August 2012 Issue | Christopher D'Adamo, PhD

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Welcome to *Functional Medicine Update* for August 2012. This issue is going to deal what I think is a very interesting topic, and that is how do we get the right database, and the right clinical support, and the right trials to demonstrate the effectiveness of functional medicine in clinical practice? That has been a standing discussion that I'm sure you've all been involved with when someone asks you: "Well, give me the references." Or, "Cite the double blind, placebo-controlled, intervention trials." Or, "How do you know what you're saying is true based upon randomized, unbiased evaluations?" Of course, often a clinician working everyday with their patients doesn't have the time to really be dredging the literature and to spend the time that is necessary to surf through all the various databases to pick out those articles and those studies that really adequately document, to a critic's capability, the nature of how this form of medicine really provides an effective, safe, and improved patient outcome basis for care.

As we look at this in a broader sense, we recognize that a number of years ago, thanks to Senator Tom Harkin and his advocacy, and then his mobilization of other colleagues such as Senator Orrin Hatch from Utah, the National Institutes of Health was funded to set up the National Center of Complementary and Alternative Medicine (or NCCAM), which was focused on support of appropriate studies and interventions that relate to complementary and alternative medicine. A component of that obviously relates to functional medicine and nutritional interventions. This month we're very fortunate to have as our clinician/researcher of the month an individual who has been actively involved in the NCCAM-funded studies, and the grant proposal process, and the outcome-based publication of these studies, which helps to build a rich and much more dense body of supporting literature for the safety and effectiveness of some of these therapies that have previously been considered non-scientific only because they were not subjected to the rigors of a good scientific study.

Joel Wallach, DVM, ND Receives Klaus Schwarz Medal

When I think of this, I'm reminded of a colleague that I've known now since the late 1980s. In fact, when I was a professor of nutrition for the National College of Naturopathic Medicine in Portland, Oregon in the late 1970s, he came in to take over my position as the lecturer in nutrition. His name is Joel Wallach. He's a naturopath. He's also a veterinary medicine doctor. He was in experimental work, working at one time for the National Institutes of Health, and he had made an observation back during his time at the NIH that I think is a very interesting observation that was considered artifactual. It didn't

seem to fit into the standard body of logic.

This was not appreciated nor held. You know, there's quite a distance in time between 2012 and the late 1970s. But over these years, a considerable body of literature has been developed and started to be much more well-appreciated that these relationships between trace mineral deficiencies and insufficiencies and problems as it relates to mysterious symptoms, including that of neurodegenerative-like symptoms, are not totally artifactual.

I was very pleased to see that in 2011 Dr. Wallach was awarded what is arguably considered the most prestigious award in the trace mineral nutrition area, the Klaus Schwarz Award.[1]Many of you know Dr. Schwarz, who was born in 1914 and died in 1978, was an investigator at the University of California, Los Angeles, and was a leading trace metal/trace element researcher and was certainly known for his discovery of the nutritional essentiality of the trace mineral selenium. So for Dr. Wallach to receive the Klaus Schwarz Award is no small compliment to the discoveries that he made early on when he was a post-doc at NIH.

I think we've started to recognize that there are all sorts of interesting associations that occur from insufficiencies of various nutrients that are hard to pin down as to the cause and effect, and even more difficult to define a specific mechanism by which those deficiencies result in certain pathologies. I'm reminded, when I think of this, that the origin of most chronic diseases from a mechanistic perspective were not known well at all, and only recently—in the last 10 to 15 years—have we started to see the emergence of pathophysiology at the molecular/cellular level start to be understood for a number of the major chronic age-related, degenerative diseases.

When we start looking at nutrient deficiencies or insufficiencies, many of these have what are called long-latency effects, meaning that the deficiency or insufficiency does not result in an immediate disease like you might have with an infectious organism (a virus or a bacterium), but rather relates to a long-term declining function, which later then produces a disease that has a long latency period, and that this disease may be very difficult to tie cause-and-effect to the deficiency of that particular nutritional element because of this long latency period. It may be sometimes many decades before something like osteoporosis with calcium insufficiency results in the adult.

I think this is one of the complicating factors when we deal with the area of nutrition and pathology, that the origin of these diseases often is masked over this long latent period. But I do want to acknowledge Dr. Joel Wallach's interesting and very, I think, important discovery that he made as it relates to selenium in primates, now going on 40 years ago, that allowed him to be the 2011 Klaus Schwarz medalist.

Physiological Distress and the Origins of Chronic Disease

And that, of course, then relates to a whole series of other interrelated questions about the origin of dominant, chronic, age-related diseases, such conditions like metabolic syndrome, type 2 diabetes, cardiometabolic syndrome, atherosclerosis, that are associated not just with dyslipidemia but with dysinsulinism. What is the specific mechanism of action or the origin of these particular diseases? I think it is easy to say, "Well, there must be a single gene that somehow is impaired or mutated, or there is a SNP that causes these conditions to occur, or there is a specific variable like an infectious organism or a toxic exposure that causes these diseases. But rather as we examine them in the light of 2012, what we recognize is that these diseases—their origins—fall into the same category that Hans Selye was talking about with stress-related diseases in the 1950s and 60s.

You recall, if you followed Dr. Selye's stress model, that he indicated that physiological distress, as responded to by an animal in response to a changing environment, disturbs the web of metabolism and physiology in such a way that multiple outcomes in terms of pathophysiology can be seen. In his animal studies he showed it could be wasting disorders and what you might call metabolic sarcopenia or muscle wasting. Or it could be such things as cardiac conditions. Or it could be such things as ulcers. Or it could be such things as diabetes. Or it could be even such things as increased risk to a carcinogenesis. So the outcome of the condition is variable. The input that causes this disturbance in physiology is the individual organism's response to their environment, seeing their environment as a hostile, threatening environment in which they mobilize, against this perceived threat, a disturbed metabolism.

