May 2006 Issue | Ruth DeBusk, PhD, RD Mahan Center

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Welcome to Functional Medicine Update for May 2006. This is going to be an exciting month following on the heels of the 13th International Symposium on Functional Medicine in Tampa, Florida, which always lifts my energy and enthusiasm as to functional medicine beginning to "have its day." And the Textbook of Functional Medicine has certainly helped to put functional medicine on the marquis.

DNA Diet: Bogus or Breakthrough?
This month, we are going to focus on nutrigenomics and the clinical application of that concept. What is nutrigenomics? What is the future of nutrigenomics? What can it do to improve patient outcome? Some of you probably saw the segment on ABC's Good Morning America recently, in which the topic, "DNA Diets, Bogus or Breakthrough?" was discussed.[1] The commentators talked about the use of genetic testing to evaluate nutritional needs. Dr. David Heber, a colleague and friend, and a professor of medicine at the UCLA Center for Human Nutrition, described this revolutionary new change in nutrition-the nutrigenomics evolution. This is probably the most remarkable thing that has happened in the interface between nutrition and medicine in decades.

Nutrigenomic Testing
There are now a number of commercial laboratories offering nutrigenomic tests that evaluate some of the genetic uniquenesses that may require specific types of nutrients or diets to be personalized to an individual's need. This becomes the birthing of a personalized medicine that is the culmination of what Dr. Roger Williams talked about in 1949 in his article in the Lancet on genetotrophic disease, and Dr. Linus Pauling's concept of orthomolecular medicine. As Dr. Heber said, this genetic evaluation testing will allow for individuals to better understand how lifestyle and diet changes could influence their functioning, improve outcome, and reduce their risks to disease.

Some experts say it is too soon to apply nutrigenomics in a clinical setting, and that we still have a lot more research to do. That is certainly true. There is no question that we are only on the front edge of this particular revolution. However, the early information that is starting to come in is giving us significant potential for starting to look at patterns of nutritional needs related to genetic uniqueness that we did not have access to before. That is a consequence of the revolution in molecular biology and molecular genetics.

With that in mind, we are going to focus our attention on the revolution in nutrigenomics, and how this information can be clinically applied. We are fortunate to have a world-renowned expert on this topic as our Clinician/Researcher of the Month-Dr. Ruth DeBusk. She has a PhD in nutrition with research experience in biology and molecular nutrition and genetics, and she is also a Registered Dietitian (a very

unique background).

Looking at the big picture for a moment, we are trying to find ways of preventing premature cell death that results as a consequence of declining function in cells, tissues, organs, organ systems, and ultimately, the whole body. This is what Dr. James Fries has talked about since around 1980-improving organ reserve, compressing morbidity, and extending the health span of the individual. When we look at the clinician's strategic objective in trying to improve health outcome by compressing morbidity and increasing organ reserve, it would be to maintain cellular and tissue function.

Cellular Processes

If we were to go inside a cell with microscopic molecular eyes, we would see thousands of processes occurring simultaneously in a time-dependent fashion and with rhythm, like the tides, that create different pulses of activity in all the different organelles. These would be generating all sorts of intermediary metabolites. Those processes would be influenced by external and internal factors in the so-called "environment." Mixtures of molecules float around, as they are conducted on a tour of the cell and hopefully, they will leave the cell as non-toxic waste products, such as carbon dioxide, water, urea, sulfate, and phosphate. That gives rise to biochemical energy leading to the organization of the cell, the tissue, and the organ to create, sustain, and direct their function. If, however, there is a buildup of non-endproduct metabolites, or debris (molecules that were not supposed to be the endpoints, but only transient in concentration and number), and they start to increase in number, a "toxic response" might occur from the non-toxic series of molecules that ultimately overcome the control mechanisms of that cell. What once was considered non-toxic becomes toxic. As Tolman's principle in pharmacology tells us, everything is toxic at some level, even air and water. It is possible to over-hydrate a person when infusing them with water. Or, a person can be hyperoxygenated as a consequence of not controlling blood gases.

What is the threshold when a toxic or adverse response to a substance occurs in a cell, leading to dysfunction? That is going to be individualized to the person's uniqueness, and this is where nutrigenomics or nutrigenetics comes into play. The signaling molecules that trigger cell death go through cellular dysfunction before apoptosis takes place. I am weaving the term "function" into my conversation. The early stages that precede cell death and cellular pathology are altered cellular function by altered metabolic processes, and altered genomic, proteomic, kinomic, and lipomic expression into the metabolome, which ultimately influences the phenomics, or function of the cell. The process of dysfunction at a cellular, biochemical, or organ-specific level ultimately gives rise to apoptosis or necrosis through adverse effects, which causes loss of organ reserve and ultimate disease.

Roles of Molecules in Promoting Apoptosis

What roles do various molecules play in promoting cell death? There is an interesting article in the *Journal of the American Medical Association*, titled "Messenger molecules and cell death: Therapeutic implications."[2] It opens the door for what we are going to be speaking about, in part, in this issue of FMU, and how it interrelates with the topic of the 13thInternational Symposium on Functional Medicine-biotransformation and detoxification.

Programmed cell death, called apoptosis, participates not only in normal physiological processes, such as the development of the immune system, when immune cells come and go, as needed. We do not constantly build increasing numbers of immune cells over the course of life. They increase in number when we need an immune response, and they die off by apoptosis when we do not need them. It has also

been found that premature, accelerated apoptosis, or cell death, is associated with many diseases-neurodegenerative disease, cardiovascular disease, and diseases associated with muscle wasting. These are conditions that accelerate apoptosis, particularly in the so-called post-mitotic tissues. These posttranslational tissues-the brain, the heart, and the muscles-do not replicate very quickly. As a consequence of injury to these tissues (as contrasted to the liver or the skin that can regenerate), accelerated loss of cells can lead to loss of organ reserve and increased risk to dysfunction. It has been implicated that increased risk to accelerated cell death in certain tissues is a consequence of exposure to various messenger molecules that produce a death message to the cell.

Bilirubin

What are those molecules? Bilirubin, often thought to be a toxic endproduct of heme metabolism, serves as a physiological cytoprotectant that may attenuate multiple forms of morbidity. It helps to protect against some of the things associated with increasing apoptosis, which are triggered as a consequence of increasing concentrations of reactive oxygen species. Apoptosis and reactive oxygen species, or what has been called oxidative stress, are very tightly tied together. Bilirubin is often a compensating mechanism for the increase in oxidant toxic molecules. As a cytoprotectant, bilirubin is not the effect, but perhaps the response to these processes.

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)

Secondly, the enzyme glyceraldehyde-3-phosphate dehydrogenase mediates a novel death cascade. This is triggered as a consequence of hyperglycemia, or poor glucose transport. In a diabetic-like situation, glucose becomes a potentially toxic molecule through the activation of the cascade of events that induces cell apoptosis. Excess free fatty acids and excess glucose in cells can induce cytotoxicity and initiate apoptosis and loss of organ reserve. Both dysinsulinism and dyslipidemia have a nutrient-toxic relationship to the accelerated cell death phenomena. That is tied together with diabetes, coronary heart disease, and even certain forms of cancer that appear to have a dysglycemic and dyslipidemic component.

