December 2007 Issue | Christoph Westphal, MD, PhD Sirtris Pharmaceuticals, Inc.

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Welcome to *Functional Medicine Update* for December 2007. Can you believe we are at the end of another year? We are now going into our 27th year and I can't believe how quickly these things go by. I think it has been a very exciting year and this issue should be a great way to finish up.

I want to remind you that we now have quite a nice portfolio of audio courses that have been produced by Synthesis. These include our autoimmune course, *Understanding the Origins and Applying Advanced Nutritional Strategies forAutoimmune Disease*; our most recent product, *Perspectives onAutism*, a compilation of interviews with Jill James, Martha Herbert, Richard Deth, and Herbert Needleman, plus commentary by me; *Applying Nutrigenomics in Clinical Practice to Reshape Your Patients' Health*; and then the last one is *Beyond Metabolic Syndrome: Dementia, Diabetes, Cardiovascular Disease, Hypertension*. These are all available through Synthesis. Our toll-free number is 866-272-5789, or you can go to the Synthesis website, which is www.jeffreybland.com.

What topic are we going to be speaking to this month? A major paradigm shift in nutritional/functional medicine, and I think ultimately in standard medicine: the concept of how nutrients and other environmental factors influence genomic expression and ultimately change the phenotype of cells, tissues, organs, organ systems, and whole bodies, and how this connects the environment to our genome and ultimately to our function and our health.

I recently authored a paper on this topic titled "What Role Has Nutrition Been Playing in Our Health? The Xenohormesis Connection."[1] This article appeared in *Integrative Medicine* in 2007, and I believe it is a nice overview of the focus we are going to have in this issue of *Functional MedicineUpdate* and the discussion with our extraordinary clinician/researcher of the month..

Let's talk a little bit about this big "X" word: xenohormesis. What does it really mean? "Xeno" means "foreign" and "hormesis" is the process of small agents producing change in systems. Xenohormesis is small levels of foreign substances producing changes in biological systems.

In the United States, we seem to be getting fatter even though we have introduced more and more weight loss diets, more and more calorie restriction, and more low fat foods than any culture has ever known in the history of the human species. We continue to see type 2 diabetes, certain vascular problems, renal failure, and neurological problems develop as a consequence of this pandemic of obesity. Could it be that these problems are not just solely a consequence of the direct application of the first law of

thermodynamics (meaning energy in equals energy out, or there is an absence of proper calorie control)? Rather, are these problems related to a combination of calories plus the information that calories bring into the body because food is information? Food contains bioactive molecules that speak to receptors to create ligand-receptor interactions that then transmit, translate, and functionally modify the outcome of cells, tissues, organs, and organ systems, and ultimately the whole body. Maybe the things that we are eating are sending inappropriate signals. This question opens up the possibility of xenohormesis.

In 2006, this topic was discussed in a provocative paper by Yun, Lee, and Doux (Palo Alto, CA) that appeared in *Medical Hypotheses* titled, "Are We Eating More than We Think? Illegimate Signaling in Xenohormesis as Participants in the Pathogenesis of Obesity."[2] I want to emphasize that the question "Are we eating more than we think?" is not being applied to more calories; the authors are asking if we are eating more information/disinformation-molecules that induce a stress response in the body, incite a foreign relationship with receptor sites, and trigger processes of alarm that may induce inflammation, macrophage/monocyte activation, and infiltration into adipocyte visceral fat mass. This process can produce unfriendly or hostile fat, which sends out signals (through adipocytokines) to the rest of the body with the message, "foreigner onboard/let's do battle." This message associates itself with a whole shift in the physiologic sands, producing, then, the dysfunction of chronic disease.

Illegitimate Signaling and the Food-as-Information Concept

It's an interesting question. This is in part the question that Morgan Spurlock talked about and showed us in his marvelous film, *Supersize Me*. In that film, he was consuming three fast food meals a day for several weeks, which induced significant changes in his physiology. In addition, he talked about experiencing mood changes, energy changes, and sleep disturbances. It was as if he was on drugs, he said.

