December 2006 Issue | Patrick Hanaway, MD Genova Diagnostics

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Welcome to *Functional Medicine Update* for December 2006. Can you believe that we are again at another end of a year? How the time flies when we are having fun.

Questions and Answers
We are very fortunate to have in the ranks of our functional medicine colleagues some people with remarkable minds. These are thoughtful and conscious individuals who are constantly searching for truth. One who stands head and shoulders above most of us is Dr. Sidney Baker. After the Symposium on biotransformation and detoxification held in May of 2006, Dr. Baker asked me a very insightful question related to the presentation of T. Colin Campbell, from Cornell. The question was about the effect of dietary proteins on hepatic detoxification processes, and aflatoxin conversion to the carcinogenic form of aflatoxin on the high animal protein diet. Why is it that in studies where animals are exposed to aflatoxin, vegetable diets do not seem to activate carcinogenesis whereas the animal protein diets do? What is going on?

I think that is a very insightful question. It raises the issue of whether it is just protein, itself, or if it is something else that might come along with protein (part of the unique personality of animal versus vegetable protein).

I'd like to cite a couple of interesting papers that bear on this. One was in the *Journal of Nutrition* in 2001, which talks about the inducibility of hepatic CYP4501A enzymes by a known carcinogen in animals fed diets that either had animal protein or vegetable protein.[1] The authors found that the carcinogen was not activated after a vegetable protein diet, but was after the animal protein, suggesting that the source of dietary protein may have something to do with the inducibility of the liver enzymes that go on to produce the ultimate carcinogens. Another paper described a difference in carcinogen activation between soy protein isolate-fed animals and casein milk protein-fed animals.

It appears as if there is something within the constitution, structure, or function of dietary protein that has an influence on CYP450 activation of carcinogens, with the animal proteins having higher activations than the vegetable proteins. This is certainly something worth further explanation. It may help us to someday understand the difference of cancer risk from differing types of diet. Thank you, Dr. Baker, for getting us pointed in this direction.

One of the things that we have learned in functional medicine over the years is the importance of the gastrointestinal tract in establishing a tone of overall systemic physiologic function, particularly as it relates to immune function. This issue-the December 2006 issue- is going to focus on gut-immune

function and also some collateral activities of the gut as a functional organ, beyond that of its being a conduit pipe that takes things from the north to the south in the digestive process. The gut has multiple functions, and those are the things we'll be focusing on in the course of this month's *Functional Medicine Update*.

As you probably recognize, one of the many functions that the gut is involved with is the synthesis of cholesterol. We often think of the liver as being the principal site of cholesterol biosynthesis, which it certainly is, but the gut also plays a role in de novo cholesterol biosynthesis.

When a person is on cholesterol-lowering medications, they are influencing not just hepatic de novo biosynthesis of cholesterol, but also having an effect on the gut function. There is a movement among some professionals to use more and more of the statin medications to lower cholesterol. Within this group there is this sense that statins are benign and completely safe and that we should use them aggressively to lower LDL cholesterol below 90, or even below 70 (based on some of the more recent suggestive data). But what are the impacts on immune function? What are the impacts on hepatobilary function? What are the impacts on gastrointestinal function of making statins a part of virtually everyone's lifestyle in order to get their cholesterol LDL levels below this target of 70 mg/dL?

I was very intrigued to see that in a 2006 issue of the *British Medical Journal* an interesting, controversial article by Swedish investigators was published titled "Should We Lower Cholesterol as Much as Possible?"[2] One of the coauthors of this paper is Mark Houston, who is a well-recognized leader in our functional and integrative medicine arena; he is a clinical professor of medicine (internist/nephrologist) at Vanderbilt University School of Medicine. I think this paper is quite a dramatic story that we should be paying serious attention to.

Statin Doses and Target LDL Levels

The article states that to evaluate whether higher statin doses are safe, and to get people down below the new target LDL level, we would have to go above the equivalent of 80 mg of atorvastatin daily. It has been suggested (from looking at various clinical studies on the use of statins) that the dose of statins would have to be more than 8 times higher than currently used to have the population achieve this target level of LDL.

What does that really mean in terms of potential adverse side effects? We know with higher doses of statins overall mortality is not reduced, because the smaller number of cardiovascular deaths in the 80 mg statin group was offset by increased deaths from other causes, leaving a benefit of fewer non-fatal cardiovascular deaths of very marginal significance. What we are really talking about is risk-benefit trade-off.

If we look at the actual number of adverse side effects that appear in these higher-dose statin trials, they are much higher (say the article authors) than we normally hear about. Muscle complaints are claimed to occur in less than 1 percent of patients taking statins, but in a study of 22 professional athletes with familial hypercholesterolemia who were treated with various statins, 16 of the 22 discontinued the treatment because of muscle side effects. We also look at other kinds of studies looking at myopathy and rhabdomyolysis and death from renal failure, and, again, in a recent review of statin side effects, 4.2 cases of rhabdomyolysis per 100,000 patient years after atorvastatin were found. If true, it could mean that the side effects are twice as common than previously acknowledged.

There are also some other issues that have been discussed in the literature, like mental and neurologic symptoms. We know that cholesterol is vital for the development of function of the brain and nervous system. We can see (in people on statins) functional changes in mental and neurologic function (things like irritability, aggressive behavior, suicidal impulses, and cognitive impairment).

In animal trials, statins have been found to be carcinogenic and alter signaling pathways for cell cycling through the farnasyl transferase reactions. This has been suggested to track against the increased cancer seen in these animals. Significant increase in breast cancer was seen in the cholesterol and recurrent events trial (CARE), and so there are these questions that sit in the literature about how safe these products are when used for a long period of time and at ever higher doses to try and get down to these "target" low LDL levels.

The conclusion of this *British Medical Journal* article was that US recommendations for low-density lipoprotein cholesterol concentrations could put most of the western world's adult population on statins. That might be very great for the companies that are producing the statins, but then the question is: What are the relative benefits versus risks? Doses of statins would have to be more than 8 times higher than the currently used levels if, in fact, the target low LDL was to be the measure from which people were going to be titrated to for their statin dose.

Increasing the dose of statins by 8 times was not found to lower total mortality. Adverse side effects in clinical trials are often underreported and any reduction in non-fatal events may be outweighed by more numerous and more severe adverse functional side effects, say the article's authors. The statin story remains, I think, controversial as it pertains to ever increasing application of that family of drugs to try to achieve more and more aggressive lowering of LDL cholesterol.