Disturbed Metabolism is Normal Metabolism—Up to a Point

Now we call it disturbed metabolism, but maybe a different way of actually contextualizing this is to say it's a metabolism that is actually responding as it should based on the genetic messages that are preprogrammed from the lineage of that organism's history (that person's history). And so what we call a disease is really the appropriate response to a foreign exposure, or let's call it a hostile exposure, that somehow gets locked in the "on" position, so that what was the normal adaptive response to a changing environment (a hostile changing environment) now becomes harmful to the organism itself, and we call that a disease.

So the disturbance of metabolism may, in the first stages, actually be the appropriate response to that perceived hostile environmental change. It's only when it gets aggravated in response or locked in the "on" position that over time it then starts to produce its own untoward effect on the structure and function of the organism that we call later a disease.

That model holds very nicely for conditions like metabolic syndrome, syndrome X, hyperinsulinemia, and cardiometabolic disorders, which we know are very closely related to this gene-environment interaction. In fact, there are a number of very nice papers that have been published over the past few years that have really tried to explore this study of genes and their relationship to environment, that then signals to the organism a change in physiological status that later we diagnose as hyperinsulinemia, glucose impairment, and metabolic syndrome.[2]

So you think of genes like, for instance, the peroxisome proliferated activated receptor genes (the so-called PPARs). This could be PPAR?, or it could be PPAR?, the one that has received so much attention with the thiazolidinedione drugs for the treatment of diabetes, which we know these drugs have been labeled as PPAR? agonist drugs. We recognize that there is PPAR?-?, and all of these have differential effects on modulating gene expression as orphan nuclear receptor signaling substances. We also know that genes like apolipoprotein E, and we know apolipoprotein E2, E3, and E4 have influences on lipid dynamics, on glucose dynamics, oxidative stress, and redox potential. Similarly, genes like glutathione s-transferase, both T1 and M1, have been identified to be very important in modulating insulin sensitivity, oxidative chemistry, mitochondrial oxidative phosphorylation and its relationship to type 2 diabetes.

We could go on and talk about literally hundreds of genes that have been implicated in different configurations and different expression patterns to be associated with the disturbed metabolism that we later label as type 2 diabetes. Now we might ask the question: Does that mean that type 2 diabetes is a singular disease? Or is it really just the manifestation of what we would call dysinsulinism and dysglycemia, of which the origin of it could have come from myriad different factors that are genetically unique to that person, based upon their gene environment interaction, and how that over a period of time (the so-called long latency period) leads to decreasing insulin sensitivity, increasing dysglycemia, and later crosses that magic boundary of a fasting blood sugar >100, which we will diagnose as diabetes and later elevated hemoglobin A1C.

The Events Associated With Disturbed Physiology

These are, I think, important philosophical questions, but more importantly I think that they are really important clinical questions, because they start asking us to look earlier in the sequelae of events that are associated with disturbed metabolism/disturbed physiology, that are reflective; kind of like Plato’s “Myth of the Cave”—we’re looking at the reflections rather than the fire. We’re looking at the shadows on the wall of the cave when we start looking at the transition in these biomarkers, things like postprandial insulin, postprandial glucose that we see with an oral glucose tolerance test; drifting towards higher levels of hemoglobin A1C, going from 5.2 to .3 to .4 to .5 to .6 and moving up towards 6, where we see increasing levels of high sensitivity CRP (hs-CRP), knowing that there is a connection between chronic inflammation and dysinsulinism in type 2 diabetes; things like uric acid that start to drift up. All of these are indicators of a disturbance in metabolism that is resulting from altered cellular physiology from a change in the gene/environment interaction. The earlier we can understand that, in the functional

medicine/systems biology model, the better off we will be able to intervene with less aggressive—less invasive—therapies to modulate that disturbance by taking away the precipitating events we call the initiators that alter this gene expression pattern into that that we later associate then with this condition of metabolic syndrome.

Metabolic Memory: A Response Pattern of the Genes

There is another kind of wild card at play here that I think, again, argues strongly for why we would want to intervene earlier with the functional medicine model. And that is it has been recognized, and you've seen this if you've been following *Functional Medicine Update* for the past few years, that the emerging understanding of epigenetics is starting to help us to recognize that certain environmental features that the organism is exposed to ultimately may lock in, or let's call it "label" with these epigenetic marks, the genome in such a way that it changes gene expression patterns. I don't want to call it adaptation to the environment. What I would call it is that genome becomes conditioned by the environment, and in so doing it becomes more difficult, then, to change the expression patterns once you've put these marks on the genome—these methylated promoter regions of genes, or change the histone acetylation patterns, or change the ubiquitination patterns, or the phosphorylation patterns that are all associated with epigenetic modulation of gene expression. Once those are locked in you then develop what might be called metabolic memory. And metabolic memory is a more difficult thing to break because now we've kind of hard-wired that organism into a certain response pattern of their genes, and it becomes more difficult, and maybe more necessary for aggressive therapy, to wipe off those marks and put on new epigenetic marks that would allow a metabolism to result that is less disturbed, less distorted.

Large randomized studies have established that early intensive glycemic control in the diabetic reduces the risk of complications, both in terms of micro- and macro-vascular disease. Epidemiological and prospective data support a long-term influence of early metabolic control in clinical outcomes.[3] This phenomenon has been defined, as I said, as metabolic memory, which I think is now starting to be recognized mechanistically as tied to epigenetic alteration over time. The genes get conditioned to that environment. By the way, this same thing seems to hold true for pharmacology—that long-term administration of specific medications have been found to alter the methylome or the epigenome, so that you've actually changed, on a kind of metabolic memory basis, the way that specific genes are expressed by long-term exposure to specific types of pharmacological agents.

This mechanism for propagating this memory is the production of species that ultimately alter the way the genes and way the proteins are going to modulate metabolic function, things—as I mentioned—like methylation patterns, acetylation patterns of the genome, even things like protein glycation, like advanced glycosylation end products, which modify the way proteins actually do their work.

