Advanced Clinical Resources (ACR): Guest Faculty Resources *The Nutritional Neuroendocrineimmune Network* with Dr. Jeffrey Bland

Transcript

Dr. Ritamarie: Hello and welcome everyone. This is Dr. Ritamarie Loscalzo and we are here for an amazing advanced clinical resources talk for our nutritional endocrinology practitioner training. I have the delight and the privilege today to have with us someone who is a pioneer in functional medicine. Many of you have started in this path of functional medicine, natural alternatives over the last decade or so, just been doing it for many decades, long before anybody else knew it and long before it was called functional medicine. That's a really cool part is that he is just, he's a pioneer. He's one of my very early mentors after I graduated and got my degrees and started practicing. Even when I was in school still I would go to every workshop that he gave in our area. He's just really phenomenal.

He's known as the father of functional medicine. Over 35 years he has traveled, I love this step, more than 6 million miles teaching more than 100,000 healthcare practitioners in the US. If they had a Guinness book of world records you would have it for this particular feat because it's amazing. Now you're pretty settled I'm sure, not doing it quite as much. But he's gone to over 40 countries teaching it. He founded the Institute of Functional Medicine. He's been the director of the Linus Pauling Institute. He's been the cofounder since 1991. I was at the second of the Functional Medicine, the IFM events, which was really cool in Palm Springs. I remember the audience being relatively small compared to the most recent one that I attended here in Austin. He's the one that got that thing all started.

He's passionate about sharing his wisdom, his knowledge, and his (in my opinion) photographic memory for this stuff. Every time he put up a study we'd be looking and saying, “Well, and there was a study back in this and so and so.” I just really have always been jealous of your brain Jeff. I've wanted it because that kind of brain is just so sought after.

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He's published in more than 100 scientific journals. He's published more than 11 books. He publishes books for both health professionals and consumers.

Just a warm welcome. We are so excited and honored to have you here Jeffrey Bland, Dr. Jeffrey Bland.

Dr. Jeffrey Bland: Well Dr. Loscalzo I'm very honored to be with you, and thank you very much for that walk down memory lane. That was pretty amazing that you could pull back that Palm Springs second IFM meeting. That's in the distant archives now being in the 25th anniversary of IFM. Thank you very, very much for all your years of friendship, service, and yourself being a pioneer in the field.

Dr. Ritamarie: Thank you. Thank you so much for being here. I love the topic that we're going to talk about today because it's so consistent with everything that we are all about here. It has to do with the neuroendocrine, the nutritional neuroendocrine immune network. It's just so consistent with what we're learning here. Take it away. Tell us more.

Dr. Jeffrey Bland: Well thank you. I feel like I'm going to be talking to the knowledgeable converted. This I hope won't undersell the level of knowledge and specification of your audience. I thought I could build up maybe a little bit of how this whole field has evolved and emerged over the last 25 to 30 years. What a remarkable transition this is forecasting into healthcare in the 21st century.

This conjoint long winded term that we can hold out for Scrabble to wipe out our opponents, neuroendocrine immune network, really represents a changing paradigm in healthcare where we're moving away from organ specific reductionistic thinking where we know more and more about less and less until we know everything about nothing. It is this new model which is a model of interconnectedness, it relates to networks rather than pathways. We see that these synthetic boundaries that we put on organs, when we did our organ system anatomy and physiology teaching, is really not the way life works. There's this cross-communication that's involved.

I think we owe people like Candace Pert a big debt of thanks for helping all of us to understand these interconnections among the nervous system, the hormone producing endocrine system, and of course the peripheral and central aspects in innate and acquired immune system.

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I think that the whole concept that there is this interconnected cross-talk among the nervous endocrine and immune system is a pretty remarkable concept because it allows us to better understand mechanistically the diverse symptom profiles that often patients present with who have chronic illness that you can't really understand when you're using just a single organ specific type of diagnosis or assessment.

On those kinds of assessments what happens is a person would have to see like 5 different specialists that are examining each organ in isolation, so you'd have your endocrinologist, and you have your gastroenterologist, and you'd have your neurologist, and you'd have your rheumatologist, and you might have your cardiologist all looking at a different portion of your anatomy, describing the origin of the signs and symptoms of their own territory of ownership, their organ system, and not understanding the nature of the cross-talk and the network inter-relationships that are causing the disturbance in all of those systems, so treating the cause rather than the effect is lost unless you ask the right questions. That's what we're going to be discussing.

Then we're going to tie that or I'll try to tie that together with how nutrition plays a role as a biological response modifier in a cross-talk and network physiology of the neuroendocrine immune system. It's a big objective over the course of the next 10s of minutes that we can hopefully get at least make a first approach and lay out the landscape and understanding how these concepts really relate clinically and how they open up new doors for successful outcome in patients with complex chronic illness that may have had a failure with the traditional organ specific types of treatment.

With that in mind, that's my long-winded intro, I promise I won't spend that much time on every slide here forth, what we're doing in slide 2 is to really talk about connecting therefore the immune endocrine and nervous system into a complex interacting network of communication an how that ties together with function of that system, that super system.

I really want to emphasize this construct of function because when we started in 1989 and 1990 to do the whiteboard discussion about the what if of medicine, what would it look like in the 21st century, we recognized at that point that the term functional as it applied to medicine was pretty much relegated to psychosomatic characteristics. It was a pejorative term in healthcare and really took people away from thinking of organic causes of concern to all in the mind.

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What I recognized in 1989 was if you looked at the literature closely you started to see the emergence of a new definition of the term functional in healthcare where it was being applied functional cardiology and functional radiology and functional endocrinology. It was moving beyond this old model of psychosomatic into this new model of the first signs of a later stage pathology being changed in the function of a cell or a tissue or an organ or in this case an organ system.

Out of that we ultimately decided to take on a new way of defining functional as it pertains to medicine. Since then now we have functional genomics, we have all these different new titles in which functional is applied to them that have really described the opening of this new conceptual framework for medicine and healthcare that's less concerned about what you call it, meaning medical taxonomy, the name of a disease, and more about how you got there, what the process is that led to it, which all originates and emerges out of altered function. That altered function is at either the level of physiology, or the physical function, cognitive function, or the emotional psychological function of the individual.

With that as a preset then how does that relate to the neuroendocrine immune super system? The next slide really describes an emerging new view of this epidemic that we've seen. We used to think it was in the western world, but now we've exported it to the rest of the developing world, which is called metabolic obesity or the whole nature of diabesity. This particular body type, this high body mass index increased wait-to-hip-ratio type male or female is an iconic view of what's gone on as it relates to the way our genes are being expressed in this early 21st century.

We recognize as we see in China with the extraordinary exponential increase in the prevalence of diabetes and cardio metabolic disease that this metabolic disturbance is seen as functional changes at the cellular, and the tissue, and the organ level, and therefore the term functional medicine really even takes on another level of support because we really can't say these conditions are yet necessarily a disease.

These are people on their way to a disease and they will get potentially one of many diseases, which can vary from everything from type 2 diabetes, to polycystic ovarian syndrome, to early stage dementia, to cardiac disease, to breast, ovarian, and prostate cancer.