Getting back to our gastric mucosal model, let's talk a little bit about the nature of NSAID-induced enteropathy and gastropathy. About 25 percent of the patients on long-term non-steroidal anti-inflammatory drugs (NSAIDs) go on to have some form of gastropathy. In many of these, the conditions can lead to hemorrhagic problems with life-threatening consequences. In a study published in the 1990s, there were at least 12,500 deaths reported annually that were ascribed to adverse effects (fatal outcomes, actually) from NSAID administration, and about 106,000-110,000 hospital admissions annually for gastric bleeding from the use of NSAIDS.[3] This is not an insignificant problem.

The difficulty is how do you know, early on, whether a person who is taking routine NSAIDs is at risk to a gastric perforation or to a serious enteropathy or gastropathy? Most people are not going to prophylactically be scoped. I have been involved (in research at the Functional Medicine Research Center [FMRC]) in looking at gastric mucosal cell models for estimating relative gastrointestinal toxicity of non-steroidal anti-inflammatory drugs, and, in fact, recently co-authored a paper that was published in *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. [4] In this paper, a method that seems to be very useful for evaluating relative toxicity to GI drugs using the AGS model-the gastric mucosal cell model for screening various compounds for relative GI safety or risk-was described.

It was found that there is a range of different GI risk factors from different non-steroidal anti-inflammatory drugs. Even the so-called selective COX-2 inhibitor drugs that were supposedly safe to the GI tract are found (by this model system) to be at some risk to GI inflammatory problems. I think there has been some relative misleading take-away from individuals in the medical world that the selective

COX-2 inhibitors are completely safe as contrasted to the traditional nonselective COX-2 inhibitors (the mixed COX-1/COX-2 inhibitor NSAIDs) that put the GI mucosa at risk.

Fecal Calprotectin Test

Some type of a functional method for evaluating individual relative risk to NSAID-induced enteropathy is needed. This is where tests like the fecal calprotectin test can be very useful. This test has been used in studies at the FMRC during the past several years to understand the association between the elevation of fecal calprotectin on NSAIDs and the relative risk that that patient might have to a gastropathy.

There can be a variety of different responses in different people to NSAID use in terms of how it affects the rising level of calprotectin, the reactive immune protein that is secreted by neutrophils in the GI mucosa. If we are able to use the fecal calprotectin test as a benchmark for looking at relative risk to injury, then we can evaluate interventions that would helpfully lower the relative risk to some kind of a serious hemorrhagic problem or a gastropathic response.

Hepatic Inflammatory Response

Because the gut is the center of the immune system, as you start having gut inflammation, you start to demonstrate localized inflammatory patterns that then can track to altered gut mucosal integrity and can lead to upregulation of proinflammatory mediators, cytokines, and chemokines. That can then deliver downstream from the gut, these messengers that can enhance liver or hepatic inflammatory response. This seems to be more and more well recognized now. Nonspecific liver injuries that relate to elevated liver enzyme profiles don't seem to track against a seropositive hep C or hep B (and the person is not an alcoholic), and sometimes we don't know what the etiology is of these liver profile elevations. We can look at things like metabolic syndrome and nonalcoholic steatohepatitis (NASH), one thing that we know causes liver infiltration of hepatocytes. Another potential cause is proinflammatory mediators from the gut. We start talking about liver inflammatory conditions as being precipitated by gut inflammatory conditions, and then you start looking at things like food allergies or antigenic-presenting phenomena that occur to the GI mucosa.

One substance that always rises up in this discussion of things with a problematic nature for the GI tract is gluten (from wheat). If a person has a nonspecific elevation of their liver enzymes and we can't identify that it is from NASH or alcohol, or a drug, or a viral infection, could it be that this liver injury is precipitated by an upstream antigen-antibody-type response at the GI mucosa? Is an upregulation of the gut-immune defense system and inflammatory mediators being produced in response? There is a body of literature that supports this contention with people who may be gluten sensitive. Once put on gluten-free diets, liver enzyme profiles go back into normal range and gut inflammatory and liver inflammatory conditions go into remission.

Chronic gut infections (sometimes euphemistically termed "dysbiosis") can also induce gut inflammatory responses, which then translate into liver-related problems. In older-age individuals, where you often get this condition called hepatic encephalopathy with psychosis developing, this can be precipitated by the gut inflammation/liver connection to the brain through the glia (the microglia). The microglia is the brain's immune system, and so there can be an upregulation and an alteration of immune function in the brain with altered neurotransmitters and increased inflammatory agents, activation of glial nitric oxide output, and peroxynitrate being formed. The result is a whole different brain milieu in terms of functional molecules.

Long-term use of antibiotics can induce changes in gut flora. Gut flora can then induce changes in gut-immune function. Gut-immune function can change the liver. The liver can change the brain. Now we have a round-robin connection between gastroenterology and neurology.

Hepatic Encephalopathy

There is a paper that describes all of this web-like connection that appeared in the journal *Medical Hypotheses* in 2005. It is titled, "Effect of Antibiotics, Prebiotics and Probiotics in Treatment for Hepatic Encephalopathy." [5] Hepatic encephalopathy has traditionally been treated by putting a person on a substance that will create hyperosmolar diarrhea, like the disaccharide, lactulose, which is generally nonabsorbable. That diarrhea then alters gut flora. It also washes out toxins from bacterial cell wall debris and lowers the load of inflammatory materials, which then lowers the effect on the liver, and then ultimately lowers the middle molecular weight nitrogenous molecule load on the brain. This can help a person come out of the hallucinations that are associated with hepatic encephalopathy. The real name for that should be "gastrointestinal hepatic encephalopathy," because it is the gut, connected to the liver, connected to the brain.

Can prebiotics and probiotics also be useful for managing this kind of a condition? There is a wide body of literature described in this review article that suggests that not just lactulose (as a substance to produce hyperosmolar diarrhea), but also prebiotics and probiotics, work together to help in proper normalization of GI-immune defense (lowering inflammation, lowering liver activation). This can lead to improved microglial function (the brain's immune system), and reduce the symptoms of hepatic encephalopathy.