Third is cytochrome C, which is released from mitochondria in early apoptosis and interacts with the inositol-1,4,5-triphosphate (IP3) pathway to elicit a large uptake of calcium across cell membranes. Calcium influx into cells is tantamount to triggering apoptosis. All the calciphylaxic processes associated with chronic stress, infection, and trauma (the conditions Hans Selye talked about in the 1960s) lead to the rush of calcium from outside the cell to inside the cell. These triggering events are associated with increased apoptosis and loss of cellular reserve.

There are many different cellular processes associated with accelerated cell death, or toxic events in the cell, such as excess glucose, excess free fatty acids, excess reactive oxygen species, excess inflammatory mediators, and excess relationships to trauma that induce calcium influx into the cell and trigger apoptosis. In people with high coronary artery calcium scores, each of the little focal calcifications are indicative of a site where inflammation has occurred in the artery wall and calcium moved from outside the cell to inside the tissue, leading to calciphylaxis. That is the point when cells died, and where there is debris. The cytoskeletons were calcified, to use an archaeological or paleological model.

I want to talk about one of the precipitating events, or triggers (to use the nomenclature of patient-centered assessment in functional medicine) of toxic events. This is discussed in a paper by Dr. Paul Ridker, whom most of you know as the father of high-sensitivity C-reactive protein (hsCRP). He is located at the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital, Harvard

Medical School, and has been actively involved over the last decade in advancing the concept that inflammation is associated with atherogenesis and ultimately, heart disease and cerebrovascular disease.

Low-Grade Chronic Infection, Inflammation, and Oxidative Stress
In Dr. Ridker's paper, published in the journal, Circulation, he talks about the triggering of the oxidative inflammatory response by focal infection, leading to cell death in the arterial system.3 We often forget about the importance of the effects of low-grade chronic infection on triggering aspects of inflammation and oxidative stress. Where can focal infection reside? There are many places in the body containing warm, nutrient-rich media where bugs like to hang out-the sinuses of the nose, the GI tract, the gingiva around the teeth, and periodontal ligaments. Bugs can harbor focal infection in all of these places. People with gingivitis or periodontitis have been found to have higher incidence of autoimmune disease and coronary artery disease (CAD). The process is similar in chronic sinus infection or chronic GI dysbiosis.

Dr. Ridker talks about the fact that if we look at inflammation and infection in the causes of atherosclerosis, there is an interesting correlation, and these are further fed by dietary variables, such as diets that cause insulin resistance and hyperinsulinemia. When there is inflammation from an infection, coupled with hyperinsulinemia, it is like a dog chasing its tail. Increased amplification of adipocytokine production, with more and more inflammatory mediators, more reactive oxidative species, and more tissue redness (rubor, color, and dolor), produces more injury to the arterial wall and the arterial intima, increasing the risk to CAD.

The point I am trying to make is that there are potential multiple environmental factors, multiple genotypes with differing susceptibilities, and multiple outcomes of pathogenesis, depending upon the organ or tissue in the individual that is most likely influenced by this process. It is a much more complicated process than that rendered by the differential diagnosis, suggesting that each disease is independent of the other. What we are really looking at is the connection of multiple diseases to the process of inflammation that is a consequence of the interaction of genes with the environment. It is the clinician's responsibility to understanding something about genetic susceptibility and the unique environment of the patient that allows for personalization of therapy to reduce the risk of inflammation-related dysfunctions. Obviously, atherosclerotic disease is only one in the family of inflammatory-connected diseases. Others fall into the same category-dementia, metastatic disorders, type 2 diabetes, and autoimmune disease. It cuts across many different areas.

How does the body regulate its response to these triggers and precipitating events? We are exposed to them all the time. No one lives in a perfect environment. Many things might trigger these events. It seems almost impossible that we could even live to the age of 60, based upon all these factors. The body has had to evolve protective pathways over millennia to regulate these insults, or exposures, so that it does not amplify the toxic response and lead to whole-body free radical pathology, or toxicity events that lead to cellular apoptosis and serious loss of function.

One system that offers protection is the body's antioxidant system, which includes enzymes like superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase. These enzymes help to defend us against the processes associated with inflammation, oxidative stress, calcium uptake across cell membranes, and ultimately, mitochondrial depolarization, energy loss, and cell suicide (apoptosis). This process also involves specific phytochemicals that act as antioxidants and are known to regulate the detoxification of environmental compounds. Many of these phytochemicals bind to the antioxidant

response element in target detoxification and antioxidant enzyme genes, resulting in upregulation of these enzymes. It is pretty interesting that these processes have a coincidental convergence. Toxicity reactions produce greater output of oxidants in the body; greater output of oxidants, in order to be quenched, requires not only detoxification of the toxic substances of the process, but also attenuation of the oxidant stress, so that the fire does not run uncontrolled (using free radical oxidative stress as a metaphor to a fire). By this interesting duplicity of effects, the substances in our food communicate chemically with the antioxidant response element, resulting in an ultimate reduction in the amount of fire.

This is described beautifully in a review paper, titled "Antioxidants in photosynthesis and human nutrition," published in *Science* magazine.[4] In this article, the authors talk about an interesting observation: how plants have evolved such a rich array of phytochemicals that are consumed by humans in minimally processed plant foods, and that gives rise to the support for both detoxification and antioxidant protection against cellular oxidative injury, damage from reactive oxygen species, and ultimately, excess apoptosis.

There is an interesting figure in this paper (Figure 5), a scheme showing how key redox-modulated pathways of signal transductions are related to human diseases and disorders, including such things as attention-deficit hyperactivity disorder (ADHD) and other types of neurological problems that are modulated through phytochemicals- including omega 3 fatty acids, as well as bioflavonoids. From basic science, applied medical science, clinical research, and animal and epidemiological research, there is a convergence of data that leads us to recognize that these nutrigenomic connections to environmental modulation are extraordinarily important in finding the trajectory that ultimately gives rise to health or disease in later age.

I have gone through this to try and make a point. Recently, I had a conversation with a well-informed, intelligent professional in our field. He is not directly in the functional medicine field, but he is in the general health field. He and I got into a vigorous discussion. To summarize what he said, his criticism was that I was promoting a plasticity of health that was not justified, and that people got sick as they got older as a consequence of bad genes, and there is little you can do about it. Basically, medicine is there to save people when they are injured, and he felt that I was unjustifiably promoting the concept that you could do something about this by trying to personalize one's diet and lifestyle, suggesting that our genes have a lot more plasticity and could be expressed in different ways. According to him, there was no science that would justify that. I was just speculating and leading to false expectations of outcome, and giving people a heightened sense of control when it really did not exist. He suggested that we should try to live our lives, eat the foods of commerce, do what everybody else does, and medicine would be there to save us, because there is really no other way out. That was the model-a kind of medical determinism.