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There's all sort of disorders that have ultimately become diseases that arise out of these metabolic disturbances, but they start as functional changes in the individual as a consequence of a mismatch between that individual's genes and their environment. Diet plays a big role in sending the signals to the genes that ultimately get translated into that body size, that body shape that we often associate with diabesity.

What we recognize is that if we go to the next level beyond the whole organism level into the tissue and the cellular level is that there are changes in the cellular architecture that are occurring at every level in individuals that have these conditions associated with diabesity. If we go to the adipocytes, the central fat mass, and we look at what goes on there we see that these become enlarge, you get a conversion of a pre-adipocytes into mature adipocytes. They then get stimulated in the production of a series of different type of hormones that are derived from these adipocytes that are called the adipokines and those hormones of which there are many things like TNF-alpha would be one, resistant being another.

These hormones or these modulator substances are pro inflammatory and they tend to blunt insulin sensitivity at the peripheral site, so you get insulin resistant, you get increased inflammation, which we call metabolic inflammation. It's a chronic state of being inflamed. You can see then ultimately the increase in the blood of certain biomarkers associated with inflammation like high sensitivity CRP.

Beyond that if we look at the immune system we see the same changes occurring there. We see the immune system getting activated. You get more pro-inflammatory macrophages and monocytes. You see a shift from the balance between Th1 and Th2 to be more Th1 dominant these pro-inflammatory cells. As a consequence you get an increase in the pro-inflammatory mediators, similar to what we saw in the adipocytes more IL-6, more TNF-alpha, more interferon gamma. These are all mediators that are associated with inflammation that occur as a consequence of the disturbance in physiology at the functional level.

In the neurons, if we go over there to brain and peripheral neurons, we see the same thing happening there, that there's changes in the cellular architecture, change in cellular physiology as gene express different assemblies of proteins. As a consequence of that we see the glial cells starting to become activated with the production of the same types of inflammatory mediators.

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Now we get a brain on fire, or our nervous system on fire, and we get more oxidative stress in the nervous system, we get more apoptosis occurring in neurons with cell death, which then leads to lowered neuronal reserve. We get peripheral neuropathies.

We see the most profitable drug sold by Pfizer being a gamma pentane product that is used to treat nerve pain from the neurological activation through this metabolic process. I'm talking about the drug Lyrica for people not familiar with it. It's the number one selling drug by Pfizer now. It works by blocking these inflammatory processes at the neurological junction that occur as a consequence of factors that activate the nervous system and the immune system. Then we get in the brain, increased crosslinking of proteins, these amyloid plaques. That then increases again the activation of genes and the production of inflammatory mediators.

Now we have the brain and the immune system and the endocrine system all in an activated state as a consequence of these changes. That is what we call the neuroendocrine immune dysfunction. It comes not as singular systems. These work together as a network. It's very common to have what we call co-morbidities. If a person has a condition in their nervous system it's often seen that they have a condition simultaneously in their immune system and their endocrine system. That's not just that they happenstance to co-locate. It's because they're all derived from the same cause. Therefore we get symptoms appearing in the nervous, immune, and endocrine system simultaneously.

With that in mind let's talk about obesity for a second and go to the next slide. Because a paper was published a number of years ago actually in the New England Journal of Medicine that I think is quite fascinating historically. At that particular time when this was published in 2004, a little over 10 years ago, liposuction was a dominant surgical procedure that was being used to treat obesity. This was by, as you know, evacuating certain amounts of fat from the body. The presumption was that by getting rid of that fat you not only would have cosmetically improved the individual, but you would reduce the burden of these fat derived materials that were creating health problems, that were associated with health problems, and so it could have health benefits as well.

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Well the result of those studies, and this is one of the more dramatic examples of an individual with a very high BMI, morbid obesity, you'll see before liposuction and you see the CT scan there in the right showing the amount of subcutaneous fat in that individual. Then after liposuction they lost a considerable amount of weight by the removal of fat. You notice that their subcutaneous fat masses significantly reduced in that second CT scan at the lower right. The interesting feature however was that although they lost a tremendous amount of weight and subcutaneous fat that their metabolic parameters were not changed at all, they still had deranged insulin sensitivity, they still had inflammation. It wasn't just removing fat that seemed to be the problem. There's something else going on.

Now let's take a deeper look at these CT scans for a second and see what we can pull out. What you see is that there was a significant reduction in the subcutaneous fat layer in the liposuction procedure. But if you look at the white stuff sitting in between the organs, the inter-organ abdominal fat, the omental fat, you'll see that it has remained constant because liposuction doesn't remove that physically. It's that fat that sits right up next to the organs and drains its metabolic activities through the portal blood directly to the liver. That wasn't changed in its composition at all.

I call this angry fat. If that omental fat, of that integral fat of the body, central adiposity it's called, is not altered, that fat then releases these pro-inflammatory mediators that come from it's being up-regulated in inflammation, directly into the portal blood that travels as you know directly to the liver. The liver then gets the first level. They have to deal with that. This is probably why we're seeing such a, increase in prevalence of what is called non-alcoholic steatohepatitis (NASH) or nonalcoholic fatty liver disease (NAFLD), because the liver is the first central organ that has to deal with this insult coming from angry fat that's present in the inter-organ area.

What we learned from this study, at least what I learned from this study, is just removing fat itself is not the solution to the problem. You have to somehow tame the angry fat, which is this inter-abdominal fat. The next slide really talks about another technique, which removes, which treats obesity, which is bariatric Roux-en-Y surgery. This is gastric bypass surgery. This is a paper published again in the New England Journal of Medicine. This is 2012, a more recent paper. What they were looking at is changes in metabolic parameters after Roux-en-Y gastric bypass.

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Now it's very, very interesting. I want the individuals who are not familiar with this data to spend just a moment with me looking at these charts because I think these graphs really are very telling.

These are ponderous people who have undergone gastric bypass Roux-en-Y surgery. These are all people that had very significant metabolic disturbances to begin with. They had elevated glycosylated hemoglobin because they were diabetic, they had cardiac irregularities, had dyslipidemia, they had increased inflammatory function. What you notice is that the rate of change in some of these parameters after surgery if you go to the number of months after surgery the rate of change of the physiological parameters, things like glycosylated hemoglobin, or hemoglobin A1C, is much faster than the rate of weight loss. In a month the person doesn't lose a lot of weight but in a month their physiological parameters can change dramatically.

Now what this points out to us is that it's not just weight loss alone that is going to correct this problem, or let's put it another way, it's not just obesity alone that causes this problem. That there's got to be something else going on and it must have some kind of a relationship to the gut, because when you bypass the gut, shorten the bowel and reduce the transit time of things moving through, and also the amount of material moving through, you get a very dramatic change in these metabolic parameters associated with inflammation, insulin resistance, and dyslipidemia.

That's been reproductively shown in many, many studies done in Roux-en-Y gastric bypass patients, many times within just a few weeks are able to come off their medications. They may have been taking a statin and anti-inflammatory and antihypertensive or cardiac anti-arrhythmic and lo and behold in a matter of just a few weeks after surgery, before they've lost much weight at all, those medications can be removed. There's something dramatically interesting about this as it pertains to how the gut interrelates to the neuroendocrine immune system and the regulation of these functions and how it connects to obesity.