We often think of hepatic encephalopathy as only being associated with ammonia-producing organisms. We often characterize it as a condition of hyperammonemia. If you look at the literature, you'll find that the symptoms of hepatic encephalopathy (the hallucinations) are not tracked closely against blood ammonia levels at all, but rather tracked against other nitrogenous putative precursor molecules to neurotransmitters, which are immune-active substances that are produced in the gut and/or liver and are associated with these gut inflammatory conditions. Encouraging the detoxification of the gut, reinoculating with friendly bacteria, and use of prebiotics appears to be part of a favorable clinical protocol. The next step is to give nutrients that are helpful for restoring proper gut-immune defense, like L-glutamine, which we know is a useful amino acid for improving gut mucosal integrity. L-glutamine is a gut fuel (in some respects), as it helps to activate in situ glutathione stores for proper redox balance and gut mucosal recovery of immune defense.

There are a lot of different parts to this story, but certainly lowering the load, getting rid of food antigens or allergens, improving prebiotic and probiotic reinoculation of the gut, and then gut restoration of mucosal integrity with nutrients like L-glutamine all seem to be part of this program that connects the gut to the liver. If we see elevated liver enzyme profiles, I think we should take a broader look at the implications other than that of just serology for hepatitis-producing organisms.

How might systemic inflammatory conditions be connected to localized gut-immune activation and enhanced immune activities of the gastrointestinal-associated lymphoid tissue (GALT)? There is ever increasing interest in the whole spectrum of autoimmune disorders that may have some connection (in certain individuals) to alteration in gut-immune defense. This connection appeared very strange about 10 years ago, but is now starting to gain more credibility between the activity and function of the mucosal-associated lymphoid tissue (MALT) and the gastrointestinal-associated lymphoid tissue (GALT) and

systemic inflammatory responses.

Are there any animal models that take a look at this connection? The answer is yes. There are certainly an ever increasing number of well respected animal models where this connection can be studied under controlled conditions. A review appeared just recently in the*Arthritis Research Journal* that is titled "The Genetics of Rheumatoid Arthritis and the Need for Animal Models to Find and Understand the Underlying Genes." [6] In this particular paper, the authors talk about new animal models that are being used for evaluating the potential of rheumatoid arthritis and the etiology of rheumatoid arthritis, how that connects to certain immune-related genetic characteristics, and what environmental modifiers can modify the genetic expression of these characteristics to give rise to an immunological inflammatory condition that later tracks as arthritis.

Rheumatoid Arthritis and *Proteus mirabilis* Infection of the Urogenital Tract

If we think of rheumatoid arthritis (RA) as an autoimmune disease, we get some sense that there could be cross reactivity from epitopes on environmental stimuli leading to superantigens. What environmental factors lead to those cross-reacting epitopes? One family of organisms to consider are those that have urinary tract infection correlation, like *Proteus*organisms.

There is an interesting paper that just appeared in *Clinical and Developmental Immunology*that looks at the relationship between rheumatoid arthritis and *Proteus mirabilis* infection of the urogenital tract.[7] The authors propose that a subclinical *Proteus* urinary tract infection could be a main triggering factor related to this molecular mimicry and cross reactivity between bacteria and RA-targeted tissue antigens that perpetuate disease through the production of cytopathic autoantibodies.

This is a complex world in which we live. There are literally thousands of microorganisms that have their own molecular personalities. On their surfaces sit all sorts of different potential hapten or antigenic components, which may then react with receptor sites on host immune tissue in genetically unique individuals to activate those cells into a heightened stance of inflammatory expression. The urinary tract may seem like a long way away from the joints, but we are all connected together through our immune system.

In this particular paper, the authors talk about how this connection may explain why vegetarian diets (diets higher in water and juices that are acidic and contain certain phytochemicals, like cranberry juice) have been useful in certain studies with patients not only with urinary tract infections, but also those who have conjoint arthritis. These patients find that as their diets change and their urinary tract infections improve, their joint pain improves, too, because there is this connection through the immune system between the reaction of receptor sites to antigens (these cross reactive materials-this mimicry, so to speak, between a bacterial antigen and a self antigen).

We are starting to learn a lot more about the interrelationships in this complex world, and how they can then be individualized to the patient's own immune system. We can't just form rules that cut across all individuals, and we can't say there is only one cause of an autoimmune disease. We are looking at modifying factors.

Gut-Joint Connection in Arthritis and Foods

Is there any demonstrable connection between the foods in our diet and their chemical personalities (as it

relates to their immunological activity) and cross reactivity with antibodies that are associated with rheumatoid arthritis? That is a question that has been discussed for several decades (at least). As we get better immunological assessment tools, this association becomes more recognized. I am now quoting from a recent paper that appeared in the journal *Gut*, which describes this connection that couples together the cross reactivity to food antibodies and ultimately joint inflammatory conditions.[8]

This is a very interesting paper. The title is "The Gut-Joint Axis: Cross Reactive Food Antibodies in Rheumatoid Arthritis." This was a study that was aimed at patients with rheumatoid arthritis who have differing severity of their condition that seems to track against different dietary persuasions or different foods that they might eat. The authors of the paper wanted to investigate a putative immunological link between gut immunity, rheumatoid arthritis, food antibodies, and general quality of the diet of these individuals who have this food exacerbation.

The investigators looked at IgG, IgM, and IgA antibodies to dietary antigens to measure the potential for food allergy in these individuals in serum and jejunal perfusates from 14 rheumatoid arthritis patients and 20 healthy subjects. The antigens that they evaluated were from cow's milk (α-lactalbumin, β-lactoglobulin, casein: the three most reactive proteins in cow's milk), cereals containing gluten, ovalbumin (hen's egg), codfish, and pork meat. In the intestinal fluid of many of the rheumatoid arthritis patients, all three immunoglobulin classes showed increased food-specific activities. Except for IgM activity against β-lactoglobulin, all other IgM activities were significantly increased, irrespective of the total IgM level (so you have to look at the individual class of IgM). The rheumatoid-associated serum IgM antibody responses were relatively much less pronounced. And compared with IgM, the intestinal IgA activities were less consistently raised, with no significant increase against gliadin and casein. Considerable cross reactivity of IgM and IgA antibodies was documented by looking at absorption tests. Although intestinal IgG activity to food was quite low, it was nevertheless significantly increased against many antigens in the rheumatoid arthritis patients. Three of the five rheumatoid arthritis patients treated with sulfasalazine for 16 weeks had initially raised levels of intestinal food antibodies. These became normalized after treatment.

