November 2013 Issue | Jay Udani, MD, CPI, FACN Medicus Research

http://jeffreybland.com/knowledgebase/november-2013-issue-jay-udani-md-cpi-facn/

DOWNLOAD AUDIO | DOWNLOAD SUMMARY NOTES |

Welcome to *Functional Medicine Update* for November 2013. One of the topics that we have discussed at some length throughout the course of the last nearly 30-plus years has been the research methods that underlie a proof of hypothesis or a proof of concept. We've talked a little bit about how complicated it is in the area of systems biology to use a univariate type of hypothesis to prove a point. In other words, if you are trying to use a model, which is one agent against one outcome, and you're really trying to look at a systemic or systems-wide effect, it's very difficult to design a study that would be appropriate to test that hypothesis using an univariate model or let's call it a double-blind, randomized, placebo-controlled, single-agent-against-single-type of approach when trying to prove a systems effect. It's not impossible, but it's certainly very challenging in terms of design.

We're going to have the opportunity in this issue of *Functional Medicine Update* of talking to an expert, Dr. Jay Udani, who is an internist who is overseeing as the director of a CRO—contract research organization—that's really focused on looking at some of these systems biology approaches and issues in the field of medicine, and particularly focused on some of the natural products areas and these biological response modifiers that are pleiotropic in their mechanism of action, meaning they have multiple hits in physiology—that they are weak interactors, but they have multiple effects on different physiological functions. So the question is how do you design studies to prove efficacy and safety? That's something we'll be discussing at length with Dr. Udani.

Beyond that, however, is something else that has come to light. It really comes as a consequence of the experiences that I've had over the last 30 years, but amplified over the last couple of months, where I've had the opportunity to travel extensively and speak with researchers and clinicians around the world. Let me just tell you how I have derived this thought.

Traveling the World, Seeing the Need for Global Changes in Thinking

During the course of the summer of 2013, I had the opportunity to be in Canada for a meeting where I was presenting before the Canadian Naturopathic Association, and so I met some of the leaders in natural medicine in Canada. Then later in the summer I had the chance to go to Taipei, Taiwan to meet with many leaders in the traditional medical circle within the Taiwanese medical community who are venturing out as early adopters into this concept of systems biology and functional medicine. I've had the privilege of going there several years in a row now. This group has grown quite large with over 200

different medical doctors from major medical institutions who are asking questions about the proof of concept within this functional medicine/systems biology model.

From there, then, I had the chance to be involved with several medical school engagements, looking at collaborative research projects with what we might consider traditional, institutional-based medicine, and where the interest really is looking at systems biology in medicine and how you actually start to define proof of effectiveness in these broad functional medicine models versus pill-for-an-ill-single-hit-type model.

And then from that I had the chance most recently to travel to London to engage in a collaborative discussion with over 400 health practitioners, many of them from the traditional Royal Society of Medicine model, and asking questions about new ways of proving success and efficacy in this new biology of the 21st century. And then lastly, a very interesting visit in Milano, Italy with a group of about 165 medical providers who are, again, heads of their medical school departments, and leaders of clinical wisdom within their communities who are again asking the same question: What do we do to prove some of these broader issues within the area of systems biology and medicine?

So it seems like, from my own personal experience, this is almost like the hundredth monkey; how many people have to think about this before we start producing global change, or, you know, the butterfly's wings in China producing a weather change in North America—that kind of concept. As I came back through all of these trips and spent some time on the plane reflecting on these conversations, I came to recognize that some of these beliefs that we've had about the single agents having single effects to produce single outcomes are fallacious; they're really not true. When we start examining with a broader lens the effects of what we think are single actions—independent actions—like a drug that hits a specific target to influence a specific biomarker, an endpoint that has a specific disease implication, we find that those are really, when we dig deeper, not actually correct. These drugs are hitting multiple things, of which one we look at. You know, if you don't ask the question, you don't get answers; you see only what you see.

Statins: The Classic Example of a Therapeutic Agent with Pleiotropic Effects

I think if you use, as an example of this, statins, which I find is probably the most predominant story, because when we first all were told about statins and the way they were discovered is through their ability to block these monocholines that were found in fungal metabolites of certain species of fungus. These monocholines were able to block or inhibit an enzyme called hydroymethylglutaryl Coenzyme-A-reductase, which basically is an enzyme that is involved with the rate-limiting production of cholesterol. So we were told that these drugs worked by blocking the synthesis of cholesterol. And by the way, they do that, so that's not to be corrected. However, with more, now, 30 years of experience with these statins, both the original Lovastatin and then the later developments of other derivatives, like the more potent statins of today, we find that they have pleitropic effects. They have biological effects other than just the inhibition of this enzyme HMG-coA-reductase. In fact, these other effects may be as or more important in their efficacy than was the singular belief that they worked solely by blocking HMG-CoA-reductase. These are the effects that they have on things like the immune system. Now we say, these statins are anti-inflammatories and they work by blocking immune reactions at the arterial endothelium, and therefore

they prevent, somehow, the atherogenic process, not just by their mitigation of cholesterol biosynthesis, but also by these pleiotropic influences on the complex interaction of monocytes and macrophages with the vascular endothelium and how that relates to lesions that ultimately become sclerosed that we call atherosclerosis.

If we use that as just a single example of where we believe that something was a single agent against a single endpoint and now we find it is a single agent against multiple endpoints, and the more we look the more we find, we can probably extend that into virtually every class of therapeutic agents, and so in some ways everything is working in a systems biology fashion; we just didn't ask the question. You can use the same logic for things like angiotensin-converting enzymes, or angiotensin-receptor blocking agents that are involved with hypertension management. We look at those and we find that these are pleiotropic molecules as well. They don't just hit angiotensin receptors or angiotensin-converting enzyme activity. They have other effects that influence multiple things such as inflammation, insulin signaling, cell proliferation, as well as hypertension.

Connecting Obesity and Diabetes: Understanding Mechanisms and Therapeutic Approaches

Where am I going with this? I'm going to shine a light on the emperor in the corner who is not well dressed, in fact maybe even a little bit naked, and doesn't look that good in the bright light of our present view because we recognize we've missed a lot of that emperor's anatomy. That there are things that are probably more important than we previously understood.

