August 2014 Issue | Dr. Bland

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Welcome to *Functional Medicine Update*. We have what I hope will be a special treat for you this month, and that is, given where we have been going in the discussion of big data and the concepts of systems biology in medicine, and some of the extraordinary insight that we've had shared with us from luminaries like Dr. Lee Hood and Dr. Eric Schadt, I thought it might be very useful to just take a deep breath this month on *Functional Medicine Update* and really go back to basics, as they say, and do an issue on what I would call bridging big data with clinical practice.

The question is, how do these two…what might appear…disparate concepts intersect to improve the quality of patient care and to address the rising need for new ways of managing the dominant diseases that not only are plaguing the United States, but really are global in their prevalence. And in so doing, when we ask that question, it takes us into a very, very interesting reflective process as to what have we learned at this point in this complex field of systems biology in medicine that really we can, with some security, say applies directly to patient care in our advocacy for patient-centered medicine? So there is the focus of our attention in this issue. And fortunately, upon reflection, I think we can say there is extraordinary news to use that we can derive out of this evolving field, and it is my hope that by the end of this issue of *Functional Medicine Update* that we'll have pinned down a few of the how-tos, as well as the whys and hows that relate to this emerging, extraordinary revolution that's occurring in medicine.

INTERVIEW TRANSCRIPT

This full-length issue features commentary by

Dr. Bland without an interview

Framingham Changed the Practice of Medicine, But How Long Did It Take?

Let's go back for a moment, if we can, and ask the question in historical perspective: how long did it take for the Framingham studies to gain traction and start to change medicine, and the concept of risk factor analysis become a dominant theme in health care? The reason I ask that question is it helps to give us

some perspective as to how long it might take for these extraordinary revolutionary concepts of big data and systems biology in medicine to infiltrate patient care and ultimately transform medicine. Well, if you go back and study the Framingham work, you recall that it was in the late 1940s that advocates really set the tone for this large epidemiological prospective study to look at the relationships of people's lives to their disease patterns. In fact, somewhere around 1948 to 1950 was the inception of the concept of this serial analyses epidemiological study that has now gone on for the better part of five-plus decades.

It took until the 1960s, however, until the concept of the now very famous Framingham cardiovascular risk factors started to emerge and become general conceptual foundations of this new medicine related to prevention and risk factor reduction that was born out of these Framingham evaluations—these epidemiological associations between disease and lifestyle. And now we are all able to recite on demand the so-called Framingham cardiovascular risk factors—the hypercholesterolemia, the diabetes, the smoking, the obesity, the maleness, the age over 40, the hypertension, the risk factors that associate themselves with specific numerical increases in relative risk of an individual to have, within a certain period of time, a cardiovascular event.

New Concepts Must Be Accompanied By New Technologies

It was that concept coupled with the emergence of new technologies, particularly the fingerstick cholesterol blood test, that led to the emergence of this extraordinary development of pharmaceuticals that really were not there to treat an existing disease, but rather to prevent a disease, and I'm talking about the emergence, first, of lovastatin, or Mevacor, by Merck—the first marketed statin drug for lowering cholesterol that was delivered to the market. And then following on, the panoply of other pharmaceutical companies that developed their own statins, including what at the time was the most successful drug in the history of the pharmaceutical industry, atorvastatin, which as we know is Lipitor.

These drugs—these statin drugs—were not really designed to treat a disease, but to treat a risk factor, which was hypercholesterolemia, which had been associated out of Framingham and then follow on studies with a variety of other kinds of epidemiological association and animal interventions and looking at the various effects of hyperlipidemia on vascular function. Eventually this became codified and made cardiology into a form of preventive medicine, because now the cardiology field had a tool called the statin drugs that they could use to not only treat disease but also prevent disease. As I said, if we really were to examine how long it took for that concept to get incorporated into standard of practice, it was somehow from the time of the late 40s—say '48—into the middle 60s, so one could say 15 to 20 years it took to incorporate these concepts.

Big Data is Here: The Steps Toward Change

So with that as a background, let's now talk about the bridging of big data with clinical practice—the present state that we're in in this concept that we see emerging called systems biology and medicine. I'll first talk about James Fries, once again. You probably recall in the extraordinary interview we had the opportunity to have with Dr. Fries recently. We talked about his landmark paper that appeared in the New England Journal of Medicine in 1980, the paper that really talked about aging, compression of morbidity, and natural death.[1] And then the follow on paper that he and his colleague, Anthony Vita, published in the New England Journal of Medicine in 1998 titled "Aging Health Risk and Cumulative Disability," in which they were able to demonstrate, after 18 years from the publication of his first paper, that this

concept of the way people treat their genes through their lifestyle and their activities of daily living—their diet and the way that they see their health patterns—translates into demonstrable improvements in both life expectancy and the reduction of disability associated with chronic disease.[2] Meaning, the age of first infirmity is longer in these individuals who self-select to participate in certain lifestyle habits (no smoking, control of weight, good nutrition, and regular activity). They have an age-to-first-infirmity that is much later than those individuals who just take the luck of the draw.

So this concept that there is something within this interface between genes and environment that gives rise to the outcome that we call our health, which may seem like a very simple-minded concept, has a powerful potential influence on the trajectory of health and disease over the subsequent future. And then we ask the question: well, how does that actually get related to the individual? Is it a one-size-fits-all, or is it a personalized patient-centered approach, and what is emerging more and more through the genomic, or 'omics, revolution that we've been seeing since the announcement of the deciphering of the human genome in 2000, is that the personalization of these messages that relate to how an individual's genome intersects with their lifestyle and environment will improve efficiency of outcome and be more effective in reducing disease than a generic, one-size-fits-all message. And that is where the new medicine has an opportunity to be extraordinarily successful.