Obviously, I do not believe that. At the core of everything we have been trying to do in functional medicine for 30 years, I think that is wrong. I do not think the data supports that view. I do not believe that the basic science, clinical science, or even the rules of reasonableness support that model. However, that model still resides in the minds of well-informed, trained professionals in our field. Somehow, they feel that to try to get involved in modulation of the environment of the patient is ill-served, a waste of resources, and it takes us away from doing good medicine, which means treating sick people, because we cannot do anything about it anyway.

That model, which still remains resident in the minds of many professionals practicing medicine today, is

a self-fulfilling prophecy. Believing that there is nothing we can do about our genes leads to believing that there is nothing we can do about our health. People believing this generally have outcomes that are determined without modification; their genes are likely expressed in probably the most deleterious way. If we take a different set of presumptions, however, based upon the nutrigenomic argument, and all the literature that is coming out that we have been discussing in FMU for the better part of more than 20 years, we see that there is a different understanding that is emerging that speaks against the model of "treat it when it's broken." It starts speaking to the fact that cellular dysfunction, which we later call pathology, and its association with things like apoptosis and loss of organ reserve, did not result as a "bump in the night." It occurred over a period of time as a consequence of the collective injury resulting in large part from the inappropriate interaction of our environment with our cellular physiology.

This is not to say that all problems could be entirely alleviated or prevented if we could optimally adjust the environment. That would suggest that what I am arguing for is pro-longevity-that people would live forever in an optimal environment. There is no evidence from animal studies to indicate that is true. There is, however, strong evidence indicating that the survival curve can be rectangularized, compressing morbidity and increasing health span when, through a better understanding of genetic uniqueness, we modify the environment appropriate to a person's needs, thus producing a better outcome. That is the model encoded as a core concept in functional medicine.

We are now seeing that nutrition and food science are going genomic. The reason is because we are finally developing the tools to start looking at genetic uniquenesses in the laboratory, outside the range of a few specialists. The new genomic tools-the gene chip models and the molecular biology assays-are becoming accessible, so that students in undergraduate curricula in universities are now doing these tests as standard routine in their studies. It is not esoteric. These technologies are being commonly used in crime labs all over the US, which can be seen by the number of TV shows now referencing molecular genetics. This is becoming rote technology, routinely done using dependable technologies, which have allowed it to develop from esoterism to the bench.

Nutrition is the recipient of this technology. The wealth of genomic information and high throughput profiling technologies are now being explored in the disciplines of food science and nutrition. Diet and food components are prime environmental factors that affect the genome, transcriptome, proteome, and metabolome, and therefore influence the life-long interaction between our diet and our bodies, such that health and disease states are the results of that interaction. For the first time, the interaction of foods and individual food constituents (so-called phytochemicals), and the relationship they have to biological system control is being defined on a molecular basis. Profiling technologies are being used in basic-science applications for identifying the mode of action of foods or particular nutrients, and we are similarly taken into the science-driven development of foods with a defined biofunctionality. We are not just moving toward foods that are "tasty," "attractive," and "stable," in the consumer world of shelf-stable foods, but we are looking at things with biofunctionality-functional foods and medical foods-the nutraceutical market that connects with specific genetic uniquenesses. Biomarker profiles and patterns derived from genomic applications in humans should guide nutrition and food science in developing evidence-based dietary recommendations and health-promoting foods. We are seeing the emergence of a personalized nutrition that was talked about by Williams, Pauling, and many others, that will deliver on biochemical individuality.

If we look at where we are heading in the application trends of biotechnology to food science, it is

happening in real time. It is not just something that is still in the planning phase that is talked about by only a few early adopters and futurists; it is happening right now. I would urge you to look at a recent article, titled "Nutrition and food science go genomic," published in*TRENDS in Biotechnology*.[5] We are witnessing the evolution of this concept in real time, and it is changing every view of nutrition and how it impacts health and disease. The textbooks that students are studying from today are already out of date, before schooling is even finished. We have gone across a one-way threshold, one that does not allow people to go back the other way. We are in the age of molecular nutrition and, in real-time, we are learning how nutrition interfaces with genomics.

Effects of a Vegan Diet Free of Gluten Improves Signs and Symptoms of Rheumatoid Arthritis
Let me give you an example of how this plays out clinically. Let's look at the effect of diet on rheumatoid arthritis. This is a very interesting connection that includes many sub-topics on which we could spend many issues of FMU, have many discussions, and undoubtedly, we will, over the years to come. I want to focus on an article that appeared in the journal, *Rheumatology*, that presented information about a vegan diet free of gluten improving the signs and symptoms of rheumatoid arthritis, and that the effects on arthritis correlate with a reduction in antibodies to food antigens.[6]

The food of one may be the poison of another. It may initiate an immunological response as a consequence of the constitution of that food, which triggers a unique immune response, principally mediated through the gut-associated lymphoid tissue (GALT), the immune system of the gut, which produces reactive substances to constituents of the diet that are perceived by that individual's own unique genes as being "foreign." As such, the body initiates an antibody response to those antigens.

In this study, 66 patients with active rheumatoid arthritis were randomized to either a vegan diet free of gluten, or a well balanced, non-vegan diet, which was maintained for one year. At the end of the year, very strong evidence was found that the low-gluten dietary modification resulted in significant improvement in arthritis symptoms. In fact, about 40 percent of patients in the vegan group fulfilled the ACR20 improvement criteria, compared with only 4 percent in the non-vegan group. This is strong evidence that a gluten-free diet with a minimally processed vegan base modulates inflammation, both by reduction of the inflammatory trigger, and by probably improving the control over oxidative stress and inflammation due to the range of phytochemicals in a vegan diet.

When the diet is "white," which means white flour, white sugar, and white fat, we have few of those phytochemicals that I talked about earlier that have evolved over time to help balance the gene expression patterns; that regulate cell signaling and intercellular signal transduction; and that control inflammation and how the body responds to the environment as a "friend" or a "foe." There are many variables at play when dietary changes are made. It is not just gluten; it is the absence of gluten in the presence of many other phytochemicals that, in a minimally-processed, vegetable-based diet, help to regulate gene expression patterns.

As we review these types of papers that have appeared in traditional medical journals, we begin to have a different perspective. We see that this dietary treatment is not just the result of a gluten-free diet alone. It has multiple variables, gluten-free in the presence of increased phytochemical intake, which are antioxidants and xenobiotic response element activators that improve detoxification, lower intracellular toxicity, alter the immunological effects, and reduce cellular apoptosis.