The authors conclude, after looking at this fairly small number of patients in the trial (14 RA patients against the 20 healthy subjects), that the production of cross reactive antibodies is strikingly increased in the gut of many rheumatoid arthritis patients. I think that is probably the most significant contribution of this study was looking at intestinal perfusates and examining what the localized production of antibodies through the activation of the gut-associated lymphoid tissue was as a consequence of exposure to their complex diet. Their food-related problems reflect an adverse additive effect on multiple modest hypersensitivity reactions. These may then promote more severe autoimmune reactions in the joints, so they come to the conclusion that this gut-joint axis is not just theoretic, this actually does exist and it is clinically demonstrable that food elimination or improved gut-immune function (normalized gut-immune function) translates to lower systemic and joint-related inflammatory conditions.

I think this is very important because often I hear people say that what happens in the gut wouldn't translate to the joints-they are controlled and isolated and compartmentalized by barriers of defense and whole different physiological control systems. That is an extrapolation of unreasonableness. Both systemic and intestinal humoral immunity is found to be apparent in rheumatoid arthritis patients, with a particularly striking elevation of cross reactive food antibodies in the proximal gut secretions. We now learn from this more recent paper that IgM reactivity against food items was increased in the serum, as

well as in the intestinal perfusate, suggesting systemic as well as localized effects.

These incremental increases in intestinal antibodies provide striking results suggesting a connection between mucosal immune activation and the pathogenesis of rheumatoid arthritis (at least, we can say, in some patients). I want to emphasize that I think that like all diseases, rheumatoid arthritis is a heterogeneous condition with many different contributing variables. We can't say one rule covers all patients, but certainly it is a characteristic that is worth looking at (the diet connection to antibody exacerbation of these autoantibodies). Food, therefore, may have an additive effect on other risk factors or contributing factors to the etiology of immune imbalance that is associated with rheumatoid arthritis. The gut-immune defense functions, environmental allergens and toxins, stress factors-these are all contributors to imbalanced immune function that we associate with these arthritis-like conditions.

What I have really been talking about in this discussion is a presaging of what our clinician/researcher of the month, Dr. Hanaway, will be saying much more eloquently. That is: What is the immune privilege of the gut in the establishment and maintenance of proper immune response upon exposure to dietary antigens and commensal flora, which can be either friend or foe? We know that the intestines represent a new site for immune privilege. In fact, as early as 1948, Peter Medawar, who was an early transplantation immunologist, coined the term "immune privilege" to refer to the experimental observation that allogenic solid tissue grafts survived for prolonged or indefinite periods of time in specialized sites of the body. This relates to immune allostasis, or control of immune function. The pregnant uterus, ovary, testes, hair follicles, and regions of the eye and brain are among those anatomical sites traditionally classified as immune privileged. This immune privilege was largely due to passive mechanisms and immunological ignorance. In other words, antigenic material was transplanted into the immune-privileged site, but hidden from the systemic immune system, secondary, obviously, to barriers (like vascular barriers) in the absence of lymph drainage. However, if you expose these tissues by opening portals of entry to antigenic insults, they can lose their immune privilege and become no longer naïve (be activated).[9]

It was later shown that traditional immune privilege sites are privy to lymphatic drainage and, more significantly, by the 1970s, it had been demonstrated that antigen placement in the interior chamber of the eye (a traditional immune privilege site) did, in fact, generate a systemic immune response, even if the response did not lead to graft rejection. As a result, immune privilege was recognized to result from active (rather than passive) immunoregulatory processes. It is how you control this Th1/Th2 type of response and maintain balance.

When we look at the gut immune privilege, it is really buttressed and affected by many factors. On the one side, there is food which contains foreign molecules that have to be digested and translated into neutral molecules, relative to the information they provide to the body (at least, not seen as hostile molecules). On the other side, there are two-and-a-half to three pounds of organisms sitting in the gastrointestinal tract that are potentially immunologically active. These organisms could be trophic and have positive impact upon immune function, or they could be parasitic and release caustic chemicals that activate the immune system and cause immunological imbalance and inflammation.

Immune privilege of the gut is really maintained by this dynamic tension and balance between intestinal epithelial barriers, phagocytic innate immune cells, tolerogenic antigen presenting cells, and regulatory adaptive immune cells. This gives rise to tolerance to this environment that is within the gastrointestinal system. Imbalances or alteration in regulation leads to dysfunction, and that can be related to mucosal

breakdown and to what we call increased permeability (or leaky gut). That exposes the gastrointestinal associated lymphoid tissue (GALT) to immunologically activating substances, imbalancing the teeter-totter of immune defense between the thymus-dependent 1 and the thymus-dependent 2 lymphocytes. What we end up getting are altered chemical communicators (cytokines and chemokines that relate either to things like food allergy or inflammatory bowel disease and activated immune system functions).

This concept that is emerging-to look at the gut as the seat of immunity-is a very important concept in functional medicine and complex chronic disease because the conditions that result from this are more than just gastrointestinal in name. We further amplify (or complicate) that with the recognition that the gut is also a very active site for the secretion of many neuroactive substances. It is the site where the majority of serotonin is secreted in the body-I think maybe two-thirds of whole-organism serotonin comes from secretion from the gut associated lymphoid tissue.

Protein Consumption and the Release of PYY Gut Hormone

We also recognize that various brain neurotransmitters (not just cholecystokinan, but also PYY) are altered by gut-immune defense and the contents of the diet. Recently, one group of investigators has found that the gut hormone PYY is released when a person eats a higher protein-containing food. Signals are sent to the brain that indicate fullness. This is in contrast to empty calorie foods that are devoid of protein, where you get lowered PYY release and a lowered satiety message that is triggered to the brain. This might explain why eating protein in adequate levels has a positive effect on controlling appetite and a feeling of fullness. This recent work has been done by Rachel Batterham and her colleagues at University College London, who have been working to understand diet and its relationship to appetite and obesity.[10]

I think we can think of the gut as the "second brain," as Dr. Michael Gershon pointed out in a book by that same name. We can think of the gut as the site for the immune system function. We can think of the gut as having a very important digestive function, in terms of breaking big to small for absorption. And we can think of the gut as controlling water content (fluid balance, electrolyte balance). It is much more of a functional organ than just a conduit-a pipe-that connects the mouth to the anus. This is the theme that is emerging and it is more fully understood if we can start thinking of the gut as a bioreactor. Gut microflora convert primary substances in foods into secondary metabolites (for instance, soy isoflavones get converted by certain enteric bacteria into secondary metabolites like equol, which has a different effect on physiology once absorbed than does the lignan or the isoflavone itself).

