

October 2007 Issue | Frank Lipman, MD Eleven Eleven Wellness Center

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Welcome to *Functional Medicine Update* for October 2007. This is going to be an issue with an unusual focus relative to past issues. I would give this issue a working title of "Structure vs. Function Connected through Cellular Signaling."

Much of the intellectual basis for functional medicine is derived from the pioneering works of Archibald Garrod, Linus Pauling, and Roger Williams. These giants, whom we have often spoken about, gave us conceptual framework for the functional medicine approach.

Dr. Linus Pauling was an extraordinary proponent of the concept of structure and function being connected to one another. He started off, obviously, with structure being molecular structure (atomic structure). He looked at the structure of the atom, then combinations of atoms to make molecules, then combinations of large molecular structures to make macromolecules, and then, ultimately, organisms made through cellular structure. One can play with the concept of structure and function at many different levels.

What I believe has happened within the constructs of medicine is that we have separated structure from function and often treat them as two entities. We have physical medicine, which treats function from a structural perspective, and then we have functional physiological medicine, which treats it from a metabolic perspective. Really (as Dr. Pauling got us to understand), there is not a separate universe of structure on one side and function on the other; they are connected together very intimately.

Intercellular Signal Transduction

Structure can influence function at a metabolic level through the pathways that we call intercellular signal transduction. When we do things like nutritional intervention, exercise therapy, talk therapy, physical medicine, acupuncture, or bodywork, we are mobilizing this connection between the outside world (either through molecules or mechanical forces or electrical forces) into inside functional changes. These changes relate to metabolic things that we often measure with laboratory tests and other methodologies (really kind of a shadow). The image that makes the shadow is the alteration in the function of that cell, tissue, organ, or organ system that ultimately gave rise in bulk to the changes that we see using our diagnostic technologies.

With that as a conceptual framework for this issue of *Functional Medicine Update*, let's talk about some examples (from the molecular up to the whole organism) that show how this structure-function duality is not a duality, but is actually a continuum. We (as clinicians) are using this continuum every day; I believe it is the fundamental underpinning of what separates functional medicine from diagnostic traditional

medicine, which is focused on the diagnosis and then the treatment of the dysfunction as a pathophysiological process. Let's look at the functional medicine interpretation of this structure-function duality.

The Influence of Cruciferous Vegetable Phytochemicals on Structure and Function

Starting with a molecular concept first, I'm going to choose some examples that are in the news recently and exemplify this principle. Cruciferous vegetables (the broccoli-cauliflower-brussels sprouts-cabbage family) contain an interesting array of phytochemicals called glucosinolates, which we have heard much about in the past several years. We know that vegetables that contain these glucosinolates can be broken down (by secondary metabolic function in the body) into a series of other phytochemicals that have names like indole-3-carbinol, diindolylmethane, 3-hydroxy-2-butene, sulfurophane, and phenylisothiocyanate.

Glucosinolates, when broken down into these secondary biochemicals (or phytochemicals), influence things like detoxification pathways. Historically, we know sauerkraut juice was used in European communities for what we would call detoxifying the body, and now we may know what mechanisms make this seem reasonable. Glucosinolates that are in fermented cabbage do, in fact, influence the balance of phase I and phase II detoxifying enzymes. Understanding how these vegetables were associated with certain health attributes occurred through observations and an evolution of thinking about mechanisms.

My colleague, Dr. Deanna Minich, and I composed a review article on this topic, which appeared in Nutrition Reviews in June 2007 under the title, "A Review of the Clinical Efficacy and Safety of Cruciferous Vegetable Phytochemicals."¹ Rather than go into the specifics of how indole-3-carbinol, diindolylmethane, sulfurophane, or phenylisothiocyanate alter phase I and phase II enzyme induction and activity in terms of detoxification, I'd like to move back a step. What's really going on with these chemicals? What are they doing? Each one of these molecules (these phytochemicals) has a specific structure.

If you were a student of chemistry in your past, you probably recall that when a combination of atoms give rise to molecules, often, in nature, this happens in a geometric configuration that is so specific it can rotate plain, polarized light. In other words, it can interact with light in such a way so that it has right- and left-handed types of light twisting capability (we call this dextrotrotatory and laevorotatory). There is a tremendous amount of information, in terms of the topology of these molecules that we eat in our diets that can influence our function by their specific structural capabilities. How they do this is by binding or interacting with specific receptors, which in themselves have specific geometric structures that are very unique. So it is a lock and key, you learn. But it is really more than a lock and key because a lock and key sounds very static (like the key is always the same shape and the lock is always the same shape). In terms of these dynamic processes of the binding of a phytochemical to a receptor, these are what we might call amorphous receptor bindings in that they can be changed by the environment in which the receptor is found. The lock is not always the same geometry. Based upon the environment in which that lock is found, it might appear as different shapes, so you might have that receptor (the phytochemical called indole-3-carbinol) binding to its receptor in different ways depending upon the environment in the cell in which the receptor is found.

Acid-Alkaline Balance and Cellular Physiology

What do I mean by that? Let's take an example from clinical medicine, a gross thing that we all know

about: pH (acid-alkaline balance). History tells us (from diets that have been explored throughout many cultures) that the residue of acid or alkaline in a diet can have something to do with the physiological effects of that diet. There are whole dietary approaches that have been built in the schools of hygiene and nutrition for several hundred years around acid-alkaline reserve and how different diets produce different residual effects on the acid or alkaline balance of the body.

What are we really talking about here? We are talking about how the constituents of that diet, in bulk, influence cellular physiology in such a way as to lead to-when the smoke clears, after the metabolism of the food, digestion, absorption, and utilization has occurred-an acid effect or an alkaline effect. We often say that the alkaline reserve foods are those that contain high levels of calcium, magnesium, potassium, and sodium. These would be things like vegetable products. Acid residue foods are those that when "burned" or metabolized in the body, lead to residual effects of more acid producing, such as sulfuric acid, phosphoric acid, or hydrochloric acid. These would generally be higher protein animal foods.

States of ill health, historically, have often been associated with shifts in cellular physiology toward the acid side: metabolic acidosis, or respiratory acidosis with the build-up of organic acids, and the shift of pH to lower values (meaning, more acid shifts). The treatment for people in a state of metabolic acidosis is what? To alkalize. You give them alkaline reserve. You can either do this synthetically by giving an alkaline material like bicarbonate, or you can introduce foods that have high residual alkaline reserve to neutralize the extra acid and reestablish appropriate intercellular pH (7.37, slightly on the alkaline side).