I find it really interesting that as we learned from Dr. Fries in our interview with him that he was a rheumatologist that really started to consider disability in his patients with rheumatological autoimmune diseases, and how he could improve their function over time. And it was through that that led him to recognize that this construct of improving function in patients with autoimmune disease that had musculoskeletal disabilities and pain and various infirmities could cross over into many other conditions, and it wasn't just specific to rheumatological diseases, but this concept of function really pertained to all diseases, and then it led him into the organ reserve concept and the maintenance of organ reserve by practicing the right types of things in one's life through good diet, nutrition, exercise, proper environmental management, to maximize the opportunity for the genes to express the function of good health, rather than the alarm function that we associate with inflammation and disease. So I credit Dr. Fries as a rheumatologist as being a philosopher cum physician, really expanding his view and perspective beyond that of his own discipline to look at the impact that these concepts had on health care and medicine in general. In fact, there's a wonderful article that appeared in the American Journal of Public Health in July of 2008, volume 98, page 1163 that talks about Dr. Fries as a healthy aging pioneer and how he really set the tone for this whole field over those years.[3]

So now we are in 2014 and watching the effects of medicine that's focused principally on diagnosing a disease and treating the outcome of the biomarkers of disease rather than implementing the Fries model of compressing morbidity and improving organ reserve. And as we start to look at those impacts they are pretty alarming. I recently read an article that appeared in Pharmaceutical Executive magazine titled "The Peace Dividend," in which the editorial talked about the rising tide of type 2 diabetes, not just in the United States, but globally—talking about the epidemic increase in type 2 diabetes that's occurring, not because the genes of these populations suddenly changed, but because their environment changed and the genes were receiving a new message: the western lifestyle of stress, and pollution, and poor quality diet that was then creating—almost overnight—an exponential increase in the appearance of type 2 diabetes.[4]

He talks, in this editorial, about the Middle East, and I was a little naïve to the severity of this same problem (the epidemic of type 2 diabetes and obesity) in the Middle East. Saudi Arabia, for instance,

recorded four hundred thousand deaths from diabetes last year alone. More than half of these victims were under the age of 60. And the cost of this is over 12 billion dollars in 2012, which is a small fraction of the nearly 120 billion dollars spent on arms purchases, I might add, but yet represent an extraordinary condition that is associated with the social and environmental aspects of the people living in these countries—their diet, their stress patterns, their environment, their pollution, and so forth. We're starting to witness almost what I would call exporting chronic disease to the rest of the world as a consequence of the adverse impact—I would call it the hostile interrelationship—between these environmental lifestyle principles that have been part of the western lifestyle, with the genotypes of other cultures around the world.

In the Lancet medical magazine, recently, there were a variety of very interesting papers that talked about improving health in the United States and progress and challenges. You know, although life expectancy at birth is now up to 78.7 years (which is 76 years for men and 81 years for women), one might say, "Gee whiz, that sounds really great. We're achieving longer life." However, if we start looking for age-adjusted death rates for the four leading causes of death—heart disease, cancer, chronic respiratory diseases, and stroke—we would say, "Yes, they're falling, but we're seeing early-age of morbidity, meaning, early-age of need for medicines and intervention." So we might be misled into thinking that although the quantity of life is increasing the quality of life is equally increasing, and that's not the case. Actually what we are seeing is a decrease in the quality as increasing infirmity starts encroaching on younger age. But we are able to keep people put together with baling wire and bubble gum—that's kind of a little exaggeration, but we're able to keep them still alive for longer periods of time, but the quality of life is not necessarily that which gives them the freedom to do what they want, the high functional capacity.

So it's this chronic disease incidence that is really the problem, the unremitting progression of chronic disease. And if we start looking at differences in health outcomes in the United States versus other countries, it's quite interesting. In 2012, you probably know we spent 2.8 trillion dollars on health care, or about $8915 dollars per person per year, which accounted for a little over 17 percent of the gross national product. And these expenditures exceed those of all other high income countries in Europe, Asia, and North America. However, in World Health Organization grading of health outcomes, we're down in the world. So, there is some interesting paradox between spending more, keeping people alive, but health outcomes are depreciated. It would suggest that maybe our model that we're using is in need of revision.

And so that leads into a very, very interesting article that just appeared in the Lancet, volume 384, July issue of 2014 titled "Prevention of Chronic Disease in the 21st Century: Elimination of the Leading Preventable Causes of Premature Death and Disability."[5] And in this particular article they go on to say that basically what we are witnessing is an extraordinary increase in many of these chronic illnesses that are plaguing not just the late-age individuals who are at the terminal end of their life expectancy, but also starting to encroach on younger-age individuals and put a greater demand on burden in healthcare delivery systems.

Things like kidney dialysis are going up dramatically. Ocular problems that relate to retinopathy are going up dramatically. Issues that are related to neurological conditions, particularly peripheral neuropathy, are going up dramatically. These are all associated risk factors with type 2 diabetes and with this insulin resistance pandemic that we're seeing not just in the United States but in the world at large. And there's no drug that has yet been developed that is going to beat back this rising tide. It requires a

different model—a different approach. And so that has to do with making primary care patient-centered in the 21st century, and there's another very, very interesting paper, in the Lancet again, volume 384, page 281—this is the July 26 issue—talking about how primary care should become really focused on managing through this gene-environment-lifestyle interaction, the individual risk factors that people have that can be modified in their phenotypic expression so that the outcome is reduction of risk to early-age-related chronic illness.[6] And I think this is something we all know. It's intuitively obvious, but then the question is: what do we do about it?