The effects of this fast food diet were more than just elevated blood lipids and altered fasting glucose. How do remarkable multiple effects occur across organ systems through the simple concept of changing the diet? The answer may be through this illegitimate signaling (through receptor site interactions that translate information from the diet into genomic expression and ultimately into function).

This is a big idea-a whole new idea about how nutrition may play roles in immunity, inflammation, appetite, blood fat levels, insulin signaling, and even cellular division and cellular apoptosis.

In this "food as information" concept, nutrition regulates what we call intercellular signal transduction, or the transduction of information from the outside world (from the environment) into inside cellular function. This relay race, or passing the baton off along these various stages of transduction, involves many, many different steps, including picking up the message at the receptor and translating that into genetic or epigenetic modulation. The message has to go through the cell cytoplasm because the genome, which is the chromosomes that are bound up in their histone proteins and super-coiled through the nucleosomes into their architecture, is in the nucleus of the cell. The genome is shielded from direct exposure to the outside environment and therefore it gets indirect messages that are transduced through the cell often by kinases. Kinases are one family of transducing enzymes that relay messages from the outside world to the inside cell. Chemokines, cytokines, or other cellular regulators are also various types of cell signaling substances that influence nuclear regulatory factors and ultimately have effects on promoter regions of genes by upregulating or downregulating the expression of these genes in such a way as to induce an altered cell phenotype.

I know this discussion sounds like a bunch of cell biology and biochemistry, but it really is a fundamentally different way of viewing the relationship that diet and nutrition have to our health outcome by looking at the flux of these xenohormetic molecules through the signal transduction process, ultimately modifying cellular function.

The food-as-medicine concept looks beyond just calories alone, and just protein, carbohydrate, and fat. The individual personalities of the myriad molecules that we find in a complex diet, or in a highly processed diet in which we put new molecules, such as partially hydrogenated trans-fats, send signals to genes and receptor sites that cause alterations in intercellular signal transduction. These illegitimate signals may work through altered kinase pathways (these phosphorylation pathways) that occur quickly in cells. These pathways can modulate function in ways that are much more rapid than what is required by selective mutation over many years of natural selection (evolution). In this model, we are talking about things that can happen very quickly.

Anti-Stress Substances in Phytochemicals

Going back to the recent article I mentioned above, it begs a question: Can we get xenohormetic substances through a minimally processed whole-food, plant-rich diet? Do we have substances within the family of of phytochemicals in a minimally processed, plant-based diet that serve as anti-stress substances? The term "xenohormetic" does not necessarily mean bad. We may have xenohormetic substances that induce the stress response, or we might have xenohormetic substances that attenuate the stress response.

Plants, under stress, will induce the synthesis from their own genes of compounds that are anti-stress compounds--flavonoids, polyphenols, carotenoids, etc.-that are there to help the plant respond to stress. These xenohormetic substances that the plant produces under stress are really anti-stress substances. When consumed by humans, these substances may be considered by similar shared pathways (or conserved pathways), to be anti-stress substances in the human-the so-called primordial shared metabolic or genomic pathways that we (through our plant ancestors) share in common.

It may be that by distancing ourselves from a whole-food diet and foods that contain phytochemicals, that we are actually uncoupling ourselves from messages that signal anti-stress. Isn't that a profound concept, when you think about it? A "white" diet (white sugar, flour, fat, alcohol) is devoid of all these other signaling substances I have talked about. This diet does not have the xenohormetic, anti-stress personalities or signatures that we see in a minimally processed, whole-food, or plant-rich diets. I think this is a very powerful concept that we are going to be learning much more about. It translates into what I call the systems biology approach towards looking at human pathophysiology or pathobiology. You can't understand this by looking at one substance at a time; you can only understand this by looking at the web of interactions of a complex environment with a very diverse genome that responds in different ways in expression to differing signatures that come from the complex environment.

