November 2011 Issue | David Jones, MD - Clinician Roundtable, Part II

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Welcome to *Functional Medicine Update* for November 2011. This is the continuation of a theme that we initiated in the October issue that I'm very excited about, which is this roundtable forum that we orchestrated on lifestyle medicine. What is lifestyle medicine? How is it applied in the clinic? What is its point of differentiation from traditional preventive medicine? And does it have value in reducing the burden of chronic disease and turning back early stages of pathologies associated with various chronic illnesses? Those were the questions that were raised during the forum.

Before we get into the completion of the discussion among the expert physicians that were present for this forum that we had in Gig Harbor, WA a month or so ago, I'd like to set the context as to why I think this is an appropriate theme for this period of time in the evolution of the functional medicine model. I think what I'm going to say is well-known for most of you, but it never hurts to have a refresher and reinforce basic principles that underlie the work that we engage in everyday in healthcare delivery.

Health Care and the Global Economy: The Impact of Five Non-communicable Diseases

How do we improve the state of the world and the people that reside in it? This particular 2011 year, the world economic forum met specifically to look at healthcare-related issues pertaining to the global economy.[1] The results of this were truly, I think, remarkable for those of us who have been living through the global economic disaster of the last few years. We have been experiencing, both in the United States and in the global economic community, these wide swings—almost whipsaw-like swings—in the economy. Through the so-called trickle-down model, that ultimately influences the daily lives of people and their ability to maintain status, both in the developed and developing world.

The question of how this all interrelates with health care and the prevalence of certain diseases is not an esoteric or tangential topic. It's really at the cornerstone of understanding how the world community is going to meet the challenges that lie ahead, in that an unhealthy population that is burdened with chronic disease cannot mobilize the kinds of necessary focus on building an economic model of success that may be required under a time of great global financial turmoil. With that in mind, what's the global economic impact of the five leading non-communicable diseases? I'm not even going to go into the HIV or influenza, or other communicable types of diseases like tuberculosis and malaria. I'm just going to talk about the non-communicable diseases—the leading chronic, age-related, degenerative diseases: cardiovascular disease, chronic respiratory disease, cancer, diabetes, and mental health issues (including Alzheimer's disease).

The result of this forum, in terms of looking at that from a global perspective, was—I think—overwhelming. The suggestion was that these particular diseases—these five diseases—could mean for the global impact on economy, about $47 trillion dollars over the next 20 years. Forty-seven trillion dollars. Which means that this deficit that we have gotten the United States into of a couple of trillion dollars would pale in comparison to the depth of the whole burden that chronic disease will make on the global economy over the next 20 years.

Mental Health Issues Are Now Included in the List of Top Non-communicable Diseases

The global economic burden of non-communicable diseases report analyzes the overall costs of these non-communicable diseases to the global economy. What it suggests is that it represents about 4 percent of the annual global GDP that is going to have to be dedicated to maintenance of therapeutics related to the rising tide of these diseases. Historically mental health was left off the list of the top non-communicable diseases, but as a consequence of the rising tide of Alzheimer's in the aging population, when you add that to the list it accounts for more than 16 trillion dollars (or 1/3) of the 47 trillion dollars anticipated. If we were to look at where we see the greatest growth of concerns and the lack of good therapeutics in this area of chronic illness, it appears it is in the chronic mental health area, particularly Alzheimer's- and dementia-related.

Poverty as a Risk Factor to Disease

More than 60 percent of deaths worldwide are due to the non-communicable diseases. Low and middle income families are disproportionately affected, as we've talked about in previous issues of *Functional Medicine Update*. You'll recall we—about 10 years ago—cited the studies looking at poverty as one of the most significant risk factors to disease.[2] We said that poverty, from this study, was more than just annual income; it was related to feeling impoverished, which was low attribution, lack of acceptance, of value, lack of love and appreciation, lack of meaning in life. This broader definition of poverty (or being impoverished) correlated very strongly with early-stage disease and death, even in the absence of traditional risk factors (the so-called Framingham risk factors). So there are many different components that relate to the rising burden of disease, including isolation, lack of attribution, and "poverty."

In 2010, 80{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the non-communicable disease deaths occurred in the countries where they have premature working age (actually taking people out of the work force and reducing their ability to contribute to the overall economic growth, or even economic stability, of their countries). The global population beyond the age of 60, as you know, is expected to double between now and 2050. This development coupled with increasing urbanization means a sharp increase in the non-communicable disease rates, and the study concludes that the cumulative bases of cardiovascular disease, chronic respiratory disease, cancer, and diabetes in low- and middle-income countries are estimated to surpass 7 trillion dollars in the years 2011 to 2025.

We're seeing a very, very significant change in what we might consider lifestyle-related diseases (lifestyle and environment). This interaction between genes, and environment, and lifestyle that gives rise to a change in the function of the organism that we, at later stage, diagnose as a disease. Is there an economic argument, then, for a functional medicine intervention earlier with, we might say "pre-clinical" signs of disease? Meaning, a trajectory towards disease: functional decrements in performance of the

individual as measured by changes in biomarkers, or psychometric performance, or physical performance that indicates a premature acceleration of loss of function associated with biological age? These are very important questions that are now really at the cornerstone of trying to address how we're going to fight back against this 47 trillion dollar expected cost to chronic disease globally over the next 20 years.

Analyzing the Economics of Disease Prevention

That takes us to a very nice editorial that appeared recently in the *Journal of the American Medical Association* titled "A Closer Look at the Economic Argument for Disease Prevention."[3] This marries itself very nicely to the functional medicine, patient-centered assessment, personalized medicine approach. This article goes on to say that disease prevention has always been the preferred option for promoting health and reducing disease rates. This health argument is the reason why people have suggested that we should be investing in prevention. Others, however, have criticized this, saying that there are really no great long-term outcome studies showing that one would be able to save a measurable amount of money in healthcare expenses by engaging in prevention, and so it lacks a proof-of-concept that preventive services will actually result in these savings as a consequence of improved health benefits over time. So these outcome studies are really kind of pivotal in people making a decision about the best way to spend dollars is on the early stage of intervention with preclinical disease and prognosis rather than diagnosis as watchwords for intervention.