So that's really the focus of what I want to talk about in the remaining time in this issue of Functional Medicine Update. It's how we take this extraordinary knowledge that's emerging from pioneers like Dr. Eric Schadt and Dr. Lee Hood and his colleagues and translate that into operational and executional practice policies that really create a different standard of care.

The Patient Value Equation is Driving Information Availability, Technology, and Business Models

Now one of the wild cards we have today that is going to help this, obviously, is the Internet. You know, we don't have the patience, probably, to wait 25 years to get all of this implemented. Fortunately, thanks to the Internet, the compression of information and timeline that we can get things out more quickly to people and informed consumers can start making decisions for themselves and this is going to become much more a patient engagement process than it's been in the past. In fact, the Affordable Healthcare Act, as you probably recognize, is pushing more responsibility back to patients to make individual decisions about health, and fortunately we have the benefit of the Internet to do so.

Recently I read a very interesting editorial—actually it was an interview—with the present CEO of WebMD, David Schlanger, who was talking about how he views (as the CEO of WebMD) the future of this information service, and of course what they see is that the patient is at the center of their universe.[7] The patient value equation is what will drive WebMD's business model over the years to come. In fact, there's a very interesting discussion about how they view the dissemination of information and patient management technologies and interfacing with wearable devices and biometrics, and start accumulating all this information in real time and providing competent data reduction and information to the consumer about how to tune up their metabolism and how to personalize their program. They see their business model—as WebMD moves forward in the future—as being one of the providers of this type of what I would call personalized, lifestyle, medical information.

Clearly this is just one of many companies that we're going to see in the fray. We know now that Apple is certainly focused on this direction. We know of Google's enterprise in this area. We've heard that Microsoft has had, certainly, interest in this area. And you will find many, many companies emerge to become the providers of health care through this big data analysis and real-time evaluation of how a person is functioning that will really transform medicine. It will provide tools for the physician to be able to better understand the warp and weft of their patients so that they can really design individualized programs for them rather than defaulting to medicine for the average. As Roger Williams said—and I've quoted this many times—"Medicine is for the real person, statistical humans are of little interest." So I think this patient value equation component is going to be a very big part of this translation of big data into patient management.

Three Fields Already Embracing Translational Medicine

So that really relates to personalized medicine moving from the bench to the bedside. And so where is it happening right now? Where can we say that we're actually seeing this translational medicine occurring? Really there are three places where it can occur, two of which we're starting to see significant change in, one of which is already a standard of care. Let's talk about those three areas.

Personalized Oncology

The first is oncology, and you can already see personalized oncology centers rising up around the country. In fact, virtually every cancer treatment center now has to have a genomics unit because we're now seeing personal tumor typing becoming the standard of care in many cancer treatment centers, where the cells from the tumors are analyzed for their specific mutational injuries and then specific drugs that are influencing that mutation can be administered. I think Gleevec and Herceptin are two really good examples of drugs that have come out of the kinase inhibitor research that relate to specific mutations or specific genotypes that are responsive to certain drugs, making this patient-centered so that basically what you get is a drug cocktail patterned and personalized to your own genetic need for your tumor type. And interestingly when this has been done—and there are companies like Translational Genomics that are doing this commercially, and many others in the field—what is found is that many times off-label drugs (drugs that were approved for other uses) may be actually effective for individual types of tumors in a person, and they are not even really thought of as oncology drugs, but they have a unique sensitivity to that specific genetic type of tumor in that person.

So this is truly a front edge of how we translate this concept of systems biology into clinical practice and start getting a personalized medicine to emerge, and we're starting to see now that full human genome can be analyzed using the aluminum platform and that the FDA has now approved genome analysis as a medical technology test/device, it has really started to open the door for this to become a fairly routine type of analysis, particularly in oncology, but moving on into other fields as well.

Now you recall this is built around an economic model to say that the analysis of the genome now is moving down to a thousand dollars or less, which makes it comparable to a standard kind of high-end laboratory test, and once this genome has been analyzed, it's kind a universal test of all tests because you don't need to analyze it again; you've got that record for the rest of your life. There might be an occasion somewhere in your life where—if you have an oncogenic event—you want to measure the tumor DNA to see if it's mutated, but in terms of a record of your book of life that stays with you for your life—your human genome.

Genetic Disease and Inborn Errors of Metabolism

I think this is another extraordinary sign of major changes as we start seeing the thousand dollar genome being able to be routinely analyzed, and then the question is, once it has been decoded, or been chemically analyzed for the nucleotide sequence, then how is that information going to be developed into a personalized program that is uniquely applicable to the individual and can be done in real life, not in a lab animal? And that's where, I think, the next area of application of personalized medicine is occurring, which is in neonatal inborn errors of metabolism (diseases of infancy). You know, we've always known about things like Tay-Sachs, Wilson's, Gaucher's, Fabry's, megaloblastic anemias, things that relate to these genetic inborn errors that we've been searching for solutions to. And now, with better understanding of the variant forms in which these exist, and that they are not always expressing the same

phenotypic outcome—use Down's syndrome as an example. I mean, Down's can exist in the phenotype in all sorts of different levels of severity. The more mild forms can be very well managed with good personalized intervention, again, a lot dealing with lifestyle: diet, nutrition, exercise patterning, visual training, intellectual stimulation, things of this nature.