I'm sure all this is just a quick history of what you already know. Now let's go back to the receptor story that I was talking about and how it relates to structure and function, phytochemicals in foods (say, indole-3-carbinol), and its influence on detoxification. If the physiology of a person is shifted towards an acid side, that acid environment (and when I'm talk about acid I'm not talking about the kind that can leech away stone, I'm talking about just very subtle changes in intercellular pH) it influences, then, the domain and environment of that local cellular milieu in such a way that it can alter the shape of the lock.

Right? So the lock, as I said earlier, which is the receptor, is not static; it is dynamic. It has multiple configurations that it can exist in depending upon the nature of the environment.

So let's say that patient has an acid residue, or they are shifted metabolically toward the acid side, slightly. That would change the shape of the lock, which means that the same key (indole-3-carbinol) would be less able to get into the lock and would have a different influence, then, on the processes that are associated with that lock and key (receptor/ligand) interaction. Therefore, its effect on detoxification could be altered.

I hope you are following my argument, here. What I am trying to say is that structure and function are intimately interrelated, even at the molecular level. But the structure is not cast in stone because the structure, in and of itself, is modified by the state of the environment.

Let's now take this and see if it really plays out, or if I'm just talking a bunch of philosophical mumbo-jumbo. Does pH, or alkaline/acid balance, have anything to do with detoxification? The answer is yes. There are many, many articles that have been published in very highly respected journals in toxicology that demonstrate that the acid/alkaline balance in a person who has been exposed to a toxin will alter their ability to eliminate that toxin (i.e. to engage in detoxification). I want to cite a recent review article that (again) Dr. Minich and I authored. This article was just recently published in *Alternative Therapies*, and it

takes this theme and describes how it works clinically.²

Let's take the example of a person exposed to a toxic chemical or maybe a recreational drug taken at toxic doses. He or she is in the throws of renal or hepatic failure, and so what would be, in a toxicology/poison center, the treatment that might be employed in this crisis situation? It would be to infuse this person with very high alkaline equivalents-in other words, to force his or her plasma into a more alkaline state.

What is the strategy? The strategy is to improve renal excretion and detoxification because when a person is in a poison situation their physiology is shifted toward the acid, with depressed respiration so they are not oxygenating their blood correctly. They are getting more carbonic acid building up in their blood, plus they may have a whole series of organic acids that are being produced in their body as a consequence of the poisoning of their metabolism. So you shift their pH in the emergency room or the treatment clinic, forcing more alkaline reserve into their blood.

That is the extreme example of toxicity, right? Now let's back it off to a much more ambulatory, chronic state of toxicity, where a person is shifted due to the consumption of high fat/high meat, processed food diets. They are not eating a lot of fruits and vegetables. They don't get a lot of alkaline reserve. They are exposed to-let's say-an OTC chemical. Maybe it is ibuprofen. Maybe it is acetaminophen. They have chronic toxicity. What do you want to do? You want to move them over to a diet with higher alkaline reserve. This changes the receptor/ligand interaction. It enhances detoxification. It improves renal excretion. And the same body exposure to that toxic material leads to a lowered adverse effect on their physiological function.

I hope I'm getting you to understand this interesting view of structure and function that is emerging and the plasticity of structure based upon the local environment, which is a modifiable environment. In other words, our environment is not cast in stone. We could drink more fluid. That hydrates us. That is a changing of our cellular environment. We can eat more alkaline reserve foods. That is a changing of our environment. We can think different thoughts. That is a changing of our environment. We can exercise or not exercise. That is a change of our environment. Each time we do something it changes the way the structure of these molecules influence our function.

Going back, if I can, then, to the indole-3-carbinol (I3C), diindolylmethane, sulfurophane, and phenylisothiocyanate story as it relates to detoxification, what was the point Dr. Minich and I were trying to bring to the reader's understanding as it relates to the clinical efficacy and safety of the cruciferous vegetable phytochemicals? What we were trying to point out is that the application of therapeutic doses can be beneficial (for example, I3C; there have been many clinical studies that have been published on the use of therapeutic doses of I3C-about 300 mg of indole-3-carbinol about once or twice daily against placebo and looking at the effect it has on detoxification of various substances, including the conversion of estrogens, 17-b estradiol into the 2-hydroxy estrogens versus the more cytotoxic/mitogenic 16-hydroxy estrogens).

If broccoli intake (or another cruciferous vegetable) is increased, will it have a favorable effect on estrogen metabolism, even in a man? We know that men are producing estrogen to some extent in their prostate glands and that has to be metabolized. Soy products would increase 2-hydroxylation. These are phytochemical characteristics of the structure of these food ingredients that influence a function of the body, which is detoxification of an endogenous chemical called 17-b estradiol. That's a really powerful

conceptual framework as an example of a more general concept of how the myriad things in our diets can influence physiological outcome.

What happens if the person who takes indole-3-carbinol, 300 mg once or twice a day, is in an acid-shifted metabolism? They are eating a diet or they are in a state where they are in an acid metabolism? Would that alter, then, the functional influence of that phytochemical on their detox? The point I am trying to make is absolutely yes. That structure, as it relates to the implication on function, would be modified by the environment.

This begs the question, doesn't it, as to how we deliver these concepts in the functional medicine treatment program? What it doesn't mean is that just one agent is given at a time, like you might give a drug. With a drug, some practitioners might say they don't care what a patient is doing because they are just going to lay this new pharmacological agent on top of whatever they are doing and the outcome will (hopefully) be what is desired.

What I am saying is that for optimizing the functional outcome in the patient, you have to look at the full physiological status of the environment of that patient. If they are an acid-shifted physiology and they are eating a high acid, ash-type diet you need to shift them to a more alkaline-ash diet. You need to improve their respiratory quotient to lower their carbonic acid build-up, and that means you need to improve the oxygenation of their blood. What does that mean? Movement, exercise. You need to signal the appropriate signals through their cellular receptor systems, lowering inflammation (which we are going to learn more about later in this issue of Functional Medicine Update --things like bodywork, massage, acupuncture, yoga). This concept calls forth what is really the hallmark of functional medicine: not just doing one thing at a time. Functional medicine is looking at the environment and domain of the patient and adjusting it to produce the optimal conversion of the structure into appropriate function.

The Effect of Soy Phytochemicals on Function

I hope I didn't lose you in that discussion. Let me try giving you one more example, beyond the cruciferous vegetable/indole-3-carbinol/estrogen connection. Let's look at soy. Soy is another interesting food that contains a whole array of phytochemicals: such as polyphenols, and isoflavones. As you probably know, we have emerged to recognize this as a remarkable plant food.

What about these substances found in soy? What influence do they have-the structure of those molecules in soy-what effect do they have on the function? We might look at things like some of the adverse results that seem to be associated with soy that people have been concerned about recently. Things like effects on testosterone in males.

