, as well. In fact, one can get small intestinal bacterial overgrowth which may be able to influence IBD and which has been shown to influence irritable bowel syndrome (IBS). There is interesting research on these topics currently going on in the field of gastroenterology.[5],[6],[7]

Etiologic Hypotheses

The hypothesis that relates commensal bacteria to IBD suggests that a person may have either persistent infection with mycobacteria or *H. pylori*. One can even have things like embedded viral infections from measles, mumps, listeria, or adherent/invasive *E. coli*(enterotoxigenic *E. coli* like H0157). All of these can create persistent infection. One can also have defective mucosal defense due to "funny" or altered bacteria in the gut that change gut immunological defense. Altered mucus 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 productive bacteria counts are decreased and aggressive, and harmful bacteria counts increased, leading to a dysregulated immune response with loss of tolerance, aggressive cellular activation, and defective apoptosis of the gut mucosal cells, leading to IBD. No two people are identical in the susceptibility of their gut mucosa to the types of imbalances just described. IBD in a susceptible individual depends somewhat on how actively regulated the inflammatory

cytokines are through messages from the gut mucosa and the contents of the gut.

Relative to flora and digested food, how do the contents trigger a gut/immune response? Individuals with hypersensitive or highly sensitive upregulated inflammatory systems experience a loss of tolerance by alteration in both the thymus-dependent 1 (Th1) and thymus-dependent 2 (Th2) components of the gut immune system, resulting in increased IgG formation, increased formation of tumor necrosis factor alpha (TNF-α), IL-1, and interferon gamma (IFNγ). As a consequence, there is much greater inflammatory potential that occurs at the interface between the luminal adjuvants, the leaky mucosal barrier, and the brush border cells.

The IBD-susceptible individual is one in whom specific triggers produce a heightened response in the inflammatory area. They experience elevated Th1 production with increases in TNF-α and IL-1β, leading to tissue destruction and inflammation, and ultimately, to the bleeding observed in IBD.

The Role of Commensal Enteric Bacteria

What is the role of commensal enteric bacteria? In studies using gnobiotic animals, that is, animals who have had their guts sterilized and, therefore, contain no bacteria, it has been shown that stimulation with an agent known to initiate IBD-like conditions in normal (bacteria-containing) animals does not induce colitis. However, if certain resident bacteria are reintroduced to the gnobiotic animal when the adjuvant is given, there is significant activation of macrophages and the Th1 immune response. Within a week, it produces serious colitis and an inflammatory condition of the colon. Many different model systems have been used in an attempt to identify how resident bacteria become triggers for inflammation. It is not just one factor at work, such as bad bacteria. It is a combination of altered gut flora with a genetic susceptibility, and other adjuvant agents that trigger immune hypersensitivity and inflammation.

There is a strong correlation between the degree of microbial stimulation and aggressiveness of the GI inflammation. This is even seen in genetically-engineered animals in which transfection studies are done that basically produce animals with well-defined bacteria composition and show activation with specific bacteria. The mechanism of these actions is starting to become much better understood. It is not just descriptive, but understood more at the cell physiological and molecular genetic level.

Results of Germ-Free Studies

The lessons learned from germ-free studies include the following: normal luminal bacteria can induce and perpetuate chronic colitis, duodenitis, arthritis, and gastritis in genetically susceptible hosts. There is the gene connection toward susceptibility. Both luminal bacteria and genetic factors are essential, but neither is sufficient for chronic inflammation alone. There is a need for both of them simultaneously. An interaction of both genes and microbial factors results in chronic diseases. We know that from food allergy and the fact that no two people have identical responses to their diet. 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. There are differing responses of the immune system to different antigenic determinants.

When the luminal contents of Crohn's disease patients are examined, different types of bacteria are found. We might ask whether the altered flora is a consequence of the disease, or does the flora cause the disease? It is the old push/pull, cause-and-effect argument.

A paper appeared in *Gastroenterology* that talks about fluorescent probes detecting increased mucosal-associated bacteria in an IBD biopsy.[8] Some good genotyping has been done relating to polymorphisms in people who are more susceptible to these types of interactions, with an upregulation of gut/immune function producing an NFκB-mediated process that activates nearly 100 genes associated with inflammation of the gut. There is immune-dysregulation with antigen-presenting cells at the gut mucosal level that is triggered through the personality of specific types of bacteria.

From both animal and human studies, there is an emerging connection with loss of tolerance as a consequence of altered enteric bacteria, which is ultimately associated with a clinical diagnosis of IBD. The question is, what is the strategy for treatment? Should selective antibiotics active against specific bacterial subsets be used, or should there be intervention trying to modify the GI environment of the host, using pre- and probiotics and altering the diet? Research on both strategies is being conducted. For instance, in experimental colitis and enteritis, a series of different antibiotics has been studied-metronidazole, Cipro, and various types of tetracyclines-to see if they have different influences on different bacteria in animal models relative to the outcome of IBD. The implications of this research are that a combination or broad-spectrum of antibiotics is needed to manage what would be considered the animal model of Crohn's disease and ulcerative colitis. We do not yet know what selective antibiotics might work on specific biota to eliminate or alleviate the inflammatory-initiated process. Antibiotics can work, but we still do not know everything we need to know. If we look at various things that have been used clinically, like metronidazole, there does not appear to be any real difference in treatment versus placebo in conditions such as Crohn's disease. Possibly altering the GI environment would be equal to, or even more successful than, antibiotic therapy in patients with chronic IBD. Those cases lead us into looking at different kinds of bacteria and modifying the gut mucosal environment to try to rebalance Th1 and Th2 immune function, and to decrease chronic conditions leading to acute inflammation associated with IBD, its progression, and its serious interrelationship with colon cancer risk.