So the question as to whether prevention saves money has been incorrectly framed, according to Dr. Woolf in his editorial. He says: "Health care, like other goods, is not purchased to save money. The dollar can be stretched further and more goods can be acquired by optimizing economic value. The proper question for preventive intervention is: 'How much health the investment purchases.'" This is measured generally in terms of cost effectiveness or cost utility, which in health care, as you know, is quality of life years, so we might ask: What is the quality of life adjusted life years that you would get by a prevention strategy for a particular disease versus waiting until it is diagnosed and you do an intervention? So we could say "cardiovascular disease prevention," meaning functional medicine improvement of cardiovascular function versus waiting until you have cardiac pathology and intervening with a hospital-based or interventional therapy. How did the quality of adjusted life years relate between these two approaches?

Those types of data are now starting to become available. Services that are ordinarily considered to have reasonable cost-effectiveness in the interventional model are between 50 thousand to 75 thousand dollars per quality adjusted life year. But payers from the insurance world will routinely cover treatments that cost more than 100 thousand dollars per quality adjusted life year. So that is kind of the benchmark that you could use to then compare functional preventive or functional early interventional studies against. If you could have data that would allow you to understand the cost of a functional medicine intervention and its relationship to quality of adjusted life years and compare that to the benchmark of a pathophysiologically-based intervention model, which is between 50 and 100 thousand dollars per quality of life adjusted years, you could then form some kind of an understanding of cost-effectiveness or benefit.

Specific Questions to Consider When Doing Economic Analysis

That's a very interesting way of approaching it, and as Dr. Woolf points out, in order to do that we might start looking at several kinds of specific things that would pertain to this. First of all, what type of

services are we talking about in terms of measuring early intervention versus late intervention? Are we talking about a public health intervention, which has to do with things like seatbelts, mammography, low cholesterol diets, or are we dealing with personalized interventional trials that relate to the individual needs of a patient-centered approach? Number two, what evidence are we going to use for determining our quality of life adjusted life year outcomes? The evidence-based clinical services needs to have objective markers for tracking benefit because the outcome that we are going to use is not going to be the endpoint called death. We're going to use something that has more functional decrements. Will we use biomarkers like cholesterol-to-HDL ratios, or will we use carotid intima medial thickness levels, or will we use cardiac performance on a treadmill test? Will we use some type of imagery of wall motion studies? All sorts of different variables might be considered important for determining how we are going to objectively measure the quality of adjusted life years for our intervention by maybe surrogate markers that are tracked against longer term outcome variables that have to do with things like life expectancy. And then next is, what is a core set of services that will be delivered? Is there some kind of a reasonable, replicable protocol that we can implement, both in terms of screening—in other words, a set portfolio of evaluative tools that are tied to the outcome treatment that we are going to employ in these preventive, functional medicine-focused services?

I think when you start adding all this together, it starts to form a system or a schema, so to speak, that would allow us to both have a replicable way of intervening in a more functional medicine, early stage, preclinical milieu, and then have ways of evaluating outcome and look at cost-effectiveness from quality of adjusted life year comparisons with more pathology-based interventions. The way that this field is evolving, if we're going to actually demonstrate at a large regulatory level, legislative level, reimbursement level, these types of data need to be accumulated so that we can actually sit down and measure apples against apples in terms of cost benefit and outcome-related studies, and what is the economic value for this functional medicine/personalized lifestyle medicine approach?

A Recent Article Authored By Dr. Bland

This has to do a little bit then with finding the right therapy and how that gets personalized appropriately. Recently an article that I authored titled "Finding the Right Therapy: A Look at Personalized Medicine" appeared in the *Integrative Medicine: A Clinician's Journal*.[4] I talked about how this whole theme had evolved since the turn of the last century, with the concept of biochemical individuality through Archibald Garrod's discussion of genetic metabolism diseases. I moved into Roger Williams and Linus Pauling with biochemical individuality, genetotrophic disease, and orthomolecular medicine, and has now moved into the postgenomic era with regard to the deciphering of the code of the human genome, and then into gene expression understanding and how we recognize the genome, in and of itself, is not the ultimate determinate of our phenotype, but rather it is the interaction of the genetic code (meaning our genome; our book of life; 23 chapters encoded in our 23 pairs of chromosomes)—how those stories in our book of life called our genes are ultimately expressed as a consequence of the interaction with our environment. Those personal environmental exposures then give rise to different expression patterns that ultimately become our phenotype: how we look, act, feel , and how our health process evolves over the course of living.

With that in mind, we then see the emergence of a concept that really is a revisited concept from the 1800's. It's the concept of adaptation, because it is not just the determinism of the genes as they are hard-wired from our parental legacy (the sperm and the egg when they met), but it is also the influence that our

environment has had on setting marks on those genetic codes that then allow different expression patterns to pursue, and this is the process that is called epigenetics, as we've talked about at length in previous issues of *Functional Medicine Update*. You'll recall the magnificent discussions we've had on two occasions, actually, with Dr. Randy Jirtle at Duke. He is kind of the father of nutritional epigenetics, and the discussion we had with Dr. Michael Skinner at Washington State University on *Functional Medicine Update* that talked about exposure in the environment to various substances that are toxins that induce epigenetic marks on the germ cells and alter, then, the function of subsequent generations. He talked about transgenerational inheritance of those epigenetic marks into the third generation. So we're starting to see a re-validation of what Jean Baptiste was talking about in the 1800s as it relates to adaptation, which now is being seen, at the molecular/genetic level, as epigenetics—these methylated, stop function, or silencing of gene functions, or the phosphorylation or acetylation or the ubiquitination of genes that are all post-translational effects that occur epigenetically to put these marks on the genome that allow only certain messages to be expressed and others to be silenced.

What Role Does Nutrition Play in Epigenetics?