Phytochemicals and Neurological Function

Let's look at the influence of plant-derived phytochemicals on neurological function. There is a rich history of the use of plant substances to alter perception and cognition and produce states of altered consciousness. But we recognize that virtually thousands and thousands of phytochemicals and plants may have direct or indirect influences on cell signaling processes that could be either directly, or by feedback processes, influencing nervous system function.

There is an interesting paper that was published in Neurochemistry Research that I think bears on this topic very nicely. This was in 2007 and titled "Neuroprotective Effects of Natural Products: Interaction with Intracellular Kinases, Amyloid Peptides and a Possible Role for Transthyretin." ³ In this particular

review paper, the authors discuss how things like tea catechins and polyphenols from foods-things that we consume in whole-food diets all the time-may have effects, through the structure of those molecules found on those plant-derived foods, on the cell signaling processes related to things like memory, cognition, states of arousal, and central nervous system affective behavior.

Historically, we have been eating foods that influence the function of our nervous system as a consequence of this interaction of the structure of molecules in the food with the function of our nervous system through a whole series of cell signaling modulations. When I talk about cell signaling, again, I am referring to the fact that the structure of these molecules in the food interact with certain receptors that then signal through the cellular functions of the nervous system to induce (or produce) states of functional change. These would be things like enhanced alertness, or alterations of cognition or memory. These discoveries are obviously leading to new food concentrate derivatives to try to improve central nervous system function, or normalize nervous system function, or to develop neuroprotective effects (like you would get with ginkgo biloba, for instance). What are the individual molecules in the ginkgo concentrate that then influence the structure and function of the nervous system? These are the frontier-level discussions that are now ongoing.

You might ask how this differs from traditional pharmacology. The difference, really, comes in the application of the concept, not in the concept itself. In traditional pharmacology as we know it, the agents within the Physician's Desk Reference are new-to-nature molecules that have been derived by multi-phasic screening processes from synthetic chemists to have very profound effects upon specific receptors or specific enzyme-mediated functions within the body. They have been tailored (or engineered) to have dramatic effects, sometimes tying up enzymes and blocking function (like H2 blockers, HMG Co-A-reductase inhibitors, or selective serotonin reuptake inhibitors). You'll notice it always has this "inhibitor" or "blocker" title to it. These drugs really tie up enzymes and cellular function at a very dramatic level as contrasted to the agents that are in natural products, which have a much more moderate effect upon cell signaling.

You might say, "Why did nature evolve molecules that we have in our foods that have only moderate effects on cell signaling, and not evolve food that contain agents that have dramatic effects on cell signaling? I think the answer to that is obvious. If every time we ate a diet that contained drug-like effect molecules, our physiology would be whipsawed around. We have evolved this relationship with these active phytochemicals in our foods that are much more moderate in their cell-signaling effects; that normalize function. It is a similar mechanism to drugs, but a different way of playing out through these intercellular signal transduction processes.

Now let's go into another part of the body's physiology: gut bacteria. One of the largest organ systems in our body is the enteric bacterial population that is not connected to us through our blood supply directly, but is metabolically active-a kilogram and a half of live organisms, several hundred different species, all vying for real estate in our gastrointestinal tract and all metabolizing, fermenting, and producing waste products. These waste products are, again, molecules that have specific structure that are produced by these enteric bacteria.; they have effects on different receptors within our gastrointestinal milieu (the so-called gastrointestinal lymphoid tissue, the GALT). These antennae that are sitting on the surface of our gastrointestinal epithelia, which are the receptors of the GALT or the MALT (the mucosal associated lymphoid tissue)-what they do is pick up these information molecules from bacterial activity in our intestinal tract and translate it, then, into functional changes, both locally and systemically. Here is where

70{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of our antibodies are produced--at the local gut level--in response to the connection between the intestinal milieu, the structure of molecules that are available to activate these receptor sites, and then how those ultimately get translated into systemic function.

Gut Bacteria and Cell Signaling Processes

With that as a conceptual framework of looking at structure-function (now I've even moved, you'll notice, structure and function away from eukaryotic cells and I'm talking about those prokaryotes that live in our gut--those bacteria and how they interface directly and indirectly with our cell signaling processes), that leads me to an interesting article that was published recently that opens up the door to how diverse these effects of bacteria in the gut can be on influencing systemic physiology. The title of this paper is "Metabolic Endotoxemia Initiates Obesity and Insulin Resistance." 4 That may sound like a very disparate set of topics to all put together in a single title. This article appeared in *Diabetes* in 2007 and says that diabetes and obesity are both known to be metabolic disorders characterized by insulin resistance and a low-grade inflammation. This is obviously something we have been talking about in *Functional Medicine Update* for some years.

This study sought to find what inflammatory factor is causative of the onset of insulin resistance, obesity, and diabetes (in other words, the key that may unlock this whole problem). This group of investigators, from the Institute of Molecular Medicine in Toulouse, France, identified a bacterial lipopolysaccharide (LPS) as a triggering factor for this process, meaning a product of a bacteria in the gut that is released from its cell wall that induces, through its structure, a functional change that enhances, then, insulin resistance, inflammation, and ultimately, clinically, can contribute to the etiology of diabetes and obesity.

Did you follow what I just said? I know it sounds pretty amazing, doesn't it? This sounds like science fiction. Somehow the personality of specific gut bacteria, when they die or release these cell wall constituents called lipopolysaccharides, interact in such a way with the receptors on the MALT or GALT to induce an inflammatory response that is systemic (leading to low-grade inflammation), which then has a signaling process through these various cell types and organ systems, that we see clinically as contributing to the etiology of diabetes and obesity.

Now you may have thought that diabetes comes from obesity, but this research would suggest that maybe there is a factor below that that contributes to the etiology of both diabetes and obesity that are connected clinically, but not necessarily one derived only from the other (that they come as a consequence of metabolic events that induce cell signaling associated with low-grade chronic inflammation at a systemic level).

To study this, the investigators took animal models and fed them high fat diets, which in these animals induced a higher level of inflammatory markers. That increased plasma lipopolysaccharide concentrations two- to three-fold, and the investigators have identified this threshold for increased LPS from these bacteria in the gut of these animals as kind of a threshold that leads to metabolic endotoxemia, a term that we have called dysbiosis for many years in *Functional Medicine Update*. This dysbiosis (or metabolic endotoxemia) associated with a high fat diet increased the proportion of the LPS-containing microbiota in the gut by changing the flora to increase the relative production of this LPS, which then induced this state of chronic inflammation. Clinically, then, these animals start to develop fatty liver, with elevated triglyceride content of the liver; increased markers of inflammation including TNF-alpha, IL-1, and IL-6;

and increased relative risk to and onset of type 2 diabetes and insulin resistance.