Recently, in the journal *Molecular Systems Biology*, a very interesting paper appeared titled "Human Disease Classification in the Postgenomic Era: A Complex Systems Approach to Human Pathobiology."[3] The investigators, who are from the department of medicine at Brigham and Women's Hospital, Harvard Medical School, talk about a change in thinking about disease, and, in this systems biology age that we are moving into, how we need to redefine how we classify disease and how we think about its remediation. Let me share this concept with you.

The contemporary classification of human disease that we know derived from observation correlation between pathologic analysis and clinical symptoms and has resulted in the diagnostic codes that we all use in medicine (the DRGs-Diagnostic-Related Groups). These are fairly empirical and observational in their origin: you see a patient who has a certain kind of anomaly. We started off with gross pathology and moved to clinical parameters that may include biochemistry and even radiology as resonant spectroscopy. Those criteria that cluster together as a series of symptoms, signs, and pathophysiologies we call a "disease," as if it were independent and isolated in time/space in that individual and you could disconnect it from other "diseases."

That model appears to be breaking down. We now recognize that conditions are often connected together, and there are no two people who have the exact same presentation of a disease. Even though you might diagnose a person with type 2 diabetes, the next patient that comes in with that same diagnosis may have a very different presentation and progression than the previous patient with the same diagnosis. Even within the same name of a disease we see a highly different set of parameters that relate to their expression.

Characterizing disease from this concept of the correlation between pathologic analysis and clinical symptoms did establish a structure that has served clinicians well up until this time. It created convenience and a teaching algorithm that is reproducible and can be memorized, as well as a systemization of the field so that standards of practice could be codified. Yet this time-honored diagnostic strategy has significant shortcomings that reflect both a lack of sensitivity in identifying preclinical disease and a lack of specificity in defining disease unequivocally.

The investigators from Harvard and Brigham and Women's have been looking at this limitation, viewing it as a reflection both of the different clinical presentations of many diseases (meaning variable phenotypic expression, as I was describing), and the excessive reliance on Cartesian reductionism in establishing diagnosis-cause and effect (single agents producing single outcomes). This perspective is really changing to now take-as a fundamental component-this systems biology approach and classifying human dysfunction and disease utilizing a broader systems biomedicine approach, looking at interaction of systems so that the mechanism and etiology of the disease becomes more important that the disease itself.

There are certain people who have been bold enough to say that we don't have diseases, we have physiological dysfunctions that for convenience we code as a disease. Physiological dysfunction is where the action is. We should be treating the dysfunction, not the disease. You have probably heard this language before through the teachings of the Institute for Functional Medicine and the *Textbook of Functional Medicine*. It is the fundamental construct of the functional medicine approach.

Recognizing that shift in the web of function is a consequence of the gene-environment interaction gives rise, then, to a whole array of altered potentials in the phenotype. If we were to look at pharmacology nutrition related to this obesity epidemic, we might say that we are moving into a new phenotype, which one author has called "*Homo obesus*." Not *Homo sapiens*, but *Homo obesus*, which is a metabotrophin-deficient species in their phenotype as a consequence of the illegitimate signals and the translation of those signals into phenotypic change that we are seeing in our population today.

I'm not making this all up (I know this sounds a little Jeff Bland-esque), This actually comes from a

recent paper that appeared in *Current Pharmaceutical Design* in which the concept of*Homo obesus*, metabotrophin-deficient species, was advanced.[4] The authors of this article state that in most countries the prevalence of obesity is now exceeding 15{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the population. This 15{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} or greater figure was used by the World Health Organization to define the critical threshold for intervention in a nutritional epidemic, so we can actually say this is a global transition in phenotype towards this *Homo obesus*.

Why? Is it just luxurious calories? Or is it the combination of calories that are inappropriate as illegitimate signals, which then alter secretory and/or signaling pathways that are related to this metabotrophic effect, and then are seen in all sorts of changes of insulin, adiponectin, resistin, inflammatory cytokines like TNF-alpha? Is this the new metabolic personality of the 21stcentury?