Metabolic Memory May Require More Aggressive Intervention

The reason I am going into some detail on this is that as you intervene with a patient that has this kind of stuck metabolism, this metabolic memory, you have to recall that you may be working uphill a little bit against epigenetic conditioning that may require some more aggressive intervention. That's why sometimes very dramatic nutrition programs are used that dramatically alter dietary habit patterns and create kind of a frame shift in the way that the genome is receiving signals from the environment. So it could be things like detoxification programs. It could be—in the chemically sensitive patient, like those who have multiple chemical sensitivity (MCS)—a completely pristine environment for a while, just to completely alter the signals the genome is getting.

A Meta-Analysis of Metformin Efficacy

The alternative of this, obviously, is polypharmacy, and we do know that polypharmacy has been used in medicine for the management of complex disorders associated with metabolic disturbances. One of the principal drugs, as you know, that is used in the management of type 2 diabetes is metformin. It's the first line of therapy. Metformin has a history of safe use, reasonably. It has a history of efficacy. But I found it very interesting that recently there was a reappraisal of metformin efficacy in the treatment of type 2 diabetes, doing a large meta-analysis of the published randomized controlled trials.[4] I want to be very cautious. I don't throw the baby out with the bathwater when I go through this because you might take away that I'm a nihilist around pharmacotherapy. That's not the point I'm trying to make. The point I'm trying to make is the nature of the heterogeneity of these conditions and how in one patient something might work very well but in other patients not. Because when you do a meta-analysis of the large-scale randomized controlled trials on metformin in the treatment of type 2 diabetes—this is 13 randomized trials with 13,110 patients—what you find is that the metformin, although considered the gold standard, its benefit-to-risk ratio remains uncertain when we look at it from a meta-analysis large perspective. There is a potential, obviously, of a statistical reduction in all-cause mortality, but this is a range of effects, all the way from that which has been proven to reduce all-cause mortality to that which has been shown to increase all-cause mortality, with the same medication. So, wide standard deviation of variation, marginal improvement when you look at the averages of these kinds of trials on the average patient, so then you start asking: Is the drug a good drug? In the right patient under the right conditions, the answer is yes.

Gut Microbiota Correlates to Type 2 Diabetes and Insulin Resistance

The point I'm trying to make is there is no one panacea for these complex disorders of chronic disease. They are heterogeneous in their origin: multiple genes influenced by multiple environmental changes. We even learned recently that environmental change called our gut microbiome is a big factor that modifies insulin sensitivity. In fact, there are now papers that are being published, one by our colleague at the Universite Catholique de Louvain in Belgium that looked at the gut microbiome in the development of low-grade inflammation and type 2 diabetes that is associated with obesity, finding that there is a very close correlation between specific types of microbiota, the interrelationship with the diet, gut permeability, and inflammatory connection ultimately to type 2 diabetes and insulin resistance.[5]

So we need to keep our field of vision wide open when we're in the functional medicine model. We need to move it to earlier understanding of trajectories towards changing metabolism. And we need to recognize that these diseases don't have a single origin. They have multiple origins from complex interactions of genes with environment that require personalization of therapy for maximum effectiveness. Whether drugs are used, or lifestyle interventions are used, or the combination, one needs to be very aware of this complexity of interaction between the environment and the genes of the patient, so that the program becomes personalized.

With that said, I think now we're ready to really talk with our clinician/researcher of the month, Dr. Chris D'Adamo, who is going to tell us a little bit about how all this plays out in the medical school environment, in the NCCAM-funded studies, and how we're starting to build a rich body of literature and clinical support for what I consider to be the medicine of the 21st century.

INTERVIEW TRANSCRIPT

Researcher of the Month

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Here we are at that place in Functional Medicine Update that all of us look forward to with great anticipation. For you it's probably a little bit of a surprise: Who will Jeff Bland choose for the interview of the month? It's not an easy thing to make these decisions. As you know, we're so fortunate in our field of functional medicine to have so many remarkable contributors—clinicians, researchers, educators, people who really bring tremendous breadth of talents and experience to the field and are really germinating the field, causing it to evolve at a very rapid rate. But I am always very impressed as we start seeing new energy come into the field, individuals who have diverse training and background. I don't want to say they are in the first part of their career, but let's say in the earlier part of their career, and they start to affiliate with the functional medicine model and bring to the field some new talent, new energy,

new capabilities that I think are going to make the field even more robust and more effective. That is, of course, a longwinded introduction into this month's researcher/clinician/educator on Functional Medicine Update.

Let me say a little bit about him. I had the opportunity to meet Christopher D'Adamo a number of years ago, and more recently we spent some time together at the integrative medical conference hosted by the University of Maryland integrative medical program. Chris is just a remarkable guy. He was not only involved with the organization of the meeting which went well—very well attended and very smoothly run—but he also was one of the keynote lecturers and was giving multiple presentations on multiple topics and connecting with the majority of the attendees on a personal level as an ambassador to what we're all about. He just struck me as the exact right energy, right enthusiasm, and right knowledge base.

As I got to know Chris a little bit better I recognized that not only is he quite remarkably talented, but his background also reflects a very interesting and diverse set of experiences, going all the way from a certified personal fitness trainer to a nutrition consultant (certified) to an assistant professor at the University of Maryland School of Medicine, with a primary appointment in the Department of Family and Community Medicine and a secondary appointment in the Department of Epidemiology and Public Health. He has his Bachelor's from the College of Holy Cross in mathematics and pre-med, but then went on and got his PhD in epidemiology. He is an Epidemiology of Aging Fellow at the University of Maryland in the Department of Epidemiology and Preventive Medicine.

Obviously I could go on and on, but I think what you'll learn as we have a chance to talk with Chris is that he has brought this wide range of diverse experiences into really the same mission that all of us are aligned to, and that is finding more effective ways to both prevent and manage chronic disease. He background and experience I think provides a very unique way of looking at what I call personalized lifestyle medicine and how that interfaces with functional and integrative medicine.

With that, Chris, we can't tell you how much we are very pleased and privileged to have you as our clinician/researcher/educator of the month, and welcome to Functional Medicine Update.

CD: Thank you. It's my pleasure. That's a very flattering introduction and I'm looking forward to the discussion today.