In this particular case, the high fat diet induced chronic inflammation, enhanced LPS-producing bacteria in the gut and the process that relates to inflammatory signaling (systemically), which then has the effect that all roads lead to NF-kappa-B reducing insulin sensitivity and associating itself with both the onset of obesity and diabetes. This is a very interesting example of the structure-function interrelationship and how the environment can influence not only the cells that we are made of, but also these residents on board that can be commensals, or symbiotes, or parasites that we call our enteric bacteria.

Let's take this a step farther. Let's look at a carbohydrate-restricted diet and what influence it has on gut peptides and adiposity signals. This was recently discussed in an article in the Journal of Nutrition that I thought was very fascinating.⁵ In this study (a human study), researchers were looking at what happens when you restrict a highly refined carbohydrate in the diet. Would this alter gut enteric peptides? The cell signaling substances that come from this interaction of food with cell receptors in the gut signal to the rest of the body things like inflammatory markers leading to adiposity or central obesity, and into insulin resistance and later into diabetes.

What these researchers found is that a carbohydrate-restricted diet lowered cholecystokinin concentrations, inflammatory markers, and adiposity signals, and had a very positive effect on compensatory control mechanisms related to things like insulin signaling and inflammatory signaling. This means that highly refined carbohydrate diets may influence cellular function through the structure of those carbohydrate molecules translating, through the cell signaling process, into induction of inflammatory mediators and ultimately insulin resistance and obesity and diabetes.

Is it just refined carbohydrate? Of course not. There are many, many other signals that come through the gut. Another example appeared in a recent paper published in the Scandinavian Journal of Gastroenterology. This article is titled "Prevention by a Decapeptide from Durum Wheat of In Vitro Gliadin Peptide-induced Apoptosis in Small-bowel Mucosa from Coeliac Patients."⁶ In this study, what the authors suggest is that there may be substances within phytochemicals (specific kinds of structural molecules within grains) that both induce an inflammatory response (that would be your traditional gliadin-like peptides that we know respond in certain sensitive individuals by inducing inflammation, both regional and systemic, that we call celiac sprue, or hypersensitivity inflammatory reactions), but that also may contain specific decapeptides that lower inflammatory response. So it is the yin and yang. It is the upregulation and downregulation. It is the activation and inhibition. A whole-food diet contains myriad of these different messenger molecules that produce an orchestrated effect on physiology.

But if we start taking specific molecules out by refining or by chemical partitioning of the diet, we get different signals that go to these receptors, producing different effects. In that case, we can produce an imbalanced effect, an aggravated effect, or an enhanced effect (like an inflammatory response not offset by an appropriate anti-inflammatory response). This begs a question: Can we find anti-inflammatory decapeptides from grain products that have a positive effect on reducing inflammation? That is ongoing research that I'm sure we are going to see more about in the future.

The point I am trying to make to you is that we have eaten complexity in our diet for decades. We have lived in a complex environment-not just for decades, for millennia. And these influence, in their complex, orchestrated way the structure-function relationship of our body.

Let's take one last example, one that I think is very valuable clinically: prebiotics and stimulating appropriate bacteria (friendly, symbiotic bacteria) and proper signaling in the gut and the reduction of inflammation. What do we know about the prebiotics? We know that one of the most interesting prebiotics that has been discovered recently actually comes out of a product that originally was grown as a northern latitude vegetable, chicory. It has been found to contain very high levels of a prebiotic called inulin. Inulin has a very dramatic influence on the personality of symbiotic bacteria that are butyrate-producing and lower the levels of inflammatory lipopolysaccharide production in the gut. This enhances insulin signaling and lowers the risk to obesity through these processes that I have described (by lowering metabolic endotoxemia suggestions).

The Favorable Effects of Inulin

Inulin, when given in adequate levels, as well as galactooligosaccharides, are extraordinarily valuable prebiotics that influence the cell signaling process. The structure of these oligosaccharide molecules in chicory induce (as inulin molecules) an appropriate cell signaling response on the other side.

How much inulin? We are talking somewhere in the range of six grams a day, probably as a threshold. Ranges could go from 6 to 10 grams, and it induces, then, these more favorable effects, and it goes along with probiotics to induce these proper gut signaling processes.

I hope I have left you with thoughts of how structure and function are very closely interrelated and connected through cell signaling. It is among the fundamental processes by which functional medicine works to control the adaptive capability of physiology against a changing environment.

With that in mind I think it is time to turn to our clinician-of-the-month who is going to take this concept of structure and function to the next level.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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Here we are again at that portion of Functional Medicine Update that I look forward to with great anticipation every issue and I think you as a listener certainly do as well: our Clinician of the Month and what expertise they bring to us in terms of their history, background and insight.

Over the years we have had the most remarkable experiences. As the person who has the pleasure of doing these interviews, I have often had epiphanies because I think I have a sense that I know how these discussions will go, and then something occurs during the interview that is just remarkable and takes it to another level.

I have a suspicion that we are going to be blessed with type of discussion today with our Clinician of the Month, Dr. Frank Lipman, who is the founder and director of the Eleven-Eleven Wellness Center in New

York City. I want to do a quick vignette of Dr. Lipman so we can set the context of his background. Dr.

Lipman is South African in his training, qualifying in medicine in 1979. He worked both in private practice as a general practitioner in the rural areas of South Africa before entering the United States. He became board certified in internal medicine, doing his residency at Lincoln Hospital in New York City, and served as the chief medical resident in his final year of the residency.

As he moved his practice into focus, he was able to bring together some fairly remarkable concepts that you'll be hearing more about from Dr. Lipman. Some of these are related to what we want to focus on in these discussions, which are related to this very interesting emerging concept of signaling through connective tissue and the extracellular matrix and how that connects to health, wellness, and also to chronic disease in terms of dysfunctional signaling. Dr. Lipman is the author of a book that I have talked about in the past on Functional Medicine Update . It was published in 2003 and titled Total Renewal, 7 Steps to Resilience, Vitality and Long-Term Health.

I know that Dr. Lipman has some apprehension because he said, "Well, you know I'm not really a researcher; I'm just a clinician." I think, for us, the word "just" is a pejorative because that is where the tire meets the road; that is what functional medicine is all about-trying to bring information to user friendliness (so-called "news to use"). So let's just strike the word "just" and let's introduce Dr. Frank Lipman to you.

Frank, thanks so much for joining us today. I can't tell you how much we appreciate you being available for this discussion.

FL: It's an honor to be on with you, Jeff, because you are one of my primary mentors.

JB: Well, thank you. That's very flattering for me, obviously. Could you tell us a little bit about your practice? You know, over the years I have gotten to know you I've been very impressed with how you have developed the personality of your practice (knowing that every practitioner has kind of a different fingerprint on their practice).