Rather than just reduce the calories, we ought to be looking at reducing adverse signals and improving favorable anti-stress signals. This even leads to changing the diet to increase the intake of these exogenous metabotrophic agents that can induce proper anti-stress or adiponutrigenomic substances that can modify the expression of genes that are associated with inflammation and stress. This has to do with things like the sirtuins-the family of genes that we are going to be discussing at great length in this issue that have been dubbed "longevity genes." They actually have effects on modulation of the outside environmental information through the epigenome into genetic expression and ultimately modulating these regulatory substances like insulin and proinflammatory cytokines and a whole array of the metabotrophic substances. Maybe we should be managing the signals more than managing the calories; that is the concept.

What I have really been speaking to is defined by a term that can be found in the literature more and more: "nutritional hormesis." Hormesis, again, as I defined, is the effect that small quantities of substances have on functional changes. Here we are talking about substances that come through the diet (nutritional substances) that modulate, at low levels, physiological function through altering the phenotype. This concept of nutritional hormesis is really gaining importance and it may explain why even small levels of new substances added to the diet through food processing or chemical transformations have resulted in more significant changes in physiology than we might have predicted.

This concept of nutritional hormesis is reviewed in a very nice paper by DP Hayes, from the New York City Department of Health and Hygiene that appeared in the *European Journal of Clinical Nutrition* in 2007[6] In this paper, Dr. Hayes describes the concept of nutritional hormesis and talks about how research along the lines of understanding how hormetic effects are modulated through intercellular signal transduction through the gene expression pattern will be the forefront of the "new" nutrition and its relationship to medicine.

With all that in mind, let's take a specific example-one that we are going to be speaking to in greater detail during this issue of *Functional MedicineUpdate*-and that is the small molecule found in peanut skins, grape skins, in a variety of skins of fruits, and to some extent also found in whole grains. That is the molecule resveratrol. You may have heard a lot about resveratrol. You may know that it is associated somehow with the French Paradox (the French, who have historically eaten high-fat meals that include foods we might even think of as cardiotoxic, historically have had very low incidences of cardiovascular disease relative to people who ate a lower fat diet-this is paradoxical if the diet-fat hypothesis is correct).

People have been exploring the French Paradox for some time. There have been suggestions that it might be alcohol that reduces cardiovascular risk in these individuals (through the consumption of wine at meals). Red wine contains polyphenols and phytochemicals such as resveratrol, which have been said to be "antioxidants and cardioprotective." What is the story that has emerged around resveratrol recently? It is much more than just the story of antioxidation.

Animal Studies and Resveratrol

Recently, a paper was published in *Nature*, a very well-known scientific journal, titled "Resveratrol Improves Health and Survival of Mice on a High-calorie Diet."[7] I think this is a pretty profound study. In this particular study, mice were intentionally fed a high-fat diet, similar to a diet that might be consumed by those eating a lot of processed fast foods. Some of the animals received a supplement with 3,5,4'-trihydroxystilbene, which we know as resveratrol, one of the principals from red wine (coming from the skins) and peanut skins.

Resveratrol was of interest because it had previously been shown to extend the lifespan of diverse species, including the yeast, *Saccharomyces cerevisiae*, the flatworm, *Caenorhabditis elegans*, and also the fruit fly, *Drosophila melanogaster*. All, when given supplemental resveratrol, were found to have an extended lifespan, as if somehow it had an effect similar to that of calorie restriction, which is the only reproducible way of extending lifespan in animals (restricting calories by thirty percent without restricting micronutrients).

In looking at how resveratrol could influence the lifespan of yeast, flatworms, and fruit flies it was found that it had an effect upon a gene called Sir2 in these species, a conserved deacetylase, which is a gene that is very important for regulating the expression of other genes that are associated with such diverse things as insulin sensitivity, inflammation, cell cycling, apoptosis, and oxidative redox potential. Even things like insulin-like growth factor 1 levels, adenosylmonophosphate-activated kinase (or APK), and PPAR-gamma (the peroxisome proliferated activated receptor associated with insulin sensitivity) all have interrelationships with the Sir2 gene.