Let me take an example now of how this fans out into the complex question of how you prove something in a systems biology model. Let's take what we all know about, or at least we think we know about, the connection between obesity and diabetes. That seems like a fairly simple question. Shouldn't we be able to just make studies in which we're looking at people with elevated BMI (body mass indices) and show that these individuals have a high prevalence of diabetes, which would then "prove" the hypothesis that obesity causes diabetes? It seems like a reasonable concept, and in fact, if you look at literally hundreds and maybe even more like thousands of papers, the assumption has been made that obesity causes type 2 diabetes. Okay, good. Thirty years of understanding, and so to treat diabetes by putting people on weight loss diets, meaning you restrict calories by some mechanism so that they will lose weight, or you increase their activity levels by having them suddenly take up going to fitness clubs or something so they will no longer be diabetic.

Now, what's wrong with this? Just as I was examining or using as an example with the statins and heart disease, it's that that model that I've just described for obesity and diabetes is not totally wrong. We know that there is a very high correlation between elevated BMI and diabetes. But an association does not prove causality. Just because two things are associated doesn't mean that one is caused by the other. They may be both caused by something else—by some other disturbance in the system—in a systems way, just as we said the reduction in heart disease incidence with males taking statins may not solely be a result of lowering cholesterol biosynthesis. It may be a result of other effects of this pleiotropic mechanism of action of statins across vascular endothelial health and immune function and inflammation. I hope I'm not losing you all here. I know I'm getting a little bit alliterative, but I believe you kind of get the drift of where I'm going.

So let's look in a little bit more detail at this obesity-diabetes connection, because I think it's not only insightful in terms of helping us to understand the complexity of developing an understanding of mechanism and therapeutic approach, but it also leads us into what might be a much better way of approaching diabetes than just to think we're going to put people on weight loss diets and they're going to get better.

Fitness and Fatness: A New Study Illustrates the Complexity of Pre-Diabetes

Let's now look at this. A recent study in this area has been published that bears light on this particular question. This is, again, like shining light in the corner on the emperor over there with no clothes. The study was collaborative work, including the department of human performance and sports science from Winston-Salem State University, and the Department of Exercise Science and the Arnold School of Public Health at the South Carolina School of Medicine. They recently published a paper titled "Fitness, Fatness, and Survival in Adults with Pre-diabetes."[1] Now, why is this paper one that I'm citing? Because I think it illustrates the complexity of this topic. Because what they found in this particular study in which they screened for individuals with metabolic syndrome, insulin resistance, pre-diabetes, whatever you want to call it—so they screened a very large number of individuals that fulfilled this criteria. In fact, over the course of the study 17,044 responded, so it's a fairly large study. This group of people had pre-diabetes, meaning they had fasting blood sugar somewhere between 105 and 126 milligrams per deciliter, so they weren't frankly diabetic, but they weren't normal glycemic; they were in that grey area. So they then asked the question, what was the mortality of these individuals who had this pre-diabetic condition? What was seen is those individuals with elevated BMIs who had high cardiovascular fitness, meaning on a standard submaximal cardiac stress tested they tested to be reasonably fit (so these were reasonably fit, overweight people, who were pre-diabetic), there was no difference in their health outcomes than lean, fit individuals. In fact, what they found is that thin, unfit individuals had a similar adverse effect as heavy unfit individuals, which was entirely different and more advanced promotion of disease than in either overweight fit individuals or normal weight fit individuals. I hope you understand what I'm saying here.

This is a fairly important study because we know from previous work that has been published that in frankly diabetic patients, people that have fasting blood sugars above 126 milligram per deciliter, that the same thing is found to be true—that there is no correlation between diabetes and elevated body mass unless you also look at fitness. level.[2] We also know, to confound this even more fully, and we've discussed this at length in previous editions of Functional Medicine Update, that in individuals who are overweight but have low normal GGT (gammaglutamyl transpesidase) levels in their blood, that they do not have elevatedrisk of diabetes. It's only in those people that are overweight and have upper-level normal or above normal GGT levels in their blood plasma, and who are unfit, that have the highest risk of diabetes.[3] So can we say that fatness causes diabetes? No, we can't. We say it is associated, but there are other factors that we have to take into account as part of the system disturbance to really understand personally how that individual has a risk of diabetes.

From this fans out all the secondary conditions of disease that are associated with diabetes. Not just diabetes itself, but nephropathy, ocular injury (cataract, for instance), neuropathy, dementia, cardiovascular disease—these are all attendant covariables associated with diabetes. Clearly, our simple-

minded univariate association between fatness and diabetes is incorrect, so that would mean that we would put a huge number of people on weight loss diets, assuming that that was the cause of their diabetes, only to find that they didn't respond very effectively. And other people, who are reasonably thin, we would say, "Well, they certainly don't have any problem with their body weight so I won't have to do anything with them," when actually maybe the cause is below both of those, and we should be looking more deeply for the personal contribution to their system disturbance we call metabolic disease or diabetes.

What this means, in fact, is if we took a hundred type 2 diabetics or a hundred pre-diabetics at random and asked what is the characteristic that defines them, what I think we would say is, we have a hundred pre-diabetics or diabetics, each one is different from the other. You cannot form one general rule, saying this produces that. You have to look at each individual patient or each individual person and ask, what's the contributor in their specific situation to lead to this metabolic disturbance? In other words, it is the interrelationship of their genetic uniqueness with their environment that produces this outcome.

Now you're going to say, "But, Jeff, there are literally tens of thousands of people who kind of get the generic treatment of diabetes and they seem to be doing just fine. Their blood sugars are normalized and they don't seem to be getting kidney failure and we're using a formulaic approach, so aren't you exaggerating your story?" I don't think I'm exaggerating my story for the following reason. If you go back and you review where people were studied whose blood sugars were tightly controlled by pharmacological mechanisms using a standard recipe, so they were rigorously controlled, their A1cs were controlled, and their blood sugars were controlled by precise use of the pharmacology of the day, you will find, on outcome-based levels—not just measuring the numbers, but how did they do over years—you'll find that their outcomes were not as good as you want them to be. These are studies that were published in top-level journals, like JAMA and the New England Journal of Medicine.[4],[5],[6]

So, how does that work? Well, it says that the rule of the averages is pretty good if you're in the average. If you're in the middle of a Gaussian curve, probably a formulaic approach will work. Good for you. But all those people on the side of the curve, the bell-shaped curve of life, those formulaic approaches for them may not work as well. In fact, they may even produce an untoward outcome. But medicine has been developed for the averages, not for the individual, so what the heck do we do? We change medicine. We can't change the individuals; their genes are what they are. We have to change the medicine to get a better outcome.