And so there are many different things—as we broaden the construct or the lens of medicine—that can be included within a personalized medical therapy other than just a pill for the ill—that we're looking at a much broader platform of therapeutics that can be deployed to the personalization of even these genetic metabolism diseases of infancy.

Chronic Degenerative Diseases

The third area is the one that has the greatest obvious consumer application potential, but also poses the biggest issue of challenge, and that's these common garden variety chronic degenerative diseases. This includes things like type 2 diabetes, and coronary vascular disease, and arthritis (or let's call it autoimmune diseases), and dementia, chronic obstructive pulmonary disorders, and this wider range of chronic diseases is where the big pay-off can come from personalization, but it's also where the challenge resides, because we recognize that not one of those diseases I just mentioned is the result of a single gene-inherited problem. They are not monogenetic; they are polygenetic. There is no gene for type 2 diabetes that sits alone in the book of life, or no gene for rheumatoid arthritis, or no gene for myasthenia gravis, or multiple sclerosis. These are polygenetic disorders that relate to genetic strengths and weaknesses and susceptibilities and tolerances that have to do with the environment, lifestyle, and situation that that person has found themselves in probably from the moment of conception on—so in utero, post-utero, and throughout their developing period. So this is a much more complex problem. But the nice thing about the problem is that even if we don't answer at all, even first steps along the path of understand can produce some significant improvements in outcome.

So I think that's how we have to approach this knowing that there is lots left to learn—and probably will be for decades to come—but even at this point in time, with our relative infancy about the genomic relationship to these disorders we're starting to pan some gold and starting to recognize how to better improve outcome and efficacy through personalization. And so that's where I want to take this next part of our discussion. And of course we learned quite a bit about this from the extraordinary interview we had with Dr. Eric Schadt, who talked to us about this clues-from-the-resilient concept. You know, we often focus all of our concerns in our genomic information about the relative risk that we carry in our genes to a disease, as if we want to skirt all risk and stay at the sidebar of life because we might have gotten a bad gene somehow stuck into our book of life. But his point is that actually we should be looking at it from the other side and say, "What are the genes that we have that provide resilience?" Because if we didn't have these resilience genes, none of us would survive to adulthood. So our genes—our book of life—has many, many strengths that we need to understand more as to how to optimize our relative expression of these strengths into the phenotype and not just skirt around through the fear of our "weaknesses" or our susceptibilities. And the way we understand more about our strengths or our resilience factors is to study those who are resilient: study the 90-, 100-, 105-year-old individuals who have lived a very healthy life, have probably gone through life not having an optimal environment at all times, but somehow are still functional and have had a great percentage of decades of their lives as disease-free, and ask, "What are those resilience factors that are within their genome?"

I think this is going to be a very powerful part of our dialogue with regard to the understanding of our genetic inheritance over the years to come. Because right now when we get our gene analysis back it's always about our relative risk to disease. Wouldn't it be neat if we got an analysis back that was about our relative strengths in the prevention of disease? And then if we actually worked on these things and we supported them with the appropriate tools that are necessary for those genes to be expressed that we would become a member of the resilient family, not a member of the disease family? And I think that's what Dr. Schadt is talking about and you recall he spoke to this very nice article that he and Stephen Friend, his colleague, authored in Science magazine in May of 2014 in volume 344, page 970, talking about clues from the resilient—how genetic information from individuals who do not succumb to disease points to new therapies and ideas about wellness, and it's about wellness that we should be focusing our attention, not just on disease risk and the Framingham old model of risk factors.[8]

The Role of Genetics in Chronic Disease

Now with that said, let's move now into how this all applies clinically. I'd like to take, for the sake of our discussion, the representative series of conditions that you are all familiar with that are dominant members of the chronic disease family. Let's start with type 2 diabetes. What do we know about genetic susceptibility to type 2 diabetes and its companion phenotypic issue, which is central obesity (central adiposity)? Now we know that central adiposity is associated with a fairly easy-to-assess characteristic, which is increased waist-to-hip ratio? So when we see people who have waist-to-hip ratios that exceed 1.2 or greater now we start to consider some type of what we call central adiposity. This is where intra-abdominal adiposity starts to become a potential health risk hazard.

Now you recall—just for the sake of review quickly—that we have subcutaneous fat which seems to have a differential impact on health risk from that of intra-abdominal fat (or visceral fat). There's actually some evidence to suggest that subcutaneous fat is associated with relative reduction of certain health risks because it provides a reservoir to soak up excess lipid in a fairly neutral way without adversely impinging upon cellular signaling that we associate with disease. So we might say subcutaneous fat is a different personality in terms of health risk than intra-abdominal fat. It's fat that sticks around our organs that is associated with what's often called belly fat is that which releases various types of mediator substances directly into the portal blood, which then affects the liver and affects systemic circulation in such a way as to produce what I would call angry fat, or a chronic state of inflammation that some people call metabolic inflammation (or meta inflammation). It's that condition that we often associate with the origin and the etiology of many chronic diseases, including, obviously, type 2 diabetes and vascular disease as well (or cardiometabolic disease).

What are the relative risk factors, or what we might call genetic susceptibilities? Are there any specific genes that stand out? There have been many studies—what are called GWAS studies (Genome-Wide Association Studies) to try to identify in large populations specific SNPs that are highly associated with this personality archetype (this metabolic personality type of meta-inflammation)? I think it is very interesting that when you look at these GWAS studies, you'll often find because of the large size of these studies, sometimes with thousands of patients that have had their genomes analyzed, that the relative significant correlation coefficients are extraordinarily strong between a specific SNP and a specific disease. And that is, I think, quite interesting because you might say, "Oh, now we have a solution to the problem."