In looking at the effect of a resveratrol supplement in animals with a high fat and calorie intake,that the study authors found they could-by supplementing with resveratrol-neutralize some of the adverse effects of the higher fat-higher calorie diet to modulate gene expression of the SIRT gene and decrease some of the incidences of shifting phenotype that are associated with diseases of aging. This is a pretty remarkable study, I would say. Not only did the authors show improved AMPK activities, improved PPAR activated receptor 1 co-activator activity, increased mitochondrial number, and improved motor function, but they also showed that some of these parameters associated with the high-calorie diet had a modifying effect on 144 out of 153 genes that were associated with the adverse effects of the high-calorie diet. Somehow resveratrol is speaking to the genes-multiple genes-through the effects that it has on this deacetylase enzyme (the SIRT enzyme) and how that translates, then, that message to all sorts of other patterns of genes (families of genes) that regulate factors that are associated with biological aging.

What about the sirtuin family of genes? There are pretty interesting new observations that you are going to hear much more about from one of the leaders in the field. I'm just setting the stage by this introductory comment because this ties back to our hormesis concept, xenohormesis, and nutritional epigenomics (in other words, how nutrients influence the effects that then regulate the promoter regions of genes to create altered gene expression in response to dietary and environmental signals).

If this sounds like new information to you and the whole landscape is changing around us, that is what's happening in the field right now. We are undergoing a paradigm shift that is second to none since Atwater made his first calorie discovery, Casimir Funk made his first discoveries on B vitamins deficiency and beriberi, the Goldbergers made their discoveries on pellagra with niacin, and Szent-Gyorgyi and his discoveries on vitamin C and scurvy. I think we are seeing the same magnitude of change in our thinking as at the dawn of what we might consider modern nutrition, back at the turn of the last century.

The idea that signals from our environment and diet, through receptor-site interactions and kinase signaling, modify epigenetic gene expression and the phenotype of cells is generating more interest in the interface between molecular genetics, molecular biology, nutritional medicine, and histopathology and disease (sometimes seen years downstream). Needless to say, the genetics of the individual plays a very significant role in the way this whole orchestration plays out. We can't divorce ourselves from the genes of the person. These modifying factors in the environment are going to play differently through different orchestras. The orchestras-and the assembly of each musician's chair in each orchestra-is determined by the genes. How individual instruments play a suite will depend on the environment in which it is played, but the obvious orchestra will be determined genetically.

To continue this analogy, what if you just happen to get a bunch of first-year musicians in your orchestra by your genetic lot? Let's say that your string section, your woodwind section, and your percussion section are all world-class performers, but somehow you have a high school brass section. If you wanted to play one of the orchestrated suites that had a lot of brass in it, you're not going to play it as effectively as you would if you had a world-class brass section. That's our genes. Our genes will determine the potential quality of each of the individual instruments in our orchestra. But how those instruments are played, and the way that they ultimately make individual music, will be dependent upon the environment in which the orchestra is playing. That's the basic concept of this xenohormesis construct: nutritional epigenomics and nutrigenomics and how that translates, ultimately, into the changing of the outcome of the health of the person.It is the construct of a person's genes in the matrix of their environment.

Now let's go back to sirtuins. The sirtuins are the so-called longevity genes. In sirtuins, "SIR" stands for silent information regulator. These related enzymes have originally been identified or defined as a family of nicotinamide adenine dinucleotide-dependent enzymes (NAD, for those of you who remember your biochemistry). Remember where NAD comes from. The precursor of NAD is from niacin, which is a vitamin B3 derivative, so that starts already telling us there is some nutritional connection to the way these particular enzymes in genes interact. So the sirtuins are NAD-dependent enzymes that deacetylate lysine residues on various proteins. These enzymes are controlled by genes that have this deacetylase role and therefore control how other genes are going to be expressed and how the enzymes and proteins within the cell work. This is a fundamental and important part of setting the stage for how the orchestra will play the suite.