If we look at the luminal microbe biological environment trying to find the right balance, the injurious organisms associated with proinflammatory effects that could lead to IBD include the *Bacteroides* species, *Enterococcus faecalis*, and the enteroadherent/invasive forms of *E. coli*. Those are the injurious proinflammatory organisms, or what we call invasive or aggressive commensals. On the other side, protective probiotics are emerging, such as specific species of *Lactobacillus*, *Bifidobacterium* and non-pathogenic *E. coli.* That opens the door for an intervention for IBD, one that would change the GI environment to a less proinflammatory state by modifying the function of enteric bacteria, and trying to reduce the activity of the aggressive commensals, while increasing the activity of the symbiotic bacteria.

We are talking about building an intestine through an appropriate relationship of commensal bacteria. I find this a fascinating topic. There is an article published in a recent issue of *The New England Journal of Medicine*, titled "Building an Intestine-Architectural Contributions of Commensal Bacteria.[9] The author discusses what we have been talking about.

"Bacterial cells within the intestine (commensal microflora) vastly outnumber the epithelial cells lining this organ. Like all bacteria, they release chemical signals with conserved patterns recognized by specific receptors-called toll-like receptors (TLRs)-of the innate immune system. It is therefore assumed that the healthy intestinal surface somehow defuses the threat of commensal bacteria to the lumen, where they thus reside undetected."

In a recent study in the journal *Cell*, Rakoff-Nahoum and colleagues provide insight into the fact that the commensal bacteria interact with the intestinal surface and, to some degree, trigger TLR signaling.[9] This interaction is required to maintain the architectural integrity of the intestinal surface. Thus, it seems that the epithelium and resident immune cells do not simply tolerate commensal bacteria, but are dependent on them-a very strong relationship. The authors used mice deficient in a necessary downstream component of the TLR pathway, therefore preventing all TLR signaling. Such mice have a profoundly exaggerated response to intestinal injury. When introduced to something like an NSAID, for instance, they were much more likely to have NSAID-induced enteropathy and injury through inflammation of their GI mucosa.

"Bacteria have proved to be a rich source of information on the function of our own mammalian cells.... The recognition that TLR signaling is activated by common bacterial products has also helped to shift the focus of study from how the intestinal mucosa becomes inflamed in disease to why surface inflammation is the exception rather than the rule.... The study by Rakoff-Nahoum et al. helps to refine the new focus because, in addition to the previously known fact that commensals may quench as well as elicit inflammatory responses, it teaches us that basal commensal-dependent signaling is also critical to intestinal health and the ability of the luminal surface to respond to injury."

The interaction we are talking about between bacteria and the GI mucosal epithelium, and translated through the GALT, becomes a key feature in better understanding the dynamics of the immune system and the balance of Th1-dependent and Th2-dependent activity.

"The importance of context has also emerged from models of spontaneous intestinal injury and inflammation in mice deficient in various signaling molecules. A deficiency in any of numerous signaling molecules can induce intestinal inflammation-a precursor of inflammatory bowel disease-indicating that dysregulation of any one of multiple pathways involved in inflammation or repair disrupts the normal homeostatic mechanisms (which include microflora) and thereby results in disease. Thus, although microflora are required for homeostasis, they are also required for the full manifestations of inflammatory bowel disease induced in most genetic models."

As we understand how to shift this, using friendly bacteria and pre- and probiotics to optimize the intestinal environment, it will help us to better manage the genetically susceptible individual who is at risk to IBD.

Bacteria in the gut can either be friend or foe. We can alter the balance by what we eat, what we drink, how we think, the medications we take, and the environmental toxins we are exposed to. All these things can influence the gut environment. There is a link between the barrier function of colonic microflora and susceptibility to disease. This becomes of great importance in both reducing the risk of and managing age-related chronic disease.

Most of our knowledge of gut microflora comes from studies in humans. Microbiologically, the gut can be thought of in terms of three principal regions: the stomach, small intestine, and colon. We have talked about the different types of bacteria that live in each region and the contribution they make to alteration in gut immune function. Most often, people have focused their interest on understanding colonic bacteria, but the small bowel bacteria can also play a role in modulating immune function, opening portals of entry through small mucosal barrier function breakdown ("leaky gut"), and delivering molecules of greater

weight to the immune system that can perpetuate its upregulation. It is now like a dog chasing its tail- leaky gut leading to more entry of these molecules that further initiate and upregulate the inflammatory components of the immune system. These molecules further break down the integrity of the gut mucosa, leading to more entry and so on down the line, leading to a spiraling effect of influence on immune function.

Food Allergy and Dementia

These effects can be either acute or chronic. I am always reminded of the interesting statistical relationship between chronic gluten sensitivity (and people who continue to eat wheat in their diet) and early-stage dementia. How would the brain be connected to the gut and the diet? The model we are describing, through the gut/immune system and imbalances and upregulation of Th1 and Th2 activity, may help us to better understand that. If a person eats a food to which he or she is sensitive, it alters the gut environment, alters the bacterial population, alters the antiinflammatory balance in the gut mucosa, and leads to upregulation of proinflammatory mediators. These mediators communicate and translate their messages through the portal blood to the Kupffer cells in the liver, which send out messenger molecules to the circulating white cells in the blood. The white cells send out their message or molecules to the blood-brain barrier, which influences the activity of the microglia, the brain's immune system, upregulating inflammation in the brain, and ultimately leading to neuronal apoptotic death, which leads to dementia. That is the emerging model connecting food allergy to dementia, or food allergy to neurological symptomatology, through activation of imbalance in the GALT and its interrelationship with altered gut flora. This is an important emerging part of the story.