FL: It started in South Africa, being trained as a regular physician and working in rural areas, in particular, and seeing results from Sangomas, the natural, traditional healers in South Africa. I already knew that belief systems and something other than Western medicine was at play because when we couldn't help patients, I saw these Sangomas helping patients. So that started my questioning of the system. I went into general practice straight after my training, where people came to me with functional problems and I couldn't help them. So I started exploring early and I looked into homeopathy because the homeopathic tradition is actually quite big in South Africa.

But interestingly enough, when I left South Africa (I ran away from apartheid), I came to America and my mentor there (the GP I worked with) gave me a book on acupuncture (The Barefoot Doctor's Manual) and he said, "Go study acupuncture." I landed in the South Bronx in New York City without knowing that Lincoln Hospital had an acupuncture clinic.

Very early on I realized I didn't want to be a doctor here (in America) because the medicine was so different-it was all about lab tests and x-rays, it wasn't about speaking to patients. But then I walked up to the acupuncture clinic and I started studying acupuncture and it was such a life-opening experience for

me to get into the philosophy of Chinese medicine, which made so much sense to me.

So it started with acupuncture in the mid-80's and from there I discovered functional medicine through you a little bit later. And when I heard you speak, you were articulating Chinese medicine from a Western perspective, so that was the next "a-ha" experience. Here I was studying acupuncture and Chinese medicine, which was completely different from Western medicine, and then Jeff Bland comes along and he starts putting the two together. That, to me, made a huge difference.

And then I started studying yoga, and yoga, to me, was another extension of functional medicine because yoga, once again as with acupuncture-I see both of them as functional medicine. I started exploring modalities that I felt were modalities that improved function. And over the years I just started using all these things together and I have developed-as you say-my own imprint, but it is focused on acupuncture.

What is interesting is that no one really talks about acupuncture as functional medicine, but to me, acupuncture is your ideal functional medicine. We'll talk about it later: how to improve cell function and how I see acupuncture which is basically a little bit different to traditional Chinese medicine which sees it in terms of energy and meridians. From the beginning I knew that Chinese medicine talks about energy and meridians, but I knew there was a Western explanation that could make sense to me from the Western perspective as you had put other parts of Western medicine into the functional medicine context.

No one was talking about what was going on with the soft tissue is what I was feeling. I was feeling all these bodies and I knew there was something apart from energy and meridians and I started thinking about acupuncture (or the meridians) as the fascial system. And if you think about it, the fascia is connected all over the body, and I thought and strongly believe that acupuncture works with the fascial system. Interestingly enough there is now research by Langevin and her colleagues in Vermont which is basically saying what I have been seeing for the last 20-odd years.

The Mechanism of Acupuncture: Cellular Signaling through Connective Tissue

JB: You have shared a couple of her (Helene Langevin's) wonderful articles. I think I should give a quote to support what you just said out of one of her articles that appeared in the *Anatomical Record*. She says, and I quote, "Acupuncture meridians traditionally are believed to constitute channels connecting the surface of the body to internal organs." However, work that they are doing hypothesizes that the network of acupuncture points and meridians can be viewed as a representation of the network formed by interstitial connective tissue. This hypothesis is supported by ultrasound imaging showing connective tissue cleavage planes and acupuncture points in normal human subjects. They mapped acupuncture points and serial gross anatomical sections through the human arm, and found an 80% correspondence between the sites of acupuncture points and the location of intermuscular or intramuscular connective tissue planes in these postmortem tissue sections.

Their proposal is that there is this anatomical relationship of acupuncture points and meridians to connective tissue planes. This is very relevant to how the mechanism of acupuncture works and suggests this signaling process through connective tissue, which we have always thought of in the past-I'm now editorializing-was more dys-structural (not having a function). I think it is so superfluous and facetious of us to think that the body has only structure separated from function. It is like trying to say the mind is separated from the body. I just wanted to interject that very interesting concept from Dr. Langevin's work.

FL: Right. To me this was such a huge high experience when I found this research. There is a concept in Chinese medicine called Ashi Points. Ashi are these local points (these local areas-they're not really points) that spontaneously become tender or painful in response to some local problem. It can be a strain, or a tear, or even drugs. I started treating these Ashi Points years ago. Even in acupuncture circles, if you treat Ashi Points, that is sort of real low-rung (or low-level) of treatment of the body. But what I have noticed from treating these Ashi Points (these local, tender fascial connective tissue points), is that people started feeling better. Not only did their ankle get better, but they started feeling better all over. So I knew something was going on, but no one was really describing it because I wasn't using meridian points, per se; I was feeling the body and I was going into tender areas.

The Concept of Integrins

The easy explanation is the ankle's swelling went down and the ankle got better, but people started experiencing other ways of feeling better, so I knew something was happening--there was some cell communication or something was happening that we weren't aware of. Langevin and her colleagues have come up with this concept of integrins, which are a protein on the cell membrane. I think you talk about them--not about integrins, but about these cell membrane proteins--which then activate the protein kinases.

I mean, I don't know if you want to talk a little bit about the integrins or the protein kinases.

JB: Can I just add, parenthetically, for people who may not be as familiar with integrins, the one that they probably have heard about in traditional internal medicine is GLP1 (glucagon-like peptide-1), which, as you know, has become Byetta (the drug, Byetta), which is the new insulin management and even weight loss drug that came out of the gila monster saliva exploration. That is an integrin signaling inhibitor. There is a whole family of these that are emerging. This is kind of the "new science" as to how outside information gets translated into inside cellular function. Excuse me for interjecting...

FL: No, thank you. What I find interesting is what she is documenting here: these cells communicate via these many projections (or these integrins) which are on the cell membrane. These integrins get deformed by overuse, misuse, abuse, or disuse, and when the tissues get crowded. When you release that crowding with acupuncture or deep tissue massage, not only is that area getting better, but you are improving cellular communication. So what this research is saying--and this is what I see clinically all the time--is that acupuncture or releasing the tissue (the local tissue) is actually improving cellular function. I still can't get over it: that we now can actually prove how manual tissue work, or releasing the fascia, is actually improving generalized function.

JB: For our listeners, I again want to just put a very important benchmark here--or maybe it is even a goalpost--that has to do with what you are saying, which is highly profound. Sometimes the most profound ideas sound so simple once you have heard them, but they have very deep implications. In medicine, we often have set up these dualities, assuming that the dualities have an impermeable separation between the two of them, like light and dark, as an example.

But structure and function often are taught and thought of as almost two different areas of medicine--as rehabilitative medicine, or structural, physical medicine being separate from metabolic medicine, which is the function. So we've got metabolism on one side, and we've got the structure (all the stuff that holds us upright against the force of gravity) on the other, and never the twain shall meet.