For example, if you look at some of the factors in *Humulus lumulus* (hops) that get converted (like isoxanthohumol into xanthohumol) by demethylating bacteria that appear in the gut through fermentation. There are certain types of enteric bacteria that create different types of secondary metabolites that modify physiological function. This story goes on and on in terms of many other examples where fermentation produces secondary compounds that have differing effects on physiology, and this is dependent upon the specific families of enteric organisms to do this. An alteration of those organisms by antibiotics or stress or altered diet or high salt or sweet diets that flatten the villi can all influence the secondary effects of these bioreactors on producing these physiologically active materials.

We are much more complicated in our understanding of functional gastroenterology than we previously have taken into account. This leads us into this month's discussion with our clinician/researcher of the month, Dr. Patrick Hanaway, who is an expert in this whole area of looking at how gut-immune defense

flora and mucosal integrity interrelate to a whole series of functional chronic health-related problems. With that in mind, let's move to our clinician of the month.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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JB: Once again we are at that place in Functional Medicine Update that I look forward to with the greatest anticipation because I have learned so much from the various clinicians and researchers that I have had the privilege of interviewing over the last 25 years. This month I have a chance to speak with a colleague I have admired and respected professionally and who is also a great personal friend, Dr. Patrick Hanaway. He is (I'm sure many of you know) a very important figure in our field of integrative medicine. Dr. Hanaway is a board certified family physician who earned his medical doctor degree from Washington University and completed residency training at the University of New Mexico. He is very skilled in what we would consider the analytic reductionistic form of medicine, having studied traditional Chinese medicine and integrative medicine. He is a true integrator in every sense of the word, but does so in a way that really, I think, exercises the best balance of both hemispheres of the brain. It is a great privilege to have Dr. Hanaway as our clinician/researcher of the month.

Patrick, I guess the first question I might ask is, how did you go about making this kind of interesting transition in your career-from being a family doctor to now being a leader in the field of integrative functional medicine?

PH: Thank you for that introduction, Jeff. It was really the extension of the path that I had when I was in college and went to medical school. I was of the belief that I was going to learn about health and healing. I had majored in both history and molecular biology. When I learned about biochemistry, I thought I was going to learn about nutrition; I thought I was going to learn about what things people put into their mouths and how that works. I didn't learn that. I read a book-by you, actually-in 1980 that helped me believe it's possible that some people were thinking about that concept. As I went through my training and became a family doctor I continued to be interested in how to apply the principles of good medicine-of connecting back to nature and eating the right foods and having vitamins and nutrients that are going to help to maintain optimal wellness because that is what I was interested in. I have had great opportunities to learn tools along the way.

JB: I know you have made a very interesting transition, professionally. You and your wife have been in practice together (she's a physician, as well) at "Your Home for Whole Family Health" in Asheville, NC. Within the last decade you made a pretty remarkable career change to become Chief Medical Officer at Genova Diagnostics, and you've really become, I think, a very well respected leader in the area of functional gastroenterology. This, clearly, is kind of what you would call a lifelong learning program. It seems like an interesting evolution of your professional career.

Bringing Patients into Balance

PH: It is. As you know, there is always a personal story behind it as well. Part of my growing into learning about functional GI illness stemmed from three months of work in Nepal in India, back when I was in my medical training. Getting very sick with amoebic dysentery certainly helped to stimulate my interest in the GI tract, and in learning how to come back into balance. I learned about Great Smokies Diagnostic Lab at that time (in the early nineties) and it helped me-tremendously-to come back into balance.

In my clinical practice, I needed to understand how to use tools. As I hung out my shingle, I needed to understand what tools I could use to help bring people back into balance and understand how they are biochemically unique from each other to optimize my healing potential with each person.

It was fortunate that I was practicing with my wife in Asheville, and the laboratory you speak of-now known at Genova Diagnostics-was in that town. I told them I would like to do some clinical research. I began to do that and began to see that the opportunity to share these approaches and these tools and this understanding with more of my colleagues was really a way that I could best use my skills to help advance medicine and healing.

JB: That's a wonderful opportunity to segue into what I think is one of the most useful articles that I have seen written in this field of functional gastroenterology, which just happens to be authored by you. It appeared in the September/October 2006 issue of Alternative Therapies under the title "Balance of Flora, GALT [Gastrointestinal Associated Lymphoid Tissue], and Mucosal Integrity." 11

I think the way you laid this article out is, in part, a manifesto for a change in thinking about integrated physiology or functional physiology. I'd like to (for the sake of the listeners) walk through some of this article and some of the citations that you've provided that give support to these concepts, because I don't believe that these concepts are necessarily held in every quarter of gastroenterology. It is very interesting to see how these thoughts have evolved through your lens and also through the field of clinical and basic science research. With that as kind of a context, maybe you can tell us a little bit, in summary, about gut flora and interrelationship with the gut-immune system (for those who are maybe less familiar with the gastrointestinal associated lymphoid tissue)?

A Summary of the Gut-Immune System

PH: I'd be happy to. It is interesting that while these things are not commonly remembered and understood, that much of it is a recapitulation of work that Ilia Mechnikov did at the turn of the last century, for which he won the Nobel Prize in Medicine. These are old concepts that we are re-remembering.

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{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} 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.

JB: I think that is a really important concept because-to go back to one of your historic experiences when you were in Nepal-obviously you had an environmental exposure that created a change, probably, in your enteric flora, which caused a change or was interrelated with a change of your gut-immune defenses, and undoubtedly you went back to where your whole system was as an early infant and some of the things that you might have been exposed to and how that developed the ability to respond to that stress. We don't all go to Nepal, but I guess inevitably we all get exposed to these stressors that then call forth these reserves.

PH: We do. Michael Gershon has talked so much about the second brain and this concept that the interrelationship between the gut and the brain. There are more neurotransmitters in the gut than there are the brain, so the stresses that we have in our life have a tremendous impact. It is not just the physical biological influences, but also the psychological stressors that can have an effect on how our gut functions.

JB: I know in your article you talk a lot about this concept of tolerance versus intolerance as it pertains to this interface between our enteric immune system and our enteric bacteria. Could you tell us a little bit about how we gain tolerance? Why is intolerance evident in other people?

Tolerance vs. Intolerance
PH: 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.

That all happens through the inflammatory process and the cycling that you have talked about (through the Nuclear Factor kB and the stimulation of the cytokine system). In the presence of pathogens (like Clostridium difficile or Entamoeba histolytica or E. coli 0157) the process stimulates a cytokine like interleukin-12. Or, it says, "Hey, this is Lactobacillus and Bifidobacter and they are friends that I want to have around," and it stimulates a counter-regulatory (a non-inflammatory) cytokine, interleukin-10, to slow things down. There are many other cytokines in that cascade, but that is how the body creates the set point.