The sirtuins are remarkably conserved throughout the evolutionary system, all the way from very primitive organisms (going back to primitive bacteria), through yeast, and ultimately into eukaryotes, or nucleated cells.[8] I believe there is something very ancient and important about the sirtuin enzymes and genes in that they are a very, very important conserved part of all life. They have a variety of cellular functions, ranging from gene silencing and the control of cell cycles and apoptosis, to energy homeostasis through the way they influence mitochondrial oxidative phosphorylation. On a whole-body level, the wide range of cellular activities of the sirtuins suggest that they could constitute potential therapeutic

targets that would allow us to possibly combat the dysfunction associated with metabolic neurodegenerative and proliferative diseases. It is this important role that sirtuins have that make them really important candidates for therapeutic intervention. And because there is a nutrition link to their expression patterns and their activity, it has opened up a new and important door for understanding how nutrients may modulate sirtuin function and may ultimately mimic some of the effects that we see with calorie restriction (i.e. the French Paradox).

This concept, I know, is very complex. I think as you hear our clinician/researcher of the month you are going to be able to understand this at a much deeper level. Lastly, before we hear from him, I want you to recognize what I mean by NAD-dependent deacetylase.

These deacetylation enzymes that take an acetyl group off a lysine and allow a protein to change its confirmation or unmask a genome so that it can be read by deacetylation of a histone protein. These particular effects that occur at the epigenome are such that they require adequate levels and delivery of NAD. As I illustrated earlier, the precursor for NAD is a niacin molecule (a nicotinic acid) that interconverts to niacinamide, and ultimately into NAD. Where do a lot of these B-complex vitamin derivatives have their function? They have their function not only in intermediary metabolism, but also at the mitochondrial level that helps to control some of the oxidoreductive processes that are involved in mitochondrial oxidative phosphorylation.

A major cause of cell death is this genotoxic stress that is thought to be due to the depletion of NAD from the nucleus in the cytoplasm. NAD depletion from the mitochondria can also be very damaging because it is actively involved in support of cellular physiology associated with energy production. In a recent paper that appeared in the journal *Cell*, a highly regarded cell biology journal, a group of investigators showed that NAD levels in mitochondria remain at physiologic levels when nuclear and cytoplasmic pools are depleted.[9] Rodents fasted for 48 hours will show increased levels of the NAD biosynthetic enzyme, Nampt, which makes more NAD from niacin, and a concomitant increase in mitochondrial NAD, which may, in part, account for some of the benefits that calorie restriction has on cellular bioenergetics. Increased Nampt provides protection against cell death and requires (as this article goes on to say) intact mitochondrial NAD salvage pathway. This is all, then, dependent on the deacetylase activity of SIRT and may help us to understand something of the relationship that the SIRT genes and enzymes have to prolongation of healthy function, relationship to the healthspan, and how that interconnects to nutrient signaling and xenohormesis.

If we were to tie together the resveratrol studies with the NAD observation, what it illustrates is that there may be a variety of different nutrients that play important roles in setting up the signals of orchestration of these "longevity genes" through these epigenetic modulations. What I mean by epigenetics is that every cell in our body has a message for every other cell. Our 23 pairs of chromosomes contain all the information needed to make every cell at every age in every tissue, so how is it that they are making only those things that they are supposed to be making (eg, the heart is not making the stuff needed in the liver)? That is controlled by masking of the genes with methyl groups and with acetyl groups that prevent genes from being read. Deacetylation, opens up the genes to be read in specific regions, which then can turn on the promoter regions of other genes and you can have a cascading effect. Similarly, methylation silences genes, particularly when methylating the promoter, and that then downregulates gene expression. It is these processes at the epigenome that can be modulated by diet, lifestyle, and environment that open or close down the genes to be read. You don't want to read oncogenes; you want to keep them silent. You

do want to read your defense genes and your anti-stress genes, and these are the things that we are learning can be modulated with a specific nutrient. It is a very fascinating chapter in our evolving understanding of how to engage in improving the health span.