Coffee, CYP1A2 Genotype, and Risk of Myocardial Infarction

Let's look at another example-coffee and its relationship to cardiovascular disease. There has been a long-standing debate about whether high intake of coffee has any adverse effects upon heart function. A recent paper appeared in the *Journal of the American Medical Association*, titled "Coffee, CYP1A2, genotype, and risk of myocardial infarction."[7] In this study, the researchers showed that individuals with a genetic polymorphism in the cytochrome P4501A2 (CYP1A2) gene-one of the phase 1 detoxifying CYP 450 isoforms-that resulted in their being "slow metabolizers" who consumed relatively high levels of coffee, were more at increased risk of MI. People who consumed five or more cups of coffee per day who were CYP1A2 slow metabolizers had a much higher incidence of sudden coronary events. There was no statistical relationship between coffee consumption and heart problems in those who had the common or rapid metabolism CYP1A2 genotypes.

Again, here is an example of a connection between a genetic uniqueness and a dietary variable-i.e., CYP1A2 slow metabolizer phenotype and caffeine consumption (nutrigenomics). We are starting to witness some very interesting ways of stratifying clinical studies to look at variant responses based upon genetic uniqueness, instead of the past method of putting everybody in one big data set, regressing to the average, and trying to come up with a mythical conclusion about the average person that did not exist in the study. No one is "average;" everyone is unique in his or her own response.

Let me mention one more example. What about metabolic syndrome? Metabolic syndrome's connection to heart disease is, in part, related to increased inflammatory mediation and increased oxidative stress, with the build-up of reactive oxygen species in the arterial wall, therefore increasing oxidation of LDL cholesterol, which is associated with the indications of metabolic syndrome-elevated triglyceride-to-HDL cholesterol ratios and increased waist-to-hip circumference ratios. These particular characteristics of increased oxidative processes leading to LDL oxidation through activation of the immune system, connect metabolic syndrome and hyperinsulinemia with heart disease risk. I am now quoting from a 2006 paper in the *American Journal of Clinical Nutrition*, in which it is suggested that this is the key to understanding the metabolic syndrome-the connection between oxidized LDL cholesterol and abdominal obesity.[8,9]

There is a clustering of metabolic abnormalities, not only in adults, but also in adolescents with hypertriglyceridemic waist phenomena.[10] In my evaluation, elevated triglycerides and elevated postprandial fatty acids are very toxic because they induce increased production of oxidant free radicals through the activation of the enzyme that I talked about earlier that is associated with cellular apoptosis-GAPDH. The upregulation of that enzyme is associated with the problems of metabolic syndrome, oxidative stress, diabetes, and ultimately, CVD.

There is a companion paper to those I just mentioned, titled "Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults."[11] What do the authors of this article say? Let me stop for a moment. Recall that we have just gone through an interesting period in which carbohydrate was suddenly considered toxic, and protein and fat were good. This is interesting, because it came out of the previous period (the 1980s), when high carbohydrate diets (the Pritikin approach) were desirable, and high-protein, high-fat diets were toxic. The pendulum swung very quickly. What actually is going on? I believe it is much more than we are hearing about. The changes in macronutrients levels, going from high protein to high carbohydrate, may be secondary to other factors that are not being discussed in these

studies. What happens when you take a lot of minimally-processes carbohydrate out of the diet?

The type of carbohydrate that Nathan Pritikin and Dean Ornish talked about in their studies was minimally processed-high complex carbohydrate and high fiber foods-the kind of diets Richard Anderson from the University of Kentucky School of Medicine talks about. These are particularly nutrient-rich forms of carbohydrate because they carry the phytochemicals initially made in plants, not only vitamins in the incorporation of minerals, but also flavonoids, polyphenols, carotinoids that get converted to retinoids, and the tocopherols (vitamin E). These myriad phytochemicals have impact upon function, as well. We often forget about that in clinical studies. We just look at the macronutrients overall. In this study, showing whole-grain intake inversely associated with metabolic syndrome, we are not just looking at increasing carbohydrate with whole grain, we are looking at the effects the fibers, lignans, plant sterols like beta sistosterol, and the flavonoids have on gene expression, intercellular signal transduction, and the relationship of that specific dietary signature as "food information" to the genes to produce a different outcome-lowered inflammation and improved function through regulation of insulin sensitivity.

If we take that argument and extend it to other phytochemicals, we come out with a similar theme. For instance, a very interesting paper was published in *Cancer Research* that showed we could help protect against aflatoxin-induced tumorigenesis by giving a synthetic substance (a new anti-inflammatory) based on a natural product found in a variety of foods that has a tremendous effect on upregulating glutathione-S-transferase and the antioxidant response element, as well as helping to protect against oxidative injury. This is a triterpenoid found in many plant foods, particularly in spicy, Indian foods, that is a natural antiinflammatory, downregulating the potential production of a toxic reaction.

What about the flavonoid, quercetin? We now know that it has a direct effect on gene expression signaling. It inhibits proinflammatory cytokine effects through reduction of tumor necrosis factor-alpha (TNFα) gene expression in peripheral blood in individuals who have been administered high oral doses of quercetin.[13] Quercetin is the aglycone of rutin; it is found in whole grains.

We are starting to witness the emergence of the connection of the genes with the nutritional environment to give rise to different outcomes, personalizing the effect of outcome and designing nutrigenomically-tailored diets that will ultimately allow people to be properly managed based upon their individual needs-the dream and objective of both Drs. Roger Williams and Linus Pauling.

With that in mind, let us move to our Clinician/Research of the Month, Dr. Ruth DeBusk.

INTERVIEW TRANSCRIPT

Clinician of the Month
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JB: It's time for our Clinician/Researcher of the month. We have been waiting for a couple of years to interview this month's guest on FMU. She is very busy, and has been making significant contributions to

the field of nutrigenetics and the interaction between genes and diet. I'm talking about Dr. Ruth DeBusk, who has a remarkable background that will lend itself nicely to a lot of questions that have come up over the last several years on the interaction between genes and diet. Dr. DeBusk has a PhD in genetics and molecular biology, but she's also a Registered Dietitian. She has been very actively involved in the American Dietetics Association (ADA) in trying to establish a different thrust for dietetics and nutrition in that organization, moving away from traditional food-based programs to individualized nutrition, nutritional counseling, and clinical nutrition, which has not been the major thrust of the ADA. Ruth has been a leader in that organization and in changing the entire field of nutrition. She has recently published what I think is the premier book in the area of nutrigenomics and personalized approaches to nutrition. It is a dynamite, must-have book for any of you who want to see where the future is going to be taking us in the field of nutrition. (DeBusk R, Joffe Y. It's Not Just Your Genes! BKDR, Inc., 2006.)

It is with tremendous pleasure, both on a personal and professional level, that I welcome you to Functional Medicine Update, Dr. DeBusk. My first question is, was it dietetics first, followed by molecular biology, or was it molecular biology, followed by dietetics? How has the thrust of your career led you to your current, unique status?

RD: Thats a great question. I started out being absolutely fascinated by the chemistry aspects of food and nutrition. I never thought of nutrition as applied biochemistry. I came into it from a food and nutrition training base. After doing the Master's/PhD Program in Food and Nutrition, I realized that what I really loved was molecular biology and the genetics base. I pursued training in that area, and was fortunate enough to land a faculty position in genetics. I focused my research on putting nutrition and genetics together, looking at the genetic regulation of nutrient absorption, and always planning, ultimately, to be able to bring those two disciplines together in practice. It seemed like it was going to take forever, so I'm thrilled that it's all of a sudden here, barreling along, with lots of good studies in progress. I think we're going to see quite an impact before too long.