So we are actually witnessing the bridge between the environment and the genome through epigenetics. That takes us, then, to the question of: What role does nutrition play in this epigenetic understanding? In the past we might have felt that nutrition was a third- or fourth-level variable that had very little to do with how our health proceeded as we grew older, and was relegated in medicine to kind of a spot way at the back of the class. Recently, however, as Randy Jirtle's discoveries have now been validated and many, many other investigators are starting to look at the role that nutrients have in epigenetic influences on gene expression, it is starting to be seen that this epigenetic concept may represent a bridge between nutrition and the phenotype of health or disease. We now recognize that nutrients can reverse or change epigenetic phenomena, such as DNA methylation and histone modifications within the genome, thereby modifying the expression of critical genes associated with physiologic and pathologic processes, and includes such things as embryonic development, aging, and even carcinogenesis. In fact, there are individuals who have questioned whether epigenesis is in part related to the increasing frequency of such conditions as autistic spectrum disorder in our society. Could it be that altered methylation patterns caused by changes in fetal stress that are seen in utero—and that stress could be chemical stress, or a variety of different kinds of inputs—that would then alter the way the imprinting of the genome occurred during fetal development, and changed, then, ultimately, the expression patterns of the genome into the phenotype that we call autistic spectrum disorder (ASD)? This has been a very robust area of inquiry and research over the last several years.

Chronic Diseases Can Be Epigenetic in Origin

We now recognize that we might be able to say that many of our chronic, age-related, degenerative diseases are in part epigenetic in origin. As was recently talked about, these might be considered long latency nutritional disorders, as contrasted to short latency nutritional disorders like scurvy, beriberi, pellagra, xerophthalmia, and rickets where you can omit or prohibit the intake of a certain vitamin for a short period of time, like vitamin C, and in a matter weeks to months, you can induce scurvy in a human. But what happens if the alteration of a nutrient intake has a much longer timeline in its effect on epigenetic modulation, ultimately of gene expression, and then the sequence of events that lead into

pathology, so that it is not just weeks or months, but it is years or decades in which that starts to be seen. How does a person know the origin of that disease (say, cardiac disease), when the origin occurred as a consequence of the cumulative influence of epigenetic changes on the genome over years of living? It might have started, actually, in utero, and then been continually re-stimulated through the environment that that individual was living, to ultimately encourage, then, the outcome that we call this chronic disease, which may be thought to have no nutritional relationship, but really if we knew its etiology from the initiation through its progression, we would see it's a functional outcome of an early stage epigenetic change.

Phytochemicals and the French Paradox

These are the questions that are being asked as it relates to the importance of nutrition and its relationship to epigenetics. It appears that nutrients and bioactive food components, which includes things like phytochemicals—this rich array of thousands of different secondary metabolites of plants that are unique in their ability to modulate cellular communication—influence epigenetic phenomena, either directly or indirectly, by influencing enzymes that catalyze DNA methylation or histone modifications, or by altering the availability of substrates necessary for these enzymatic reactions. The one that we've probably heard the most about recently is the so-called sirtuin gene family that regulates aspects of histone acetylation/deacetylation, and therefore the folding and unfolding of the genome to be accessible to reader enzymes.

You probably know that this marries itself very closely to what we call the French Paradox, where it has been said that people in France eating a traditional high fat, but natural, French diet and drinking red wine have a very low incidence of cardiovascular disease. When they consume a more highly processed diet that is less natural and contains less phytochemicals, their incidence of cardiovascular disease goes up. So the suggestion is that fat in and of itself is not the causative agent, but rather it is the kind of diet that brings information that alters the expression of genes that in the absence of those nutrients then results in pathology. So French Paradox, red wine, resveratrol gave birth to the increasing ordering at restaurants of red wine. It was wonderful for the red wine business because everyone said, "Oh, yeah, I'm drinking red wine for the health value now—for these phytochemicals."

Resveratrol Modulates Genome Structure and Function in an Epigenetic Way

The resveratrol story is a very fascinating story as a concept that lies within this epigenetic theme that is emerging (nutritional epigenetics) because resveratrol is just one of many phytochemicals that has been identified to modulate various aspects of genome structure and function in an epigenetic way. Resveratrol has been shown to influence the regulation of function of the SIRT1 gene in mammalian eukaryotic mammalian cells, and as a consequence it leads to alteration in histone deacetylase, one of the enzymes that is responsible for taking off acetyl groups from the histone proteins, which then allows these proteins to open up and to say "Read Here" (transduce or to basically translate the message of that gene into

messenger RNA ultimately into protein). So this particular phytochemical—resveratrol—is one of a family (a literally large family) of specific plant-derived materials which influence genetic structure and function in such a way as to alter the phenotype (meaning alter the communication in that cell that produces its function.

This is a very dramatic shift in our thinking, isn't it, about diet? To think that somehow there are information molecules within our food that can influence specific regions in a very kind of tailored, lasered way. The regions of expressions of genes by epigenetic modulation of their structure/function. "Epigenetic" means "above" the actual code itself. We're not altering the ATGC kind of pairing in the DNA code; they remain constant. What we are changing is the way that that code can be read: either by silencing the genome by allowing certain messages not to be read (or prohibiting them from being read), or activating certain other genomic messages to be read by acetylation, for instance, which is known to open the genome to being read.

Will Epigenetics Research Lead to Treatments?

These are very, very interesting changes in how we view the interrelationship between diet and ultimately function and health of the individual. So could there be the emergence of treatments focused on either prevention or dietary management of specific epigenetically modified functions that give rise to what we see later stage as long latency disease, like cardiovascular disease, or Type 2 diabetes, or cancer, or arthritis? The emerging understanding of this field seems to suggest the answer is yes, that is where the data is taking us. In fact, there is a very interesting review paper that was published on this whole topic in *Advances in Nutrition* in 2010 that talks about this bridge between nutrition and health as connected to nutrient modulations of epigenetics and how these phytochemicals in food can modulate intercellular signal transduction, meaning alter the way the environment speaks to genes to regulate gene expression.[5]

Small Inducible Inhibitory RNAs

This particular epigenetic revolution that is occurring goes beyond just things like methylation and acetylation of the genome. It moves itself also into another topic that we discussed previously (two years ago) in *Functional Medicine Update*, that for many was probably very esoteric and seemed to have little clinical application, and that was an interview I did with a primary investigator at the Scripps Institute on the small inducible inhibitory RNAs (siRNAs). You'll recall—if you go back with me for a moment—that he indicated that what is being seen in cells is that there are literally thousands of differing RNA molecules that are produced specifically by a cell, many of which have unique inhibitory functions on the expression of genes. It is like they are blocking RNA fragments from the ability to read specific

messages. So this is another part of the epigenetic regulatory pathways—that cells are producing these kinds of jamming messages that prevent specific regions of the genome from being read.