With that in mind then let's talk about the immune system specifically. Let's take a look at this so-called M1 and M2 macrophage immune balance. We have these 2 personality types of macrophages. The classical activation form of the M1 macrophage is called the dark side.

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I don't want to really necessarily call dark and light, because these functions are important when they're in balance on both sides, so we can't say one is good and one is bad. But if you have the over accentuation of the M1 personality archetype of the macrophage …

Now what am I really talking when I say personality archetype, what I'm talking about is that the genes of that macrophage are turned on in such a way as to produce an up-regulation and an increased production of various kinds of pro-inflammatory mediators, like TNF-alpha, IL-1, IL-6, IL-12, and that increases in the reactive oxygen species and the reactive nitrogen species, so you get into oxidative stress and you get into pro-inflammatory condition.

The other family of macrophages are worse factors active a different series of genes in the macrophage. These are called the M2 macrophages. You can sort these by various types of cells, or in technologies when you're doing studies, and these produce a different family of adipokines. They produce interleukin-4, interleukin-13, TGF Beta, and these are involved with a different kind of functional effects on the body, more anti-inflammatory effects, immune suppression and tissue repair.

Now clearly you need both of these capabilities in your body to maintain good health and good function, but they have to be in balance. If you have an imbalance of M1 to M2 macrophages then you shift the teeter-tooter over into a pro-inflammatory state, this kind of state of metabolic inflammation or meta-inflammation as it's often called. That's what you see in these patients that have a lot of angry fat, this omental fat, is they're often when you take biopsies of their fat you'll find it's infiltrated with a high level of M1 macrophages that are associated then with the adipocytes in the fat mass that are turned on to be pro-inflammatory. That's what I call angry fat.

The immune system and the endocrine system and the nervous system obviously are all interconnected as it pertains to the production and maintenance of this state of immune vigilance or what we call metabolic inflammation. The next slide talks about how this leads to a cascade of events, this inflammatory cascade because it doesn't just stop locally, the blood is going to take these various chemokines, and adipokines, downstream and they can attach themselves to receptors of tissues at a distance. This is I think locally, act globally, type of thing.

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We can see that the vascular endothelial cells that line that one-cell thick lining of all of our arteries, that they are also capable of being affected in their function by these materials because they have receptor sites that pick up on their receptors these particular adipokines and cytokines that were produced elsewhere in the body. That turns on locally then affects that then influences atherogenesis, or the production of the first stages of arthrosclerosis, and you start getting then foam cell formation and lipid uptake and the cascade of events that then we associate with the start of the atherosclerotic process.

Now we've got the arteries connected to the adipose tissue, connected to the immune system, connected to the liver, and as you know within the liver 10% by weight or volume in the liver is occupied by what are called Kupffer cells. Kupffer cells are embryologically they originate from the immune system. That's the liver's immune system. The liver picks up these messages too and it is transitioned into increased inflammatory injury as well.

The Kupffer cell, next slide, then sends out its messages into the blood. Those messages in the Kupffer cell, those immune activated messages then do what? They alter the gene expression of the Kupffer cells so it is going to produce more of its own inflammatory molecules that it alters cholesterol synthesis and conversion to bile salts, and now we start to change lipid levels, we start to change the production of apolipoproteins in the liver and then the transport of lipids in the blood.

Now we start to see a person shift their patterns where they never had a cholesterol problem and now suddenly start getting increased cholesterol and increasing LDL, increasing stickiness of platelets with increasing risk to fibrotic problems. You've got a whole series, a cascade of networked events that cut across many different organ systems, that produce distant symptoms that as I mentioned earlier are probably seen by different subspecialists who are all looking with their own lens at individual organs and it's saying, "Okay, well, we're going to give a drug for the treatment of this problem for this organ."

Now in this slide entitled "Hepatic Kupffer Cell Activation Cytokines and Metabolic Inflammation" there is a word on that slide that I want to bring into our attention and that's the word called *endotoxin*. Because there's another part of this network of events that I think is very important to understand. Activating upstream this whole process are triggers.

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If you think of the functional medicine model we talk about antecedents, triggers, mediators, leading to signs and symptoms. There are triggers therefore upstream that activate this whole process within the neuroendocrine immune system. One of those activating substances, not the only, but one is called endotoxin.

Endotoxin is the debris of gram-negative bacterial cell walls that contain certain types of cell wall materials that attach themselves when released to receptor sites called the innate receptors, so called toll-like receptors that appear throughout the body but certainly are in very high concentration in the mucosal cells on their apical surfaces. These toll-like receptors pick up the debris from gram-negative bacteria, these so-called lipopolysaccharides or LPS that is what is an endotoxin.

This LPS then binds to these receptor sites on the surface of cells and it then sends a message through the membrane of the cell, through the cytoplasm, through a very elaborate process called the kinase network to the genes of that cell through nuclear factor-kappaB and other kinds transcription factors that turns on the genes to then produce things like TNF-alpha, IL-6, and these other pro-inflammatory mediators. Therefore the initiating factor in many of these cases of metabolic inflammation that cuts across the neuroendocrine immune system, is the relationship between the gut microbiome and the activation of these toll receptors.

Then one has to ask, in this chicken and the egg argument, well, where does the gut microbiome get its information? It gets it from a complex series of different events, this matrix of literally thousands of different kinds of bacteria that live in our intestinal tract. One of the major sources of information that the gut bacteria get comes from our diet.

Therefore diet plays a role in modulating the gut microbiome, which then modulates endotoxin levels, which then influences the innate immune system, which then influences the production of these toll-like receptor activated inflammatory cytokines that then travels down through the portal blood to the liver, and whoa-be-it, now we start getting a shift in the body of a combination of the angry fat and the endotoxic events in the gut that lock a person into a spiral. I don't want to call it a death spiral. That sounds a little bit gloom and doom, but certainly into a negative health spiral as it relates to this metabolic inflammation that cuts across all these organ systems that are associated with the neuroendocrine immune function.

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Now we've gone from tissue pathology to a functional state that relates to multiple clinical symptomatologies. We can back ourselves up to understanding where some of the origin of this may have been derived and it leads us into kind of a wonderful Sherlock Holmes detective story as to what in an individual patient was the triggering factor that started this whole process. Because you have to take away the things that are triggering it and then you have to add back the things that the body needs to rebalance the neuroendocrine immune system. This is a functional medicine approach to these problems. Rather than treating the downstream disease we're moving to the upstream understanding of its origin.

Now move to the next slide with me and here's where this starts to connect into the traditional view of specially, sub-specially medicine. This is a paper that appeared in the journal again, a little over 10 years ago that was entitled "Clinical implications of the Osteoprotegerin/RANKL/RANK System for Bone and Vascular Diseases." Now that's a pretty sophisticated title and you almost have to go to the medical dictionary just to look up the words to figure out what they're talking about. Let me if I can demythologize it slightly.

RANKL and RANK stands for the receptor of NF-kappa-B ligand. Therefore these are receptors that sit on the surface of various cell types and various tissue types that are activated by inflammatory processes. Osteoprotegerin is one of the signaling molecules that is produced that then regulates, to some extent, the activation of the RANKL/RANK system. We know that bone loss in association with osteoporosis, is in part, related to activation of the RANKL system and therefore we can say osteolytic osteolysis, which is bone resorption, is in fact an inflammatory process that's associated with the activation of these inflammatory mediators, specifically in the osteoclast.