The model that you are describing, which I think is very powerful, drawing from several thousand years of history, is that this duality/separation between structure and function is really incorrect--that structure

interfaces with function, function interfaces with structure, and which ever way you enter into the system, you are influencing both. In this case, we are talking about a mechanism that through structure sends signals to function, which has implications on metabolism and physiology. Am I paraphrasing this correctly?

FL: You have articulated that so beautifully. That is right on. Thank you for doing that. That is exactly what I am saying; you just say it so much better. I have seen that, clinically, through yoga and acupuncture; I use both of them a lot. Why do people get so much better through yoga, not only physically but emotionally? And the same with acupuncture? Thank you for articulating that so beautifully.

JB: Let's take an example. Over the years we have had conversations, and I have the benefit of drawing on those past exchanges. Let's take fibromyalgia. Fibromyalgia is a very interesting clinical term that relates to patients who experience these very hot, tender points, which often happen to be coincident with what (historically) might be considered some of these meridian points or active energy points on the body, going way back (as you said) to Traditional Chinese Medicine.

If you look at the literature on fibromyalgia, in journals such as Arthritis and Rheumatism, it has fallen within the prevue of the rheumatologist. This is an autoimmune-related family of disorders, and it has something to do with a disturbance of the hypothalamus-pituitary-adrenal axis because we can find alteration in neurochemicals and stress chemicals in patients with fibromyalgia.. These patients have a centrally mediated difficulty of the HPA axis and that, then, translates into a neuromuscular problem.

Now from what you are saying (and I'm being a little presumptuous here, so I hope I'm not misleading you), it would suggest that maybe we could turn that around and say fibromyalgia is a condition that is associated with certain kinds of dysfunctions of this cellular communication process (mechanical signaling through connective tissue). Really, then, rather than coming from top-down, it comes from bottom-up, and that influences, in turn, the HPA axis function that is responding to the block in energy flow and so forth. It turns this whole concept of the etiology of fibromyalgia around on its head.

Is there any validity to this model that I just stated?

FL: It could be. It's hard for me to say because when I treat fibromyalgia I use both together: I always use acupuncture and I always suggest yoga. But I will work, from a functional perspective (metabolically) as well. But, yes, it could be.

I do think that the fascia, per se, is the forgotten organ system and it doesn't get much credibility. Western doctors definitely ignore it. Even functional medicine doesn't address it that well and hopefully that will change now. I mean the European osteopaths have developed many procedures to correct these functional problems by working closely with it. It's the European osteopaths more than American osteopaths.

That could be correct; it is hard to say. But clinically, there is no question. When I work metabolically and use the acupuncture and use some yoga (or something like that) patients respond really, really well. But it is hard to say whether it is up-down or down-up.

JB: As you have gained all these years of clinical experience and become an expert in this area, have you

(through your hands) learned (when you touch a person) where you can feel these kind of irregularities of the extracellular matrix?

FL: Absolutely. Any body worker can tell you that when you touch a body, you can feel it. You know, you had once asked me, how I measure this. I don't know how to measure it in terms of what tests or what blood levels are going to be off; I can just measure it by my hands. You can feel the tissue change; it is really interesting. So that has been my measurement over the years: the touching. I don't know any other way of measuring this except the feel of the body and any body worker you speak to will talk about that.

JB: When a patient comes to visit you, undoubtedly they already know something about the unique way that you approach these problems, so they are not coming in to you for kind of a traditional internal medicine blood screen, physical, history and then a prescription for a drug. How do you walk them through what is obviously (from my perspective) a very highly evolved functional approach using both the connective tissue components as well as the metabolic components coming from both directions?

FL: As you say, I think I'm lucky in that most people are referred by other patients and when they come in they are already believing that I'm going to help them. I think belief, or the placebo effect, or whatever you want to call it is a really important part of the healing process. When people come in believing in you as a practitioner I think that makes a big difference. It is much easier for me. And a lot of what I'm doing is reframing the way patients see their problems.

They come in with a diagnosis. My first intake is a long intake because I honestly believe you get most of what you are going to get from the history, or a lot of what you are going to get comes out in the history, even before I feel the body, so the first visit is trying to get a really good history, and at the same time I am trying to reframe the way patients see their problems. And I often put it in a functional medicine perspective. It is easier for me because I have the luxury of having that type of referral practice where people come in thinking they are going to get better. I'll take a good history first.

Because acupuncture is so intimate--patients have to take off their clothes and you are touching them--this is also an advantage. In Western medicine and Western culture, we don't touch a lot. A nonsexual way of touching is not really part of our culture, and I think so many people need to be touched in a nonsexual way, so it becomes a very intimate experience because these patients are taking off their clothes and I'm touching them.

So I have a lot of good things going for me for people to get better before I even put a needle in or before I even give them a supplement. I know it sounds crazy, but I really believe that's part of the healing: the intimacy and the touch. I'm very functional medicine oriented--you have taught me a fortune and the way I practice is largely influenced by your philosophy and your teachings--but then I will incorporate the touch and the body work and the needles.

That's what I do. I rarely do tests. I used to, in the early days, do more functional medicine testing. Now I work clinically. Occasionally, if someone doesn't get better, I'll start doing tests, but I am always weary of getting lost in test results, so I'm usually working clinically. And the other luxury I have is people coming back after a week, a couple of times, for a month (for four or five treatments), so I'm seeing them every week (you know, four or five times). I'm seeing if they are getting better or not, and I have the luxury of adjusting things week by week. And that's how I work.

JB: I would like to focus for a moment on the extraordinary process of acupuncture and what is evolving to be better understood. There is this sense that I have heard from some people that you can get the same benefits that you get from acupuncture without penetrating the skin. In other words, no needles. However, the mechanistic work that is evolving around acupuncture suggests strongly that the mechanical influence on the cytoskeleton, by penetrating the skin with a needle in the right rotation and kind of mechanical forces, plays a huge role in sending these signals through these membrane-coupled cell mediators, like the kinase families, and triggering downstream metabolic as well as neurophysiological changes. So it would seem that the mechanism implies that penetration of the skin in the appropriate place at the appropriate depth with the right rotation of the needles and the techniques of acupuncture is intimately important for the outcome versus just stimulating an acupuncture point transcutaneously.

FL: I would agree with that. I do think you need to penetrate the skin. My experience has been that the results are much more powerful, although there are people who don't think you need to penetrate the skin. I think there is something to relationship beliefs working energetically, but I think that penetrating the skin is crucial to getting better results.