Clearly we're still witnessing the emergence of understanding of how inhibitory RNAs actually play roles in physiology. But there are big research projects going on at many institutions now to find out how to harness specific siRNAs to block the production of certain oncogenic proteins associated with cancer. So this is being seen as a potential new route towards cancer treatment by modulating cellular function at the siRNA level. The interesting theme of this is that these small inducible inhibitor RNAs are also produced by plants in their regulatory machinery (it's not just seen in human cells), and these small inducible RNAs have just recently—in 2011—been found to be consumed in the diet of plant foods, and have been found (at least in the case of rice) to actually be seen in the blood after consumption, meaning that these micro RNAs actually can survive digestion and end up being transferred across the GI barrier into the blood, and therefore may have influence (and I want to emphasize "may") on modulating, through epigenetic mechanism that occurs through the diet, the expression of certain genes in the host organism that has consumed that food.

Now this is a pretty dramatic observation, isn't it? Because what it is saying is we're getting information from food that could potentially modulate gene expression through an inhibitory mechanism that is specific to regions of the genome that would alter health or disease patterns. The title of the article is quite esoteric: "Exogenous Plant miRNA-168 Specifically Targets Mammalian LDL Receptor AP1."[6] There is evidence from this study of cross-kingdom regulation by these micro RNAs. This appeared in the journal *Cell Research* in 2011. It's pretty amazing, really.

Previous studies from this group had demonstrated that stable micro RNAs (miRNAs) in mammalian serum and plasma are actively secreted from tissues in cells and can serve as a novel class of biomarkers for diseases, and they act as signaling molecules in intercellular communication at an epigenetic level. In this particular paper, however, they went on to report what I think is an absolutely fascinating finding: that exogenous plant miRNAs are present in the serum and tissues (and I want to emphasize "tissues") of various animals that have orally consumed these plants, and that those exogenous small inhibitory RNAs are primarily acquired orally through food intake. The specific example that was chosen in this study was this small inducible micro RNA 168A. It is abundant in rice, and is one of the most highly enriched exogenous plant micro RNAs in the sera, as found in Chinese subjects consuming rice. Does this have any role to play in gene expression? When they did the in vitro functional studies (and in vivo), they demonstrated these micro RNA 168A could bind to human/mouse low density lipoprotein receptor adaptor protein (or so-called LDL RAP1), inhibiting then the expression in the liver and consequently decreasing LDL removal from the mouse plasma. These findings, they suggest, demonstrate that exogenous plant micro inhibitory RNAs in food can regulate the expression of target genes in mammals.

Let me let that set in just for a second. You want to talk about a shifting paradigm? This is one. This has us really looking at diet and food and its relationship with information and gene expression and how that translates out into non-communicable chronic disease in a very, very remarkable way. In fact, it even suggests that epigenetic changes are not just hard-wired; they can come and go based upon the type of dietary intake a person has and the presence and exposure to these micro inhibitory RNAs in their food.

So what can we say about this extraordinary discovery? Investigators at the Max Planck Institute of Developmental Biology in Germany really have discovered what might be the first comprehensive inventory of how spontaneous epigenetic changes can be brought about through food, and that these changes could be considered reversible as diets change, which means that epigenetic changes may not always last; they may come and go as it relates to the changing diets of the individual.[7]

Now if you tie this together with my previous discussion concerning phytochemicals that influence genomic structure, like resveratrol and the SIRT1 genes, you're starting to see that this regulatory series of pathways that ultimately regulate how genes are expressed and become our phenotype is much more related to environmental factors than we previously have acknowledged. Therefore, the concept of a personalized lifestyle medicine intervention program that is functionally based is starting to have a molecular/genetic and a cell/biological explanation that is absolutely profoundly intelligent when we start asking the questions, how, why, when, and what do we do? We are really starting to develop a new medicine that translates ultimately into studies that would allow us to look at cost-effectiveness of personalized intervention (early stage), based on certain new emerging biomarkers, and then tracking that against quality of adjusted life years so that we start to see, for those who are planning health economies and health expenditures and are really trying to deal with the broad-brush questions of 47 trillion dollars to be spent for the next 20 years on non-communicable chronic diseases, how this could move the needle, how this could improve outcome.

I was very impressed when I looked at a recent paper that appeared in the journal *Cell*, which reports a very nice study of the influence of 30 days of supplementation of resveratrol on metabolic parameters and body fat in obese humans.[8] This is a very interesting study in which resveratrol—the same compound I was talking about, a constituent of grapes and grape skins—which is known from previous studies to affect energy metabolism and mitochondrial function, and has been suggested to serve as a calorie restriction mimetic. These are themes we have talked about earlier and we interviewed, as you recall, Dr. Christoph Westphal, the CEO of Sirtris Pharma years ago, before they were acquired by GlaxoSmithKline, who had really been exploiting the discoveries of David Sinclair at Harvard related to resveratrol in the SIRT1 gene.

Results of a Human Trial on Resveratrol

In this particular study, researchers treated 11 healthy obese men with a placebo and 150 milligrams per day of a special form of bioavailable resveratrol in a randomized, double-blind, crossover study for 30 days. What they found after the 30 days with this group of 11 individuals who were randomized was that resveratrol was found to significantly reduce sleeping and resting metabolic rate, and in muscle resveratrol was found to activate adenosine monophosphate kinase (or AMPK), which is kind of the energy thermostat of the cell. You'll recall we've talked about it previously as having a direct effect on mitochondrial oxidative energy production. It was found to increase SIRT1 expression and increase citrate synthase activity without change in mitochondrial content, and improve muscle mitochondrial respiration on a fatty acid-derived substrate. It was also seen that resveratrol was found to modulate or influence intramyocellular lipid levels, and it decreased intrahepatic lipid content (meaning lowered fat infiltration into the liver), and it lowered circulating glucose, triglycerides, and liver enzymes like ALP, and it also reduced inflammatory markers like hs-CRP.