By the way, the new anti-osteoporotic drug that Amgen has now had approved by the government, which is an injectable drug, is a drug. This is Denosumab is what I'm talking about. That drug actually blocks the RANKL system. It is an antibody that lays over that receptor that prevents activation in the bone of this inflammatory process and thereby reduces bone resorption.

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The interesting thing that this article points out, and this an aha, this is like a functional medicine 1A diagram, is that the same mediators that activate this bone loss through the RANLK system, that would be the top picture in the diagram labeled A, *Skeletal System*, those same mediators that are pro-inflammatory that activate in bone loss if you go down to the next middle diagram this is what happens in the immune system. In the immune system associated with rheumatoid arthritis you see the same exact mediators activating the RANK/RANKL system there associated with connective tissue loss and the dysfunction that's associated with joint degeneration in rheumatoid arthritis. Then go to the third C, bottom panel, and what you see is the same exact thing going on in the vascular endothelial cells with the same mediators.

Therefore one mechanism, this activation of the RANKL system, is associated with 3 very different diseases, osteoporosis, rheumatoid arthritis, and coronary heart disease. That begs the question then where do these come from. They came from imbalances of the neuroendocrine immune system, they came upstream from triggers that could have either been from the gut through endotoxins, or through activation of angry fat, through various factors that are associated with activation of innate immune system receptors that ultimately downstream signals to these various organs specific activities or tissue specific activities that result in what we see pathologically as osteoporosis, rheumatoid arthritis, or coronary heart disease.

This begs the question, doesn't it? It begs the question whether a person who has osteoporosis would have a higher probability of having rheumatoid arthritis and coronary heart disease. Or vice versa, a person with rheumatoid arthritis, do they have a higher risk of osteoporosis and coronary heart disease? This is called comorbidities or disease adjacencies and the answer is absolutely yes, that these come together often and that patient or that person might be seeing 3 kinds of practitioners for 3 different individual diseases.

They might be seeing a rheumatologist, they might be seeing an orthopedist, and they might be seeing a cardiologist to treat each of these individual conditions that emerge from this process and not recognizing that the cause of this is upstream and if you treat the cause and not the effect maybe these downstream mediators will not then have these tissue specific activities that we call these diseases. That's the functional medicine model of how we would look then at the clinical application to the neuroendocrine immune system.

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What is then the source of this chronic inflammation? That's my next slide question. You probably recognize that we are saying that there are these triggering events that could be the ultimate kind of places that we would want to place our bets as to where these things emerge. Next slide talks about endotoxin, inflammation, and mitochondrial uncoupling, because these bacterial cell wall debris that I talked about, these lipopolysaccharides that induce endotoxemia are known to enhance then inflammatory processes and these pro-inflammatory mediators do none other than uncouple mitochondria. In other words they cause energy deficits in the tissues affected.

It's like putting a short circuit in the wires of your electrical system in your house. You might have the voltage coming into the house but it's not getting to where you need it to light the lights or turn on the heater. So you get mitochondrial uncoupling. That produces oxidative injury. Oxidative injury activates capsis and other proteins in the cells, it causes cell suicide which we call apoptosis and now you're in a degenerative mode, that person is in loss of organ reserve and they are accelerating their biological aging.

We recognize that there are these concepts that relate to the origin of these problems that interrelate to alternative function of the neuroendocrine immune system, and how they downstream influence in function of tissues. What are the triggering events for these processes to occur? The next slide takes you down the road a little bit of understanding, probably more than you ever wanted to know, as to where these things come from.

One of the most interesting places that won the Noble prize in medicine and physiology a number of years ago was the discovery of these receptors called the innate receptors or the toll-like pattern recognition receptors. These sit on the surface not just of mamune cells, but these toll-like receptors sit on the surface of immune cells and of nervous system cells as well, neural cells. They share cross-talk and communication in a network.

These receptors are called TLRs, toll-like receptors. The one that I want to focus on just for the sake of this discussion is toll-like receptor 4 or TLR4. TLR4, it's ligand, and the thing that activates is the lipopolysaccharides that come from ground-negative bacteria cell walls.

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Again, gut dysbiosis inducing endotoxemia activates toll-like receptor 4, which then triggers this downstream process of gene expression that is associated with inflammation.

Now is LPS the only activating agent for TLR4? The answer is no. Another known activator, which has been discovered recently, is palmitic acid, a long chain saturated fatty acid that is found in diets that are high in animal products that contain high levels of palmitic acid. That also is known to activate TLR4 downstream gene expression patterns of inflammation.

Another family of emerging substances that activate them are certain types of persistent organic pollutants. This interrelationship between pollution or let's call it outside exotoxins and inflammation can in part be rationalized or understood through activation of these toll-like receptors and how that then works together with things like endotoxemia.

You can imagine this is a system where you start layering things on. You have dysbiosis, then you have a high saturated fat diet, then you're exposed to a lot of toxins, persistent organic pollutants, and what you're doing is layering on triggers for these toll-like receptors that then is shifting your gene expression patterns towards inflammation, shifting macrophages to the M1 state, and shifting your adipocytes towards pro-inflammatory reactions. That has a neuroendocrine immune system effect throughout the whole of the body.

How this whole field is emerging to be understood at a mechanistic level, it's quite a remarkable I think advancing in our understanding. Again, we have to go back down to the gut slightly to understand how the gut immune system plays a role. The next slide talks about specific gut microbiota derived compounds, these LPS's and how they're able to trigger metabolic inflammation through the associated immune system, the macrophages sit right there adjacent to the surface of the immune system and this is the so called gastro intestinal associated lymphoid tissue.

You might think of your gut talking to your adipocytes, talks to your liver talks to your vascular endothelium, talks to your nervous system, and talks to the endocrine producing cells in your adrenal glands. All of these things are then interrelated to the recognition that dysbiosis is associated with diabetes, that dysbiosis is associated with dementia, dysbiosis is associated with cardiovascular disease.

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These don't occur mysteriously. They have a connection through this alternative cell cycling or cell signaling, excuse me, that is associated with these inflammatory messages that were derived from the gut dysbiosis relationships.

How do we know that? Well let's go to studies in twins. This was published recently in Science Magazine. I think it was a very interesting study entitled "Gut Microbiota From Twins Discordant For Obesity Modulating Metabolism." What we're looking at, again this is a very controlled study in animals because all the variables can be controlled, and these are animals that are derived from the same litters and they show the same genes. We're looking then at the role of gut microbiota in lean animals that are transplanted to fat animals and how those gut microbiota from these lean animals transfer to fat animals then will alter the gene expression patterns in the animal based upon the level of dysbiosis that occurred in the transplanted microbiota.

You have 2 twins. One twin gets a sham transplant. The other gets a transplant of the biota from a metabolically disturbed animal, and lo and behold you end up getting obesity and inflammation and diabetes appearing in the animal of the twin that got the transplant of the biota from the disturbed animal. The sham animal remains lean and remain insulin sensitive and remains absent of inflammation.