This study that I was describing about fitness and diabetics and pre-diabetics I think is a very telling study because it suggests that the way we should start doing research is to cohort stratify. We don't just throw everybody in a big lump and call them 70-kilogram humans and assume they're going to respond the same. We have to look at cohorts of individual susceptibilities or individual responses to environments and ask, what's best for that group? You're going to say, how thinly do we need to cut the cohorts? Like, is everybody a patient unto himself, so everyone is an individual study? Maybe that's a little too ambitious at this point in our technology, although I think in the future that's the way we will go. We'll have the data from Big Data on each individual that will allow their programs to be very personalized to their need, but in the absence of having all of that information available today, which may be available more quickly than we think, but today maybe we don't have it, so we have to use the best information we have available to stratify.

Let's start asking how we would stratify, in a study, to evaluate the influence of body fatness to diabetes and its secondary side effects. I've described a couple of ways we might stratify. One way would be to stratify on fitness levels, because maybe those individuals who are unfit, their primary therapy should be improving their fitness levels. Maybe more so than drugs. Maybe more so than anything, that's what they need. Their prescription should be principally a fitness prescription. Maybe that is a takeaway that is more important than any pharmacological or nutraceutical intervention that a person can get if they have that status. Or, let's assume that these are individuals that have elevated gammaglutamyl transpepsidase, which is a surrogate marker for what? Toxicity. That these people have accumulated in their bodies a burden of toxins that their glutathione pathway is trying to detoxify and they are at constant risk to this mitochondrial interruption from toxic burden of their energy powerhouse in the cells, including their pancreatic beta cells, the insulin-secreting cells, so maybe for those people the first important thing is to put them on a detoxification program, to liberate from their body the burden of these toxins that are inducing mitochondrial inhibition and causing insulin resistance. Well that's an interesting concept. So, who, then are those people? Well, we need a different set of screening tools to know who those people are who have the principal problem of toxicity, and that's where GGT levels in the blood might be useful as a first-level screening tool.

Well, what about another one? How about endotoxemia? Oh my word, now we really get into the netherworld. Endotoxemia, meaning maybe some peoples' origin of their diabetes starts in their intestinal tract because they have a gut inflammatory condition going on as a consequence of funny bugs in their microbiome that are releasing cell wall debris, which we call lipopolysaccharides, that are powerful proinflammatoriy substances produced in their gut, and punch holes in their gut epithelial lining, which leads to what? A portal of entry for other toxic molecules that then activate their immune system and triggers insulin resistance induced by systemic inflammation. And that systemic inflammation, I might add, is principally delivered through the relay race of macrophages and monocytes—these white blood cells that are sitting around in the liver getting information from the liver's immune system, which is called the Kupffer cells. So the Kupffer cells are saying to the circulating white blood cells, "You know, I just got a message upstream from the portal blood coming from the intestinal tract that we've got trouble on board and you ought to be really alarmed, so take that message out to the rest of the body." So these macrophages and monocytes circulate out into the blood, and where do they end up? In part, they end up in the fat mass, which is called the adipocyte mass, particularly the central adipocytes, the intra-abdominal adipocytes, the big waist-to-hip ratio adipocytes, right? And what do those adipocytes do? They are also derived from the same family lineage as are the white blood cells, the Kupffer cells, and the intestinal mucosal immune cells. They are all from the same family line, so they get the information from these macrophages that are embedded now in the fat mass that are saying, "You know, the intestinal tract tells us that it's pretty upset with the way it's being treated. You ought to be upset, too. And the way I say it is, it's as if the fat cells say, "I'm fed up and I'm not going to take it anymore." Right? Using kind of a double entendre.

And so what do those cells do? Those fat cells, they have the ability to upregulate their genes to express a message called adipocytokines. And what are those adipocytokines? They are alarm molecules. They have names like TNFalpha, tumor necrosis factor alpha. Just the name alone kind of suggests what its activity is. Or interleukin-6, one of these proinflammatory cytokines. So they circulate out in the blood and where do they end up? They go everywhere. They go into the vascular endothelium. They go into the brain. They go into the muscle. They induce lipotoxicity. And they can even activate, in the brain, the embedded immune system, which is part of their relatives, and what are those cells called? Microglia. So

if the microglia pick up an alarm message in the blood that has come from the fat cells, which has come from the liver, which has come from the intestinal tract, what do you think the brain immune system says? It says to the neurons—its adjacent cell type—"You ought to be upset, because everybody else is upset." That's called neuroinflammation. That leads to dementia. Is there a connection between insulin resistance, diabetes, and dementia? Yes.[7] So we start understanding a mechanism here that cannot be identified by one agent against one outcome. I hope you see what I'm saying. You've got a pattern of disturbance, here. You've got a system of disturbance.

In that case, if a person has endotoxemia, where do you want to focus your attention? You want to focus your attention on normalizing gut immune function. You know, if might seem in a traditional medical model like, what? You're now in gastroenterology trying to treat diabetes? That sounds like crossing the barrier between two different medical disciplines that are independent of each other. They are not independent. They are all part of the system of communication that relates to insulin and glucose regulation.

If you take the most recent issue of *Nature Medicine*, in a very, very nice little article titled "Microbes, Metabolism, and Medications," what they talk about is the key role of intestinal flora, known as the gut microbiome that we've discussed for years—in fact, from the dawn of creation of *Functional Medicine Update* we've been talking about the microbiome.[8] It seems like I've been living and talking about this as long as Ilya Metchnikov at the turn of the last century. This article goes on to say that this gut microbiome, or the intestinal flora, is a very, very important component in establishing the integrity of the mucosal barrier in the intestinal tract and it contributes to immune function and epithelial growth and differentiation. We call this leaky gut. Now the term leaky gut is gaining traction and in fact what used to be considered like the grounds for disbarment if you brought up leaky gut in a traditional group of medical physicians, now leaky gut is quite fashionable and everybody is talking about it. In fact, the head of the Italian gastroenterological society has made his claim-to-fame in Italy by being the chief researcher on what he calls leaky gut.