So this was a very interesting study in humans. Again I want to suggest that this was an early stage-type trial (we're only talking about 11 healthy obese men randomized between resveratrol and placebo, with the resveratrol being 150 milligrams per day of this unique formulation of resveratrol that was made more bioavailable). By the way, 150 milligrams a day would be equivalent to something like 70 glasses of wine, so we are talking about an amount that is more pharmacologic and less nutritional because you're not going to pick up 150 milligrams in a food and beverage delivery system under normal conditions. In that nutritional pharmacological intervention with resveratrol in these modestly obese, presumably healthy individuals, it appeared to have very salutary and beneficial effects on modulating expression that ultimately was seen as lowered triglyceride, lowered inflammatory markers, lowered glucose, and improved liver function. I think that these are very, very exciting kind of clinical takeaways from the discussion we're having concerning nutritional epigenomics and genetics—whether they really play a role or is it more of an esoteric academic topic as it pertains to the burden of disease and the rising tide of chronic non-communicable diseases in the world.

How does that relate, then, to this discussion among the experts that you are going to hear in the remainder of this issue of *Functional Medicine Update*? It really relates directly to the question of the efficacy of a functional medicine approach towards personalized lifestyle intervention. Does it really deliver the goods? Is it more than just a feel good experience? Does it have an outcome that really can reduce the progression to more serious pathology? Will it be cost effective? Will it increase the quality of adjusted life years of the individuals? All of these are very, very important questions that appear to me, from the way that the literature is emerging and how things are being developed, to have a revolutionary conceptual affirmation for this model.

A Published Study by Dr. Bland's Research Team on a Phytochemical Formulation

In fact, recently the group that I am very privileged to work with at the Functional Medicine Clinical Research Center just published a paper in *Nutrition Research*, volume 31, page 347 in 2011, reporting on

the role of the complex phytochemical formulation that contained hops iso alpha acids, berberine, vitamin D3, and vitamin K, having a very profound and favorable effect on bone biomarker profiles in postmenopausal women who have metabolic syndrome.[9] This particular study demonstrated that by giving a certain concentrated mixture of bioactive phytonutrients that are known to influence certain gene expression patterns, you actually can enhance the osteogenic potential within certain cells that would help to prevent bone loss and help to maintain proper bone integrity. So we're talking here about giving more than just calcium and vitamin D to mineralize bone, we're really talking about the active process of bone formation and bone resorption—that balance between osteogenesis and osteolosis—and how that triggering event of that equilibrium is in part controlled by the environmental exposure to certain phytochemicals that can modulate the gene expression patterns. This is sometimes called hormesis, as we've talked about in previous issues of *Functional Medicine Update*: small amounts of the right things hitting certain regulatory nodes on the gene expression patterns can have a larger effect clinically than we would have predicted. Hormesis.

These concepts of berberine, and vitamin D, and vitamin K, and rho iso alpha acids from hops having unique gene personalities to enhance the orchestration of the phenotype of cells that are associated with bone integrity and maintenance is, I think, another of the myriad of examples that are coming out in the literature recently as it pertains to improvement of function with the appropriate information from food. So it is food, exercise, stress management, the reduction of exposures to environmental xenobiotics or chemicals or heavy toxic elements—all of these things then play extraordinary roles in sending signals to cells that ultimately create expression patterns that become the phenotype.

INTERVIEW TRANSCRIPT

JB: I've got two last questions I want to ask each of you, and they can be probably fairly short answers. The first one, which comes up frequently in conversations I have with individuals who may be considering integrating a portion of lifestyle medicine into their practice, is: What are my peers going to think of me? This is a guild—medicine is a guild—it's really passed down from the Medici family in Italy. It has had generations of refinement, but it's still a very strong guild of internecine communications. What happens when you start breaking the guild, and how does that have an impact on you, and your life, and your vision, and your identity? Maybe it could be none, but my experience is that it is generally something.

David, I'll start with you.

DJ: I wonder about that question because lifestyle changes in my clinic included doing home births with a midwife. Ashland is a small town of 18,000, but we're right next to the large referral center, so you have no idea how people think about you. I go merrily along my way delivering babies at home and going about doing lifestyle medicine, and eventually we got into what we call functional medicine. So managed care comes along, and all the doctors are scared because they can sit with a patient and make decisions about that patient that is a life-and-death decision, but when it comes to confronting an insurance company that holds your money purse, somehow they just…I've never seen such change. It was a bipolar experience for me watching how doctors dealt with managed care. They actually came to me to be their president, to help them with the insurance companies, because somewhere in there they realized,

“They’re going to ask us to do something about prevention, and we don’t know anything about prevention, and David, we’d like you to come.” It surprised me because I thought I was considered more radical than that. To have that kind of respect in the community when you think of yourself as, “That Dr. Jones over there in Ashland, he’s pretty weird.” So I had exactly the opposite experience: making decisions about my patients, the way that I referred patients, and what the patients said about me.

Now I had other doctors in the community that came out of medical school and they felt such a sense of betrayal that they created a certain disharmony between the establishment and themselves. For whatever reason, I had such great respect for the skills (that I could refer my patients to people with skills in areas), but I also knew what not to take from their advice. And over time there was a respect that was developed, and I was their president for 10 years until I came and was asked to be the president of IFM. So I didn’t have a bad experience being the granola doctor in Ashland.

Establishing Respectful Relationships Among Colleagues

JB: I think you said something very, very important, and I’ve observed this not only with you, but other very successful people that swing over this and have feet in multiple areas of activity. You really create a relationship with your community of respect. You never passed a sense of disrespect for people that did things differently. In fact, you honored their skills in areas where you needed them, and didn’t look through their liabilities and limitations as the major barrier. I think that’s a really important lesson because, as you said, there are some people who get into this field and they have the conversion experience, and then everything that they did before was wrong, and all of the people in that field are wrong, and suddenly we end up with a polarity and now it’s a fight.

JB: So Graham, how about you? You’ve made this transition from Oakland Raiders team doctor all the way up through the years of dealing with a myriad of different medical referral specialists. How has it been for you?