But actually what has often happened is when you take that information and you try to direct a certain pharmaceutical for that SNP, it doesn't prove to be very successful clinically, and the reason for it is that although there is a high association of that SNP with that disease, it's also associated with many other genes. It doesn't work just by itself. So correctly just one gene doesn't solve the problem as it relates to these chronic illnesses. It's a complex network biology disturbance, so I call this disturbed metabolism, and disturbed metabolism is a consequence like if you pull on a net: if you pull on one little frame of a net it distorts the whole net, it doesn't just distort that one little area that you're tugging on (that corner of the net). This is the way chronic disease really manifests in genealogy (in gene expression patterns)—disturbance or distortion of one portion of the web creates a perturbation in the web at large. So just changing one cell doesn't change the whole of the pattern.

However, with that said there are certain genes that do appear to be prominent in terms of their SNP connection to cardiometabolic disease and this metabolic inflammation, and those are genes that relate to mitochondrial oxidative phosphorylation, oxidative stress, energy economy (bioenergetics, in other words), which takes us back once again to an interesting confluence of how energy is produced within cells (like the endocrine beta cells of the pancreas or cells in the neurons that are highly rich in mitochondria, or cells in the heart, which, as you know, seventy-five percent of the volume of a cardiocyte is occupied by mitochondria, which are the energy powerhouse of the cells). I don't want to say that all paths lead to enlightenment, but what I do want to say is that this mitochondria/bioenergetic connection to chronic disease across a wide range of clinical diagnoses, including diabetes and heart disease and dementia and even into inflammatory autoimmune diseases, is an interesting unifying principle, and what is it, then, that causes dysfunction with regard to these bioenergetic pathways? Well there are many factors that I guess we would tease out from a functional medicine perspective. There's a very nice review paper on the genetic susceptibility to type 2 diabetes and obesity, the follow-up from findings over the last ten years of the genome-wide association studies. This appeared in the International Journal of Endocrinology in 2014 in the July issue.[9] I think it's a very good overview of both some of the positive things that we've learned from these association studies, but also some of the things that demonstrate to us that these chronic diseases are much more complex than single monogenetic disorders.

Will Drugs of the Future Address Genetic Expression Rather Than Symptoms?

We need a systems approach to diabetes is really what comes out of this. The single drug for a single outcome, although we've got the DPP4 inhibitors, we've got the integrins, which are things like the GLP-1 analogs, we've got metformin, we've got the TZDs (the thiazolidinedione drugs for diabetes), we have insulin, obviously, sulfonylurea. So there's a variety of different classes of diabetic drugs, but none of them really treats the disease, they treat the effect of the disease, and so the question really comes down to, can you move upstream from these through a systems approach to diabetes to actually improve the expression of genes that are associated with a downstream phenotype that we call diabetes? And that model is starting to gain some traction. I think this is the new "ah-ha" that is emerging out of this systems biology approach to health care that Dr. Hood and Dr. Schadt were speaking to in their concepts. In fact, in a very nice review article that appeared in Frontiers in Genetics just recently titled "Perspective: A Systems Approach to Diabetes," the authors go on to talk about how the modulation of a variety of factors within the environment can improve genetic expression into the phenotype, improve insulin sensitivity, reduce demands on the beta cell to produce insulin, reduce lipogenesis and hypertriglyceridemia, and significantly reduce postprandial area under the glucose and insulin curve.[10] Here we're starting to say maybe the treatment of choice for type 2 diabetes is not the single drug or poly-

drug therapy, but rather this complex systems approach that we have talked about as personalized lifestyle medicine.

Personalizing the Diet is Just as Important as Personalizing Pharmacology

So what are the tools that we have? Well, fortunately we've learned quite a bit over the years. Dr. David Jenkins, University of Toronto, Department of Endocrinology/Gastroenterology, is the father of the glycemic index, which was the first approach to try to understand how diet puts demands on beta cell secretion of insulin and has an effect, then, on glucose metabolism. I think that that contribution to our understanding was the cornerstone of building this new view as to the extraordinary impact that diet has and the components of diet and the ingredients and the constituents within our diet on the regulation of insulin signaling and what's called intracellular signal transduction that leads to GLUT-4 receptors, ultimately transporting glucose across cellular membranes and controlling mitochondrial oxidative phosphorylation processes and glucose metabolism.

From the glycemic index was developed the glycemic load concept—that glycemic load is the postprandial effect of a diet or a meal—not just one food at a time, which was the glycemic index, but a complex meal—on the postprandial excursion of insulin and glucose. And what we found is you can start measuring glycemic load effects of diets and compare them from individual to individual, and we found that not all people respond to the same pre-prepared meal in the same way relative to their management of that glycemic load. So this gets into personalization. And people say, "Well what's the best dietary approach? Is it the high protein/higher fat/lower carbohydrate approach, is it the Paleo approach, is it the Pritikin/Ornish approach high complex carbohydrate/low fat/high dietary fiber approach, or is it the Atkins approach, or is it the Sears approach of the Zone? What is the way that we should move on doing this?" And my answer is, "It's probably all and none of those particular approaches. Meaning, the individual has their own response to the macronutrient composition and the physical nature of their diet. It's built on their unique genotype.