We are seeing a frame shift, a real paradigm shift in understanding the gut is the central therapeutic focus for improving insulin sensitivity and treating type 2 diabetes. So if you have a person who has gut endotoxemia, or let's call it postprandial dietary endotoxemia, then you would want those patients—the individual—to have their primary focus not on fitness maybe, or not on systemic tissue insulin sensitivity or beta cell insulin secretion, but on improving integrity of the gut mucosa to prevent leaky gut and transference of potential immune activating substances across the gut mucosal barrier and activating the gut immune system, the so-called gastrointestinal-associated lymphoid tissue. This again shows you the nature of thinking from a systems biology approach, that you need to get beyond thinking of one agent for one outcome. Your agents may have multiple effects. Particularly when you start talking about lifestyle intervention or diet intervention, you're not just hitting one target. You're hitting many, many different targets, so you wouldn't just put a person on a program solely for their gut mucosal effects. You would put a person on a good nutrition program that would re-nourish the gut mucosa, but it would also simultaneously have positive effect upon multiple other factors, systemically, really, that relate to physiology.

Dr. James A. Levine and the Concept of Non-Exercise Activity Thermogenesis

Let's go back for a moment and just look at this fitness part of the equation. Because whenever I say fitness, in the mindset of many that conjures up this view of joining some kind of marathon training group or something, like it's a boot camp. You're going to have to go to cruel and unusual levels of commitment to improve strength, endurance, and flexibility in order to get a positive benefit. I had the privilege of hearing a lecture and then speaking personally with Dr. James A. Levine at the Mayo Clinic, who is a world leader in development of a concept called non-exercise activity thermogenesis. Non-exercise activity thermogenesis. By the way, for those of you who are interested in learning more about this, there's a wonderful review paper that he has authored with his colleagues at Mayo that appeared in the journal *Arteriosclerosis, Thrombosis, and Vascular Biology*. This was actually back in 2006, volume 26, page 729.[9] It outlines this concept, which he abbreviates as NEAT—it's a NEAT concept—that stands for non-exercise activity thermogenesis (NEAT). The subtitle of this article I think you'll find interesting. It's "The Crouching Tiger Hidden Dragon of Societal Weight Gain." That's kind of an interesting metaphor. And what he is saying is that you don't have to be out running around the world training for marathons and involved with extreme athletics, or pushing the envelope into the area of aerobic/anaerobic debt of the wall to get extraordinary benefits. The way that this group proved this—you might be familiar with this—is really tremendously innovative work. They developed a set of underwear for men and women that then contain, in regions around the underwear—this would fit around the torso, all the way up to the chest and down through the buttocks, sensors (piezoelectric sensors). Let's call it accelerometers, so to speak, that would measure XYZ coordinate movement. So these were able to measure in real time and transmit data to a collecting device that would then be able to model exactly how a person was moving throughout their day. So that would be like moving in sleep, moving at rest, at work, moving whatever—24-hour movement profile. What was found was this component of calorie expenditure that was not very well understood until their work, which is called non-exercise activity thermogenesis, meaning there is about a six-to-eight hundred calorie difference among people who move around. Some people call this fidgeting, but it's not really fidgeting. It's getting up and moving your body, not just sitting in the same position in front of a computer screen for like eight-to-ten hours a day, not moving. This can contribute up to 800 calories of energy expenditure. It would be like running eight miles additionally per day if you were jogging at eight minutes per mile. It would be like that level of energy expenditure. And that's the difference in these people that maintain leanness and those people that don't. It is this non-exercise activity thermogenesis.

From those studies, what they found is, okay, how do we induce it? How do we make it easy? This is where the whole concept of walking became so important because they found that if a person would just walk after every meal for 20 minutes—after every meal they would go out for a short walk (15 to 20 minutes)—that it blunts the postprandial blood sugar.[10]

They developed all sorts of ways in schools for kids to move and stand up in classroom orientation so they weren't just sitting for long periods of time without movement. They took this to the workplace. They developed standing workstations—you've probably seen them—and even treadmills, where you can work on your computer standing up and you can walk slowly while you're working. They have these workstations in many companies where you can go and plug in your chip and you can work for a half hour or an hour at that workstation while you're slowly walking. When they looked at the group overall aggregate body composition, they found unbelievable improvements. So what I'm trying to say is simple things that come out of complex thinking through systems thinking produces extraordinary breakthroughs in therapeutics, rather than just if all you have is a hammer everything's a nail, kind of one univariate thinking.

With that in mind, we're going to be talking to Dr. Udani about how do you actually address these things in experimental methods to prove them and to actually move this ball forward so we're not stuck in this old model of one agent against one outcome, and we can actually propel medicine forward based on a systems biology approach?

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

Jay Udani, MD, CPI, FACN
CEO and Medical Director, Medicus Research
CEO, SysteMedicus, Inc.
Medical Director, Northridge Hospital Integrative Medicine Program
www.medicusresearch.com

November 2013

Well here, once again, we're at that place in Functional Medicine Update that I think really defines the topic, defines the focus of each of our issues, and that's our clinician/researcher of the month, and we're very fortunate this month to have a person who really fulfills both of those criteria. I'm speaking about Dr. Jay Udani, a medical internist, who is founder and CEO of Medicus Research, which is a contract research organization working within the natural products and natural health product regime and really looking at the clinical safety and effectiveness of things like botanical drugs, dietary supplements, and functional foods. As you probably know, Dr. Udani, whose reputation precedes him, is from Cedar Sinai (was a resident there) and then moved over into a program, which he has been very, very principally responsible for, which is this innovative clinical research program at Northridge Hospital in the San Fernando Valley. He works at the Geffen Institute at UCLA, in the medical school, and has been very actively involved as a clinical associate there as well. And he is certainly seen as one of the bright lights in the whole field of clinical research in the natural products area. An eloquent speaker, a very clear speaker, and a person who has really started to help us understand how clinical research will play a bigger role in defining proof of concept and proof of principle as it pertains to the safety and effectiveness of natural products in managing chronic illness.