JB: As I look at your background, I see that our chronologies match up very closely. Your undergraduate degree was just a year after mine. Your PhD was a year after mine. Your post-doctoral work, which you did in genetics and molecular biology, and nutrition and food science at Florida State, was an interesting dual specialization. Then, you moved into physiological chemistry at the University of Wisconsin, Madison and became a Registered Dietitian. All along the road, I imagine you had people asking you what you were trying to do. You must have had a very clear vision as to where you wanted to take your career.

RD: I felt like Joan of Arc many times-a voice in the wilderness. Most people saw one discipline or the other. They couldn't see what one had to do with the other. That's frustrating, because genetics is absolutely fundamental; it under girds everything we visibly see and can now measure biochemically. Genes make the proteins that control an organism's structure, its metabolism and ultimately, its function. That has to have profound effects on any aspect of health care that I can think of. Nutrition is so much more than cold food; it's the bioactive, dietary components in the food and the way they communicate, not only to the genes within the cell, but as signals from the environment into the genetic material and ultimately, turn gene expression on and off. That's such a powerful connection, and something that organisms have had from the very beginning. It's a very fundamental, biological process.

JB: It's interesting. I notice that early on, you did quite a bit of work in an organism that I talked about,

which is Neurospora crassa, the red bread mold. In medicine, people often ask why we would think it's interesting to do research in yeast, bacteria, mold, and fungi. That seems so simplistic, but a lot of the genetic pathways we are describing are conserved up through time immemorial. Perhaps you can tell us a little about what you learned about Neurospora crassa that can be applied to humans.

Research with Neurospora crassa

RD: It's amazing, but most eukaryotic cells are very good model organisms for much more complex organisms. The beauty of Neurospora crassa was it's haploid, so you could introduce a mutation and directly look at its effect. And, you could define the environment it was in, manipulate that environment, and look at the impact on the gene. You could look nutrigenetic-wise at what the effect was of changing the genes on the organisms that they will need to function, and then you could do the reverse, which is more in the area of nutrigenomics, looking at the impact of change in the environment on the organism's function. Then, you have a system you can manipulate and try to take apart in very systematic ways, compared to a very complex organism like the human. I think what we may not appreciate is just how similar these organisms are. We like to think we're a lot more complex than single-cell yeast or Neurospora crassa (even the bacterium), but it's amazing how many things are conserved. Even now, the organism of choice seems to be the mouse, which has a great deal of homology with the human. Thank Heaven we have these model systems, because we can't just do selective breathing in humans like you can do with model systems, and really look at the impact of changing the genes or changing the environment.

JB: I'd like to go back and build up this discussion for the person who is not as familiar with the topic as we are and first, talk about the difference between nutrigenomics and nutrigenetics. Maybe even before that, I should ask you, is it "nutra" with an "a," or "nutri," with an "i," genomics?

Nutrigenetics versus Nutrigenomics

RD: It's nutri. As you know, in any emerging field, the terminology evolves. It's still in a state of confusion, but I think it's starting to sort out. I think of nutrigenomics as short for nutritional genomics. What is the interaction between dietary components and our genetic makeup? Within that, there are sub-disciplines. Nutrigenetics looks at the effect of an individual's unique genetic makeup on their nutrient requirements. Your genes and my genes are, obviously, basically the same, because they're both of the same species, but there are some three million base pairs that are different between us. All of the characteristics that make us unique come from those genes. In addition to our hair color, eye color, intellectual capacity, etc., there's a difference in how we are going to be able to use particular nutrients, as a result of structural differences in the enzymes that are coded for in these genes. That's nutrigenetics. It has an impact on us in terms of how much of a particular nutrient or bioactive food component we need in order to function optimally. That's going to be slightly different for each person.

Nutrigenomics, in addition to being a whole broad field, also refers to looking at how food molecules from the environment impact the genetic material itself, turning expression on and off, or modulating it up and down. I look at nutrigenetics as "inside out"-what's in the individual and how they respond to various nutrients in terms of levels required, and metabolites required. Nutrigenomics is sort of "outside-in," looking at the impact of the environment on the particular expression of the genes that individual has.

JB: That's a great definition. Let me see if I have this right. Let's take apo E4 as a genetic polymorphism. That would be a nutrigenetic characteristic that might make that person more susceptible to certain kinds of diets or environmentally-related disorders. Would that be correct?

RD: Correct.

JB: Whereas a glucosinolate in a cruciferous vegetable, such as indole-3 carbinol (I3C) and how it impacts detoxification of estrogen, would be more of a nutrigenomic relationship.

RD: Yes. That's a good way of thinking about it. I've told people not to get hung up on definitions. When nutrition and genetics come together, however they relate, I call all of that nutrigenomics. I think at this point in time, if people got that, it would be great.

JB: Let's go from there to what is becoming another part of the emerging story. The community of molecular geneticists and biologists almost expressed surprise when Celera and the NIH mutually disclosed the structure of our chromosomes and the sequence of DNA nucleic acids. It turned out there are only about 30,000 genes, which was very surprising. People thought there would be so many more than that. Then, they said genes are not expressed one at a time; they're expressed as specific families of genes connected to non-coding regions we used to call "junk DNA." Maybe the principal difference between humans and other organisms is in the non-coding regions, and we better throw away the term "junk," because it's not junk.

RD: Exactly.

JB: Would you tell us a little bit about that-how genes get turned on through the other loci?

Understanding Single Genes
RD: That whole story is fascinating, and it's very much in its infancy in terms of unraveling it. There's so much to consider and, from a scientific basis, we always tend to start with the simplest part, try to understand that, and then look for more complex explanations. Most of the current focus is on trying to isolate one gene and understand it. What is its protein product? What's the function of that protein, and how do various environmental factors impact that function and the expression of that gene? We've got quite a bit of work to do in that area. Overlaid on that is the growing understanding of just how complex it is. Not only do you have a single gene able to make multiple proteins and protein interaction, but potentially gene/gene interaction. I think most people are probably ignoring that as much as possible, because it's so complex. Thankfully, there are some great researchers who are working hard to understand those dynamics. I'm not sure that I know all of the intricacies of that.

JB: Let's move to what has been a term in our literature for some time that is now gaining some better understanding as a consequence of the work you're describing. That term is "conditionally essential nutrient." We can put on that list things like coenzyme Q10, lipoic acid, taurine, and carnitine. These are substances that our body makes, but perhaps under certain conditions, can't make enough to meet the needs of an individual, so they become conditionally essential. I would presume the concept of conditionality relates, in part, to the nutrigenetic relationship, individualized to the person. Is that correct?