No Single Dietary Approach Will Work for Everyone

So we shouldn't lock ourselves into one dietary approach for all. Again, it's just as dangerous as saying there is one drug for all—that statins work on everybody. We need to recognize there is extraordinary difference among response in individuals to the same diet. If you take the same, what we consider "good" meal—let's call it the low-glycemic load, modified Mediterranean diet with no gluten—and you give that to a hundred people, all of whom have some degree of glucose intolerance, will you get the same result in all 100? Of course you don't. You get a wide range. Some people have elevations of their postprandial glucose on that approach. And other people—in fact actually most people—will have fairly significant lowering of their insulin and glucose response from that kind of dietary approach. So I think what I'm trying to really advocate is that we should become students of all of these kinds of dietary studies that are relating macronutrient composition and the physical nature of an unrefined diet (or minimally processed diet) on insulin and glucose, and be able to harness those concepts for individualization of the diets of the patient. Not just say, "Here is one sheet we give to every patient and that's the program you're going to be on and—come hell or high water—that's the answer to all questions." I don't think there is such a diet for all people that is the answer to all questions.

But we do know there are certain dietary principles that are important, and minimally processed is one.

Diets higher in plant-based foods is another (complex plant-based foods). The third is not to be overly attentive to the worry about excessive fats, but try to stay away from excessive levels of the long-chain saturated fatty acids. These are the fats that easily solidify at room temperature (become solid). I think we want to move more to the oils and fats that are liquid at room temperature. These are the mono- and polyunsaturated fats of differing families, omega-6 and omega-3. I'm not saying that a little bit of saturated fat in the diet is going to create serious problems. I'm just saying that if we were to look at fat overall, a significant percentage of it should be that which is liquid at room temperature if we were to isolate it. I think that this also falls into things that we call medium-chain triglycerides. Those are lower melting than the long-chain fatty acids that I described earlier (the saturated long-chain fatty acids). Your medium-chain triglycerides or medium-chained fatty acids like propionic, butyric, caprylic—those particular fatty acids have a different physiology. They are more easily regulated by mitochondrial oxidative phosphorylation than these long-chain saturated fatty acids.

So I think there are certain principles that we can employ, recalling also that dietary fiber is a very important component for flattening out the postprandial glucose curve and putting less demand on the beta cells to secrete insulin, and specific soluble fibers—there's a whole range of these—that can also serve as prebiotics, so you get a double-barrel benefit because they also can be food for friendly bacteria and we know how important the microbiome is for modulating insulin sensitivity, so you want a friendly microbiome to give friendly communications between insulin and your cells. So, you get a double-duty benefit from use of certain prebiotics: arabinogalactans, large fructans, various types of what we consider non-metabolizable carbohydrate that's often called plant fiber that's soluble. These are all beneficial for smoothing out the glucose postprandial curve.

We also recognize that there are forms of starch that can be more resistant to immediate breakdown by amylase enzymes, and this resistant starch slows the release of glucose into the blood and therefore has a salutary or beneficial effect on flattening the postprandial curve. There are all sorts of dietary variables, right? And by the way, when I talked about fiber and starch, I'm obviously talking about plant foods. You don't get a lot of fiber and starch in animal products. That's why I think that this concept of a very high plant-based diet makes very good sense on many levels, particularly if we were going to talk about the additional benefit that phytochemicals have, which we're going to be discussing. And also, minimally processed, plant-based foods bring a lot of good vitamins and minerals with them, too. Magnesium obviously is part of chlorophyll—a very important regulator of glucose tolerance. And we have things like biotin, which we know is extraordinarily important, and thiamin, which is very important—in fact, these can be given in supplementary doses to improve glucose tolerance in a person that has insulin resistance. We know that therapeutic doses of biotin can be helpful. Similarly with thiamin. Benfotiamine is a derivative or an analog of thiamin, which has been found also to be very useful for improving glucose tolerance in individuals who have insulin resistance. So we know there are a variety of nutrients in the mineral family. Of course it's legendary, the Klaus Schwarz work done on chromium and its effect as a glucose tolerance factor in helping to regulate insulin sensitivity. So you get these substances in higher levels in minimally processed plant-based foods. Again I want to emphasize, let's not lock ourselves into a religion about diet; let's look at the dietary principles that give rise to improved insulin sensitivity.

What I have been summarizing is a very interesting paper that is titled "Prevention and Management of Type 2 Diabetes: Dietary Components and Nutritional Strategies." This is authored by Frank Hu and his colleagues at Harvard School of Public Health, who is a world leader in this complex understanding of diet and its relationship to chronic disease. This article appeared in the Lancet, volume 383, page 1999 in

2013, so I think this is another very interesting citation that helps us to understand the important role of how you personalize an approach towards these chronic diseases.[11]

Dementia: Examining the Question of Genetic Risk versus Lifestyle Factors

Let's move from there to brain aging and dementia, because we now know from Suzanne Craft, who you probably recall was one of our clinicians of the month that talked about the interrelationship between insulin resistance and hyperinsulinemia and dementia and that it cuts across both diabetes and dementia. In fact, there is now evidence to call this type 3 diabetes with Alzheimer's disease. So there is a greater and greater need for us to recognize a cross-relationship between the comorbidities of type 2 diabetes and dementia, and there is a very interesting question as to whether all of this dementia is really just a consequence of our inheritance: did we just inherit in our genes the risk to dementia? And of course there is some relative risk that's associated with certain genetic susceptibilities. The one that is most commonly talked about is the apo-E double 4 allele with Alzheimer's disease. It's interesting, however, to note that the apo-E4 double allele is also associated with a significant increase in risk of cardiovascular disease, which suggests that they share common etiological pathways of some aspect of oxidative injury and inflammation. And so this is an example where a double E4 requires a very vigilant review of diet and lifestyle. And these are individuals that are very sensitive to high saturated fat intake. In fact, the evidence would suggest that they translate high saturated dietary fat quickly into oxidative inflammatory injury when they carry this double E4 allele. So these are people that need to rigorously exclude high saturated fats from their diet. They need to be very assiduous about the higher complex carbohydrate/higher fiber/low glycemic load-type approaches with higher amounts of plant-based protein and improved intake of plant-rich polyunsaturated fatty acids.