JB: I think that for a lot of us in the clinical world, the concept of cellular biology seems very abstract and not very clinically relevant. If we think of what's going on as you have described (your procedures and intervention using yoga and acupuncture), you are really, in those technologies, influencing (at a very fundamental level) the dynamic state of balance that relates to the function of the cytoskeleton. I think people don't understand that cells (individually) have an internal skeleton that is made out of protein; it's not like bone, it is made out of various types of proteins that can form in aggregate and disaggregate, so it is kind of chimeric. It can be changed, and as it changes its structure by changing the environment, all sorts of things change—electrolyte transport and intercellular voltage gates (as it relates to electromotive force), for example. In other words, you are fundamentally capable, through the changing of the cytoskeleton, of changing the metabolism of the cell. If multiple cell changes create changes in tissues, then you get demonstrable whole body changes. I think the concept you are talking about has such profound implications of using the structure of the body to speak to the function through these altered dynamic states of cellular structure function.

FL: Right. This is what Langevin's research is showing. I don't read too much research, but that's the way I understand her research.

JB: Yes. I think, in fact, one of the papers that she and her colleagues published (this was the Department of Neurology, as you mentioned, from the University of Vermont), appeared in the FASEB journal, which is the Federation of Applied Biology and Science, and they talk about the fact that in these studies in animals with insertion of acupuncture needles, they can actually demonstrate alterations in things like extracellularly-regulated kinase, or the ERK.⁸ And that connects to inflammatory pathways.

So from a cell biological perspective, we are now able to start delineating mechanisms that go down ultimately through things like cyclooxygenase enzymes and lipoxygenase, and can turn off or turn on fundamental things that we observe as inflammation or immunological parameters. It's a really dramatic interface between two disciplines. It appears if they were separate in the past they are now being seen as part of a continuum.

FL: Absolutely. For me to see that happening (because I've noticed this clinically over the years) for me

to see research on this and see these changes happening--is very exciting.

JB: As your patients, then, proceed along the path of recovery, do you find that there is kind of a recidivism--there's a relapse--and they need to come back in periodically for a tune-up of this whole connective tissue/extracellular matrix, or does it last. What are the residual effects?

FL: Well, it's interesting. First of all, acupuncture is interesting because one way to see it is as irritating the nervous system. You know, acupuncture is obviously working somehow through the nervous system; you are basically irritating it. And if you irritate it a little bit too much, like any stress, you can damage it. But if you just give it the right irritation, which is usually not much, the body heals itself. So I think the art of acupuncture is not overtreating, which some people do, and not undertreating.

I think you can affect changes through acupuncture, but if a person doesn't eat well, exercise, keep moving, maybe doing yoga or some type of body work, they are going to need to come back for acupuncture. What I tell patients is that they should have three or four treatments a year, but as we get older (and I see this in my body as well), I try to go for body work once a week, or once every two weeks, or whenever I can. I try to catch problems early, so I really encourage my patients to come in whenever they feel something is off. In other words, if they sprain their ankle, don't wait for it to heal because oftentimes it will heal but it won't heal properly, so I would encourage them to come in straight away and then they'll only need one treatment or maybe two treatments. So I do encourage my patients to come in every now and then for a tune up because I don't think it lasts forever.

JB: Frank, what you have given us in this discussion--I know we have just touched the surface--is just a wellspring of powerful information. You know, as I'm reading the articles by Dr. Langevin and her colleagues, she closes one of her articles with a very interesting kind of summary which I think, from a scientific perspective, is a way of describing what you have beautifully described from a clinical perspective. To paraphrase, what she says is that this acupuncture theory was based on empirical observations made over 2000 years ago, and the field of mechanical transduction is emerging to now provide scientific grounding for this ancient form of therapy. She says that acupuncture provides an important clinical application for the current explosion in basic knowledge of the diverse biological effects of mechanical signaling, as to how pressure in the right place and mechanical-electrical stimulation of tissues can signal, through these intercellular signal transduction processes, altered cellular tissue organ and organ-system function, which then produces a functional change in the organism, not just locally, but it can be systemic.

I think what you have observed, which is where the reality exists, can now be explained from this emerging cell signaling perspective. What an exciting time we are in. This is just an amazing breakthrough of understanding. So where would a person start if they want to start down this road and develop some the skill that you have developed in your practice and world over the years?

Acupuncture Courses

FL: I think the most exciting acupuncture training that I have recently found out about is being done by a Spanish MD in Canada, Alejandro Clvalho, near Toronto. (I have never actually trained with him.) He is teaching acupuncture but calls it "functional orthopedics." He is teaching a type of bodywork that goes with acupuncture, which I think fits right into your philosophy of functional medicine. It is really an extension of the functional medicine--this "functional orthopedics" model he has. When people call and

ask for advice, I actually send people up to his training. The website is acupuncturecourses.com. I know it is right near Toronto. Not to put anyone else down--I had wonderful acupuncture teachers--but in terms of the functional medicine approach, I think he comes closest to it.

JB: Well, thank you. We'll make sure we put that on the summary card for referral. To leave us with some thoughts as we close this discussion, what you have helped us to understand (or at least open the door for many of our listeners, probably) is a whole different perspective about fascia, connective tissue, extracellular matrix, how acupuncture and bodywork trigger systemic metabolic and physiological changes, and why the worlds of structure and function are not separate; they are actually part of a continuum. If we can get that concept, alone, across in this discussion we have done a big service to advancing medicine from a functional perspective. I want to thank you very, very much. This is the start of a journey, I'm sure, for many of us as we have heard you speak about your experiences and background.

FL: Thank you for having me on, Jeff.

JB: It has been our great pleasure.

Issue Synthesis

Let me do a recap of what I consider the take-home value of this month's *Functional Medicine Update*. We started off talking about this duality of structure and function and then redefined it as a continuum. Structure influences function and function influences structure, and these two terms are really connected through cellular signaling.

We then talked about various ways that you can influence this process by altering the environment through the alkaline/acid balance, saying that as you shift toward an acid pH it changes receptor binding and changes ligand/receptor interaction to alter cellular signaling. By using an alkaline-ash diet, you shift towards improvement in detoxification, enzyme function, and metabolic function. This is what has historically been seen clinically for many years (that an alkaline-residue diet has these positive impacts upon function). So the environment is plastic, and it alters the way that cell signaling occurs.

Then we went from that to talk about specific small molecules, or phytochemicals, found in whole foods and their influence on cell signaling processes. I talked about indole-3-carbinol, and phenylisothiocyanate, and sulfurophane that are found in cruciferous vegetables. These molecules can influence detoxification and the conversion of endogenous molecules (like 17-beta estradiol) into nontoxic metabolites, which can also be used as parts of the signaling process to induce specific cellular function.