The particular model I have just described was discussed during a recent presentation at the WALTHAM International Science Symposium, titled "Nature, Nurture, and the Case for Nutrition." The title of the paper is "Bacteria in the Gut: Friends and Foes and How to Alter the Balance,"[10] published in the *Journal of Nutrition.* It offers a good indication of how differing substrates influence different bacteria, and how different bacteria can influence gut immune function. In this article, the authors talk about probiotics, as well as prebiotics. I want to differentiate a prebiotic from a probiotic.

Prebiotics versus Probiotics

Prebiotics are substrates that specific bacteria can ferment or live upon. An example of prebiotics would be fructooligosaccharides (FOS) or arabinogalactans. These are specific types of carbohydrates unique for the fermentation support of specific bacteria. The key with a prebiotic is to feed the food useful for the bacteria that one wants to promote at the expense of starving the bacteria one does not want to promote. The combination of pre- and probiotics has been used to create enhanced GI proliferation of friendly bacteria, altering or lowering the pH and increasing short-chain fatty acid production. These would be things like butyrate, a gut fuel used by the colonocyte for its metabolism. Increasing butyrate production by stimulating probiotic organisms through the use of effective prebiotics enhances physiological outcome.

Substrates for Gut Colonic Bacteria

In the *Journal of Nutrition* article, the authors talk about the different kinds of substrates used for gut colonic bacteria, or enteric bacteria. They talk about FOS versus high-maltose corn syrup versus cellobiose, isomalto-oligosaccharides, lactose or maltose, and high fructose-containing corn syrups, raffinose, stachyose, and sucrose. When looking at different microorganisms, one can see that some proliferate when fed the appropriate substrate. For instance, *Lactobacillus reuteri* had virtually no growth

on sucrose, but had very high growth on oligosaccharides. One would want to feed the appropriate type of substrate as a prebiotic, along with a probiotic to improve the function of the specific family of bacteria. That becomes part of what we have often called in functional medicine parlance, the "4R Program."

Recall the four Rs: *remove* the unfriendly bacteria, parasites, and food allergens; *replace*digestive enzymes and acid, where necessary, to acidify the chyme; *reinoculate* with friendly pre- and probiotic organisms; and *repair* using nutrients such as glutamine, vitamin E, zinc, magnesium, and pantothenic acid, all of which are helpful for repairing gut mucosal integrity.

Small Intestinal Bacterial Overgrowth

What about small intestinal bacterial overgrowth? That is another interesting part of the story. IBS is highly prevalent in our society. Eleven to 14 percent of our population suffers with IBS. It is a diagnosis made principally on the basis of meeting clinical criteria. The symptom-based approach has been used because no consistent biological marker or unifying framework has been available to explain the different symptoms. Constipation, diarrhea, pain-diarrhea-constipation are predominant symptoms in IBS. It is basically more a symptom definition than a pathognomonic diagnostic marker in defining IBS.

Another way to look at IBS symptomatology may be to emphasize the differences rather than the similarities in patients. There is a close correlation between IBS and other conditions like chronic fatigue syndrome (CFS) and fibromyalgia (FM). We reported this over ten years ago and it seems to be well characterized in subsequent studies that the chronic problem of gut function appears to be tied to other types of energy/fatigue-related disorders and alterations in the hypothalamus-pituitary-thyroid-adrenal axis (HPA). It is now well recognized that the GI and immune effects of small intestinal bacterial overgrowth provide a possible unifying framework for understanding frequent observations seen in IBS. These include postprandial bloating and distension, altered motility, visceral hypersensitivity, and abnormal brain/gut interaction that produce fatigue- related and sleep disorders, autonomic dysfunction, and immune activation.

One might say that what I just discussed sounds like something out of a functional medicine textbook. When I talk about small intestinal bacterial overgrowth being associated with that wide a range of symptomatology, including postprandial bloating and distension, it is fairly evident it is a GI-related function. What about visceral hypersensitivity or abnormal brain/gut interactions leading to sleep disturbances and what has often been called "foggy brain syndrome" and fatigue-related syndromes? What about systemic immune dysfunction? Those conditions sound less likely to be commonly associated with an IBS diagnosis, and probably do not fit into a traditional medical model. Yet, that particular collection of symptoms I just described is actually a list I quoted out of a recent paper in the *Journal of the American Medical Association*, titled "Small Intestinal Bacterial Overgrowth. A Framework for Understanding Irritable Bowel Syndrome."[11] It contains an interesting recapitulation of what has been talked about in functional medicine for over ten years relating to the interrelationship between bacterial overgrowth, altered flora, and alterations in gut immune system, which also has effects on cell signaling to neurotransmitters.

This particular association takes us across a wide range of function. Dr. Mary Ellen Sanders, our Clinician/Researcher of the month, will share with us later that various types of probiotics can ameliorate arthritis in animal models and can have systemic antiinflammatory effects through signaling in the gut. I am quoting from a paper that appeared in the *Journal of Nutrition*.[12] Alteration of gut signaling through

flora can alter glucose tolerance. Increasingly, we are realizing that insulin resistance may be associated with altered gut flora, as well. I am now quoting from two papers that appeared in *Current Opinion in Clinical Nutrition and Metabolic Care* on glucose tolerance and the gastrointestinal tract.[13],[14] The authors talk about the proper maintenance of gut flora and proper GI tract immune system function for improving glucose tolerance.