Dr. Udani, it's a great privilege to have you as a Functional Medicine Update clinician of the month and thank you for your time with us today.

JU: Thank you, Jeff. You're a great inspiration to me and one of my mentors, so it's my pleasure to be here.

JB: Let's start right down the trail, here, Jay, as I often do with individuals, and ask them how they got on their path, on their journey to this point. You probably didn't just start by saying, "Hey, I'm going to start a contract research organization to do clinical research in the area of natural products." How did this arrive in your career and your focus?

Establishing a Contract Research Organization to Conduct Studies of All Sizes

JU: Well, you know, it's a confluence of many things. I've been doing human clinical trials since working at a local hospital in Chicago, where I was running a clinical trial for a neonatology unit, and so I had been doing research all along in undergrad, med school, and residency. A couple of things happened in my residency, which was very traditional internal medicine, and I had planned to go into one of the internal medicine subspecialties and be firmly on the allopathic track. The first was my fiancée, now wife, Amy, had mentioned just off-handedly one day that she was having a bit of an acne breakout and was going to go to her Chinese medical physician in downtown LA and get some herbs and some other treatment— possibly acupuncture. Being chief resident of internal medicine at the time, I very calmly responded, "What are you talking about?! When you're engaged to the chief resident of internal medicine at Cedars Sinai you do not go see some quack downtown." She, of course, being right, as she always is, said, "Why don't you open your eyes to what's going on out there?" And this was in the mid-90s where this really hadn't broken the surface, at least within the medical community, about what was going on. And I did. I started looking around and I said, "Holy cow, people are using dietary supplements and alternative medicine. They really had no—from my standpoint—authoritative medical guidance at that time about what they should use or not use, and what was safe and not safe. Serendipitously, at the same time, Eisenberg came to Cedars Sinai to deliver ground rounds on his groundbreaking research, looking at the number of people in this country using alternative medicine.[11] And I sort of figured out this is something that is going to be big and also in conjunction with all that our chief of medicine announced that they were going to be starting an integrative medicine program at Cedars Sinai. So I volunteered and said, "Look, if you're starting a program you're going to need a fellowship. I'll be your first Fellow. I'll write the curriculum. I'll put all this together." I had an opportunity to work with Dr. Mary Hardy in starting that up, and really while finishing up a health services research outcomes fellowship, focused on research methodology and design for alternative medicine. Not just for dietary supplements, but for how you research alternative medicine paradigms, like traditional Chinese medicine or chiropractic, in the context of only looking at the reductionist model of pharmaceutical drug development. How do you effectively document and track and compare efficacy of whole systems versus with standard-of-care approaches. That really was the genesis of it, and when I came to Northridge Hospital to start their integrative program, I began doing some clinical trials there and eventually spun off what is now Medicus Research, which is a independent contract research organization doing, as you said, clinical trials for natural health products, but in the context of always knowing that these products have a certain risk-benefit ratio, which is that the benefit may not be as immediate or abrupt as pharmaceutical, but the risk profile is—in my opinion—so far superior that it is worth doing. And then along the last 12 years now, you've seen yourself the evolution of the industry. The first clinical trials were a pastime in that very few companies would support them. If you didn't have academic or government support, there really were no clinical trials to be done. But as regulatory pressures have been changing, as enforcement has stepped up, especially in the last four years, the demand for this work as a solid business, if you will, has really taken off, and so we've been preparing for all these years—again, the last 12 years we've been doing nothing but this—and now have the ability to help these dozens and dozens of companies in designing and running their clinical trials.

JB: I really want to compliment you. I think your prescience in being able to look forward to what is going to be needed in the way of designing appropriate trials to do proof of principle or proof of concept I think was really, really very forward thinking. I think it might be useful for our listeners just to go back. You know, you have over 20 publications on different ingredients and different products in different human clinical trials. Maybe we can review a few of those just to kind of give people an idea of what we're talking about. Let's start back, if we can, with a trial that you were involved in, which I think is

very interesting, looking at the interface of psyllium and plant sterols in hypercholesterolemic individuals. This was published back in the Journal of Nutrition in 2006.[12]

A Study on Psyllium Delivered Via Chocolate Chip Cookie

JU: Sure, and that's an excellent study to talk about because we deal with companies of all sizes and shapes, from the largest of large to this study, which was, in fact, funded by two registered dietitians. I mean it was literally an in-the-garage type of thing. They had a very unique delivery vehicle, which was a chocolate chip cookie. They put the sterols and the fiber into the cookie and found a way to make it taste good, so we were looking at what it was going to take to design and run that study. The main challenge was the placebo cookie. The psyllium and sterols do add and change some of the mouth feel. It's a lot easier when you are taking something in a capsule to blind people to the intervention, so we had to look for certain ingredients and certain baking processes that would at least make the two cookies roughly equivalent, and that's an important part—when we're looking at blinding, again, to contrast and compare pharmaceutical studies with natural health products. In pharma you have a pill, tablet, capsule, whatever and it's manufactured and you simply manufacture a placebo that looks identical. In what we deal with, you have foods and other things that have flavors, that have mouth feel, that have taste, that have smell. If you open up a bottle containing fish oil, for example, it's going to have a certain smell. If you open up a bottle containing turmeric, it's going to have a certain smell. So we had to learn over the years how to mask, how to add additional smells and flavors, and try to make our blinding as good as possible, and the concept there is sensory equivalent if not sensory identical, meaning that in some cases it may be impossible to replicate a certain smell—let's go to fish oil or turmeric—but you can add another smell that is as strong and doesn't carry connotations that are so different, so that when a clinician or a patient is taking it, they can't tell, "Oh, this one doesn't smell at all. It must be placebo. My friend has the one that smells. He must be on the real thing."

Anyway, to go back to that particular paper, we did see statistically significant differences in a reasonable time period for the endpoints we were looking at in cholesterol and also especially we were looking at LDL subfractions. It's been well known that psyllium and sterols have this impact, but it is the combination of the two together and it was the unique delivery vehicle of the chocolate chip cookie that I think made that article most interesting.