JB: Let's start like I do with all of our invitees/interviewees, and that is with the question about how your path of life took the tributary or took the juncture into the University of Maryland, the integrative medical area, and ultimately into the position that you find yourself as a faculty. It must have been a very interesting journey. Tell us a little bit about how you got there.

Lifestyle Issues Did Not Play a Role in Hospital Care

CD: It has been an interesting journey with a lot of different stops along the way. You know, you trace some of it in your introduction. I was math/pre-med in undergrad. I had always wanted to be a physician and had followed that track. I was fortunate to have won a fellowship at Johns Hopkins Hospital going into my senior year of undergrad in medicine. The experience was eye-opening and enlightening in a number of ways. During that experience it became clear to me that I was interested in a different style of medicine. I had always been a lifestyle enthusiast. I was an athlete, so I believe in the virtues of exercise

and eating right and I had been learning a little bit about stress management, and I came to witness that didn't play a very big role in what I was seeing in the hospital. To me, I was a little more interested in proactive prevention of disease and promotion of health and a less reactive approach. It kind of threw me a little bit. I had taken the MCATs, I had done all the steps, and I decided not to go into medicine and I took a divergence into healthcare management consulting, which was also a pretty enlightening experience in many ways, just to see how the business of medicine and health care worked. But at the end of the day, I was still very interested in the science and helping people and the lifestyle component, which again wasn't really there. So I decided to take up personal training in my spare time on weekends and got some certifications in that and nutrition as well. I worked with clients and was really just blown away with the results I saw from basic lifestyle interventions. Getting people off their blood pressure meds, losing weight and so on, which you'd expect and I think that is very important, and then the ability to kind of ameliorate autoimmune disorders that people were having, digestive problems, and I really saw how this lifestyle stuff is pretty powerful. I wanted to kind of "up" the level of education I had in that and study it more formally, so I chose to get a doctorate in epidemiology at the University of Maryland School of Medicine to apply rigorous methods to the study of lifestyle medicine, mainly exercise and nutrition. That's what got me started on this path, and I can say that functional medicine principles—reading the blue textbook several years ago—was very formative for me. I was very fortunate to get hooked up with Dr. Brian Berman at the Center for Integrative Medicine and it's just been a real blast so far.

University of Maryland has Support from Key Government Officials

JB: Let's talk a little bit about that connection with Dr. Berman. Those of us in the field recognize both he and his wife as really fundamental pioneers in this whole integration of these concepts that fall under integrative and functional medicine into a medical school teaching environment and clinical environment. It's quite an ambitious project that the two of them undertook and were successful. I was very impressed at the conference when I saw the number of influential people in the government within the state of Maryland who are supporters of the center and who have been very actively involved in making sure that it has adequate funding and support for its go-forward future. Tell us a little bit about how the center is disposed, how it interfaces with the medical school, and your role and your present position would kind of juxtapose between those two.

Education, Research, Clinical: A Three-Pronged Approach

CD: Absolutely. We've been around for 20 years. We celebrated our 20th anniversary last year. It's essentially a three-pronged approach to what we do. We've got a robust education program for medical students. The bread and butter has probably been the research, where we have really led the way in terms of bringing rigorous methods to the study of integrative medicine, acupuncture, mind/body medicine, nutrition, and so on. And then we've got a clinical presence as well, where we see patients. We have physicians, many of whom have followed the functional medicine model. So it's three-pronged and I can tell you it is very exciting to see how integrated we've become in the school of medicine. We have an elective course, which I can talk about in more detail, for fourth-year medical students, but we have exposure at all levels. Everybody in the second year is taught some principles of integrative approaches to pain management, which is a big problem that mainstream medicine doesn't have all the answers for, as well as stress management. We're working with shock trauma quite closely, as you recall from the conference, and we were very happy to have you there. Dr. Tom Scalea is the head of our shock trauma

center and has welcomed us with open arms and an integral part of what they are doing there is bringing these modalities into the trauma center. We're forming collaborations in different departments. I've got an appointment in epidemiology and public health, so we bring our perspective there. We've got people in psychiatry. The ideal goal is almost to lose the label "integrative medicine" and just become ultimately "good medicine." I think the way to do that is to get assimilated into all the other departments and reach them with evidence, and that's one of the main things we've done: the modalities we talk about, and treat patients in the clinic, and teach and research are backed by evidence.

JB: I want to really compliment you and the whole team there with Brian (Dr. Berman). I think that you have really accomplished that—being the image of integrating your concepts into the body of medicine at the larger scale, and I think that takes a lot of skill to bring something that's different into a form that can be created or assimilated into peoples' other systems of learning or systems of observation, and sometimes they don't even know it's happening. It's almost like the Trojan horse model. I think you have done this very, very effectively. I also was very impressed, at the meeting, with the advocacy of Senator Mikulski from Maryland, who clearly has a tremendous amount of respect, and admiration, and support for the program that you are engaged in there, and being a person of extraordinary importance in the Senate—being on the committee that relates to health care, being one of the senior members in tenure—it seems that that relationship has been very vital. Can you tell us a little bit about how you handle things like government relations? It sounds like you're doing a good job.

Some Law-Makers Understand the Need to Change the Healthcare System

CD: Sure. Senator Mikulski's one of our biggest supporters. She spoke at the health and wellness conference this year, and she spoke at our 20th anniversary last year. It is critical to have that backing. I think she and many others understand that the current healthcare system can't continue on the way it is. It's not financially sustainable. The modalities that we're talking about, and self care, and lifestyle medicine, it's unquestionably more cost effective to prevent disease than treat it, and if we get to these biological underpinnings then it just makes sense that that's how we're going to quell the bleeding in the healthcare system. She has been a great supporter and I think it has been very helpful for us to have her support and the support of others in the federal government. That includes the National Center for Complementary and Alternative Medicine, which has funded quite a bit of our work over the years. We're an NIH Center of Excellence, which helps get buy-in within our own school of medicine, but the greater model, as well, is to have credibility in a sense from doing good research and having the backing of people like Senator Mikulski.