Arthritis and its relationship to gut inflammatory disorders, the relationship of glucose tolerance and insulin sensitivity to such wide-ranging dysfunctions as the gut/brain connection that relates to "foggy brain" or dysphoria or fatigue-related symptoms, and perhaps even activities related to energy production in myocytes associated with FM-all of these have been implicated as having a gut immune-related functional connection.

There is an interesting model emerging for immune system modulation, using the gut immune system as the triggering or signaling device. By focusing therapies on this organ through adjustment of the environment, implementing the appropriate "4R Program," and using the appropriate pre- and probiotic intervention tools, we may see remarkable species-specific alteration in immune function leading to the remediation of many age-related chronic disorders.

We are ready to move into a discussion with our Clinician/Researcher of the Month, who will take this platform to a whole new level of application using the gut and probiotics as a tool for modulating systemic function

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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JB: There is one therapeutic area of intervention in medicine that has been getting more and more attention recently, and that is the area of probiotics. For years, I have been thinking that we need to do an issue of FMU on this topic with a leader in the field of probiotics who can help us to understand what this category is all about. What is a probiotic, how is it defined, what are its standards, how does it work, and what does it do?

We are fortunate to have a colleague with that knowledge in her experience base-Dr. Mary Ellen Sanders, a consultant at Dairy and Food Culture Technologies in Centennial, Colorado. I've had the privilege of meeting Dr. Sanders on several occasions. She has a broad-based background in probiotics, going back more than 20 years. Her experience brings to bear the techniques and tools that define probiotics as an important category in therapeutics. With that brief history in mind, I would like to introduce Dr. Sanders to our FMU audience. Thank you for being with us, Mary Ellen. For those who might not be familiar with probiotics, I would like to begin by asking you to define the category, and discuss its origin and history.

MS: Thank you for having me on FMU. I appreciate this opportunity to share some information on

probiotics. 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.

JB: In the human GI tract, there are hundreds of different species of live organisms, and in our food, there are hundreds more species. This leads to a potential cornucopia of things that could be of benefit or of harm. How did one seek out those that were considered favorable probiotics, and what are those species?

Favorable Species of Probiotics

MS: As you mentioned, there is a wide range of microbes. Some that inhabit our intestinal tract are pathogens that are clearly bad for us. There are other microorganisms, those that constitute the majority in the GI tract, that probably have neither harmful nor necessarily beneficial effects. There are microorganisms on the other end of the spectrum that seem to show very positive effects. 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 on trying to specifically delineate the advantages of particular strains of those groups of bacteria.

JB: There is a wide range of taxonomic varieties of microbiological organisms. You have defined two families that appear to be quite important. How do we know what we have? What is the mechanism used to define what we have?

Microbiological Techniques for Identifying Components of Microbiota

MS: Microbiological techniques have been in the process of development for over 100 years. Microbiologists now have tools to sort out and select for different microbiological components of the GI tract that help them identify specific components of microbiota. There is also a variety of culture techniques. For example, growth on culture medium, and then plating on agar-coated plates specifically designed to be selective for particular groups of microorganisms, have helped microbiologists identify the presence of different components. Over the past 10 or 15 years, we have also seen an explosion in techniques based on the genetic complement of particular organisms. Now, we can use DNA-based techniques to probe for particular organisms that we are looking for as part of the group of microbes that inhabit the GI tract.

JB: Not too long ago, I recall reading an editorial in which the authors discussed a molecularly-engineered or genetically-engineered bacterium that had specific favorable characteristics in the GI tract. Is there a trend toward genetic modification of these organisms, or are we still looking for the most favorable organisms through the natural selection process?

Genetically Altered Microbes

MS: Natural selection is the backbone of most procedures, but specifically designed, genetically altered microbes are being considered, probably more for specific therapeutic applications than, for example, applications through dietary supplements or in food products. Another area of research includes studies targeting delivery of certain antiinflammatory cytokines through probiotic bacteria, and delivery of certain vaccine epitopes through bacteria that are orally fed. I think we will see genetic development of very targeted probiotic bacteria, but those will likely come out in a range of therapeutic products, initially at least.

JB: Is there a dividing line between products considered as drugs in the area of probiotics versus those considered as dietary supplements or food, and labeled GRAS (generally recognized as safe)?

MS: Yes and no. A genetically engineered probiotic bacterium would not be considered a GRAS organism that could be used as part of the food supply without required review by the FDA. I'm not a regulatory specialist. However, my understanding of regulatory issues is this: whether a probiotic is considered a food, a dietary supplement, or a drug, has a lot to do with how it's labeled and presented to the public. It also has to do with what types of claims are made for its use, where the organism is isolated, and what types of natural selection screening processes were conducted to select it. For example, certain types of intervention would preclude an organism from being used in food without evaluation, such as genetic modification. The same microorganism might be considered as a food, a dietary supplement, or for therapeutic use, depending on how it is labeled and what types of studies were done to support its use.

JB: Is it safe to say that the probiotics now commercially available are non-GMO (genetically modified organisms), based on what you just said? Or, are there GMO-products that have found their way into the market place?

MS: I don't know of any GMO probiotics currently being sold. I would say that's very likely. They are all non-GMO at this point.

JB: Let's move to physiology. Presumably, each of these species of organisms has its own unique biochemical machinery, as determined by its genetic lineage. Each produces different primary and secondary metabolites, which has something to do with their influence on physiological function. Would you tell us about the influence of some of these organisms on physiological function?

MS: Probiotics cover a range of bacteria. I mentioned two different genres-Lactobacillus and Bifidobacterium. These are commonly used as probiotics. They have different metabolic capabilities. All Lactobacilli have a certain number of traits in common, but within the genus Lactobacillus, there are dozens of different species, each of which can be distinguished based on other types of traits. Sometimes, those are certain physiological or metabolic characteristics. And sometimes, it has to do with variation in the way they evolved and the genetic complement that allows them to be split into different taxonomic groups.