For most individuals, however, the genetic linkage to dementia is fairly low. And in fact there is a very interesting paper that just appeared in the Current Opinions in Psychiatry in March of 2014 in which they looked at the Swedish twin studies.[12] As you probably know, because of the socialized medical system and medical record-keeping in Sweden and in other Scandinavian countries, that there is very good ability to interrogate identical twin and health information over the course of living. And there is no better control, from a genomic perspective, than your identical twin.

And so the question is, what's the concordance of diseases like dementia between pairs of identical twins? The answer to that is that there is very little concordance for mild-to-moderate dementia between pairs of identical twins, suggesting that the environment plays a very important role. So there's not a high hereditability of the mild-to-moderate forms of dementia. These co-twin control studies support the role of mid-life lifestyle factors as being the most important determinants for cognitive aging and late-in-life dementia. I think this is a very important point for us to keep in mind.

Pathology-Supported Genetic Testing

And so when we start looking at the pathology-supported genetic testing and treatment of cardiovascular disease and Alzheimer's disease, it leads us into new conceptual frameworks. Now what did I just say? Let me stop for a moment. I said, "pathology-supported genetic testing." Now what's that mean? What it means is that having a gene that you ascribe as a risk or a susceptibility factor to disease, does not mean that that gene is expressed into the phenotype of the disease. It just means it's there. It doesn't mean it's expressed.

So how do you know if it's expressed? You do the expression by looking at the phenotypic markers, don't you? Which is the pathology-supported genetic testing. It's the combination of genotypic testing and phenotypic testing. So, for instance, you might say you have a gene SNP for a specific form of interleukin 1-beta, which gives you an increased susceptibility to inflammatory disorders. But if that gene is not expressed, then you will not see in the phenotype higher levels of inflammatory mediators, like TNF-alpha, or IL-6, or hs-CRP. You need the combination of understanding the relative susceptibility, which is your genotypic analysis, and then the pathology-supported phenotypic marker to see if it's really expressed. It's a combination of the two.

So it's not just what's in your genes alone. It's what is expressed in your genes that's really the most important feature, and that is a very important takeaway from what we've learned in this whole field of genomics or 'omics (how genomics gets translated into the 'omics of proteomics and ultimately into metabolomics into phenomics). This article that I'm really speaking to, which is in Metabolism of Brain Disorders and was published in 2012, talks about genetic relationships between cardiovascular disease and Alzheimer's disease.[13] Because it is now recognized that individuals who have CVD in middle life have a higher incidence of Alzheimer's disease because they share co-variable susceptibilities for the etiology of both diseases.

So, what do we know is one of the major susceptibility factors? Well, I talked about one: apoE. Apo-E4 double allele is a major risk factor. It's not a death sentence, but it's a susceptibility factor that one has to manage by rigorous lifestyle intervention. The other one that you're familiar with is methylenetetrahydrofolate reductase (MTHFR). MTHFR also plays a very important role in relative risk to both cardiovascular disease and Alzheimer's disease, and we know, don't we, how to manage a polymorphic change—say a CT677 SNP—for MTHFR. We do so by increasing folate intake. Now, the best way of increasing folate, based on evidence that's been published over the last few years, is 5-methyltetrahydrofolate versus folic acid itself. 5-methyltetrahydrofolate will not mask, by the way, vitamin B12 deficiency, which folic acid will. So you won't get alterations in MCVs with 5-MTHF. My suggestion whenever you use 5-methyltetrahydrofolate as your folic acid, is that you also just for security give concomitantly methylcobalamin. That's a methylated form of vitamin B12, or at least hydroxylcobalamin. And you also give pyridoxine and you give betaine. Betaine is a methyl transfer agent. They should be given in combination.

So what would be a good formula that one might consider? It would be a formula that would deliver a thousand micrograms of 5-methyltetrahydrofolate, something on the order of 5 milligrams of pyridoxine, something on the order of 100 to 500 milligrams of betaine, and it would deliver something on the order of a hundred micrograms of methylcobalamin or hydroxylcobalamin. That's kind of in the range of what I would consider to be early-stage therapeutic range, not into heavy hitting therapeutic range. You might use, in some cases, several thousand milligrams of 5-methyltetrahydrofolate for a real resistant MTHFR polymorphism, but I think as a get-started cocktail of nutrients, that's a fairly good range of balance between the various members of the 1-carbon pathway (the nutrients that influence the transfer of methyl groups through s-adenosylmethionine). And you probably recognize that a surrogate marker in the phenotype for this concern is methylmelonic acid. Methylmelonic acid can be evaluated as well as homocysteine, so those two analytes that you can measure in the blood, homocysteine probably being the more common of the two in terms of routine clinical evaluation, both give some evidence and allow to interrogate the sufficiency of intake of those nutrients that are associated with the folate cycle.