JB: Yes, very interesting. Thank you. Another example is the really interesting study you did on adding to white bread a white bean extract to study the effect it had on glycemic index. That was a 2009 paper in Nutrition journal.[13] Tell us a little bit about that. That's another interesting study.

JU: It's an alpha-amylase inhibitor—a proprietary one—called Phase 2, and it binds competitively to alpha-amylase in the gut (alpha-amylase is a pancreatic enzyme). They bind to the carbohydrate itself, or in this case they are binding to the primary enzyme responsible for digestion of long-chain complex carbohydrates into shorter chain sugars, which are more easily absorbed. What we found in this case is there does appear to be a dose-response curve, and possibly even a threshold effect, meaning that you have to give enough of the product to overwhelm and bind to all of the alpha-amylase in the gut that is released in response to a meal in order to adequately reduce the effect of glycemic index of the bread and allow the long-chain polysaccharides to move into the small intestine rather than being broken down and absorbed quickly. I think the overall absorption rate will probably not be dissimilar in terms of total caloric intake, but if you can reduce the rate of that absorption and have a more slow and steady digestion

and absorption of the carbohydrates, you lower the effect of glycemic index. It's not turning Wonder bread into wheat bread, but it's making the bread perhaps not so harsh on the insulin axis and allowing the body to deal with the amount of carbohydrates that are being delivered in a more time-sensitive fashion (over time, that is). So, we found that interesting, and again, one of the things we have talked about is that a lot of times when we do clinical trials or if you review third-party literature, there are doses that are very, very important, and it's also important when correlating your ingredients that you are using in practice, that you're using the doses that were used in the clinical trials because there may be these differences. It may not be that 50 percent dose will give 50 percent response. It may be that there is a certain threshold below which the dose will give no response.

JB: Yes, I found that that study design was very, very interesting in that paper, in that it was really a dose-ranging study. I think you looked at 1500, 2000, and 3000 milligram doses. I think that's a very nice way of kind of getting a bead on kind of where is the therapeutic threshold. I compliment you. I think that's taking some of the good stuff from pharmaceutical science and applying it to the natural products clinical review area, so good work. Let me move to another one, which is this area that we are at least semi-familiar with, and that's these prebiotics that are known to be non-digestible carbohydrate sources. One of which that has gotten a lot of attention is larch-derived arabinogalactans. You've been a principal on a really interesting study, again published in Nutrition Journal back in 2010, looking at an arabinoglactan extract from larch and its effect on antibody response to pneumonia vaccine, which I thought was a very interesting study design.[14]

The Challenges of Designing a Study on Immune Health

JU: You know, immune health is such a challenge to study because what does a healthy immune system mean? In my reading it means immunomodulation, the ability to respond to an outside threat. Raise the alarms, activate the immune system as appropriate, take care of the threat and then bring itself back down to proper levels. I don't think that necessarily I would want to have increased levels of circulating cells at all times. I think that the "upregulation" may not be healthy in the long run, but immunomodulation is a better response. The challenge there, in an in vivo setting, is how do you standardize the antigenic challenge? How do you take a group of individuals and ensure that they are all exposed to the same antigen in a way that is precise and you can measure the benefits or changes? We were looking for standardized antigenic challenges. I thought about the vaccine model and said, "Okay, pneumococcal vaccine is a bacterial vaccine. The good news is that most of the population under the age of 50 has not been exposed to this vaccine, which is different than, for example, tetanus or influenza, because it is generally given to the 50-plus population, and so we were able to identify a group of individuals who had not previously received a vaccine. We primed their immune systems with 30 days of the larch arabinogalactan or placebo, and then gave them the vaccine and watched the antibody responses to that. It was, I think, a 22- or 23-valent vaccine, and what we found was that there were subtypes of the antibodies in response that we looked at, and we found that there were statistically significant improvements compared to placebo, meaning that the subjects who had received the larch arabinogalactans for 30 days prior to vaccine showed higher antibody response rates than those who had not. So in some ways it could be considered a vaccine adjunct, especially as we look at an aging population with a senescent immune system that simply doesn't respond—doesn't pick up and respond as well—to antigens and vaccines. But I think, moreover, it was really meant to show that this product helps the body respond appropriately to this particular antigen and not generically to, you know, cause a response by multiple arms of the immune system. In fact, we had measured other arms of the immune system—not just the adaptive, but the innate,

looking at white blood cell counts and other things—and did not find elevations in those because there was no reason for those to be elevated. But within this adaptive arm, within the specific antibodies that we looked at, we did see this. I hypothesize these long-chain polysaccharides activate the gut-associated lymphoid tissue as they traverse through the gut, and that these arabinogalactans may mimic in some way the bacterial capsule in some of their structure, which may have been priming the immune system. So it's a very interesting study and a good model for testing the immune system.

JB: Yes, I absolutely agree. I think it was a very novel design. I think this concept of challenge testing, where we start looking at a body's response to a challenge, just like we do with, say, stress testing for cardiovascular function, or oral glucose tolerance testing for glycemic insulin response. I think these are really very powerful tools for evaluating function versus pathology. I believe the model that you've used here really is a very novel way of looking at immune system reserve and function and, as you call it, adaptation to a challenge. Great design and great study. You've published recently—in 2013—another very interesting paper that opens up another chapter in the types of studies that can be done with a different study design in the natural products area, and this is what sometimes would be called a screening trial, or an open label trial, or a participation trial, in which you've looked at fish oils and their relationship to health outcomes over a period of time in kind of an open label trial. So this is a different, not the controlled placebo-type trial, but it's more something you can do in a population-based study. Could you tell us a little bit about that? I think it's an interesting approach. You published this in the Journal of Nutrition in 2013.[15]