GR: Well, a couple of things. I’m a nut about leadership reading and I love the stuff that Einstein said, you know, “What the solutions are you had that brought you to the solution today are not necessarily applicable to the problem you’ll have tomorrow.” The issue is that we’ve got to continue to have a dynamic of change and not be caught up in finding out what the next thing current therapy says we should do, but we should also not ignore that. We should live in it and past it. So it is easy to do one thing, I think, in medicine, but we fail to embrace the system that parented us. It parented us, and if we disrespect it, then you run a risk of now feeling as though others really can’t associate with you because they’re frightened about this. So I end up doing this: I gather consultants around me. Covey says: “Every breakthrough must first start with a break away.” That’s a vital part of everything we do: every breakthrough has got to start with a break away. But it doesn’t mean a break with things out there that you have been trained in. It means break with their control over you. The big thing is: Who is the person we need to fix most? It’s me in the mirror. That’s who. I’ve got to fix me first.

The next thing, I think, is I have a phrase for patients: The difference between good and excellent care could be the miles on your car. I really don’t care much about it. I’m sorry about that—that gas is high—I know that, but the point is: I’m going to find you the very best consultant, is what I’m going to do. I have my nurse practitioner and 27 consultants that she will, in the next four months, come to see. They’ll be here. They’ll be around. They will become an integrated partner and they know that. I sent 380 patients to

our orthopedic group in Seattle because I had so many. We did 600 MRIs and CTs because by the time because by the time they get to us they are already pretty damaged. In that regard, those people already know how I think. They'll come back and say, "That's great because he knows how to fix this food for you, because if you don't do the food you won't get better." What you are doing is you go home and you gained all this weight and now you've got this knee and you want me to fix the knee. I can't go, "Darn it, I can't fix that knee unless I can cut and fix it, but it will not make you well."

Those are the people we gather around us, and they become both purveyors of the truth (in my mind) and our truth. It's a shared truth. It's not one that comes from me; it's one that is given out easily. I'll say: "You get to go see one of the best guys I know or one of the best gals that I know. You get to do this." I'll pick up the phone in front of them and call and say, "Scott, this is who I've got. This kid's been at this, he's come in today, he's got four-and-a-half weeks on his ankle today. The physical therapist said the doctor said he could play three weeks ago, but he's having a hard time walking." This is the fun part: somebody said, "Who referred you?" And he said, "All the coaches in the area."

I said, "Well, the problem is you have a little fracture. We did the digital x-ray." So I said, "You can play tomorrow and this is what the brace is for and this is why. But you'll not be good, so you have to play as a wide receiver— a wide receiver, not a defensive back. You have to stay on the left side, so you play at this end. You do not run out in the middle. If you don't do this, you can play. But you can act like everything's fine. You're just fine. Just stay on the left side. Tell the coach. Go tackle all you want, but if a guy goes on your left, you're dead." We do that in basketball, we do that in volleyball, and the point is you become a participant in their life, you become a participant in their sport, and they, all of a sudden know, "You know what I'm talking about!" If you're playing tennis, don't rush the net. I'm getting too carried away, but anyway it's about living in their life with them.

JB: Jay, how about you? You've transcended many different boundaries. Anything that you would offer as kind of your observations?

More Controlled Clinical Studies on Lifestyle Medicine Needed to Increase Acceptance

JL: I think a few points come to mind. One is that I would like to see more of the kind of research that we heard about earlier today and see controlled, double-blind studies. It is very difficult to sort of contextualize functional medicine and lifestyle medicine in terms of a clinical study, but we really have to do it, because in order to effect change and allow ourselves to adopt these important principles we're going to have to show the research that it does matter (even though we know that it does matter). I think that there is obviously a hurdle that—again, Graham, I think very eloquently talked about—which is that in order for us to effect change in medicine we have to effect change in ourselves and see where our own roadblocks are in terms of how we operate and how the things that we accept as being true are not necessarily so, and that's a difficult thing for people who are smart like we are: to accept the saying that "We know what we know, and we know what we don't know, but we don't know what we don't know." A lot of the alternative medicine is in the area of "we don't know what we don't know," and that's something that we're all uncomfortable with, but in order to help overcome intractable problems we have to embrace the unknown. So it is really two-fold. One is discovery of evidence-based practice and showing that it does improve outcomes. And two, it is willing to accept that there is just a lot we don't know about health and disease, and having an openness to things that take us out of our comfort zone are important to listen to and to have an open mind to.

JB: Thank you. Jim, as you made this transition, is there anything that you have observed with your colleagues?

JW: Yes, I've gotten beaten up a couple of times, but I would say not from anybody who I respect, and from people who I do respect, never for a good reason and when I have called them on it or talked to them about it I usually get an apology because they did it for the wrong reason or lack of understanding or something. It was very important to me going into this that I not be thought of as a kook, so I'm very careful about making sure what I do is evidence-based. That's what we've been taught. When I sit down and have the thoughtful discussion with my colleagues who are not necessarily on the same page, I can usually prove to them that what they are doing is not the best medicine on the basis of evidence. I would say I haven't yet had the experience where I was beaten up for the right reasons.

In Orange County they have this Lipid Alliance. They have a yearly conference. One year, a year or two ago, I went to the conference (it's a one day conference) and there was a lifestyle medicine lecture that was terrible, frankly. So I have been talking with one of the two organizers of the conference. Hopefully I'll be able to give the lifestyle medicine conference to a roomful of mostly cardiologists and primary care physicians, to tell them what the truth is and what they need to know based on the evidence, which is what they are there to hear.

JB: You have a pretty good referral practice with Hoag, right? With Hoag Hospital, which is really one of the big medical centers in the area?

JW: Yes, that's essentially the only hospital I use for my patients.

JB: And have you had reasonable acceptance when you go and you do your visits there with the staff and the people that know you are doing a little bit of this kind of medicine?

JW: Honestly, I really transitioned my practice and I do very little in-patient work now. There is this wonderful thing called intensivists and hospitalists and they get woken up at night and I don't get woken up any more. So I haven't had that experience because I really don't do that much anymore.

JB: Great. Ken, any thoughts about your transition with your peers (if you want to call them peers)? Members of the community?