This paper in a controlled animal study demonstrated that these effects are not due to altered calorie intake but related to the metabolic influence that the biota is having on the immune system that influences then nervous and endocrine function in such a way ultimately to cause calorie gain, poisons mitochondria, reduces oxidative phosphorylation and the fire of the body, the energy powerhouse of the body is reduced so the body then starts storing these calories for a rainy day that never comes and so you start seeing obesity.

It's not that we say that having gut bacteria necessarily causes obesity. It's having this what I would call endotoxic producing bacteria that induces these processes that are associated with obesity. This is a whole new emerging understanding of how this obesity epidemic may be related to microbiota and how that interconnects to the gut immune system, to the nervous system, and ultimately to the endocrine system.

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I recently was involved let's say a 15 months long project where we had our gut microbiota examined 4 times throughout the year, we had our genes fully analyzed, and we had several thousand different biomarkers analyzed on us over the course of the year-long study. There were about 100 people in this study. What you're looking at in this next slide is the example of species diversity of the gut microbiome. You have the green is one of the predominant types of family of bacteria you have which is the firmicuties. Then you have the pink which are the other dominant family which is the bacteroidetes.

What we generally say is that the healthier individuals are the ones with the greatest species diversity, the more diversity of bacteria the better. We also say that you don't want to have a preponderance of firmicuties. It appears as if those people who have very high level of firmicuties are individuals who have higher levels of these dybiosis, endotoxic, chronic problems. You want to be balanced in this.

You'll notice in these 100 people that are represented, each one of these horizontal lines is a different person, you'll notice that there is a very significant diversity of the speciation of these families of bacteria. Some people have almost all green, almost all firmicuties. Other people have almost all pink at the ends of the scale. Then there's variations on a theme in the middle with different types of other diversity of the proteobacteria and the verrucomicrobia bacteria as well.

I would say that the takeaway from this answer as we start looking at a healthy microbiome is diversity and species balanced between the firmicuties and the bacteroidetes. We don't want to have too many of those green at the expense of the pink in our microbiome.

Then the question is how do you vary your microbiome? Well the next slide looks at what we called the diversity score. You want your species diversity to be as high as possible. My particular microbiome is that little blue dot there on the … This is 100 and some people that were analyzed. Some people had very low species diversity and other people had 3 to 4-fold greater number of species in their microbiome than others.

There's a tracking of increased species diversity with increasing stability. This is almost like an ecological principle that diversity means stability in an ecosystem.

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The higher species diversity and the proper balance between firmicuties and bacteroidetes appears to be principles that are important for maintenance of good health and lowered inflammatory potential.

Now the question is what's the best way of getting your microbiota to be in a healthy balance? I think there's still a tremendous amount of work that's being done in this area, but certainly we know that prebiotics are very important, those selective substrates upon which the friendly bacteria, the symbiotic bacteria live, these are things like basically some of your fructans and your larger arabinogalactans. These are the non-digestible branched-chain carbohydrate molecules that are fermented selectively by your friendly symbiotic bacteria.

It appears as if the prebiotics are more important in species diversity than are the probiotics actually. I'm not saying probiotics are unimportant. They are important. We would generally in a gut restoration program we generally recommend clinically that you give both prebiotics and probiotics. But if I had only one to give I would have to say the prebiotics are probably from the clinical work that's been done to date more important in affecting species diversity and speciation type in your gut microbiome than is the administration orally of probiotics. The combination of the 2 good but don't forget prebiotics. They are very, very important part of a dietary intervention program for establishing improved gut biome, microbiome health.

We also recognize that there are a variety of other nutrients that play important roles in this immune system potential that interfaces with the nervous and endocrine system. Just some of the dominant nutrients that probably most people are familiar with are vitamin A or retinol which can come also from previtamin A or beta-carotene, which gets converted in the presence of thyroid hormone I might add at the gut mucosal level beta-carotene gets converted into retinol. You need proper levels of thyroid hormone to do that.

Vitamin A, zinc, very important and often a nutrient that's not in adequate level. This may be a place where people need some degree of supplementation. Folate as we all know is so important, particularly 5-methyl-tetrahydrofolate that allows for a stepwise improved function in the production of S-adenosylmethionine within cells. Vitamin B12 cobalamin, vitamin C, and of course vitamin D which is on everyone's marque right now.

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All of those nutrients are well-known to have very important roles to play in modulating immune systems function at this level of M1 and M2 macrophage differentiation.

We've connected the gut and the so called gut associated lymphoid tissue activity, together with the gut microbiome and with nutrients that come from the diet that are there to activate gene expression patterns that are associated with healthy inflammatory balance. We've also talked about the role that activating substances play such as saturated fatty acids and persistent organic pollutants, both of which we want to reduce to lower the activation of these innate immune system activated pathways that are associated with the upregulation of neuroendocrine immune inflammation. Now we're starting to develop a clinical model from this information that's very different than just giving an anti-inflammatory and hoping for the best.

Now the last part of this then is what about phytochemicals that are present in vegetable products? Do any of these thousands of different phytochemicals play roles in modulating this neuroendocrine immune system function and this cascade of events that we've talked about that's associated with inflammation? The answer to that of course is yes. We now recognize that food is much more than we thought about when we thought of it as calories and essential nutrients, and vitamins and minerals, proteins, carbohydrates and fat. We now recognize that food is also information. Various nutrients that are found in vegetables, these phytochemicals have evolved. They have a very interesting relationship with us to activate or to support gene expression patterns associated with anti-inflammation and insulin sensitivity.

If we were to break the family of phytochemicals down into different types this is one type of schema that one could consider as to the different members of the families of phytochemicals. On the next slide is a discussion of terpenes and phytosterols and phenols and glucosinolates, or thiols, because they have sulfur-containing residues in them, indoles, isoprenoids, and lipoic acid and coenzyme Q10 would be quite known. All of those would be representing then various types of phytochemicals, each one of these families having a different effect on cellular gene expression and cellular function.

We obviously then could take this down even another level. Let's take phenols as an example, polyphenols.

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Under that family you've got further differentiation into phenolic acids, flavonoids, tannins, like various types of molecules that are involved with catechins, polymeric catechins, stilbenes, the one that's probably most familiar in the stilbenes family is resveratrol, and lignans and like equol that are found in plant foods.

That would be a way of differentiating phenols. Then under flavonoids to even get further differentiation are sub families of flavonoids. We have flavones, flavanols. Then we have isoflavones like genistein and daidzein that are found in soy, and anthocyanins. All of these have different physiological processes and different effects on gene expression.

Now why am I making this so complicated? What I'm trying to say is that within our plant kingdom are a series of these secondary metabolites of plants that cut across thousands of different name chemicals that plants elaborate from their own genes that we have been consuming in the human diet for long time and we have evolved a relationship with them so that they actually influence in selective ways our gene expression patterns.

It doesn't mean every phytochemical has identical effects to every other phytochemical. In fact, no, they're differentiated based upon their structure in function and how they influence various receptor sites and how they can modulate then cellular signaling in unique ways. Each one of these families of phytochemicals and each member within those families is now known through these series of studies that have been in the field over the last 10 years in nutrigenomics and in cell-based essays that these phytochemicals play a very important role in orchestrating many of these processes that are associated with neuroendocrine immune system function.