JU: Several challenges face the industry and validating response and sample size is one of them. In a well-controlled setting where you can stress the body as we did with the vaccine or some of the other things that we do, like joint health studies—running people on stepmills—you can define the magnitude of effect and have a power calculation that helps you see, within a relatively smaller sample size (maybe 50 people, maybe 100 people), that you can see a response in a placebo-controlled setting. Generally, though, for some of these softer outcomes—patient-reported outcomes, quality-of-life outcomes—the sample size required can be quite large. One of the challenges of that is that there is simply a cost associated with seeing patients in the clinic, recruiting them and getting them in. We have designed, and are running several now, what we call remote studies, in which we have online screening tools, so they go through an online informed consent, go through the screening process (the inclusion/exclusion criteria), and go through a telephonic review with one of our clinical staff. If they meet the criteria we ship them study product and have them track their endpoints using electronic means, whether they are iPods, iPhones, or computers, and track things like SF-12 or satiety, or this and that. In this particular case we looked at the SF-12, and we did a large population of individuals that were given the omega-3 supplementation for a period of time, and demonstrated after 120 days that we saw statistically significant improvement. The idea is that you can get several hundred individuals and you can do it in a cost effective manner for sponsors of natural health products, and see statistically significant results in this sort of setting. Now this could be done in a placebo-controlled manner as well, but these type of data become part of the totality of the evidence, and even though the randomized, double-blind, placebo-controlled trial is the "gold standard," there are other legitimate study methodologies and designs which are appropriate and can be very helpful in, as I said, in substantiating claims and adding to the overall claim substantiation file.

JB: Yes, I think that's beautifully stated. Again, a very creative and novel approach towards getting your numbers up so your power increases. You lose a little specificity, but you get a return in terms of the

power, and ultimately if you get enough people the statistics can be your guide. So I compliment you. I think that's a very astute alternative way of approaching some of these problems, as you say, with softer endpoints. Jay, after looking at this research and listening to your, I think, highly introspective review of the different methodologies that one can use to examine the weaker effects that natural products have, meaning you've got some challenges in the way these studies have to be designed in order to look at outcome against a control, and you need to do it in a systems environment. How does one manage the data in this particular type of approach? Because it would appear that you might have to use different kinds of algorithms or different types of statistical methods for evaluating these systems effects than you would in a strong effect in a single outcome univariate type experiment where you have one variable and one placebo and it's one endpoint. Are there other ways that one goes about looking in a systems model at the data?

JU: Sure. We have a team of biostatisticians who look at this and we try to come up with our statistical plans in advance. One thing we do is we try to stratify enrollment and we do secondary variance, meaning when we're looking at our inclusion and exclusion criteria we're going to eliminate anybody who has a condition or some sort of variable that would potentially affect the primary endpoint. Also we would stratify. Again with a smaller n, you don't want to find that certain effects like gender or age end up skewing your data on one side or the other, so we'll try to ensure that both groups have equal representation of male/female—not that it's 50-50, but if there are, for example, 20 percent men in a study, at least half of those men are in one arm and half of them are in another arm, so that we don't find out later on that it was the gender effect which skewed the data one way or the other. We tend to apply stressors, as we talked about, in clinic—with the vaccine or this and that—so that we can control for the time and date upon which the body is most responsive to the effects of the product. In an ideal world we would have metabolic wards where we could lock people up for 30 days, control diet and exposure to other things. I'll give one quick example. We were running an antioxidant study, and the data didn't look quite right, and when we started pulling it apart we found that there was a time interval effect on the data in that there was a certain two-week period in August where everybody's variables had gone in a certain direction. It turns out that it was because there were extensive fires in southern California during that time, so the particulate matter that was in the air was reducing everybody's oxidative stress capacity regardless of which treatment they were on. So then you have to go back and decide what you're going to do with that data. We used a modified protocol, including anybody who had had at least one post-treatment exposure visit. In some cases we'll do intent to treat with last observation carried forward to look at things. You know, all those traditional statistical methodologies, but really in a more academic style of looking at the data and saying, "What does it actually mean?" Take a look at the whole data set. Look at trends. Look at deeper dives. Look at subgroups. So, for example, responders analysis. It's not realistic to think that 100 percent of people are going to respond to anything. You, leading the torch of personalized medicine, are showing that that's clearly the case, and so a more blunt form of personalized medicine is to simply say a certain percentage of individuals will respond to this treatment, and a certain percentage will not. Now, within those people who did respond, what did their data look like, and how is that different than, perhaps, case control matched on the placebo side? These are all things that are very interesting and tend to really show what does the product do, and not just fill out a box and a checklist of how to design and run a study and say, "Well, it worked or didn't work." There's a lot nuances here that are often missed in a more traditional setting.

JB: Yes, I think you really said, in that array of different alternatives, a beautiful description of the landscape of the difference between really understanding how to design and manage a study versus just

doing some rote project where you just recruit people with a certain set of characteristics and give them something versus a placebo after randomizing them and look at the results in kind of a statistical T-test. I think that the way you've described this is much more compatible with these weaker effects that have been seen with natural products. In fact, there's a very interesting thing that I've observed—I'd like your comment on it—and that is we have two confounding variables. When you have weaker effects, then some of the things that occur as it relates to the biological variability you were talking about, or so-called single nucleotide polymorphism differences among individuals, become more problematic in your response. When you are using a very strong acting substance, something that has a very tight binding of the molecule that you're using to its ligand, it kind of overwhelms the subtle differences among SNPs, and so you wash that out. But when you're dealing with a weaker interaction, these SNPs then start to become more problematic, which then gives you the possibility that cohort analysis, as you mentioned, or stratification of the data set becomes more important. And of course that then creates the difficulty of the numbers needed to get power in any single arm of that stratification. As you've indicated, all of these things have to be taken into account as you're doing studies on these weaker, longer-term acting substances in natural products. Does that seem reasonable, from what you were describing?