KB: Colleagues…Looking back, the primary care physicians in town kind of look over the paper, because they are kind of interested in what we are doing because they hear things from patients. The high school teacher that you talked about earlier—his brother is a well-known family practice doc in town. I tried to reach out to my fellow primary care physicians and say, "I don't need more clinical patients but I'd love to take care of those metabolic syndrome or type 2 diabetic patients that you don't necessarily want to. I finally realized that they didn't do it because they were fearful that they would lose their patients. As I mentioned earlier, our office is a beautiful 1902 heritage house with a big wraparound porch, and when people walk around there they are going to go, "Why do I need to go anyplace else?" The staff treats them well. So I got over that.

Recently I was invited to a hospital…kind of a staff meeting…well, it wasn't a staff meeting, but sponsored by the hospital. There were interventional cardiologists, some vascular surgeons, and a handful of family

docs. It was about peripheral artery disease and doing PAD screens. So they all went and said their piece, and one of the cardiologists says, “Let’s ask Browning what he does because he does things a little bit differently.” Fortunately I had been preparing to go speak up in Grants Pass, Oregon, so I had all my stats ready to go. In fifteen minutes, I was doing it, and I felt really good about it, and I told them why we were different, and shouldn’t we be treating the whole person? My server came up to me when she was giving me another glass of wine and she goes, “Great talk.” I thought, “That was very cool.”

My other encounter was with another cardiologist at the hospital. The hospital does ask us to speak often to employee group meetings or luncheons—things like that. We have picked up a lot of the ER nurses. We’ve picked up a lot of the cath lab nurses and management nurses. They come to us and they get better, and so we’ve tried to worm our way into the hospital to do things—similar, I think, to what you’re doing.

But this cardiologist got up and spoke after we had spoken and he says, “You know, I could sit here and tell you—as a cardiologist—you need to quit smoking, and you need to eat better, but if you really want to get well, go see Dr. Browning.” And that was unsolicited and it was like, “Wow. Thank you very much.”

DJ: They do recognize it (in the community). They do recognize when you do the respectable work in the community, as long you aren’t bad-mouthing them and saying, “Why aren’t they doing it?”

KB: Taking care of people.

JB: Kristi, how about you, as a naturopathic physician? That’s Mayo territory up there. What’s been the general sense that you see?

Patients Will Carry the Message about Successful Treatment

KH: I am just starting my 14th year in private practice. The first 5 to 6 years, the focus was on the patient, not as much the healthcare community, because most of the healthcare providers had never heard of a naturopathic physician where I live. I was the sixth in our entire state; this was back in 1997. I let the patients do the talking for me. After that first five years/half decade passed, all of a sudden the results that the patients were getting—under the care of other physicians for 10, 20, 30, 40 years—was really what opened the door for me. In my own personal community, I allowed for the patient results and the patients to really carry the message for me. I continued to focus on the patient—their goals, their needs—and do patient education and a lot of community education.

As you pointed out, a lot of my first pass patients, when I look back to my first few years, they were nurses, they were not physicians, but they were other healthcare providers in the system, who worked in the system and knew the system was broken (as they would say) and coming in looking for other options. So I would say the community (breaking through) hasn’t been nearly as challenging as speaking on this topic to medical doctors, to osteopathic practitioners, to multidisciplinary practitioners, and having my own naturopathic provider say: “What are you doing teaching naturopathic medicine to the other guys?” That has probably been one of the most interesting journeys I have gone through because as many of you know, functional medicine has some very strong naturopathic principles within it, and naturopaths do lifestyle medicine. That’s what you spend your four years of medical school focusing on: all lifestyle medicine. My skin has had to get a little bit thicker. I’ve had to toughen up, more against my own team I

would say, because they want to know: What am I doing out there teaching them all of the secrets? And I just look back and say: "Why would you not want to empower every physician to just go back and transform ONE patient? Just one patient's life with a little something you had to say?" I'm taking the high road on this one. I truly believe in some of the key foundational principles. "Docere" means "teacher." You teach the patient, you teach the doctors, you teach the community, and from there you are going to pay it forward.

JB: Thank you. Really, that's a model. So Mark, clearly in your academic environment, maybe the swirling guild is a little bit tighter. I don't know. Have you experienced any kind of interesting conversations with your colleagues about this whole model?

Practice Teams Can Have More Impact on Patient Success

MM: I think one of the major things is the concept of teamwork has now become so clear. Meaning that we as physicians essentially dictate to our patients, but now the conversation that we have had is that really if you are going to have an impact on patients, it really takes a whole team. You mentioned your life educator and your nutritionist. They are the ones who are—in their day in and day out—really doing the motivational interviewing, and helping patients change behaviors, and really empowering them as well. Likewise, patients themselves. There are some group settings that we utilize. Other patients are tremendous assets to each other. They quite often learn a lot more from other patients than they will learn from me as a physician. I've heard that likewise amongst our physicians as well. And the families—they can have a very positive role. If there is a mother who is trying to change behaviors and eat correctly, she needs the support of her husband as well as her children (if she doesn't have that support). So I'm just a small piece. We, as physicians and clinicians, are just a small piece of the whole pie that we're developing. Likewise, the researchers are in the background who give us the real tools to help change behaviors and to have an impact. Teamwork. I really think that's key.

JB: That's a really nice message. I want to ask one quick question. This is going to be a sound byte. I'd like you to each think about this. I'm going to give you a magic wand and I'm going to give you one wish to be realized—granted—for the successful implementation of improved patient outcome in your practices with chronic ill patients. What would it be? This would be your sound bite wish. David?

DJ: I don't understand the question.

JB: Let me give it to you again. If you could be granted one wish to make your patient population more successful than they are today in outcome, what would it be?

DJ: I still don't really think I understand the question.

JB: You can frame the question any way you want. You can answer it any way you'd like to frame it.

DJ: What I have found is the most important thing, when I see transformational change in my patients, is that I have the faith to create a context where I don't have the answer—where I walk into a room and I just simply let the answer emerge. Because I come with a lot of information. I come with a lot of knowledge. I have a certain architecture I use for sorting that. But to actually go into a room and create context where something happens—that emerges—between us just talking and listening, where I am not the answer man,

where I let that one go, and have the faith that something will emerge that will change my life while it is changing their life. That's the hardest thing for me, because my training is that the buck stops here, that I have to somehow play 62 card pickup until I pick up the right card, and I'm a good doctor if I figure out which card it is. It's not like that. The big things, where the walls fall down and something magical happens, is where I'm just there. I just happen to be a witness to what's happening. And to have the faith that that will happen and not get into that thing where it's my reputation, I don't want to be embarrassed—all those things—that I just simply say, "Together we're going to find an answer. I may have some of that. I know that you're probably the one that is going to come up with an answer. And we're just going to have a dialogue here until we figure this out." And then something happens.