The fascinating thing is that we do see that there are some people who are more predisposed because they have alterations, either in their toll-like receptors or in their inflammatory cascade, where they will mount an inflammatory response in the presence of normal organisms. There is a whole subset of Crohn's disease that is associated with the NOD2, or toll-like receptor gene, associated with that form of

developing inflammatory bowel disease.

JB: I know that an article that just recently appeared from an author that you are very familiar with because I think you have had personal contact with him, is a very prominent gastroenterologist, University of North Carolina School of Medicine, Balfour Sartor, who talks about the mechanism of disease (colitis, IBD, and so forth) in Nature Gastroenterology in 2006.12 He has proposed kind of a model that seems like it has general applicability to many of these disorders of immune dysfunction that cut across different diagnostic criteria. Could you kind of summarize what he was speaking to in this article?

PH: I'm kind of smiling because the first time I heard him talk I actually thought I was at a Jeff Bland functional medicine meeting because he said the reactivation of disease occurs when environmental factors trigger changes-trigger a break in the mucosal barrier (so-called "leaky gut")-and they stimulate immune responses and alter the balance between beneficial and pathogenic bacteria in the gut. I have just read a statement from the summary of his review in Nature Clinical Practice Gastroenterology from 2 months ago, and that is something that we have been talking about in the functional medicine arena for more than 15 years. It is fascinating to me to see that the cutting-edge researcher (he is an immunologist and a GI doc), who is speaking to thousands and tens of thousands of people, is converging at the same idea of where balance and imbalance arises from.

JB: I remember a number of years ago, we had the fortune of having Dr. Michael Gershon at the Institute for Functional Medicine annual symposium to talk about his "Second Brain" concept and the gut-brain connection. One of the things he was talking about, obviously, was irritable bowel syndrome, which he spent quite a bit of time researching. Out of that seemed to come a connection of functional gastroenterological diseases before you get to this acute pathology that we often think of in gastroenterology (they are always dealing with more the acute illnesses of the GI tract). These functional illnesses have more subtle symptom profiles and may be connected to alterations in the hypothalamic-pituitary-gut axis. I think there is a more recent paper that I just saw in the American Journal of Gastroenterology a year ago talking about the HPA connection to the gut-immune defense and cytokines.13 For the sake of our listeners, could you differentiate kind of a functional gastroenterological collection of disorders from that of a pathologic? What types of things are we actually looking at, clinically?

A Continuum of Disorders

PH: I would first state that it is my emerging view that these really constitute a continuum and that there is not a set of functional disorders and a set of pathophysiologic disorders that are going on. When we see something that is called a functional bowel disorder, like inflammatory bowel disease, or the new term for kids is "recurrent abdominal pain-RAB," which are these garbage cans of symptoms that we don't know what is really going on and so we call it a functional disorder. What we see is there is actually probably something on the order of one in ten people who have IBS who go on to develop inflammatory bowel disease. It may be a precursor in some situations because it is a further extension of that imbalance between the environment and the individual (that gene-environment interaction that is going on).

The functional disorders that Michael Gershon talks about are focusing on how we understand this symptom complex of irritable bowel syndrome that now is present in about 15{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of all Americans; it is

extremely common. We know intuitively that this has to do with the kinds of foods that we are putting into our diet. My own belief, more and more, from a clinical perspective, is that the alterations in gut flora are so extensive that our immune system is not working properly, the gut flora are not doing their normal transformation, detoxification, and metabolic activity to help us to stay in balance with our environment. In more extreme cases, that will then manifest itself as ongoing inflammation that we see in Crohn's and colitis. As a side note: the Crohn's and Colitis Foundation has been working with Kaiser Permanente and they are going to be publishing (in the next year) data that shows that the rates of Crohn's and colitis have doubled in the United States from 900,000 to 1.75 million over the past 9 years-amazing information.

JB: This continuum that you are describing sounds like the trajectory that people might travel is through less severe conditions of dysfunctional gut-immune system, and then ultimately moving into more pathologic states, which then means they could pass through things like what we generally call "IBS-like" symptoms. I was very intrigued to see in Gastroenterology in February of this year an article talking about plasma cytokines as a potential biomarker for IBS, again showing a unified concept of inflammation even at the early stages of IBS. Has that been your experience when you have looked at some of these patients with less severe GI dysfunctions?

PH: Exactly. We also see that there is a subset of those who have post-infectious irritable bowel syndrome. Those are people who have mucosal markers like fecal calprotectin also being elevated, showing that there is an inflammatory process that goes on that then moves in from the mucosal lining into the submucosa and into the smooth muscle where it interrelates.

There is further work out of Canada showing that where the nerve cells come in is right next to where the mast cells and enterochromafin cells are releasing histamines and serotonin. That gives us an understanding of why-when there is an inflammatory process (a low-grade inflammation that is going on)-that there is stimulation of changes in gut motility, bloating, a sense of pain, a sense of fullness associated with IBS. You can see how that inflammatory process, at a low grade, is really generating much of the symptomatology that is going on. In addition to that, when we have that process of low-grade inflammation, this breakdown in mucosal barrier integrity (what the GI docs will call intestinal permeability and what the naturopaths will call leaky gut-describing the same phenomenon), then creates the opportunity for other autoimmune phenomena to occur.

JB: That leads us into a clinical question. How does a clinician assess the need of the patient for intervention? Are there specific tests or do we go off clinical presentation as the principal, or is it a combination of functional tests with clinical presentation?

Tools for Clinical Assessment

PH: It is always a combination of the two. In order to understand the biochemical individuality of a person who is coming in, so that we can use the tools of functional medicine to be able to help bring them back into balance, we can use our tools of understanding the history, listening to the story, seeing how the pieces fit together, using our physical exam to see what imbalances may be going on, and using laboratory testing to give us a further sense of where we are going to get the best opportunity. I forgot to mention the family history, as well. Where do they have a genetic predisposition of having imbalance? Using all of those tools together to be able to drive and apply the right therapeutic modality-that is the thing that is going to get the biggest bang for the buck.