We are at a phase in molecular taxonomy where people who like to split up groups into different ones based on homology are ruling the day, and more and more species are being identified. This is sometimes based on genetic complement and homology, more so than clearly identifiable, specific functional metabolic or physiological traits of the organism. But, clearly, there are many species and they all have different characteristics. Interestingly, there is a tendency in the field to try to attribute certain capabilities

on physiological effects in the human, or in the host, and tie that to a specific species. We've found that the different species are almost as important as the different strains, each of which may have its own individual characteristics. The analogy I like to use is that of different breeds of dogs. All dogs are the same species, but different breeds of dogs have very different characteristics. The German Shepherd might be a good watchdog, and the Golden Retriever might be a good hunting dog. They are all the same species, but they have individual unique traits that better suit them for different characteristics. That's the same type of thing that can go on within strains of particular species of particular genres of probiotic bacteria.

JB: That's very helpful. Metchnikoff undoubtedly was using Lactobacillus vulgaris, or some genre species of that type. Now, we have become much more precise in how we define some of the individual strains within those species. What do we currently understand about the strains' specific activities?

Evolution of Research on Probiotics

MS: 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 show 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 the modern, molecular techniques to identify what strains are being used and what is being documented for those particular strains.

JB: Before we discuss the clinical effects of probiotics, I'd like to talk briefly about potency and quality assurance/standards-related issues. In 2002, you were elected by your peers to be the first president and chairperson of the Board of The International Scientific Association for Probiotics and Prebiotics, a group that is working hard to understand what constitutes the standards for these products, these organisms. Would you tell us where we are in that process and whether we agree or don't agree about what the definitions are?

Standardization of Probiotics

MS: We are closer to a fairly agreed-upon definition of probiotics. There was an international consultation assembled by the Food and Agriculture Organization (FAO) branch of the World Health Organization (WHO) back, I believe, in 2002, which put forward a definition for probiotics which I alluded to earlier. "Live microorganisms, when consumed in adequate amounts, confer health benefits on

the host." It doesn't seem like a very difficult thing to do, but there have probably been nine or ten or more published definitions of probiotics, all of which all varied slightly in terms of the requirements. That definition was put forward by expert consultation and it has received fairly good acceptance worldwide, although there will always be dissension among certain people in the scientific community.

In terms of standards, at least on an international basis, they do not exist. I think anyone in the probiotics industry understands what it takes to market a responsible product, but in terms of having standards imposed by government agencies or other types of watchdog groups, they don't occur, at least to my knowledge. For example, in the United States, you can buy a probiotic product and there really isn't anyone watching. There aren't any standards you have to meet that require what levels or what specific types of bacteria are contained in your product.

However, there are very general recommendations for standards. In the United States, you have to label your product in a truthful and not misleading fashion. Exactly what that has meant for the dietary supplement industry in the United States has been open to interpretation by the manufacturers. The FDA has not taken action against supplement manufacturers unless their products are labeled as drugs or are deemed to be unsafe. For example, a company is not held accountable for meeting claims of particular potencies in their products, or to meet standards requiring that the types of organisms in their products match what is claimed on the label. We have a long way to go, domestically as well as internationally, to get enforceable standards in place. There are guidelines, however. There was an FAO action that did publish some guidelines for the production of probiotic products that are available.

JB: We have talked about potency (the number of organisms per gram), that the organisms have to be bile-acid resistant, adhere to the GI mucosa, and be able to proliferate within a medium consistent with the GI environment, i.e., be viable. Are these reasonable standards for evaluating how they are going to work clinically, or are none of those four standards that closely tied to the clinical arena?

Clinical Evaluation of Probiotics

MS: In terms of doing a clinical evaluation, you have to know, as I mentioned earlier, what organism or blend of organisms you are looking at. You have to know the genus, the species. You have to have some handle on strain-specific patterns that you can identify and what organism you're testing. Those are the minimum criteria. One of the things that's confusing in the area of probiotics is what many people have asserted are "requirements for a probiotic." In the published literature, you'll see many papers describing what a probiotic "must be," followed by a list of things. Common to those lists are phrases like "of human origin," "must be bile-resistant" (for survival in the small intestine); "must be acid resistant," (for survival in the stomach); "resistant to pancreatic enzymes" (for survival in the small intestine); "must be able to survive transit and be isolated from human feces"; and "must be able to adhere to intestinal epithelial cells."

I take a much more pragmatic approach. There are many well-documented probiotic strains, for example, from species that are not normally thought to be indigenously associated with the human GI tract. Therefore, saying that a strain needs to be of human origin and, by that, I assume what they mean is that it is a normal inhabitant of the intestinal flora of humans, is not necessarily a prerequisite for probiotic function. Sometimes, these organisms traveling through the intestinal tract are able to exert influence on the physiology of the host.

Regarding other attributes I mentioned, such as surviving stomach acid or resistant to bile, if the

physiological effect you are looking for as an endpoint is the ability for them (probiotics) to replicate in the colon, then that would be true. They would have to be resistant to acid and resistant to bile. But there are certain characteristics, for example, of probiotics that have been found to help decrease Helicobacter pylori colonization of the stomach. Bile resistance would not be a trait important to a probiotic targeted to the stomach.