JB: I think that's a great segue, Chris, to the next question. You talked about the three-prongs that you are involved in. Let's start with prong one, which you've already segued to, and that's the NCCAM sponsorship of research and how you focus your research, the kind of projects you're engaged in. Could you tell us a little bit about that, because you're really doing some very interesting things across a wide range of topic areas?

NCCAM-Funded Research

CD: Right. The center in general has done an incredible amount of work in acupuncture. They've published studies in the Archives of Internal Medicine and other high-impact journals.[6],[7] They've done quite a bit of work with stress reduction and so on. My personal interests are in nutrition and

exercise. I've done work in the past—published some papers—looking at the carotenoids and vitamin E and how those predictors function in older adults.[8],[9] I've looked at those same micronutrients and showed they are associated with lower levels of inflammatory cytokines. We know that inflammation is an underlying cause of many diseases. I know this is an interest of yours as well. Nutrigenomics—I've started to get into that a little bit more and we're looking at those same micronutrients. We're interested in vitamin E and the carotenoids because they've been associated with lower risk of a host of diseases, and we're looking at variance on SNPs that predict higher and lower concentrations of those. We've seen that two people can eat a tomato and you'll have very different levels of lycopene and so on. Apo B and apo E seem to have some impact on serum levels of these micronutrients. I really think getting to the biological individuality of people, I think this is one way to kind of really say it's not one-size-fits-all, both when it comes to nutrition but also to these other modalities. Those are some projects. I've got a real interest in nutraceuticals. We've got a couple of studies. One with a mushroom blend of shiitake and maitake mushrooms, looking at how that prevents the common cold. We know these particular mushrooms and the alpha and beta glucans contained within them stimulate the immune system, and lots have been traditionally used for cancer and many other conditions. That's a really interesting study we've got going on now. Another is a probiotic formulation to improve symptoms of acid reflux. People are very quick to reach for the proton pump inhibitors. We're starting to see now that they can deplete B12 and inhibit vitamin B12 absorption, which can lead to H. pylori infection and perhaps some risk of bone fractures. We're really looking at some nutritional solutions to problems that are affecting many. That's some things I've got going on at the moment.

Is Nutrigenomics Dead?

JB: Let's go back and pick up a little more detail. You've given us a pretty good smorgasbord there to select among. Let's talk first about this nutrigenomics issue. I had a very interesting conversation last week with the woman who is the senior professor in charge of the nutrigenomics efforts in New Zealand at the University of New Zealand in Auckland (and at the medical school). She had made the point in a discussion that we had that it is now thought by people in the New Zealand power structure (in terms of the government) that the concept of nutrigenomics is dead. Its day has come and gone. It never really achieved its highly touted importance, and it was just a fad of the moment. What's your thought about that? By the way, I can go into more detail about why some people are saying that. She doesn't clearly believe that, but I'm wondering what your thoughts are.

CD: That's the first I've heard of that notion. I think it's alive and well. In my eyes, I feel like we've just scratched the surface. The study that we're doing is looking at predictors—these SNPs or variance on SNPs to predict concentrations. But I think if you look at some of the other literature on the way that certain foods impact genetic expression—if you look at NF?B and curcumin—a lot of good research there. One of the studies I really like was looking at broccoli, sprouts, and sulforaphane and its potent HDAC-inhibiting properties. I think it's pretty clear that foods, and food components, and nutraceuticals can have an impact on genetic expression. As far as it being a dead area that has come and gone, I personally don't view it that way.

JB: Yes, I think that your point is well taken. The individuals who are criticizing, I believe are taking a very monotonic view of it. What they are saying is that these SNPs don't really tell us exactly what the phenotype for the individual is. They just really tell us about the landscape of potential, and therefore they are really kind of useless because you really need to know more the phenotype in order to understand how

an individual will get sick or be well. I think they are missing the point that the landscape is in part determined by the potentiality of the genes and their susceptibilities and strengths. And the environment interacting with those genes is what gives rise to the expression, which gives rise to the phenotype. You don't want to throw the baby out with the bathwater and say that the genes and their uniqueness are not important. Mendel is still alive and well in terms of understanding aspects of inherited characteristics. How would you respond to someone that says: "Well, the genes are just there. It's really how it is expressed and we don't really care about the genes." How would you respond?

JB: I think I would agree with the points you made. It may be not seeing the forest for the trees. I think we've really only scratched the surface and as the methods continue to evolve we'll be able to answer the questions perhaps more directly and with a little bit more precision. I think it is kind of missing the point in many ways, so I would agree with your retort.

CD: You made another very interesting point about your research, which I think almost supports what we're talking about, and that is the apo E and apo B genotypes. Often people feel, I think, that the absorption of nutrients just occurs passively. So you just increase the concentration of a nutrient in the intestines and somehow it pushes its way, through passive diffusion, into the blood so it improves bioavailability. But as you pointed out, there are—for many, many nutrients—transport proteins and very conducted-tour-type of absorption processes that are not so simple as just mass action. They actually have pumps that pump things in and pump things out, and these are controlled very tightly by regulatory proteins, and those are then obviously intimately connected to the genes of the individuals. So if you had an apo E4 individual, they have a very different absorption for specific types of fatty substances than does an apo E2 or 3. I think you have already, through your research, started to confirm it's a combination of these genetic archetypes with their environment. In fact, maybe you can tell us a little bit about what you're seeing in terms of bioavailability and apolipoprotein genotypes.

Teaching Medical Students About Popular Diets

CD: Our results have not yet come in, but looking at the literature that is there now, I think it is pretty clear that these things have an impact. Where I would really like to go with this is to a macro level. There is some evidence, looking at the macronutrient composition of diets, that some people respond more favorably, based on SNPs, to lower carbohydrate diets versus higher carbohydrate/lower fat diets. At this juncture we're looking at the micronutrients, but I'd like to see it applied to whole diets. It's one our educational endeavors—actually teaching popular diets and getting into what's really practical. Ultimately it is what can a physician tell his or her patients? What's the right diet for them? I think it goes beyond the absorption of particular micronutrients, but I think this work that we're doing now will build towards looking at diets on a grander scheme and seeing genetic predictors of response to diets. There have been some studies. I'm not sure if you've read the one, but I think there was one that showed certain variants people responded better to a lower carbohydrate diet and others responded better to a lower fat diet. I think that is where I would like to take this on a grander scheme ultimately.