JB: Are the tests that are used for measuring gut mucosal integrity a value in this kind of assessment to know how to both track the patient and what treatment regime to use?
PH: Certainly. I know you have spoken of Ingmar Bjarnason, before who has done more recent research, not only on NSAIDS and their role and relationship in increasing gut permeability and causing problems with inflammation there, but previous work that he did helping to develop tests like the double-sugar test, looking at intestinal permeability. Those are useful tools to see if there is a breakdown in the gut mucosal integrity occurring. Is there inflammation that is going on? Using tools like calprotectin to be able to tell that. Are there changes in the gut flora? I am excited about work that is being done around the world right now, being able to begin to really describe the microbiome of the gut. Understanding, what are the 400-plus species that are there and how do we help bring people back into balance? In 2006 we are relying on stool culture to give us an idea if the right amount of beneficial bacteria are present in the right balance and are there other bacteria that are not pathogenic, in and of themselves, but in combination (when there is an alteration of the gut flora), they cause a dysbiosis that leads to further inflammation.

JB: I'm so excited to hear you talk about that because I recall-this is one of those "back to the future" reflections-a series of lectures that were given back in the 1970s, when I was first starting in this field, by a gastroenterologist from Santa Barbara (Ventura, California) who spoke about stool cultures as a way of assessing functional GI disorders. Obviously, back in the mid-70s that was pretty strange for a gastroenterologist to hear. It seems a little less strange now in 2006-2007 than it did then, but that was pretty advanced (talking about culturing the stool to see if you could pick up imbalanced organisms).

PH: I go back to Mechnikov and the work with probiotics (the work with commensal flora and yogurts and natural fermented products). They are-in my belief and in my practice-critical tools for helping to bring balance back to a system that fundamentally becomes imbalanced in most young children during the first 2 years of life, through the use of both vaccines, antiseptic birth conditions, significant amounts of antibiotics, and even the antimicrobial herbs that cause alteration; the lack of breast feeding in our culture, and the introduction of solid foods in a far more rapid phase than our gut (evolutionarily) was meant to be exposed to.

JB: I'd like to just go back for a minute to the assessment phase because for some people who may be new to this field, they don't understand the double-sugar test you described, the lactulose-mannitol challenge test, nor do they probably understand the fecal calprotectin test and how those give different bits of information in clinical management. Could you give us a summary of both those tests?

A Summary of Functional Testing
PH: Sure. The test for intestinal permeability, developed back in 1985, is pretty simple in nature. You give someone 2 sugars (we give them lactulose and we give them mannitol). Many MDs may remember lactulose as a treatment that causes an osmotic diarrhea. I'll give small, small amounts of that; lactulose is a relatively large molecule and wouldn't normally go through the gut wall. Mannitol is a smaller molecule and would commonly go through the gut wall.

We can measure, in someone's urine, how much lactulose and mannitol there is at time 0, and then 6 hours after we give the drink, how much lactulose an mannitol there is, and that tells us how much was absorbed through the gut. We see conditions when there is a breakdown of paracellular junctions; zonulin and other measures are broken down, are not working properly, and the gates open up. These large lactulose molecules are able to move through and we can find them in the urine. Conversely, some people

will not only have problems with the lactulose coming through in high amounts, but they will also have inflammation, which causes a breakdown of the villi, the finger-like projections that come out from the lining of the intestine that are part of the absorption process. When those are broken down, it can't absorb the mannitol properly, and so we can get an indication not only of intestinal permeability, but also of malabsorption that goes on from this very simple test.

JB: And how does that connect to or give different information from the fecal calprotectin test that you alluded to earlier?

Calprotection: A Quantitative Marker of Inflammation

PH: Calprotectin is something that I have been working with in the GI community. We got FDA approval on that just earlier this year and I have been working with GI docs around the world doing research on that marker. It is a marker from the white blood cell, the neutrophil. Sixty percent of the protein in a normal white blood cell is going to have this zinc binding protein called calprotectin. It is released by the white blood cell as a defense mechanism to help bind zinc so bacterial enzymes are not able to work, so it acts as a bacteriostatic measure within the cell.

We also are able to use it as a quantitative marker of inflammation. We can find out how much inflammation is going on, determine if irritable bowel syndrome has an inflammatory component in it, use it to be able to determine who (which children, especially) might have not a functional bowel problem but an inflammatory bowel disease going on, and who should be scoped. Further studies are now looking at it as a monitoring tool to follow patients with inflammatory bowel disease. It gives us an insight.

There is one other new finding on that that is really fascinating, which takes us out of the realm of the gut, but into the overall inflammatory processes-its role and relationship with disease that you've talked about. Calprotectin can be used as an indicator of who's at risk for developing a myocardial infarction when measured in the plasma; it is more sensitive than hsCRP (data from Circulation in August of this year from Dr. Dan Simon at Harvard).

JB: This is again showing unified mechanisms, isn't it? You don't just have action in a local area; you have a "think locally, act globally" type of phenomena going on here. You talked earlier (and also very nicely in your review paper) about the use of probiotics. I think most people in our field have some familiarity with these. I was very intrigued when I read this gastroenterology article in February 2006 talking about plasma cytokines as biomarkers for IBS. In that paper they talked about the use of probiotics at the dose of 3.6 trillion organisms per day, which, by most people's assessment, would be a pretty massive dose of probiotics. Do you have any thoughts about very high dose probiotics, and, if so, what you are really doing? Because it sounds like it may be beyond just reinoculation; you may be actually adding trophic factors or some bioactive components at that level.

Probiotics Research

PH: Clearly. I think that we have learned that we have been (at least within the probiotic strains that are available commercially over the past 20 years) dealing with more homeopathic dosing patterns, and that in order to really be able to get in to true therapeutic ranges with probiotics we need to go to larger doses.

Now, commonly, we see people using 50 to 100 billion colony-forming units with patients with IBS. Data with VSL#3 out of Italy now looking at 450 billion colony-forming units, and they are doing research, as

you said, much, much higher at 2.7 and 3.6 trillion colony-forming units as ways of being able to really act as anti-inflammatory measures. When we recognize that the gut has 100 trillion bacteria present in it, using a dose of 2 or 3 trillion is not unreasonable and I think the higher doses of probiotics I've found to be very effective and there is still a large margin of safety, using probiotics in this way.

There is one thing I also want to acknowledge in this arena of looking at probiotics and imbalances in our gut and it has to do with celiac disease. In the course of my career, from the time I was in med school, celiac disease was first said to be 1 in 3000, and then 1 in 1250, and now the last data says 1 in 133 people have it, and probably 1 in every 50 people who have IBS have celiac disease with true changes going on in their tissue transglutaminases. But data out of Italy also shows us that when people have the right amount of commensal flora, all of the enzymes necessary to breakdown gliadin and gluten are present. Maybe it is not just a genetic factor going on that we are uncovering, but maybe it is that there are such changes in our gut flora that we don't have the capacity to breakdown wheat like we did before. And those people with the genetic predispositions of DQ2 and DQ8 are those who are at highest risk for not being able to effectively breakdown wheat in their diet.