Conditionally Essential Nutrients
RD: Absolutely. I believe that a lot of our terms are going to fall away because they were descriptive back in a time when that's the best we could do. We could just describe what we observed. I'm thinking of terms like "penetrance" and "homozygous." Our vista is changing as we learn more at the molecular level, and the idea of conditional essentiality was geared toward the "average person." As we come to

understand that there's no such thing as an "average person," and that we have to deal with the genetic uniqueness of each individual, I think we're going to find those sorts of terms falling away. We were compelled to define an "average" so you'd have a starting point, and here is the amount of nutrients that an "average" person needs, without taking into account all of the variations on either side of that. If we had just understood and kept a more open mind about how different everybody is, I don't think we would have gotten so lost into "this is the level everybody needs." Clearly, it's not conditionally essential for that individual. That is what they need, but it's conditionally essential from the standpoint that we define some arbitrary average for "the population." But even "the population" makes no sense, because there are all these sub-populations, and there may be an average for a particular related genotype, but I have a real problem with "average." I agree with you in that a nutrient may be essential for an individual and they may need 100 mg a day. Somebody else may need 300 mg a day. It depends on what the particular gene variations are and the protein variations that result.

JB: That's a very nice explanation. Let me use an example, and perhaps you can walk us through it. One of the polymorphisms that has been very heavily studied and discussed in the literature is the methylenetetrahydrofolate reductase polymorphism, C-677®T, that leads to changing folate requirements. I've had a lot of doctors tell me over the last few years that they understand this polymorphism, but if you have the heterozygous type (let's say your mother had the allele for the sluggish MTHFR, and your father gave you the one that was the common form, or the wild type), why do you worry about it, because won't the father's common one take over from the mother's slow one, or vice versa? I think there's a misunderstanding going back to the Mendelian concept of dominant recessive genes. Would you tell us a little bit about that?

The Methylenetetrahydrofolate Reductase C-677®T Polymorphism
RD: That's exactly the kind of terminology that is not going to make any sense. For the longest time, we thought that if you had anything except two impaired genes you were normal. If you had the common form, or had at least one of the normal alleles-a heterozygote (a carrier)-that it was the same as being totally normal. That made sense at the observation level, and as we began to develop chemical measures and ultimately, molecular measures, it started not to make sense because we realized that there is co-dominance. Both of those copies, or alleles-one from the mother and one from the father-were both contributing some sort of function, either no function at all, or maximum function, or something in between. We started to see that the carrier individual has not quite fully impaired, not quite fully wild type or normal, but something in between. Particularly, if you stress the organism and put it under conditions where it absolutely must have a robust supply of folate, you're going to see the inability of that carrier to supply enough methylated folate cofactor for the needs of that individual.

It looks like there's a pretty generous amount of enzymes produced in the normal individual. We may find there are control mechanisms that read the level of enzyme activity that exists, and see that we need to regulate the normal allele more to compensate for the lack of production by the variant alleles. Those sorts of questions certainly still remain to be answered. I have a real worry about the carrier individual that we've just lumped over into normal, because at the clinical level, they don't seem to be quite as robust as the normal person.

JB: That's a very important takeaway for our listeners. Two conditions come to mind that I learned about in school that I thought were like on/off switches. One was phenylketonuria (PKU), and you either had it or you didn't; the other was Gilbert's syndrome, which is a glucuronosyl transferase polymorphism. I

learned that these were point gene mutations and you either had them, or you didn't. If you didn't have PKU, you were fine. Now, as you say, we're learning that there are variant forms of both of those conditions-Gilbert's and PKU. You might not end up with the dementia of infancy and the mental retardation that's seen with frank PKU, but you may have a latent form of a milder PKU that expresses itself with dopaminergic neuron changes and affective changes in mid-life.

Varient Forms of Polymorphisms

RD: You might be further stressed if, for some reason, your environment puts particular pressure on you. Maybe you're in an environment with a high phenylalanine content. Maybe you didn't realize that one of the artificial sugars was also in the diet drinks that you just love, which are high in phenylalanine. That's going to further stress that carrier individual who thought he or she was fine. I have a real worry, and I'm always looking for red flags within the GI area for things like celiac disease-gluten-sensitive enteropathy, or hemochromatosis. Even individuals who are not stressed in their environment with excess gluten or excess iron seem to function just fine. We've been thinking that these are not very common diseases. Again, it's a misnomer-the thought of a genetic disease. In my mind, there's no such thing as a genetic disease. It's virtually all genetic. We need to be thinking about how a person is functioning. Someone who has one normal and one impaired gene typically doesn't process some of these trigger molecules as well as the wild type might. What we're seeing clinically is an enormous rise in the amount of gluten sensitivity. The carrier rate for both of those disorders is something like 1 in 8 to 10. That's very much an undetected problem.

JB: That is a superb clinical example, because many of our clinicians have heard people say that the frequency of gluten sensitivity in our population is 1 in 1000. They see a lot more than that in their practices. What we're dealing with are people who have gene characteristics that are only expressed in the phenotype when they're under environmental stress, and we start to see all sorts of different things appear.

RD: And look at our diet. I think the diet is probably a major environmental stress, because it's so wheat-based.

JB: That's a very interesting point. This years symposium was on biotransformation and detoxification. One of the themes that came out of that whole area was whether diet can influence detoxification. Certainly, what we're speaking to has some relevance to the inducible detoxification enzymes. Would you tell us where you see the diet/detoxification connection as it relates to the nutrigenomics concept?

The Diet/Detoxification Connection to the Concept of Nutrigenomics

RD: It's a really critical area, and one that I encourage nutrition professionals to get a handle on. They get all excited, and there's so much to learn, so everybody's on a learning curve right now. They want to know what they can do right now, and staring us in the face is the whole detoxification process, which is an area where diet meets genes head on. It's an area that's not addressed and understood in terms of how much nutritional demand detoxification places on an individual, particularly in today's environment-for instance, anyone who is on any kind of prescription drug, over-the-counter medications, or dietary supplements. A lot of the toxins are contained in our food, beverages, or the air we breathe. It's seems like our poor liver is under constant demand and both the phase I and the phase II reactions are very dependent on nutrients that we supply in order to optimize those reactions. Any number of those enzymes-certainly the cytochrome P450s-come in a number of isozymes which hark back to particular gene variants. That determines how well people do or don't do from the phase I reaction, and the ability to move that highly reactive intermediate on through phase II. Again, you've got the glutathione S-

transferases, which are genetically variable. If there was just one area we could test for and have information about, I'd be happy if we'd focus on detoxification. What is this patient's phase I activity for the key cytochrome P450s? What are their phase II gene variants? What can we know about particular nutrients that upregulate or downregulate, depending on what's needed, with the particular variants that patient has? How can we manipulate those, diet-wise? For example, if you have a sluggish phase II and you need more of it, then certainly the cruciferous vegetables with their glucosinolates are directly in order. If you're a nutrition professional, you've got to figure out how to get people to eat cruciferous vegetables (it might not be their favorite thing to do), but there are lots of ways around that.