Let's use just one as an example to illustrate this and that's the Sirtuin-Histone Deacetylase story. This has to do with specific phytochemicals that modulate this gene expression process that's associated with sirtuin and histone deacetylase. What is that all about? Well, I'll try to not get too technical here. If we ask the question what is the mechanism by which calorie restriction seems to have a beneficial effect on cellular aging, how animals that are put on calorie restriction then have improved life expectancies and lowered metabolic disease it appears through activation of this family of genes called sirtuins.

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Sirtuins are involved with the regulation of how our genome unfolds to allow certain genetic messages to be expressed. It has to do with the reading of our book of life.

One of the regulators or one of the family members of the sirtuin family is called SIRT1, which you've probably heard of because it is a signaling mechanism that is regulated in part, upregulated actually by resveratrol, a great skin and peanut skin phytochemical, polyphenol. What SIRT1 do is they influence gene expression patterns of things like PGC-1alpha, NF-kappa-B and FOXO3, which are all very important signaling processes that are associated with regulation of inflammation, obesity, insulin sensitivity, and cell cycling.

That means that these particular signals that are regulated or influenced by the phytochemical like resveratrol have a principle regulatory mechanism on processes if accelerated that we associate with enhanced biological aging. So they kind of mimic some of the effects that we would see with calorie restriction.

There are a variety of different phytochemicals that have influence on this deacetylase activity and the Sirtuin1 function and those include things like epigallocatechin gallate found from green tea, or genistien the isoflavone found in soy, or allicin found in garlic, or lycopene found in tomatoes. These are all known along with obviously curcumin, sulforaphane, resveratrol, phenyl isothiocyanate that comes from broccoli and Brussel sprouts, all of these phytochemicals are known to favorably influence in the regulation of the sirtuin pathway and ultimately the regulation of things like S-adenosylmethionine and antioxidant function in cells.

I think we're starting to actually get a very important mechanistic understanding of how a complex vegetable-based diet or a vegetable included diet can have such dramatically favorable effects on processes associated with insulin signaling, inflammation, cell cycling, and replication.

With all of that in mind, how can we can apply that to some specific dysfunction of the endocrine system? Let's apply this phytochemical story and how it interrelates with the neuroendocrine immune system through the elegant work of Dr. Elizabeth Rogan at the University of Nebraska. She has done some just fantastic work.

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She's a professor and chair in the Department of Environmental, Agricultural Medicine To Public Health there at the Eppley Institute for Research in Cancer and Allied Diseases. She's an individual who's been studying estrogen metabolism in women and now more recently in prostate glands of men for some decades.

She reminds us, in the next slide, that if we look at estrogens that there are families of estrogens from 17-betaestradiol to estrone, and then there are these hydroxylated derivatives of estrogen, like the 2-hydroxyestradiol where there's a hydroxyl group that's been attached at the 2 position of the A-ring of the estradiol molecule. Then there's estriol, which we've heard a lot about E3, so we have E1 estrone, E2 estradiol, and then E3 estriol, and we know that modestrone in estradiol can be further hydroxylated to form the 2-hydroxy form, or as shown in the next slide can be 4-hydroxylated to form the 4-hydroxylated estradiol and estrone.

Now what's the difference between a 2-hydroxy and a 4-hydroxy? Well, this is a little bit like an accelerator and a brake mechanism in terms of cellular gene expression. I'm going to generalize here and it's probably not going to be scientifically precise but I think you'll get the drift to where I'm going. The 2-hydroxy estrogens are like the brake. They retard a gene expression of cell cycling and so they slow down cell replication. The 4-hydroxy estrogens are clastogenic and they are like accelerators, the 16 and 4 both have an accelerating function on gene expression and can alter gene expression, and can even be considered clastogenic and as such mutagenic, and potentially pro-carcinogenic.

You want to lower the production of 4-hydroxy and you want to increase the production of 2-hydroxy estrogens. Now how does this relate to my story then of phytochemicals modulating the neuroendocrine immune system? Well in this specific example the production of the 2-hydroxy estrogens are activated by polyphenols that occur in glucosinolates that occur from certain vegetable products, particularly the one that has been studied the most is glucosinolate, called indole-3-carbinol or I3C, and its downstream metabolite diindoylymethane, DIM.

Those particular cruciferous vegetable derived phytochemicals increase the activity of the cytochrome P450 that activates the 2-hydroxylation processes. This is actually been shown in women who have cervical dysplasia and are then placed on a broccoli-rich diet that delivers about 400 milligrams a day of indole-3-carbinol.

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It's shown that they have a reversion to normal cellular architecture as a consequence of increasing their intake of broccoli, because it's activated in the 2-hydroxylation pathway and it's decreased the 16 and 4-hydroxilation pathway.

Here's a classic example of how the endocrine system and its interrelationship with the immune and nervous system are modulated by a dietary variable, in this case bioactive phytochemical components from the cruciferous vegetable family, cabbage, cauliflower, broccoli and Brussels sprouts. I think these are really extraordinary new developments as it relates to how we actually empower then functional changes in the neuroendocrine system by dietary modification.

In fact, there is a clinical trial that was published in 2000, the year 2000 in Gynecology Oncology, looking at a placebo control trial of indole-3-carbinol in the treatment of this cervical dysplasia type situation, showing that when women as I said were administered higher levels of indole-3-carbinol for 12 weeks that they had a reversion or a regression of the dysplasia. I think that this is not just theoretic. This has been proven through clinical trial to actually be functionally important.

Nutrition has a very important role to play on neuroendocrine immune function and it even goes into things like reversal of cognitive decline. There's some wonderful work that's being done by Mark Mattson at the National Institute of Aging. There's work that we have the privilege of interviewing the individual Dr. Martha Clare Morris who is the principal investigator in the Alzheimer's Research Center at Northwestern and Rush University of Medical Center looking at this influence of what they've called the mind, M-I-N-D diet and how that was associated with reduced incidents of Alzheimer's disease in a clinical trial. This is a high phytochemically dense modified Mediterranean diet that they're using as their intervention diet that has demonstrated in individuals improve neuroendocrine immune function and a reduction of dementia risk.

Similarly we interviewed Dr. Dale Bredsen who's the director of the Mary S. Easton Center for Alzheimer's disease research at UCLA and he has also been intervening with an extraordinarily important complex diet and lifestyle program for individuals that present with early stage to mid stage Alzheimer's.

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He's published a recent paper that actually demonstrates that he can show regression of Alzheimer's disease in these individuals who've been placed on these personalized or tailored programs in which they are using diets that are much higher in phytochemicals and balancing their hormones and improving their neuroendocrine immune function at the gut level. I believe that we're moving from a stage of theoretic to a stage of clinical application as it pertains to these principles of neuroendocrine immune function.

Then lastly we've put this all together into this diagram that talks about the nutrition connection to the neuroendocrine immune system function. You have the Western diet and lifestyle, which is high in saturated fats, high in sugars, high glycemic index, and it activates then the gut immune system. You need to make a dietary change. You need to reduce the exposure to these persistent organic pollutants – POPs – and various antigens, maybe even gluten in certain people that have gluten sensitivity.