When I get in the way—like when a patient comes back a couple of times— I will sometimes say, "I just can't figure this out, so I'm going to step out of the room, and I'm going to ask Dr. Brown to come in the room, and then you explain to Dr. Brown what Dr. Jones doesn't know." Then I'll come back into the room and say, "Dr. Jones sent me in here." And every time, the patient—within two minutes—tells me what the answer is. Creating that context where something like that can happen has become probably one of the greatest joys because it's like I don't have to carry that heavy responsibility—that mantle that I was given (when I finished medical school they put a mantle on me—a green sash—and I was the answer man). I don't have to do that if I have enough faith that if I let it happen it will happen.

JB: So let me make an observation. First of all, you did answer my question, because what I take away from your response is that if you had this wish granted, what you would do is you would wish that the context of healing was established in every interrelationship you had in that privileged moment of the exam treatment room.

DJ: That's what I've always loved about you. I can say something and then you can translate it.

Establishing a Context for Healing

JB: And vice versa. And you also said something else that I want to really emphasize for the group and for this discussion. That is the abilities that you have, and your colleagues who are at this table who are all masters in their areas, to establish context is deeply studied and developed; it didn't just happen magically. This isn't like some kind of a divine process where you spiritually came down from the mount and you suddenly had the wisdom to create the context. All the things that you have done throughout your career and in your personal life create, then, the environment for establishing the potential context for many different people to have that experience. So I think this concept of deep training—we don't know exactly where it takes us, and the architecture of learning, and the constant pursuit of wisdom, and all of those things that go into "I don't know the answer" that keeps driving you, creates a context that is an expanding the opportunity for healing. That's really was Osler was talking about in his writings about really great medicine.

DJ: People around the table have talked about the sacred nature of what we do. For me that sacred nature is where something emerges between the two of us and it's sacred, but I didn't do it.

JB: But you prepared the soil.

DJ: I may have prepared the soil, but mainly I get the hell out of the way.

JB: So Graham, you've got your magic wand. Is there anything that you would say? Anything you would like to have to complete the circle?

GR: I was saying some of it before, when we started the evening. I'm 74 and I've got so much more energy than anybody I know at 74. I'm just kind of getting started in a whole lot of this. I have a lot of phrases I use with patients a lot. For instance, I say: "My job is to teach you not to need me, so I'm busy helping you do this. I'm doing techniques and studies (lab studies). I do a blood count so in one minute I know whether you have a virus or a bacteria. And I'm not going to give you an antibiotic, but in case don't this is what you do. You take the CBC. If it's 3000, you don't have that. If it's 10 or 15 thousand, you do. You'll know, in the future, that we'll start with vitamin C, 3000mg three times a day for three days, and then if indeed you are still sick and really coughing, then I will help you with this antibiotic. You don't need to come back if you don't want the antibiotic, but if you do think you need the antibiotic we'll check your blood." We empower them. To teach them not to need me. That's one thing.

The second thing is I need to be present to the moment when they call. I give all of my patients my cell number. Every one. All my coaches. Everyone has my cell number. I maybe, once a month, have violators. In a total week I might get 7 to 8 phone calls. Total. That's a gift. Partly because they feel free to call and they don't want to interrupt me because they know there are other people I'm with. I tell the staff, "Be present to the sacred invasion of their lives." I love the phrase "invasion" and I love the word "sacred." It is a sacred and it is a hallowed moment. I want to honor that, and then I want to help them discover the multiplicity of their diverse gifts, because they have many gifts and I want to broaden their life spiritually, to move their life from being full to being fulfilled. "What would help you be fulfilled?"

JL: I'll be very succinct and paraphrase a French philosopher: To grant the potential for consciousness to jump over its own shadow.

JB: That's really powerful.

DJ: Say it again.

JL: To grant the potential for consciousness to jump over its own shadow.

JW: I don't know if I can follow that. For me, the question is "What? What do I do? Doc, what do I do?" I always say, "More important that the 'what' is the 'why.'" For me it comes down to education. It's very important to educate people about why they should do what we have been talking about. Because once they understand that, then the "what" is easy for them to be compliant with. If I had my magic wand, it would be to know what that hook is for each patient before I walk into that encounter.

JB: Thank you. Ken?

KB: "Hook" is the word I use, too, but the magic wand—for me—is to take all of the data, the communication, and be able to process it concisely (or even have it make sense) and give it back to the patient in a way that they get it. Does that make sense?

Clean, Colorful, Affordable Food

KH: If I had a magic wand…I live in the middle of an agricultural hub in the middle of Minnesota, so I would say since my principle is food first, I would want clean, colorful, affordable food because that would reach everybody and I think that would do my patient populations the greatest good.

JB: Mark, you can round us out. Run us through the stretch.

MM: It's hard to follow all of these wonderful comments, but I think, if I had a magic wand, I would restate the ability to listen. It's not only to the patient, but also to the community. When you are working, sometimes, in the environment that I am (in the emergency room, for example), you have your hand on the pulse of the patient, but you also have your hand on the pulse of the community and what's going on in that community, and also in the corporate environment as well. All of those are interacting together to impact the health of our patients, so I need to be able to listen to all of those inputs and to synthesize those in a way that can actually help the patients. That's the wand that I would like to have.

JB: Thank you. We obviously way exceeded the hour that I said we were going to have, but I should have known that with this group of deep thinkers and experienced souls. This has been a privilege. David, Graham, Jay, Jim, the two Brownings, Kristi, Mark—thanks. This has really been one of those magic moments. We often don't get this chance. This is like the great circle that, probably, chautauquas were built around (the Indian tradition of great sharing). This will be shared with many other people and I hope it will be as inspirational for them as it has been for me. Thank you very much

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