JU: It does. It's very interesting. There is still an art to this. It's not just purely the science, and the art is to really start connecting the dots from the very beginning about what are the claims? What are the mechanisms of actions? And where might those two connect? Within that, then, we look at what are the other influencers of that particular mechanism? And, ask you say, would they be overwhelmed by somebody's genetics or other outside variables. Your talks on diet really are important, here. It is possible that people with different types of diets may respond differently, or if somebody changes their diet, or takes a certain type of food. Even that, itself, could overwhelm the more subtle effects of the supplement. We also use a methodology called adaptive design, in which if the calculations are difficult to understand because that substance in that extraction, for example, has never been tested in this population for this endpoint, then taking third-party literature and making power estimates is of marginal benefit. I don't know if I can rely upon that, and if you do rely entirely upon that third-party power calculation you could be way off. So in our adaptive design methodologies we may institute an interim analysis in which data are still collected in a blinded manner and one member of the statistical team may, after the interim analysis is completed, unblind them and take a look and see where are we in terms of achieving differences in the primary endpoints, and it may require additional power added to the study in the middle of the study, and this is a methodology used extensively by Big Pharma because as you can imagine you've got ten million, fifty million, 100 million dollars on the line for a clinical trial. They don't necessarily want to wait until the very end to find out that it didn't work.

JB: I have one last question and that may be a difficult one to focus in on a specific answer, but I'd love to get your opinion, and that's the regulatory environment of the Food and Drug Administration, and also how this is being seen in terms of changing regulatory environments in Europe and Asia and Australia and New Zealand as well, as it pertains in the States, of things like the Draft Guidance Document on the New Dietary Ingredients of the FDA, and the mandates as it relates to different research proof of claims that are being required, and the new medical foods guidance document that came out that becomes very much more restrictive and sounding much more pharmaceutical-based for genetic metabolism diseases, and how all of this is, in your perspective, going to influence the necessity for companies that are producing, marketing, and selling natural products to be prepared for doing business under these new regulatory environmental conditions?

JU: The evolving regulatory state is something that I have foreseen and been watching over time with great interest. A lot of it is not actual changes, per se, in the regulation but enforcement or interpretation of the guidance documents. It's becoming clear that yes, first of all, primary substantiation is becoming an expectation, so reliance upon third-party literature is less viable because there is a big concern about matrix assessment—what about everything else you put in there, and doesn't that potentially impact the effect of the ingredient. There is a much more pharmaceutical approach at one end of that spectrum that appears to be, in many ways, overly restrictive and does not allow certain things that are fairly common knowledge. In other areas, you don't design studies that allow or restrict a certain regulatory area but are meant for all of the regulatory environments, and the main challenges there are if you run a study on disease subjects or not, and everybody says, "No, they can't be diseased individuals." So then how do you make that effect be seen and so that goes back to all the other conversations we've been having. It's very clear that if you expect to be selling, going forward you have to have clinical trials. I had one distributor tell me you can sell a small amount of anything but if you expect to get the type of distribution that you really want to make a big splash in the market, you have to have clinical trials because now it's being demanded by the distributors at all levels, and not only from the regulatory side, but unfortunately from the class action lawsuit side. Those lawsuits have as large an impact on the necessity for clinical trial as the evolving regulations do.

JB: That's very, very insightful. I want to thank you, both for this commentary that you've given us, but also for the years of service that you've provided in raising the bar and giving us all a foundation and footprint for what is really truly authentic in terms of these bioactive components that are found in food and spices and herbs. We know that they have physiological effects, but sometimes quantifying them and having the proof of concept at hand has been the missing link, and I think what you're doing is really helping to raise the bar and provide the tools that are necessary to close that gap. Thank you so much for all you're doing and we'll look forward to keeping up with you. This is obviously a changing domain on a daily basis, so keep up the great work. We really appreciate it.

JU: Jeff, thank you. It's been a pleasure and an honor.

Bibliography

[1] McAuley PA, Artero EG, Sui X, Lavie CJ, Almeida MJ, Blair SN. Fitness, fatness, and survival in adults with pre-diabetes. *Diabetes Care*. 2013 Sept 23. [Epub ahead of print]

[2] Helrich SP, Ragland DR, Leung RW, Paffenbarger RS. Physical activity and reduced occurrence of ono-insulin-dependent diabetes mellitus. *N Engl J Med*. 1991 Jul 18;321(3):147-152.

[3] Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, et al. Gamma-glutamyltransferase and diabetes—a 4 year follow-up study. *Diabetologia*. 2003 Mar;46(3):359-364.

[4] Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, Ali F, Sholley C, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA*. 2010 Jul 28;304(4):411-418.

[5] Mitka M. Aggressive glycemic control might not be the best choice for all diabetic patients. *JAMA*. 2010 Mar 24;303(12):1137-1138.

[6] ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, et al. Long-term effects of intensive glucose-lowering on cardiovascular outcomes. *N Engl J Med*. 2011 Mar;364(9):818-828.

[7] Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. *Arch Neurol.* 2011 Jan;68(1):51-57.

[8] Maratos-Flier E. Metabolic disease puts up a fight: microbes, metabolism and medications. *Nat Med*. 2013 Oct 7;19(10):1218-1219.

[9] Levine JA, Vander Weg MW, Hill JO, Klesques RC. Non-exercise activity thermogenesis: the crouching tiger hidden dragon of societal weight gain. *Arterioscler Thromb Vasc Biol*. 2006 Apr;26(4):729-736.

[10] Manohar C, Levine JA, Nandy DK, Saad A, Dalla Man C, et al. The effect of walking on postprandial glycemic excursion in patients with type 1 diabetes and healthy people. *Diabetes Care*. 2012 Dec;35(12):2493-2499.

[11] Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med*. 1993 Jan 28;328(4):246-252.

[12] Shrestha S, Volek JS, Udani J, Wood RJ, Greene CM, et al. A combination therapy including psyllium and plant sterols lowers LDL cholesterol by modifying lipoprotein metabolism in hypercholesterolemic individuals. *J Nutr*. 2006 Oct;136(10):2492-2497.

[13] Udani JK, Singh BB, Barrett ML, Preuss HG. Lowering the glycemic index of white bread using a white bean extract. *Nutr J*. 2009 Oct 28;8:52.

[14] Udani JK, Singh BB, Barrett ML, Singh VJ. Proprietary arabinogalactan extract increases antibody response to the pneumonia vaccine: a randomized, double-blind, placebo-controlled pilot study in healthy volunteers. *Nutr J*. 2010 Aug 26;9:32.

[15] Udani JK, Ritz BW. High potency fish oil supplement improves omega-3 fatty acid status in healthy adults: an open-label study using a web-based, virtual platform. *Nutr J*. 2013 Aug 8;12(1):112.p>