There are probiotics that have been tested and shown to decrease the incidence of dental caries in children. Again, bile resistance is not going to be an important trait for a probiotic organism used in the mouth or oral cavity. From my point of view, the list of required probiotic traits is a pretty small one. My list would include that the organism has to be alive; it has to be safe for human consumption; and it has to be able to be technologically produced in a manner that can deliver the viable organisms in the final product at high enough levels to be effective. Short of that, the rest of the list becomes very host target-site specific, if that makes sense.

JB: That was a helpful differentiation. That leads me back to the question of relative potencies-the number of organisms per gram. Is this a pretty good standard to use for the evaluation of potency or, is that also subject to question?

MS: I think it's the best we can do right now. A probiotic organism, by definition, is a live microorganism that is delivered to the host. Therefore, we need a handle on standardizing the organisms in terms of numbers delivered. That will always be part of the story. Another issue to consider, however, is that potency, in terms of how many are required, can be different for different applications and for different microorganisms. When I'm asked how many are needed, I always tie it back to how many were used in the scientific publication that documented the effect. Then I can tell you how many you need to use in your product. The number used always has to be tied to the scientific study documenting efficacy. That may be different for different strains. You may be able to deliver 100 million of some strains and achieve an effect, but for other strains, you may need to deliver 100 billion in a day to achieve an effect. That needs to be tied to the specific studies that show the impact. Therefore, I would not necessarily be a supporter of broad scale recommendations or standards that state one needs to have a minimum number in a product. More important is that the product has to labeled accurately and has to deliver an efficacious dose, regardless of what that dose is.

JB: That's also very helpful. It appears there are at least two broad mechanistic approaches to physiological activity of probiotics in the host. One could be the release of secondary or primary substances from their metabolism that influence physiological function of the host in some way. Another could be an interaction between cell wall constituents and, as they travel through, they interact with receptor sites on the GI mucosal surface, which has an intracellular signaling process. It doesn't require any release of substances; it's more the environment of whatever the messages are on the cell wall of that specific strain. Can we make sense of how probiotics work mechanistically?

Mechanisms of Action

MS: Both of the mechanisms you just described are exactly what people are focused on. It's the ability of the organism to interact with cells as it's traveling through the intestinal tract. That's a general description, because there are many, many different types of cells. Therefore, there are many different types of potential interactions that can occur. Very clearly, these organisms have been shown to have the ability to influence immune cells, and there are many different types of immune cells. The gut is the largest

immune organ in the body. Therefore, the types of interactions you mentioned very clearly take place. Interactions with different types of intestinal cells have also been shown. In cell culture work, an interaction has shown enhancement of mucus secretion ability of intestinal epithelial cells. These organisms have the ability to decrease pathogen colonization and growth at different sites. That may be a function of competitive exclusion using, as you mentioned, metabolites and end products of growth by these organisms. They produce quite a few organic acids and other types of short-chain fatty acids that can interfere with pathogen growth. Or, it may be steric hindrance in terms of interfering with binding sites on the cell surfaces. It could be an enzymatic interaction where toxins or toxin receptors are degraded by these organisms. There are a variety of mechanisms that have been suggested in terms of how they might interact and ultimately exhibit their effects. You gave an excellent summary of the two possibilities.

JB: We have discussed the isolation, the history, the characterization, the standardization, and the potential mechanisms of probiotics. It's time for the payoff. Tell us about the clinical effects-the range of things these organisms may be useful for as therapies.

Health Promotion Capabilities of Probiotics
MS: Before I begin this discussion, I want to say that when you talk about probiotics, a general discussion can be very misleading. Oftentimes, generalizations are made to the category as a whole. If I start listing attributes or health-promotion capabilities of particular strains of probiotics, there may be a tendency to think that all probiotics can do all of these things. Of course, they can't. Even if they could, we haven't done the studies to show that they can. As I go through a discussion of the types of very exciting research that's been done to document physiological effects on humans, the listener has to keep in mind that any one of these effects has probably been documented with only one or a handful of different probiotic organisms. It's not a function of taking any probiotic available today and seeing these benefits. That's the underlying thinking that has to go into a discussion about effects. However, I will try to delineate some of the areas of research that have been the most promising with probiotics. It's up to people to make sure that any product is scrutinized for its documentation.

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. 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. Dairy products can be better tolerated by people who are consuming certain live microorganisms, either as part of yogurt or a probiotic 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. There are 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 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 that can help control many of the different problems.

JB: I think I've seen a paper or two recently discussing the role of probiotics in atopy and allergy in children. Is that another area of research?

MS: Yes, and I meant to mention that. I put that in the category of regulation of immune function. There have been some excellent studies done in children showing the downregulation of the allergic response. One study published in Finland showed a dramatic decrease in the incidence of atopic dermatitis in infants whose mothers, when they were pregnant, had been administered a probiotic, and the children received it up through the first six months of life.[15],[16] It was a randomized, double-blind, placebo-controlled trial. The control group had twice the level of atopy at two years of age as the intervention group did. It showed a dramatic ability of the flora and the particular probiotic intervention, to downregulate the allergic response and to appropriately gear the immune system for normal responses.

JB: Let me ask you about the up- and downregulation of the immune system. For instance, if the wrong strain is used, one that upregulates the immune system in an inflammatory patient, it might exacerbate the problem and result in a negative outcome.

MS: That's a very fair comment. I think we're going to learn a lot more in upcoming years about how particular bacteria interact with each other. In animal studies, there does seem to be some evidence that one particular component of a blend may either modulate the ability of another probiotic component to engage in certain functions with the immune system. I don't think the story has been told yet about how those are going to interact. In dealing with people within a reasonably normal range of capabilities, there doesn't seem to be any evidence of hyperstimulation of immune function, or downregulation of inflammatory activity to the point of not being able to appropriately respond to some type of a pathogen infection. There seems to be more of a modulation effect.