JB: That's a really important point. I'm really glad you brought that up. In this whole HLA genotype and its connection to these kind of preformed diseases of allergy tends to, I think, reduce some of the other modifying factors, like you have just described, that could influence the expression of that genotype as a phenotype. I think that is a very useful observation and helps us to understand the increase in prevalence of some of these conditions. It is not just sandpile genotypes that we are talking about, it is environmental factors that have modified the expression.

That leads to a similar clinical question that I often hear and I know you do as well. Do some of these marker organisms represent the cause or are they effect? Like we hear of Candida infection. We hear about Blastocystis hominis infection. We know these are opportunistic organisms. Do they represent, necessarily, the cause of these problems, or do they come associated with the problems of an imbalanced Th1/Th2-disturbed immune system?

PH: I'm looking at the board in my office which has a chicken and an egg on it, which is what that question reminds me of. It really comes down to changing the way we think about health and disease to one of homeostasis and balance-something you have been talking about for years.

When we look at organisms, even Blastocystis or Candida, we find that people normally have small amounts of Candida in their gastrointestinal tract; it is not unusual at all. It is about being in the right relationship and in balance with those things. It is when we become out of balance that we have problems. From a laboratory perspective it is sometimes difficult because the people who authorize laboratories don't want to talk about something that is imbalanced; it is either a pathogen or it is not a pathogen. We find that high amounts of Klebsiella in people who have certain kinds of genetic predispositions and inflammatory processes with leaky gut where those antigens are being presented, are going to have an increased risk of developing some autoimmune disease. That data has been around and published for the past 30 years, and yet it is not to say that if you have small amounts of Klebsiella in your gut that you have to use high-dose antibiotics in order to eradicate it. That's foolish. It is about how we use our food and our nutrition to help bring us back into balance.

JB: That leads, Dr. Hanaway, to really the last question. I wish we could continue this on indefinitely; we

have only touched the surface of all the resources you represent. Let me, if I can, talk about these environmental modifiers of GI-immune defense process or function. Clinically, we often hear not just about probiotics but we also hear about prebiotics, the selective substrates from which these commensal (or symbiotic) organisms can selectively grow. You shared with me a very interesting article that opened up a whole new thought for me that some of these prebiotics might play and that has to do with function of the GI-immune tract and biofilms, and how biofilm environmental oligosaccharides might relate to an outcome in the phenotype of favorable immune balance. Can you tell us a little bit about that? That emerging concept of biofilms and the GI system?

Biofilms and the GI System

PH: It is not only the gastrointestinal tract, one-cell thick and as big as a doubles court, that is actually covered by a film (a film that includes the bacteria). Oligosaccharides are also present; they are helping to create a further barrier function with what goes on in the normal gut. They are a part of the process of how we effectively relate and defend ourselves from our environment. In the paper that you talked about, from BMC Microbiology earlier this year, what they did is they looked at various strains of bacteria and they found that the wild-type strain of people had a good expression of biofilm that was associated with the colonization of normal, good bacteria (normal, good Enterococci in the gut).14 And that the presence of those oligosaccharides in foods (such as you talked about-as prebiotics) can actually influence the formation of that biofilm. So it is not only feeding the bacteria, which is they way in we have thought is the primary role of prebiotics (disaccharide food sources for bacteria), but also in the development of this layer that helps to coat the gastrointestinal tract and helps it to be safe. So there is a whole series of things and we are at the very beginning, at nascent phases, of learning the interaction between prebiotics and probiotics that I heard Mary Ellen Sanders talk about a year-plus ago on this very show.

JB: So really when you get to introduce this concept then it starts to connect with this whole mimicry issue of HLAB27, possibly, and by forming the right biofilm you may cover over certain receptors in such a way that you reduce the potential for mimicry. It sounds like this whole communication process with the gut as antennae for the rest of the body's immune system and how those antennae might be tuned in different ways, depending on the local environment.

PH: Exactly.

JB: I can't thank you enough for sharing this time with us. This is-obviously-just the start of what needs to be an ongoing, continued evolution of this discussion. As you point out in your review article, things like the Hygiene Hypothesis and how that interrelates with early stage atopic disorders in children-how that may relate to things like autistic spectrum disorders and how that connects to the Andy Wakefield concepts of immune imbalances in lymphoid nodular hyperplasia in children in autistic spectrum disorder. And how that then relates later to attention disorder, hyperactivity disorders in adults-there is a tremendous connection across many functional characteristics that knows no boundaries in disciplines. This is not owned by gastroenterology, obviously.

PH: No, it's not, and I want to actually give a plug to Joe Pizzorno and our naturopathic colleagues who have helped to champion these ideas and really bring them to the fore, as well, from a clinical perspective because they work.

JB: Dr. Hanaway, I want to thank you for helping us with this review paper that appeared in the

September/October issue of Alternative Therapies under the title, "Balance of Flora, GALT, and Mucosal Integrity." I think if people read that article carefully and go back over it they are going to have a whole level of education about this connection that can open up new important therapeutic doors with patients with complex chronic illness. Thanks for all of your contribution, and I hope through this discussion people will be more inclined now to start down the path of functional gastroenterological testing and using some of these tools to assist restoration of the immune defense.

PH: Thank you, Jeff, for being there and helping to bring these ideas forward.

In the range of clinically useful tools that we have discussed over the years in Functional Medicine Update, I can't help but feel that this discussion with Dr. Hanaway ranks right at the top because it is so applicable to virtually every patient that comes in with complex chronic disease. The disorders that we have in the late 20th century/early 21st century in chronic disease are immunologically related and certainly the gut plays such an important role in establishing immune defense function, systemically as well as locally, in the GI tract.

This whole model that Dr. Hanaway shared with us is critically important and translates directly into clinical practice. We know that you can actually evaluate gut microflora based upon peoples' diet. You can see that GI mucosal bacteria cluster around certain diets. We know that the immune privilege of the gut is so tightly related to environmental factor of eating and stress and alcohol and chemical exposures and so forth. I think this is one of those extraordinary opportunities to both listen and learn and then to do and start making a difference in your patients. Thank you, again, to Dr. Hanaway for his very lucid and insightful comments.

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