JB: I think that's really well said. In fact, I think just recently in the American Journal of Clinical Nutrition, the DIOGENES study was published that is evaluating exactly what you are talking about: looking at genetic patterns in SNPs that associate themselves with better response to certain types of diets, which once again reconfirms what you said—that there is no such thing as the perfect diet for everyone.[10] There are individual responses based upon these metabolic characteristics. I think where

you're heading is exactly where the field is heading.

CD: That was the study I was referring to. And this applies even beyond diets. I think that this could provide a mechanism for the fact that it's not one-size-fits-all for a lot of things. That applies to certain exercise modalities, and that would apply to mind/body approaches, or meditative approaches work better than others for certain people. You see certain federal dietary guidelines trying to make it one-size-fits-all for everyone. I just feel like it's not as simple as that and we'd be better served to really personalize our approaches with lifestyle based on both personal preference and perhaps informed genetic associations as well. Throughout our education, research, and clinical efforts, none of our approaches are one-size-fits-all. We have to really look at personal preference.I In my practice as a personal trainer and nutritionist I saw that too. Some people respond and really enjoy resistance training. Others don't. Others might prefer yoga. Me, if I try to do yoga I end up getting stressed because I'm so bad at it, but I love doing resistance training. So I think we need to take that approach across the board, and really remembering it's not one-size-fits-all across all the modalities that we recommend to patients and that we work into our own lives.

Recent Controversy About Curcumin Efficacy

JB: I'd like to go back and pick up another interesting thing you had mentioned earlier, and that's this curcumin story. If we were to look at the phytonutrients that have a reasonable amount of science based on their effect on cellular physiology, I think curcumin would rank right up in the top few, and maybe licorice would be up there too, and a couple of others. But certainly we would see curcumin. There has been a pretty significant controversy that has bubbled up here the last few months, unfortunately around one of the principal investigators in the curcumin area. That's Professor Aggarwall. And it's kind of put a little bit of a color on the curcumin literature. Do you have any opinions about curcurmin, or about this literature, or about this controversy?

CD: Yes, well, it is a little unfortunate because I think there is a kind of potential there. We hosted a CME training in Ayurvedic medicine this past weekend for physicians. Turmeric has played such a role in Ayurvedic medicine for thousands and thousands of years. And the turmeric, from which curcumin is derived, to me is something that I think does have quite a bit of potential. It's unfortunate what's happened there, but I still think it holds great potential. There's a lot of talk—I'm not sure how relevant this really is—about the absorption. There have been studies that have shown that when you administer curcumin with pepper the absorption is increased.[11] We have now looked at some fat delivery vehicles also. I think people would be well-served to at the very least include turmeric in their diet. If you look back at the traditional ways it was consumed, it was typically consumed with ghee, so there you get your fat to enhance the absorption of lipid soluble curcuminoids, and a lot of times with pepper. So I think it is an interesting example of how if you look back at history and traditional usage of many of these herbs, the science is now corroborating what had been practiced for thousands of years. I think curcumin holds some real promise. There is some evidence with autoimmune conditions, and certainly with inflammation it's powerful. I think it is something to consider.

JB: I think you are hitting on some really important points. I had the pleasure of meeting, and actually spending a couple of days at a meeting with Dr. AJ Goel. Dr. Goel is a gastroenterology researcher at Baylor School of Medicine in Dallas, and has published many papers that are really quite dramatically precise about gastrointestinal function, and carcinogenesis, and colon cancer (this is his specialty research area).[12] But he has also done a reasonable amount of very good work—published work—in the curcumin

area (curcuminoids and GI function).[13] One of the things that we talked about is that it is always assumed that these phytonutrients must be absorbed into the blood like a drug in order to be effective. But as he points out, the curcuminoids have a very powerful effect on receptors that reside within the gastrointestinal lumen (on the cells of the gastrointestinal lumen). And these mucosal cells pick up information and they can be signaling cells to the rest of the body through the information that is translated through the curcuminoids on their membrane-bound surfaces, and therefore you may not require a high level of absorption to actually have a physiological effect. The effect may be mediated through signaling that occurs at the GI mucosal level. I think that these questions are still open, and I believe that the pharmacological models that we've used—you look at pharmacokinetics absorption and then you try to track that to physiological effects or potency—may be somewhat limiting as it relates to some of these nutrients that are signaling through the gastrointestinal immune system. So, just a thought as we see this field opening up that maybe absorption is not the full answer to the question.

CD: I couldn't agree more. I think we're trying to fit a square peg into a round hole, so to speak, and trying to make it fit the current pharmacological model. Take turmeric, for example. The curcuminoids are part of it, but there are other beneficial components there as well. It may not be a story of maximum absorption to get maximum benefit. I think we're focusing on something that may not be of utmost importance, and so I agree.

JB: Let me ask you a question about the NCCAM research award process. Have you been…I don't want to say pleased because anybody that's involved with grants can't always be pleased because it's a very competitive process, but let's say have you felt satisfied that the NCCAM grant process for complementary and alternative medical research is still robust, or do you feel like it's a dying breed? Where are we right now?

NCCAM Funding Reflects Choices Consumers are Making

CD: That's a good point. I mean, it's challenging, and it's becoming more challenging as time goes on as the budgets are not being increased. These are important research questions. There was a relatively scathing commentary recently about someone saying that NCCAM funding—I think it was in the New England Journal of Medicine as an editorial—should be reduced, because of some claims that they weren't finding positive results.[14] But the fact is, these are important research questions.Dietary supplements is one of my big areas, and you've got half the population taking a dietary supplement, and many people taking several dietary supplements. We need to find out how well these work, and that's where NCCAM comes in, so the criticism, to me, was missing the point. These are important research questions. People are using integrative medicine modalities—70 percent, actually, according to a National Health Interview Survey—at least in some form.[15] Mind/body techniques, nutritional therapies, yoga or movement, so we need to find answers to these questions. I think the criticism is really missing the point, and it is challenging. We're very thankful that NCCAM is there. I mean, we feel the funding needs to continue to really bring evidence one way or another, so we can determine the modalities that are effective and distinguish those from those that aren't.