You then need to gut restore with proper synbiotics, which is a combination of probiotics and prebiotics. That then influences in macrophage function and we're trying to reduce then the production of inflammatory molecules so you need to have your diet high in anti-inflammatory phytochemicals, the families that I've already described in the previous slides. You also need to have regular exercise because we know exercise sends a signal that also has anti-inflammatory potential.

We also recognize that proper thyroid function and the conversion of T4 to T3 is really important in regulating these processes at the adipocyte level. We also recognize now from recent work that cold exposure has a very important role to play in activating brown fat thermogenesis and mitochondrial function through what's called UCP1, uncoupling protein1. Also cold exposure, and it can be short term cold exposure along with proper thyroid and proper exercise, and then this low-saturated fat, low-glycemic load, high-omega 3 diet, all of which together then starts to form a program for supporting proper function of the neuroendocrine immune system.

I hope what I've given here in a very rapid fashion is a history of how we got to where we have gotten, where we are today, and maybe a little bit of a look into the future as we start to do microbiome genetic analysis and we start personalizing care based upon the genes of that individual and the genes of their microbiome.

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We can start to really develop a precision based approach towards what I would call a system's medicine intervention for imbalances of the neuroendocrine immune system, so less treating the disease and more treating its cause. I think that's probably a good place to stop and hopefully I've given some news to use.

Dr. Ritamarie: You have given us an enormous amount of information. A lot of it, what comes to me as you wrap it up and come to the end, so much of what we're already doing in our program with our pillars, our foundations, and the kinds of things we're doing the right things. Understanding the research and the underlying mechanisms and some things at a deeper level gives us the ability to really stand behind those recommendations when people are baulking at those recommendations because they don't want to change their diet, and they don't want to move, and they don't want to do these things, just supports everything that we've been talking about.

What we're going to do is I shot a message off to our assistant and said we need a transcript of this, because I know that you guys, you talk fast, you're brilliant and you present so much great information. I'm trying to take notes and I can't keep up with taking the notes.

What we're going to do, we will provide you guys with a transcript. Hopefully the transcriptionist will understand some of the technical lingo that you put in there. It was awesome. I just loved the way you came full circle and came back to the phytonutrients in the plants which I'm really big on a plant strong diet and I like the way you put it, a vegetable based diet, a vegetable strong diet. Because that's really key. Not just any plants, not just filling up on wheat and rice and all that other stuff. That's not it. It's really those vegetables that are loaded with so many of these phytochemicals that you identified and probably thousands more that we have yet to identify.

Dr. Jeffrey Bland: Absolutely. I think what you're doing in your education and your networking is exactly what has to happen. It takes like 30 years for medical clinical practice to change after the discovery of a new idea, whether it's the stethoscope, or blood transfusion, or the EKG. It takes about 30 years for stuff to translate down in the clinical practice. What you're doing is so brilliant. You're accelerating that transition and compressing the time, which is what we need because there's so many people in need. I just can't compliment you enough for what your efforts are all about.

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Dr. Ritamarie: Thank you very, very much. Thank you. We know how busy you are and how much in demand you are. I just really appreciate you taking time out of your busy schedule, putting together this amazing slide presentation, and just being here with us and really allowing people to see that we're all in the right place, as frustrating as it may be sometimes when people are baulking at this and a lot of their doctors are saying, "What? This doesn't make any difference. Just put them on a stat," and they're just put them on metformin or whatever.

We know, and when we have the science to back it up, and that's why this program came into being, is so that we understand the science. We're not just doing protocols with people. We're understanding how this works and we can go back to this and back to this and back to this and really understand how some of the simple interventions that we're doing and some of the more complicated interventions are actually doing. I wanted to ask you, do you have a few minutes to answer questions-

Dr. Jeffrey Bland: Oh I sure do. Absolutely.

Dr. Ritamarie: … if anyone has any questions? Because I want to ask the first.

Dr. Jeffrey Bland: Sure, please.

Dr. Ritamarie: There's a lot of push right now towards more of a paleo type diet. A lot of people are pushing a lot of animal products and saying that plants are just condiments. I've heard this and it's like, "Wait a minute, what do you mean plants are condiments?" But there's also some situations where there people are pushing a SIBO diet for example or the FODMAPs diet or the specific carbohydrates where they're just pushing out the plants because of specific bad interactions of specific polysaccharides et cetera and monosaccharides et cetera with individuals.

I just wanted to hear your take on it. For me it's like it's almost like you're throwing out something, you're making generalizations and it could be harming people, but yeah, there could be transition periods where people do have to be careful about the broccoli or whatever because of the oxalates, the FODMAPs et cetera. I'd just love to hear your take on that.

Dr. Jeffrey Bland: I think I agree entirely with the way you just laid that question out because it implies a very good answer to your own question, and that is we recognize the diversity in humans.

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We also recognize that we are a society in metabolic stress right now and that metabolic stress is occurring as a consequence of many variables I think including our environment, including our lifestyles, including our diets and all sorts of variables that are influencing the genes that are turning us into a pro-inflammatory state. Things that we might have gotten away with before people may become more sensitive to today.

However, with that said I believe that there is always the right balance to find for a person rather than going to a rule. I think we hate to hear people say they have the answer as if the means their program.

Dr. Ritamarie: Amen.

Dr. Jeffrey Bland: Because that really speaks against the diversity from person to person. There are people who may be sensitive to certain cruciferous vegetables, there might be people that can't stand garlic, there may people that are reactive to certain isoflavones. But by looking at the individual and what they can tolerate I am personalizing their diet to their need. One can almost always come up with a very robust library of phytochemically rich foods that will be in balance with their need, and not have us be on the extremism of oh that's bad and this is good so never touch this because we put a red label on it.

I think that finding that midline that personalizes the individual need is really the difference between people who know what they're doing and people who are one-day wonders or just sending out information because they think they have the answer. The really great clinicians know how to balance the persons' need and find the right solution and put the right key in their keyhole to find the answer.

Dr. Ritamarie: Thank you. Thank you very much for that answer because it's where my heart is and where my movement is and what I teach in terms of the personalization. We can't make generalizations. Even the stuff we say is great may not be great for some people at a particular point in time. Maybe it'll be great a year from now when you clean up the leaky gut and get rid of all the dysbiosis and what not.

Dr. Jeffrey Bland: Yeah, and I think even words that we use like Mediterranean diet or paleo diet, I mean those mean very different things to different people. I mean the Mediterranean diet from the north to the south is vastly different. What Mediterranean diet are you really speaking about?

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Or the paleo diet can be everything from Konner and Eaton's discussion of Paleolithic humans living in caves to, "Well, we're going to go to the shopping market and we're going to buy all the steaks that we can get." It's a very, very different view. We put the same label on it and it means very different things.

Dr. Ritamarie: Exactly. Thank you. Thank you. If anybody does have questions star 2 on your keypad will raise your hand. Star 2 raise your hand if you have a question. I know you might be like feeling like, "Whoa, I think I have to sit with this and listen to this again and again before I have questions," but seriously if you have questions just star 2 and if … There's some. I'm looking to see if there's any questions typed in if you have typed in. Jamie says, "What's your view on metabolic typing, i.e William Wolcott for assessing multiple diets based on ANS oxidative rate dominance?