JB: You've raised a clinical "tire-meets-the-road" question. That is, are we ready for prime time in nutrigenetic testing? There have been many different articles written on that recently. Some have said we are absolutely not ready. But there are commercial companies offering tests that can evaluate some of the more commonly understood genes associated with nutritional regulation. What's your thought, as it relates to 2006?

Nutrigenetic Testing
RD: That's a hard question for me. The academic in me says, oh, no; we need 20 more years of work before we can possibly do those. The clinician in me says that people need it now. I've more of a mind to take what we have, however limited it might be, and use it to the betterment of the patient if it's not going to be harmful. I think there are some good tests that are soundly developed and validated that are really helpful. It's very helpful to know what a patient is feeling. Typically, if you're not doing functional testing, you're not seeing a lot of the characteristics beneath the surface in that individual. You can really get a good feel for what's going on if you can add in not only functional testing, but nutrigenetic testing, as well. I'm thinking of things like the cardiovascular-related genes. We have these conventional things that we do that we wouldn't do if we had genetic information. You put people on a low-fat diet, or on a salt-restricted diet. Does that make any sense if this person has the apoE1 variant that's going to give them high HDL levels? Do they really need to be on a low-fat diet? Maybe they are an apoE2 genotype that doesn't respond particularly well to a low-fat diet. They may have a particular variant in apoE1 that requires their polyunsaturated fats to be above an 8{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} level. All of that factors into nutritional intervention, and there's no way you can get that kind of information, certainly from conventional clinical assessments or, for the most part, even from functional testing. I see that as being enormously helpful to the clinician in terms of getting underneath what's really going on with a patient.

JB: For people who are listening who want to fill in the gap, your book, It's Not Just Your Genes! would be a very good place to start. Where can people find the book? It was published this year.

RD: It's readily available from amazon.com, which is probably the easiest way to get it.

JB: Great. I know that also, just a couple of years ago, you were a principal author on the book, Genetics: The Nutrition Connection, for the ADA (The American Dietetic Association; 2003). Is that book beginning to have an impact on teaching dieticians and the practice of dietetics?

RD: Yes. It's gotten to the point where people are excited about it, but they don't know what to do about it. What we're trying to do now is forge a career path. This is so fundamental to nutrition, to virtually any aspect of food or nutrition practice that a dietician would get into. It's going to be absolutely essential that

they get a solid background in genetics, but I would like to see a particular career path analogous to the nurse practitioner that develops a very well-educated, very competent practitioner in nutrigenomics; a nutrigenomics practitioner that can take charge of this area, do the genetic counseling, do the testing, and do the therapeutic interventions and prevention that ultimately will be developed, and just be responsible for that area so they're a valuable contributing member of the healthcare team. And it's one less thing the physician has to worry about. From my perspective, its so much easier to teach genetics to someone who has a very broad base of food and nutrition, than to try to teach that base to somebody that has competency in genetics. I see a real niche at a high credentialed level-very skilled, but very unique, and very much needed within the healthcare team.

JB: That's a tremendous model. I never thought about the nurse practitioner model. It makes very good sense. Let me close with one last question. You've been very kind to give us this amount of time. You've been actively involved in the chapter of the ADA called "Nutrition and Complementary Care" which, by virtue of its definition, may be an anachronism when they think of the stereotype of the ADA. Would you tell us a little bit about this sub-group and its activities, and whether you feel it's having an impact?

Nutrition and Complementary Care Sub-Group of the ADA
RD: ADA is much more progressive than they get credit for. It's so hard in a large, very old organization to turn things around. I just spent last night with the incoming president, Dr. Judy Gilbride, who is very much a proponent of nutrigenomics, and who has worked hard to get that on the table, to the extent that it's now one of the top priorities for ADA. Again, we're moving into a whole new area. We're talking about a whole different type of credentialing, so how do we get all these details together? The Nutrition and Complementary Care group came about five or six years ago to deal with all of the unconventional aspects of nutrition and food. At the time, probably a major emphasis there was dietary supplements, which is clearly applied biochemistry and nutrition, but it was not something that conventional dietitians had embraced. That group has been very progressive, I think. Their whole mission is to educate members about what this is all about. What is the science behind it? They're trying to keep it as solidly financed a base as possible. They want to know what different modalities are out there. It's not all snake oil and hocus-pocus. Here's the science and heres the effects that practitioners are having. I think it's moved us away from a very conventional, conservative stance. As you know, change takes time.

JB: Absolutely. As we bring this interview to a close, I'd like to give you the opportunity to speak to our listeners (who are principally clinicians) about anything you feel they should keep their eyes and ears open to, or that they might want to consider as they start to integrate these concepts into their practices.

Recommendations for Clinicians
RD: I think it can be totally overwhelming. We're dealing with a whole new language. I can make the analogy of trying to learn immunology. It has its own language and its own alphabet. Once you've finally mastered that, it starts to make sense. Understand that genes underlie all of function. Ultimately, virtually everything that's going on with your patients harks back to their genes. It's going to become more important to look into the genes and figure out what particular variants they have and what the impacts are. Personal health is a continuum between wellness and illness. Where we function on that spectrum is directly related to our lifestyle choices. That's very empowering to a patient. With education, you can learn to make the best choices that will optimize health and total function.

For a clinician who is just getting into this, I would try to remember the tremendous impact this will have

and how fundamental it is to the health of patients. In order to feel comfortable with it, I would pick some area that's of interest to you, whether it's your practice, perhaps a chronic disease that runs in your family, or something you're really concerned about, start at one corner, and build a base of knowledge around that. Start to read the literature that deals with particular genes. Look at the impact of a gene or two and how dietary manipulation can enhance or improve the function of that gene. Just try it out. I find patients are very receptive if you just lay it out. We don't have all the answers we'd like to have, but this is what we know, and this is what I think will be helpful for you. Let's try it.

JB: That's a marvelous message. I can't tell you how much we appreciate your time. Again, your book, It's Not Just Your Genes, is a very good place to start for a person who is moving down this path.

Thanks a million, Ruth. You are truly a pioneer and a leader. I think well look back at this interview ten years from now and say that this was where it all started in the early 20th century, and that Dr. DeBusk was right at the head of the class. Thank you so much.

Effect of a Low Glycemic Index Diet with Soy Protein and Phytosterols on CVD Risk Factors in Postmenopausal Women

It might seem presumptuous to add anything to Dr. DeBusk's eloquent discussion, but I thought it might be useful to complete this month's visit together with a review of a paper we just published out of our own research group, which is quite germane to the topic. This paper appeared in the journal, *Nutrition*.[14] It is the work of Lukaczer, Liska, Lerman, Darland, Schiltz, Tripp, and myself, titled "Effect of a low glycemic index diet with soy protein and phytosterols on CVD risk factors in postmenopausal women." Let me summarize the results of the study and how it relates to what Dr. DeBusk was talking about.