You might say, “Well what would be considered a level of homocysteine that would be of some concern?” I think when you get above 11 nanograms per mil of homocysteine that you’re into a range of concern. We also are concerned about homocysteines that are too low, and there are examples. You know, the edge of the bell curve on both sides is an indication of dysfunction in metabolism, so if you get homocysteines that are below 5, then you probably also are experiencing defects in methyl transfer. So too low a level of homocysteine or too high a level of homocysteine is a surrogate for further evaluation of the sufficiency of these pathways that regulate 1-carbon methyl transfers through s-adenosylmethionine. A very, very critically important pathway for neuronal and cardiovascular function, for hormonal function because this is the methyl that is used for metabolism of adrenalin into noradrenalin, so we start getting into very important regulatory pathways that are associated with the MTHFR (the methylenetetrahydrofolate reductase pathway). And as you probably recall, this is the fundamental best-understood area of nutrigenomics presently because we recognize that something on the order of 30 percent of the population at large has a mixed MTHFR genotype between the wild type and between these SNPs that are lower activity transfer agents for folic acid methylation. We also recognize that about ten percent of the population has the double allele of MTHFR CT677, so that would be your double hit, which has even a more serious adverse impact upon methyl transfer reactions.

So the MTHFR 677T polymorphism contributes to increased risk to both vascular disease and dementia. There is a variety of very important studies that have been published over the last few years that show this relative risk factor, one of which appeared in the Journal of Neurological Science in volume 294, page 74 that shows the co-variable relationship of risk to these two diseases—vascular disease and dementia, and of course vascular dementia—and the appearance of this particular SNP, and also how this can be modified through augmentation of those specific nutrients that are necessary to overcome this genetic kind of weakness or block.[14]

A companion SNP in this pathway of methyl transfer is the enzyme catechol-O-methyltransferase, or COMT. We recognize that COMT polymorphisms also can contribute to increased risk to these disorders, and also contribute to increased risk to things like fibromyalgia pain and other chronic pain syndromes, and this probably has to do with the effects COMT has with catecholamine metabolism. So what do you do if you have a slow COMT? A SNP that slows your COMT activity? Again, activating your levels of s-adenosylmethionine, which is the cofactor, helps to drive that equilibrium of a sluggish COMT to completion. So how do you do that? Again, you come back to augment the intake of these folic acid active nutrients, which is 5-methyltetrahydrofolate, methycobalamin, pyridoxine, and betaine to improve the conversion to SAM, which then, as a cofactor for COMT, helps to drive COMT to improved methyl transfer reactions. And it’s been shown that the COMT gene polymorphisms are associated with chronic human pain, particularly in fibromyalgia and some of these other chronic pain syndromes. This is in Pharmacogenetics and Genomics in volume 22, page 673, that made these associations.[15]

So we know, then, there are certain genotypes that do have increasing relative risk based upon their SNP presence, but we also recognize that you can overcome many of these chronic SNP associations by augmentation of your nutritional intake. This recent advance in understanding of how nutrition plays a role in driving genetic sluggish enzymes to completion is really a consistent concept with that of Dr. Roger Williams and that of Dr. Linus Pauling years ago. You probably recall that Roger Williams has this genetotrophic theory of disease in the 1950s and Dr. Pauling talked about orthomolecular medicine. Similar concepts of using these natural precursors to help improve enzyme function in the individuals with specific genetic limitations. And in fact, there is a very nice paper that appeared in the Proceedings

of the Nutrition Society in volume 71, page 581, talking about how nutrition can be utilized in therapeutic levels to modulate the expression of genes that are associated, then, with improved brain function/brain health, and treat things including potential mental disorders like schizophrenia.[16] This, of course, is Abram Hoffer's work that we were so fortunate to have as a clinician of the month years ago, now deceased. But Dr. Hoffer was really one of the founding fathers of the field of orthomolecular psychiatry and the use of things like niacin and pyridoxine and ascorbic acid for the management of certain neurological diseases.

Modulation of Gene Expression by Phytochemicals

Now since then we've recognized that plants contain substances that help to augment this function as well. These are called the phytochemicals associated with xenohormesis, and you recall we had Dr. David Sinclair from Harvard, who was discussing the xenohormetic concept with us as it pertains to various plant phytochemicals that can modulate, favorably, gene expression, and he talked specifically about epigallocatechin gallate from green tea and he also talked about curcumin from turmeric and he also talked about resveratrol from grape skins and peanut skins and how these are phytochemicals that xenohormetically modulate the inflammatory pathway and things like the sirtuin pathways. The sirtuin pathways are NAD-dependent reactions that relate to genomic structure and allow opening up of the genome so certain regions of it can be read. And the person who has probably done the most work in this area as it relates to neurological diseases and phytochemicals is Dr. Mark Mattson at the National Institutes of Health. He has a wide range of papers over the last ten years that really talks about hormetic phytochemicals and neurological disorders, one of which is a very interesting paper in Neuromolecular Medicine titled "Hormetic Dietary Phytochemicals" and talking about the role that higher levels of intake of these particular phytochemicals like curcumin can have in reducing the risk of neurological degenerative disorders, including Alzheimer's and Parkinson's disease, and that these modulate pathways like the nuclear regulatory factor 2 antioxidant response element pathway (NRF2-ARE), which is a fundamental pathway that is engaged in mitochondrial function that has to do with both detoxification and protection against oxidative stress.[17] And that these particular phytochemicals—curcumin, epigallocatechin gallate, and resveratrol being three examples—are very powerful in their ability to help regulate the intercellular signaling that regulates the NRF2 expression and the antioxidant response element expression

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