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.[17]

JB: That's very helpful information. For the clinician, that's probably the best guidance. They are obviously not able to spend the time you would spend understanding all the research subtleties in the literature. A question they might ask is, what is the published work for this strain against the condition of my interest? It seems that everything we've talked about distills down to that question.

Thank you very much, Dr. Sanders. This has been most interesting and it's been a good synopsis that many of our listeners have been looking for related to this category of therapeutic agents. For many people, it might have sounded strange to consider administering a live bacterial culture orally to someone when they were trying to treat bacterial diseases with antibiotics. This offers a different approach, using the appropriate symbiotic personality of these organisms to do something favorable. You've given everybody the foundation they need to gain more confidence as they move ahead with this category.

MS: It's been my pleasure.

JB: We wish you the very best and we'll check in with you in the future.

Yogurt and Gut Function

Once again, we want to thank Dr. Sanders for a superb description of this complex category and her help in raising our level of understanding. She mentioned something I thought would be worthwhile closing on, and that is the relationship of probiotics to the yogurt connection. As she mentioned, Dr. Metchnikoff was probably responsible for first introducing these cultured milk products. In recent years, numerous studies have been published on the health benefits of yogurt and bacterial cultures used in the production of yogurt. In the United States, these lactic acid-producing bacteria include species of *Lactobacillus* and *Streptococcus*, and they have been discussed in a variety of publications. Yogurt is one of the best known of the foods containing probiotics and it is defined by the *Codex Alimentarius* of 1992 as a coagulated milk product that results from the fermentation of lactic acid in milk *by Lactobacillus bulgaricus* and *Streptococcus thermophilus*. It has this characterization, a history of safe use, and a standard identity. Therefore, is giving yogurt the way to do probiotic therapy?

Other lactic acid bacteria species are now frequently used to give the final product unique characteristics. We have talked about *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, but there may be other organisms that have been used, depending upon the manufacturer and what they have spelled out on their labels. A carefully selected mixture of these *Lactobacilli* species is known to complement one another. We are beginning to see yogurts that have mixtures of species to optimize the low pH and high acidity of the GI environment. One might ask if probiotic therapy, giving yogurt, is the same as giving concentrated organisms as a therapeutic agent. It depends somewhat on whether we are talking about the prophylaxis

and prevention versus the therapeutics, as Dr. Sanders and I discussed earlier. If we are talking about a high-potency product going to a dewatered viable concentrate of organisms, that will result in a much higher potency per dose than yogurt. However, if the organisms are viable and have not been pasteurized and killed, yogurt can have some positive benefit as a prophylactic with general immunological-balancing properties pertaining to GI function. Numerous studies suggest beneficial effects of yogurt consumption on GI health. However, results have been inconsistent, which may be due to differences in the strains of lactic acid-producing bacteria, routes of administration, and investigational procedures used in these studies.

If we were to examine the clinical applications, it would appear that the more highly defined concentrates that have published research with specific dosages is preferable to that of using yogurt in clinical therapy, but it does not suggest that yogurt is of no value at all. Yogurt does have value, certainly in the general area of gut health. If you would like to read a good review paper on this topic, Drs. Simin Meydani, Robert Russell, and Oskar Adolfsson-investigators at Tufts University Medical School, USDA Human Nutrition Center on Ageing-have published a paper in the *American Journal of Clinical Nutrition*, titled "Yogurt and gut function."[18] This article contains a good overview of the effect yogurt consumption has on fecal flora. The authors also talk about some of the clinical applications of yogurt in diarrheal disorders; reducing the risk to colon cancer; helping with milk sugar digestion by supplementing lactase, the milk sugar digesting enzyme in individuals with lactase deficiency; and helping patients with IBD so they have less susceptibility to relapse. All of these are interesting discussions of differing strains of bacteria that have been recently been employed in yogurt, and how they might also play a role in the functional food approach toward improved GI health.

Thank you for being with us this month. We will see you in 2005.

I would like to follow up on Dr. Kellman's clinical comments about borderline subclinical hypothyroidism and its importance in health care, and talk about dysphoria and later dementia in postmenopausal women. The thoughts Dr. Kellman shared with us about the role thyroid metabolism plays in central nervous system (CNS) function is germane to the increasing number of women in the current postmenopausal age group who have historically been candidates for taking conjugated equine estrogens (CEEs) and synthetic progestins—also called hormone replacement therapy, or HRT—for the management of postmenopausal health risks. Women were told that CEEs would reduce risk to bone loss, lower the risk to cardiac disease, improve cognitive function, and lower the risk to dementia. It was a clinical approach that appeared to be the "be-all and end-all" for managing problems associated with postmenopause.

Now that the data from the Women's Health Initiative (WHI) studies have been published, we know that panacea was not realized. There is now a more cautious view of the role of mixed CEEs. It is not that they have no value; it is that the kind of excessive support for their application has diminished considerably in light of some of the more recent evidence. That also holds true as it relates to estrogen and dementia. Recently, in the *Journal of the American Medical Association*, two back-to-back papers were published that discussed the issue of HRT and dementia or mild cognitive impairment in postmenopausal women.[9],[10]The editorial that followed those two articles sums it all up. The author states that there is no evidence from the WHI data that the implementation of mixed CEE intervention did, in fact, help protect against the loss of cognitive function. The author further states that there may be some evidence that CEE intervention increased the loss of cognitive function.[11] That was not good news. The final message

appears to be—do not use CEEs to try to improve cognitive function in postmenopausal women, whether alone or as part of HRT.