JB: When you set up research designs, sometimes the way we might approach an NCCAM research hypothesis or question might be very different than using a double-blind randomized placebo-controlled trial, which is often that methodology of research that is very suited for single agents against single endpoints. How do you deal with some of these complexity issues in setting up your research designs?

The Importance of Comparative Effectiveness Research

CD: If we look at the acupuncture research history that would be indicative and convey the point well. Again, it doesn't fit the reductionist single molecule paradigm of RCT (double-blinded, randomized, controlled trial), because what they've done with acupuncture is they have had more and more elegant ways to do a sham control, where there is no actual insertion of the needle, it just touches the skin, and it is a very elegant method to respond to a criticism that this is placebo. But the issue is that that experience in and of itself has some therapeutic benefit, just the interaction with the practitioner, the touching of the skin, and so on. It's not a single molecule. The RCTs work very well for studying drugs or single molecules, but it doesn't work very well for something like acupuncture, or whole diets in my opinion either. It's a challenge, and as we get more into comparative effectiveness research I think we can look at whole medical systems—a functional medicine approach, an integrative medicine approach, Ayurvedic medicine, traditional Chinese medicine—where we are comparing the entire practice as opposed to very standardized single modality-type approach that just doesn't work very well for non-pharmacological interventions, to be quite honest.

JB: I think you, again, did a very nice job of describing that. This concept of comparable effectiveness versus biomarker modulation as an endpoint is a very interesting philosophical difference of how you approach. And seems to tie also to the increasing concerns that some people are having about what appears to be research misdirection, research that comes back positive that doesn't actually prove to be correct later. People are now saying: "You really need longer term outcome studies. You need to look at endpoints that are not just a number of a biomarker, but how did the person do?" You might change the biomarker and they died at the same level or maybe even sooner. I think what you are raising about comparable effectiveness is a very important point. I'm sure it is something you have to do a little education on to people who are very imbued or imprinted with the RCT model.

CD: You're right. We believe in individualized medicine, and I think there is great recognition that that is the approach we need take. By definition, in an RCT you want to have as standardized an approach as possible and that's sort of in conflict with the practice of medicine—the individualized practice—that we are all starting to recognize (or many of us, at least) is most beneficial. Comparative effectiveness study—in research you've got your paradigm of efficacy, which is an ideal control situation. Everyone gets the same thing and the same control situations versus effectiveness, which is sort of a real-world, how-does-this-thing-work type of approach. Comparative effectiveness research is much closer on that spectrum on the effectiveness side. Let's take someone with back pain, for instance. That involves different etiologies, and if we apply the same approach to everybody with that, chances are you're not going to find out from a result, whereas if we really get to: is it someone's stress, is it a highly inflammatory diet, or is it lack of movement? In an individualized approach you could distinguish that with a discriminating eye, and then you can study this on the whole-system level. That's what comparative effectiveness allows you to do. It's not as controlled. It's more of a real-world environment. And there is a movement towards this. We heard a little bit about it with comparative effectiveness in the sense of comparing drugs. There was some talk about it a year or two ago and it didn't really pan out, but as far as studying whole medical systems and practice styles, I think comparative effectiveness is really the future. Recently there was the Patient-Centered Outcomes Research Institute (PCORI), a federal agency that is going to fund comparative effectiveness research. This is really the way it needs to go to reduce healthcare costs and to improve patient care.

Introducing Integrative Medicine to Medical Students

JB: Let's move from this kind of focus on the research base to prong number two, or platform number two, that you discussed, which is education. You had alluded to earlier the fact that you've got this very interesting elective course on integrative medicine for fourth year medical students. Tell us a little bit about how that has been picked up. Is something medical students look forward to? It is good it is in the later year; it is not in the basic science first two years where they are just totally overwhelmed. Tell us a little bit about this experience.

CD: I've got to tell you, it's an incredible experience, simply put. We have about 15 students per year. We keep it that way. It is highly competitive to get a spot because it is an experiential course. It focuses really on self-care, lifestyle medicine, all the modalities. So some of the things we do: they learn about acupuncture, they learn about TCM, they learn about mind/body medicine, meditative techniques. My focus in the class is on nutrition and exercise, so I look at dietary supplements, and I lead a popular diets whole day where we look at the Mediterranean diet, Atkins diet. I talk about alternative laboratory testing, so the functional medicine practitioners—what's of interest to them. We do Metametrix, Genova, all those tests that are out there. We do integrative oncology. And I do an exercise session, so I actually lead the students in a home-based exercise session because they're so busy. That's one of the things we see with exercise—people say they don't have time. But I can teach them a 15-20 minute exercise program that they can do from home and they can recommend to their patients. It's just highly experiential, and the feedback that we get on the class is not only has this expanded their tool set with modalities that they can bring to their patients, but they themselves reduce their stress because they're doing guided imagery, they're getting to do healing touch, they experience all these things. We even have equine therapy where they go out and interact with animals. So it is something to really broaden their horizons beyond kind of the standard pharmacological approach that they get during the first three years of medical school. We like it because they're going to be out practicing the next year and they've just really enhanced their skill set. It is really a fun experience for those of us that lead the course, and the students have given incredibly positive feedback on it.

JB: Do you have ways of measuring any degree of competency as people go through this course, or is it not really directed towards developing competency, more developing understanding, and you would recommend then someone go on, say, to the Andy Weil fellowship program after, or the functional medicine certification? What place does it play in their education and development, I guess would be my question?