I think we are ready to move to our discussion with our clinician/researcher of the month, who is someone of the type that we've never had in our 25 years of previous interviews. He is Dr. Christoph Westphal, from Sirtris, and I think you'll find his discussion to be very important and of high relevance to this topic.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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Once again we are at that place in Functional Medicine Update that I think all of us look forward to: our clinician and/or researcher of the month. We are very privileged this month to have someone who represents what I think is the cutting edge-where the action is-right now in the advancing frontier of nutrition and that is Dr. Christoph Westphal, MD, PhD who is the CEO and Vice Chairman of Sirtris Pharmaceuticals.. Fortune magazine featured a cover and article on the company in the February 12, 2007 issue under the title of "Drink Wine and Live Longer." We are going to be talking, in a moment, about the Sirt gene, the French Paradox, resveratrol, and all sorts of things that I'm sure you have heard something about.

Dr. Westphal is not only really exploring and moving towards commercialization of these concepts as CEO of Sirtris, but he is also a medical doctor from Harvard Medical School, and he has a PhD in genetics from Harvard. He graduated with his BA, summa cum laude and Phi Beta Kappa, from Columbia University and was formerly a consultant with McKinsey.

Sirtris, it is a very interesting biopharmaceutical company that is focused on discovering and developing proprietary, orally available, small molecule drugs to treat chronic-related diseases associated with aging such as type 2 diabetes. You are going to hear more about that and how that interrelates with diet and lifestyle and, I think, a new paradigm for the pharmaceutical industry.

With great pleasure, Dr. Westphal, we welcome you to Functional MedicineUpdate. Maybe you could tell us a little bit about your background and how you-through this interesting road we all travel in our lives-got to Sirtris.

CW: Thank you very much, Dr. Bland, for inviting myself and Sirtris to join you on your program. As you mentioned, I have a technical background, having done an MD and a PhD at Harvard. Previously, I had started with Phil Sharp, who is the founder of Biogen, a company called Alnylam, which publicly traded on NASDAQ, and also (with Bob Langer and Paul Schimmel) a company called Momenta (again,

a publicly traded company).

About four years ago, I became very interested in resveratrol and in the sirtuins, based on a set of papers that were published in Nature, Science, and Cell (those are very well-known publications in the academic research world). A young researcher named David Sinclair at Harvard Medical School had published what I thought were quite extraordinary findings which indicated, first of all, that SIRT1 was a gene that appeared to govern the aging process.

It has been known for a long time that calorie restriction, or the reduction in calorie intake by about 30-40 percent, extends healthy lifespan in a wide variety of organisms including yeast, worms, flies, mice, and rats. It was shown in 1999 and 2000 by David Sinclair and Lenny Guarente at MIT that SIRT1 governed the beneficial effects of calorie restriction. By that I mean if you deleted the SIRT1 homolog in these various organisms, they no longer lived longer under calorie restriction, and conversely, if you overexpressed SIRT1 in these various organisms, even in the absence of calorie restriction you were able to extend healthy lifespan.

Research by Dr. David Sinclair
And so about four years ago, David Sinclair published a paper in Nature showing that resveratrol, which is a component of red wine (and many of you have heard of the red wine French Paradox), was able to activate SIRT1, and on its own, extend lifespan in yeast.10 When I saw those findings I thought, "Well, it's not that far from yeast to worms, to flies, and on to mammals." In fact, the data for calorie restriction was very strong all the way into humans (that it would increase healthy lifespan), and so we decided to start a pharmaceutical company to develop FDA-approved drugs seeking to target the aging genes, such as SIRT1, to treat chronic disorders such as type 2 diabetes. So that was really the origin of Sirtris.

JB: When we look at the SIRT1 gene, it is a member of the family called the NAD-dependent deacetylases, which has something to do with the epigenetic structure of the genome (the nucleosome structure). Could you help us understand that connection? I think that is a very interesting evolving frontier (this whole epigenetic connection to environment and diet).