And then from there we talked about soy--the small molecules that are found in soy and the influence they can have as isoflavones, or polyphenols, or lignans on the effects of function, including things like lipid synthesis, insulin sensitivity, anti-inflammation, and hormonal metabolism. From there, we talked about the fact that if you think of foods in their whole form they contain a whole rich array--a library-of substances that can influence cellular neurological function, and can have neuroprotective effects (with ginkgo biloba obviously being the one that is on the minds of most individuals, but there are literally hundreds of foods that have central nervous system active, neuroprotective substances that interact with

intercellular kinases and alter cellular signaling).

Then we moved from small molecules in food to talking about the gut. What about the gut and bacteria and the influence that they have on cell signaling and structure-function? I spoke about this extraordinary study that had looked at endotoxemia and how it initiates obesity and insulin resistance. By altering bacteria type and number and metabolism, we can alter the function of the body through altered cellular signaling. We talked about agents that would modify, in a favorable way, enteric bacteria and altered cellular signaling, like removal of highly refined carbohydrate in the diet and increasing certain probiotics, like inulin-containing substances that induce friendly bacteria, lowering LPS and lipopolysaccharide levels and inflammatory mediators and improving insulin sensitivity.

We talked about agents in whole foods that can induce inflammatory response at the gut level and can have systemic implications, like gliadin (found in cereal grains), but there are other substances in those grains that might have anti-inflammatory effects. I cited the decapeptide from durum wheat that appears to have anti-inflammatory effects.

Coenzyme Q10 and the Prevention of Hepatotoxicity

We talked about traditional nutritionals, or biochemicals, or what might be called by Dr. Pauling "orthomoleculars" (natural molecules found in our diet, like coenzyme Q10). You might say, "How does coenzyme Q10 help to prevent hepatotoxicity?" There is a very interesting paper that was recently published, looking at the effect of coQ10 in liver cells on the protection against injury to the cells when exposed to high-dose simvastatin (obviously a statin is a HMG-CoA inhibitor drug). This article appeared in *Toxicology and Applied Pharmacology* in 2007 and is titled "Reduced Mitochondrial Coenzyme Q10 Levels in HepG2 Cells Treated with High-dose Simvastatin: A Possible Role in Statin-induced Hepatotoxicity?"² The authors of this article conclude that as coenzyme Q10 levels are depleted within hepatic cells, this insufficiency or deficiency plays an important role in statin-induced hepatopathy and that coenzyme Q10 supplementation may help protect against hepatic cell injury from this complication of statin exposure.

So what we are really talking about, again, is a molecular effect (this is an endogenous chemical that is biosynthesized in the body-coenzyme Q10), and the influence it has on function of the mitochondria (in this case, an intracellular organelle), which then regulates oxidative injury and oxidative stress-related cell apoptotic events (in other words, cell suicide events) that are associated with oxidative stress. As coenzyme Q10 levels are depleted due to interruption in endogenous biosynthesis due to exposure to a statin, it enhances, then, the relative cell signaling process, shifts the balance toward oxidative injury, which then triggers in that cell (through its gene expression patterns) the potential for cellular suicide, which we call apoptosis, and that is hepatopathy. So I think this is, again, another way of taking data and observations that we have made for some time and projecting it through the lens of structure-function and looking at how, then, the appropriate environment leads to the proper structure-function relationship and outcome in that patient. It is not that statins, in and of themselves, should be avoided at all costs; it is constructing the appropriate environment in that individual to modify the functional changes that occur in these systems as a consequence of the perturbing structure of that molecule called the statin molecule.

And then lastly, of course, we moved to a whole other level in this discussion in the eloquent and amazing history and description by Dr. Frank Lipman of the extracellular matrix and fascia and how that

is an environmental translator of agents outside to the inside cellular function, through these same cell signaling processes I've been describing-through the kinases, the extracellular matrix proteins that then take information that may be things like baromechanical pressures or electrostimulation (mechanical electrostimulation) that occurs with acupuncture and translates it over into alteration in cellular signaling so that structure and function are modified. I think this plays out to produce a unified conceptual framework of how therapeutic interventions work to serve both as a preventive and therapeutic series of tools that work in concert with one another through similar mechanisms to produce outcomes. So it is not just one agent at a time. It is not the double-blind, placebo-controlled, randomized trial (hold everything constant and just change one thing and then look at the outcome). It is a pattern of changes that then alters our function through the structure of those events that then cause the genes to change their expression patterns, the signaling processes to occur, so it is work locally but act globally, as kind of the outcome from this framework.

So I hope we have left you with some new thoughts and tools as it relates to how the playing field of functional medicine derives from all of those agents that modify from this very subtle and important interrelationship between structure and function. Thanks for being with us. We'll look forward to sharing again in November.

Bibliography

- 1 Minich DM, Bland JS. A review of the clinical efficacy and safety of cruciferous vegetable phytochemicals. *Nut Rev.* 2007;65(6):259-267.
- 2 Minich DM, Bland JS. Acid-alkaline balance: role in chronic disease and detoxification. *Alt Therapies.* 2007;13(4):62-65.
- 3 Bastianetto S, Brouillette J, Quirion R. Neuroprotective effects of natural products: interaction with intracellular kinases, amyloid peptides and a possible role for transthyretin. *Neurochem Res.* 2007;32(10):1720-1725.
- 4 Cani PA, Amar J, Iglesias MA, Poggi M, Knauf C, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes.* 2007;56:1761-1771.
- 5 Hayes MR, Miller CK, Ulbrecht JS, Mauger JL, Parker-Klees L, et al. A carbohydrate-restricted diet alters gut peptides and adiposity signals in men and women with metabolic syndrome. *J Nutr.* 2007;137:1944-1950.
- 6 Silano M, Leonardi F, Trecca A, Mancini E, Di Benedetto R. Prevention by a decapeptide from durum wheat of in vitro gliadin peptide-induced apoptosis in small-bowel mucosa from coeliac patients. *Scandinavian Journal of Gastroenterology.* 2007;42(6):786-787.
- 7 Langevin HM, Yandow JA. Relationship of acupuncture points and meridians to connective tissue planes. *The Anatomical Record.* 2002;269:257-265.
- 8 Langevin HM, Churchill DL, Cipolla MJ. Mechanical signaling through connective tissue: a mechanism for the therapeutic effect of acupuncture. *FASEB.* 2001;15:2275-2282.
- 9 Tavintharan S, Ong CN, Jeyaseelan K, Sivakumar M, Lim SC, et al. Reduced mitochondrial coenzyme Q10 levels in HepG2 cells treated with high-dose simvastatin: a possible role in statin-induced hepatotoxicity? *Toxicol Appl Pharmacol.* 2007;223(2):173-179.p>