In this study, we recruited a group of 59 postmenopausal women who were experiencing increasing lipids and body weight. They were not morbidly obese; they were not diabetic; and they did not have cardiovascular disease. They were in the "increased risk "category. The average age of the subjects was about 55. We randomized them into two groups, one on a low- glycemic index diet that included 30 grams of soy protein and 4 grams of phytosterols per day (LGID), and one on the American Heart Association Diet (AHAD). Both groups were isocalorically managed and they received approximately the same calorie amounts. Both received the same exercise regimen-a regular walking program. Both groups received the same consultation with a trained nutritionist/dietitian, and both groups had approximately the same fat calorie percentage and similar protein calorie percentage, although the AHAD diet resulted in increased carbohydrate calorie percentage to that of the LGID (54{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} to 43{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}, respectively). Clearly, even though there were no major differences in the total amount of calories, there was a difference in the kinds of foods that were consumed by the two groups, one receiving the AHAD, the other the LGID.

The point I want to make here is, there is a theme that still resides in our culture that calories are the name of the game, and that as long as you adjust the calories with the right protein, carbohydrate, and fat percentages, there will be a favorable outcome. For years, many of us have been saying that is not the whole story. For the story to be more complete, it needs to include what those calories deliver in the form of information. Morgan Sperlock, in his classic video, "Supersize Me," had more than just supersizing of calories. He had supersizing of bad information from toxic food that was inducing different gene

expression patterns. It was not just the calories, in and of themselves, that created the multiple effects he saw in his body over the weeks that he ate "fast food."

By the same token, we wanted to ask, if you hold the calories comparable, and you hold the percent of calories as protein, carbohydrate, and fat comparable, would you change the information coming from the food between the two groups? Would there be a difference in outcome between the two groups? The result was absolutely unbelievable. I've been involved in these types of clinical studies for the better part of 20 years and for me, this was the most remarkable outcome I have witnessed. The results were so dramatically different that you could not help to recognize the power of nutrigenomics.

The AHAD group did experience improved outcome: they lost about the same amount of weight as those in the LGID group: their total cholesterol was improved; their triglycerides were improved; and their body composition was improved. But, these changes paled in comparison to the members of the LGID group, who had the same calorie intake and the same exercise, but had a different level of phytochemical intake and a different diet persuasion. These individuals had a 46 percent reduction in their triglyceride-to-HDL cholesterol ratio, a significant reduction in total and LDL cholesterol; a significant reduction in high-sensitivity C-reactive protein (hsCRP), a significant reduction in fasting insulin, and a significant reduction in glycosylated hemoglobin. Every one of those variables was extraordinarily better after intervention with the LGID diet. This demonstrates the power of nutrigenomic tailoring and getting the right information to send to the genes to produce the right outcome.

I cannot tell you how impressed the whole clinical staff was in seeing the difference between these two groups. In fact, I went to the literature and asked what drugs these patients would have to be on to produce these same effects. The answer was that if you put people on statins, metformin, and ACE inhibitors, you would still be able to get the same dramatic effects seen across the full range of parameters studied found in these dietary interventions (based on the published literature). Therefore, the LGID diet group had results that represent the *best* medicine-not alternative medicine, not complementary medicine, not integrative medicine, but the *best* medicine. The best approach with this group relative to risk factors to the major cause of heart disease in postmenopausal women (not drugs), based upon evidence of comparison, was a personalized, nutrigenomically-tailored diet focused on improving insulin signaling, lipid management, intracellular signal transduction, and lowered inflammation. Both the AHAD and the LGID groups lost about the same amount of weight. Therefore, it is not solely a weight-loss argument; it is not solely a calorie-restriction argument; and it is not solely a protein/carbohydrate/fat percentage argument. It is an argument related to what information is sent to the genes.

I have recently heard people talk about the toxic effects of soy. I find this ironic, because there are hundreds of clinical trials in humans published in the literature that demonstrate the beneficial effects of moderate amounts of soy in the diet. Our study is one of many showing that with appropriate intake of something like 30 mg of soy isoflavones (part of the soy protein isolate found in the beverage), and in the context of an overall, well-balanced, low glycemic-index diet rich in plant foods, there are no toxic effects. There is a highly desirable effect on every lipid, glucose, insulin inflammation connection that was studied.

We are witnessing the emergence of a new form of nutrition, as Dr. DeBusk discussed-personalized nutrition based on the interaction between nutrigenetics and nutrigenomics. This is an exciting new chapter in the story of the evolution of medicine, and it will result in the *best*medicine in the future-that

which derives from old concepts in new ways by personalization of the diet.

Thanks for being with us. We look forward to our next visit in June.

Bibliography

1 http://abcnews.go.com/GMA/Atio/story?id=1718017

2 Sedlak TW, Snyder SH. Messenger molecules and cell death. Therapeutic implications. JAMA. 2006;295(1):81-89.

3 Ridker PM. On evolutionary biology, inflammation, infection, and the causes of atherosclerosis. Circulation. 2002;105:2-4.

4 Demmig-Adams B, Adams WW. Antioxidants in photosynthesis and human nutrition. Science. 2002;298:2149-2153.

5 Rist MJ, Wenzel U, Daniel H. Nutrition and food science go genomic. TRENDS Biotechnol. 2006: In Press. :

6 Hafstrom I, Ringertz B, Spangberg A, et al. A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens. Rheumatol. 2001;40:1175-1179.

7 Cornelis MC, El-Sohemy A, Kabagambe EK, Campos H. Coffee, CYP1A2 genotype, and risk of myocardial infarction. JAMA. 2006;295(10):1135-1141.

8 Knopp RH, Paramsothy P. Oxidized LDL and abdominal obesity: a key to understanding the metabolic syndrome. Am J Clin Nutr. 2006;83:1-2.

9 Weinbrenner T, Schroder H, Escurriol V, et al. Circulating oxidized LDL is associated with increased waist circumference independent of body mass index in men and women. Am J Clin Nutr. 2006;83:30-35.

10 Esmaillzadeh A, Mirmiran P, Azizi F. Clustering of metabolic abnormalities in adolescents with the hypertriglyceridemic waist phenotype. Am J Clin Nutr. 2006;83:36-46.

11 Sahyoun NR, Jacques PF, Zhang XL, Juan W, McKeown NM. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. Am J Clin Nutr. 2006;83:124-131.

12 Yates MS, Kwak MK, Egner PA, et al. Potent protection against aflatoxin-induced tumorigenesis through induction of Nrf2-regulated pathways by the triterpenoid 1-[2-cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole. Cancer Res. 2006;66(4):2488-2494.

13 Nair MP, Mahajan S, Reynolds JL, et al. The flavonoid quercetin inhibits proinflammatory cytokine (tumor necrosis factor alpha) gene expression in normal peripheral blood mononuclear cells via modulating of the NF-kb<β system.>Clin Vaccine Immunol. 2006;13(3):319-328

14 Lukaczer D, Liska DJ, Lerman RH, et al. Effect of a low glycemic index diet with soy protein and phytosterols on CVD risk factors in postmenopausal women. Nutr. 2006;22:104-113.p>