Dr. Jeffrey Bland: Thank you. I think that metabolic typing has always been a chimeric objective since I've been in this field for 40 years. We've had probably I wouldn't even hesitate to estimate the number of people that have come up with their solution to metabolic typing. I think each one of these is a voice in an evolving understanding of how we get a handle on the unique needs of a person. I don't think we've completely wrestled this to the ground yet with security, but I think the more that we can ask the questions about our individual uniqueness the better off we will be.

That's one of the things that I try to do in my recent book, "The Disease Delusion." I included a variety of questionnaires that we had been using in our clinical work and our research over the last 20 years that really start addressing questions that help the person. Because the answers we get depend on the question we ask, don't they? You can't get an answer to a question you never ask. I think it's asking the right question to help guide a person to their right answers.

I don't have the recipe but I think an assembly of the right questions gets a person to think about, "Oh, gee, I've never thought about my response to that. That's a good point." Now from that information that becomes … Information is power. It becomes empowering for a person to make the right choice. I think typing is a good objective but I wouldn't throw all my eggs into one basket.

Dr. Ritamarie: Got it. Got it. I love it. Yes, thank you. We do have a question on the phone. We have Steph I think it is, right, from Vancouver. Steph is that you?

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Steph: Hey, yeah it's me. I just want to say I'm like on the edge of my feet. I was so excited I spat out my soup and I yelled, "Yes," scared my entire family. I'm having such a good time. Thank you so much for this interview. Yeah, if I wanted to learn as much as I possibly could about the interactions between the byproducts of specific gut bacteria and different parts of the immune system where would I go, where would I start?

Dr. Jeffrey Bland: That's a very good question. There's a lot of really good books that have been written recently on this topic that are getting rave reviews. I think I read about 10 of them recently from different authors who are really experts in the microbiome and it's in a relationship with the gut immune system. One person that's been on our field for many years that has a new book out is Gerry Mullin. I don't know if you don't know Dr. Mullin but he's at John Hopkins. He's a gastroenterologist and he's been a leader in functional medicine for many years and he has a very nice book. I wouldn't call it like super sophisticated. It's more like intermediate level book to get people to understand how this new information can be applied clinically. That might be one that you could google or go to Amazon and find more information about.

Steph: Cool. Thank you. What if I really want to geek out on heavy duty?

Dr. Ritamarie: Jeff is a geek. Jeff is our microbiome functional microbiome geek.

Dr. Jeffrey Bland: Let's see. In geek-tam land of which there are many if you go to uBiome, you probably have been there, they have a really interesting reading list of books and articles actually as well that are the latest cutting edge in this whole field that that might be a good place to start to look at their list.

Steph: Cool, yeah that's a good idea. I haven't done that. Thank you.

Dr. Ritamarie: Super. Thank you. Thank you Steph. Anything else?

Steph: No it's all good. Thank you so much.

Dr. Jeffrey Bland: Thank you.

Dr. Ritamarie: Thank you. Anyone else? I don't see any hands up. I'll check one more time on the Q&A to see if anybody typed anything in, but I think we've just really filled everybody with lots of amazing information. Again, I just so appreciate you being here. As I said before I mean I remember sitting and I was still in school taking notes at your seminars, writing as fast as I can and wishing I could go back and listen again.

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Here we have the opportunity, we can go back and listen to this again and again, and take notes and fill in your notes, and we'll have a transcript. This is like what I dreamed of when I was back in the early days of learning.

Dr. Jeffrey Bland: Oh thank you.

Dr. Ritamarie: So thank you so much.

Dr. Jeffrey Bland: Well you know I think you said something to me that's very for me personally is quite interesting. That is a lot of individuals I think as they go through their careers they eventually feel like they've either maxed out or it's like groundhog day, they're hearing the same things over and over again and maybe it's time to move to a different discipline or to retire.

I think I've been very, very fortunate to have selected a field over my now 40 years in this discipline that every day is being recreated. I mean this is like the Golden Age right now. I was always hoped that I might still be professionally active when this started to happen, this transformation, this shift that we're … It's a seismic shift that we're feeling right now in healthcare in the basic understanding of the origin of disease.

It's just a really, really privileged time to be involved and it's so exciting to share this with people like yourselves that have been on this trail for many years. We're all going to be holding hands as we start seeing this thing unfold. The most important thing is reducing the burden of disease in people that have been in search for so long for solutions that I think solutions will emerge out of this and already are emerging where people … I mean I have more than my fair share of responses of people saying, "You saved my life," or, "That just turned me the other direction. I've had 40 years of bla-bla-bla and now I'm over it." That's the purposeful living that I think we all … It's the most important part of probably our whole experience of life.

Dr. Ritamarie: Right. I think we all because we're here, we share the same passion which is we want to just see our broken disease care system revamped into a true healthcare system. I think that the answers are here. You've been talking about them for decades and I have for less decades than you but for decades still. I think a lot of it, and it don't mean to oversimplify it because by any stretch it's not oversimplified, but we just keep coming back to the power of these plants, the power of the vegetables, the power of the herbs.

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Now we're understanding why they're so powerful and we can use that to encourage more people to engage and to drop those habits, to drop the modern factory farmed and factory produced food substitutes, or fake food that most people eat, and adopt back to what our ancestors did but with a greater understanding of how we can manipulate the environment, and how we can prevent preventable infectious disease which they didn't have that knowledge about, and how we can eat for our genome and so many things that we can use our modern scientific stuff. So much of it goes back to the ancient human wisdom that's been with us for millennium.

Dr. Jeffrey Bland: I think that's beautifully said. You just reminded me of an interview I did in my functional medicine update series a number of years ago with a professor from Oxford University in England. He had just published a series of papers about the traditional British diet and the rising tide of chronic disease. He had done something quite remarkable because they keep very, very meticulous records, health records in Britain that go back for centuries actually. He went into the archives and dusted off these old records back in the Georgian period and in the Elizabethan period and right on up into Modern times.

It was his belief in reviewing the health records in Britain that the health decline of the country occurred when this farming nation went basically into white flour and highly processed grains and went away … He'd actually studied or calculated the reduction in overall phytochemical consumption per capita. He equated the decline of health of the British public and the rising tide of chronic illness almost directly related to the decline in phytochemical consumption during the age of industrialization, because remember that's where it all started, was in Britain with industrialized food production. It's a really interesting support for the model that you're … for what you're stating.

Dr. Ritamarie: Yeah. Wow. Well thank you again. I can't thank you enough for being here. It was just an honor and a privilege to have you here. Just keep doing what you're doing. We all appreciate you very much. I'm going to open up the line so everybody can just really say a few words of appreciation for Dr. Bland here. Interactive, there we go. Yeah go ahead and just say thank you.

Audience: Oh my god, it's so amazing.

Audience: Thank you.

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Dr. Jeffrey Bland: Oh what a treat.

Audience: Thank you so much.

Dr. Jeffrey Bland: It's been my great privilege and fun and keep up the great work all of you. We're all pioneers shepherding this thing forward.

Dr. Ritamarie: Absolutely. We're privileged to be a part of this that you were such a pioneer in, so thank you.

Dr. Jeffrey Bland: Thank you. Bye-bye.

Dr. Ritamarie: Bye now everybody.

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