Nutritional Intervention in Postmenopause

What are the alternatives? How do we keep mood, mind, memory, and behavior intact? Some individuals have suggested that nutritional intervention with soy proteins containing phytoestrogens that function as selective estrogen response modulators (SERMs) may be an alternative. There is a paper in the *Journal of the American Medical Association*, titled "Effect of Soy Protein Containing Isoflavones on Cognitive Function, Bone Mineral Density, and Plasma Lipids in Postmenopausal Women."[12] In this trial, 25.6 grams of soy protein containing 99 mg of isoflavones were taken daily versus milk protein as an alternative. The authors conclude that this double-blind randomized trial does not support the hypothesis that the use of soy protein supplements containing isoflavones improves cognitive function, bone mineral density, or plasma lipids in healthy postmenopausal women, when started at the age of 60 years or later.

I do not want to throw out the baby with the bath water with this study. Clearly, there is a considerable body of literature that indicates there are many benefits in terms of improved endocrinological function, using diets that include soy protein and isoflavones at normal dietary cultural levels. But soy isoflavones, at least at that level, are not a panacea to help protect against the loss of function that occurs postmenopausally. What other nutritional associations are linked to bone loss, cardiac function, lipid panels, and CNS function? Once we ask that question, it comes back to looking at thyroid function. Therefore, intact thyroid function is very important. There is an estrogen/thyroid connection, a connection of calcitonin and thyroid function, and a connection of T3 to CNS function. The story begins to evolve as a functional web to support continued high-level CNS function in postmenopausal women.

We should look at things that might lower thyroid activity—food allergies, and gluten and its association with autoantibodies against the thyroid gland. We should look at selenium in the diet to make sure there is adequate conversion of T4 to T3. We should look at zinc, another important mineral for the proper sensitivity and metabolism of thyroid hormone. We should look at iodine to make sure it is adequate but not excessive in the diet to support proper thyroid hormone formation. We should look at things in the diet related to support of proper adrenal function. We should look at exercise, stress management, and things that help lower excessiveadrenal output of cortisol. We should look at things that help to stimulate insulin sensitivity because that will have a salutary benefit on thyroid hormone metabolism and sensitivity. We have discussed some of those things in previous issues of FMU, such as a diet with a lower glycemic load; cinnamon for improving insulin sensitivity; and lipoic acid, another insulin-sensitizing or supportive nutrient. What I am speaking to here is, as Dr. Kellman pointed out, broadening our perspective—moving from a slit to a window of opportunity. Often in medicine, we go from big and are trained to think small, rather than starting with small and going to big, and connecting the issues that may control the outcome of the variable we are analyzing in a patient.

There are many nutritional associations we should be attending to in conditions of bone loss, dyslipidemia, and CNS dysfunction in postmenopausal women that go beyond estrogen. Thyroid function, metabolism, and activity, and its interrelationship with insulin, cortisol, calcitonin, and things relating to parathyroid function, are all extraordinarily important. Parathyroid function takes its message, in part, from the calcium and phosphorus ratio of the diets. Women who drink a lot of soda pop and other synthetically sweetened beverages, may be getting a fairly high dose of phosphorus as the phosphates in

cola drinks, but fairly low levels of calcium. They have an interrupted calcium-to-phosphorus dietary ratio that may induce secondary hyperparathyroidism, having an adverse effect upon thyroid hormone balance and calcitonin.

All of these things are interwoven. That is the excitement of functional medicine—putting the system into a context for clinical management so the whole person is being treated, not just the disease. The challenge is that it requires making a lot of thoughtful connections that may be more complicated than simply jumping to the conclusion of a diagnosis. I hope that Dr. Kellman's message came across strongly—that the payoff for that cerebral process for developing those relationships, is better patient outcome and solutions to complex, chronic age-related dysfunctions that are not amenable to polypharmacy.

There is an interesting paper in the *American Journal of Clinical Nutrition* which examines nutritional associations beyond soy isoflavones, having to do with bone loss, serum lipids, and CNS functioning in the postmenopausal transition.[13] These are things like calcium, flavonoids from fruits and vegetables, and various vitamins and minerals, as I have previously described.

Asking the Right Questions

A lot can be done once we ask the right questions. There is a common theme that comes through in every discussion we have had to date in FMU and that is, the questions you ask determine the answers you receive. If you do not ask the question, it is unlikely you will receive the answer. In functional medicine, one of the principal components of our teachings involved in gaining competency is learning how to ask the right questions. Once you ask the right questions, there are a multitude of places where you can find the answers. With the advent of the worldwide web, and accessibility of Medline and PubMed to virtually anybody with a computer, we can now find answers if we know what questions to ask. The difficulty in medicine has historically been to distill down the number of questions to a very few so that one will get "the right answer." That lowers reinforcement for asking questions and begins to make it a disadvantageous part of a daily practice. The fewer questions one asks, the better off and more efficient and effective one should be. That is antithetical to the functional medicine model, which basically states that the more questions one can ask to help connect important strategies for the management of complex symptoms in the patient, the more successful one will be in the outcome. That is what Dr. Kellman was referring to regarding how he approaches thyroid-related dysfunctions.

Thyroid function is an example of both the complexity and simplicity of functional medicine. There is a tremendous amount of information about the thyroid. We have only scratched the surface. We could discuss the topic for tens of hours. But through drilling deeper into the understanding of the thyroid, we start to explore and understand other connections as well, such as those of insulin, cortisol, testosterone and progesterone, and estrogen, which help us to understand how the body functions to improve the efficacy of patient outcome.

I hope I have provided you with some good takeaway information about using the thyroid panel and how to evaluate patients with subclinical borderline hypothyroidism.

We will see you in December.

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