CD: We consider it kind of an introduction to these therapies. Some people have pursued further functional medicine training. It has opened peoples' eyes. It's designed to give the students a sense of, at least, to whom they should refer: "You know, you've got this problem. Perhaps you should consider guided imagery. Here's a resource for it." Or, "You might want to consider movement." But we have found that it has enlightened people and they've decided to pursue it. That is very gratifying. They are somewhat self-selected because they've enrolled in the course, but it gives them confidence that this is something they can do for a career, they can practice this style of medicine as a career.

JB: Let's move to the third prong, which is the clinical side. I know you see patients on consult. I know the program there within the center sees people. Tell us a little bit about how the people find the center or the clinic, what kinds of patients you have, what your methodologies are for managing through

complexity.

CD: It operates as a primary care model, actually. People find us in a variety of ways. Many times it is word of mouth. A lot of times they are frustrated with their current medical treatment. I think the things that we see people for most often are chronic pain, chronic digestive disorders, and stress and the many repercussions and correlates of that, such as depression and other conditions for which conventional medicine doesn't always have the right answers. We see people and they get a full experience. Our primary clinic physician, Dr. Lauren Richter, is a functional medicine doctor; that's what she practices as. So we run a lot of nutritional tests, do the stool tests, salivary, adrenal, hormones, urinary, neurotransmitters—looking for the real underlying causes of these multifactorial problems. It's something that people have really found benefit from.

JB: It's interesting. When I hear you talk, there seems like such an interesting consanguinity of thinking, and probably even the way that the clinical experience seems to the patient between what you all are doing and what Mimi Guarneri and Robert Bonakdar and their team are doing over on the other side of the country over in Scripps in La Jolla. They have the integrative cardiology, but it really deals with similar types of patients: chronic pain, stress, depression, digestive individuals and how that interfaces with things like dyslipidemia and cardiometabolic syndrome. Have you all exchanged information or have you done any collaboration because it sounds like you've got similar ways you are approaching these issues.

Relationship between the University of Maryland and Scripps Center for Integrative Medicine

CD: It's funny you mention that. We think very highly of the integrative Scripps program and in fact we had an Ayurvedic medicine training that Scripps had had the previous weekend, so we are developing a relationship with them. Brian and Mimi have been friends and colleagues for a very long time. It is similar. They sort of have a focus over there—it's my understanding—on cardiovascular disease, and they've done a great job improving peoples' lives. We have a primary care model, and also this relationship with shock trauma is growing, so I think that's going to be another way that we kind of focus our efforts: bringing integrative medicine to the shock trauma setting. They've got their cardiovascular focus. That's an area of focus we're actively pursuing.

JB: That obviously leads to a follow-on question. In medicine we have what are called the resistant syndromes, things like insulin resistance, leptin resistance, and so forth. In the sociopolitical word, we have intellectual resistance. I'm wondering if you have observed or have seen a great degree of resistance to what you are trying to do within the broader politic of medicine there in the center or in the medical school or the local environment, and then how you treat intellectual resistance?

CD: When I first came on to the center, I anticipated more resistance. But we've had much less than you might think when it comes to these kinds of things, because we approach with evidence. We speak the common language of: Here's the evidence supporting whatever we're hoping to do. I think a lot of this stuff resonates on an intuitive level. I mean, again, when you talk about metabolic syndrome and insulin resistance, lifestyle is really the solution to that. Getting to get people to cut down on sugars, and refined carbohydrates, and other bad dietary components; moving a little bit more; managing their stress. It hits on an intuitive level. There is good evidence as well. Those are the kind of things, and we've hit much less resistance than, again, I would have thought. There are detractors out there, but I have found them to

be much fewer and farther in between than we anticipated. Again, the clinical results speak for themselves, and the research we are doing just provides stronger support, I think, among those who might initially be skeptical. I can tell you one of the great things about the elective course is that the students are incredibly receptive to the stuff we're doing. The state of nutrition education is, as you know, quite poor in a medical environment. I think there was a study that showed that only 27 percent of US medical schools met the 25 hours required of nutrition education: three days over the course of four years, which is just in my eyes abhorrent.[16] But the medical students want this stuff. I mean, they are so engaged and receptive to it, so I think as we go forward and as we increase our educational reach there is going to be even less resistance. As we go forward people are going to say: "Hey, this is the stuff that works, this is what is going to help my patients." The resistance is not as bad as I thought it would be, and I think it is only going to be less as we go forward.

JB: Chris, you've really done a tremendous job of painting a very broad landscape for us in the research, education, and clinical areas. I guess my last question is: As a very up-and-coming, highly capable individual in this field, how do you view the future? What's your view? I look at it maybe with eyes over the last 35 to 40 years, you're looking at it with eyes going forward into the 21st century. Tell us about your perspective going forward.

CD: I love the term lifestyle medicine. We were, at one time, called alternative medicine, where it was an alternative to what was being practiced. That sort of evolved into complementary and alternative medicine, and now we're integrative medicine. What I would love to see is that it is just ultimately good medicine, getting a doctor to reach not just for the prescription pad but to say, "Hey, these are some dietary things you might want to try. These are some exercise modalities." I think just really having the healthy lifestyle tenets that underlie functional medicine and what we all believe in—have that become medicine, have that become conventional medicine. You know, there will be resistance, but I feel like it just makes such intuitive sense, and as the evidence evolves, what I would love to see is that this is what medicine is: It's no longer integrative medicine, it's just medicine.

JB: I think that's an absolutely fantastic way to close this discussion because I think that's what we're all aspiring to do: create a more effective healthcare system with outcomes in health, not just outcomes in disease treatment improving. It's a bright light you're shining on that future. By the way, it also gives me a great sense of confidence when I see people like you coming up in their careers that this field is going to be very robust. It will be grounded in facts, not fiction. We'll ultimately know more than we say rather than say more than we know, and we'll have an authenticity about this that really delivers the goods. I want to thank you for your tireless work and for all of your colleagues there at the University of Maryland program. What I say is good on you. Let's continue to move this thing forward.

CD: I agree and I'd like to thank you for all of your work over the years. It inspired me to get into this field. I agree the future is bright and I very much enjoy interacting with you and it has been my pleasure.

JB: Thank you so much. Best to you. We'll talk soon.

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