CW: Yes, absolutely. What we are very excited about at Sirtris, and what I think our SAB (our Scientific Advisory Board-which has about six National Academy of Science members/Nobel Prize winners) are excited about is that a lot of what we are doing seems to be mimicking a natural process, and specifically addressing your question regarding NAD (of course your listeners will be aware that NAD is an intermediate in metabolism).

It was very interesting to David Sinclair and then to Sirtris that NAD controls the activity of the sirtuins, specifically of SIRT1, and provides really a compelling link between this long-standing observation that your nutritional status (your level of calorie intake or calorie overload on the one hand, your glucose levels/insulin on the other hand) and your NAD levels ultimately in your cells control the activity of the genes that appear to control the aging process. When we started Sirtris about three-and-a-half years ago, we started from a very simple precept that the sirtuins seemed to be beneficial enzymes, they seemed to control the response to calorie restriction, and they seemed to control, really, a downstream signaling cascade of proteins that ultimately would appear to be a great way to treat type 2 diabetes. So that was really the origin of the company.

JB: When we look and think of NAD, obviously we think of redox and its connection with NADH and NADPH and how that is related to the reduction oxidation quotient of a cell, which then takes us back to mitochondria, so there is this whole interesting story of connecting the energy powerhouse of the cell somehow to signaling to the epigenome. Could you help us to understand that a little bit?

Sirtuins and Mitochondrial Biogenesis
CW: Yes, it's a great question, Dr. Bland. It's just such a fascinating science story and we have begun (with our SAB member, Eric Ravussin) human studies. We have really shown this natural pathway, which is reduction of calorie intake, increasing SIRT1 activity (SIRT1 being the founding member of the sirtuin family which is dependent on NAD), apparently controlling the mitochondrial activity. So when you turn on SIRT1, you increase the activity of the key regulator of mitochondrial biogenesis, a gene called PGC-1a. When you turn that on, you seem to increase the number and function of mitochondria by about 30 percent.

We published a paper in Cell in November of last year-the senior author is Auwerx-where we showed that when you treated mice on a high fat diet with resveratrol, which activates SIRT1, you increased the activity of PGC-1α and you turned on mitochondria such that those animals then had lower glucose, lower insulin, and in fact they ended up having higher performance as measured by a treadmill.11Then, thinking therapeutically (since we are a drug discovery and development company), we moved those compounds into human clinical trials. We have now dosed more than 200 volunteers and type 2 diabetics with our formulation of resveratrol.

I probably need to add here a cautionary note that the general media did pick up on early on, which is that nutritional supplements containing resveratrol, or, in fact, resveratrol from food stuffs, has been published in the literature to not reach therapeutic blood levels in man. We have now, in the last several months, reported at scientific meetings and will publish in the academic literature our findings with our formulation of resveratrol, which basically has a smaller particle size and excipients that stabilize resveratrol, and we've shown that we can reach therapeutic blood levels in man with our formulation and linear pharmacokinetics.

The next step, of course, is to look at effects on diabetics and, in fact, we have several phase 1-B and a phase 2-A study currently enrolling and expect to begin reporting data in early 2008, so it is really a very exciting time for Sirtris right now.

JB: I would say so. I'd like to go back, if I could, to how Dr. Sinclair made the discovery of resveratrol in the sea of different interesting phytochemicals that might have been chosen. I'm sure that his discovery process was very interesting. Could you give us an insight into that?

CW: Well it is one of these fascinating science stories. I always like to think that if it is a natural process and if you are right about your science, you happen to end up being fortunate when you look under the lamppost. And so the original discovery, which in itself is just a really exciting and fascinating discovery, was that single genes could control the aging process.

Until the late 90s, it was frankly heresy for researchers like David Sinclair and Lenny Guarente when they said, "We believe there will be single genes that control aging." Most people thought aging would be too complex a process. They then went into model organisms such as yeast, which are tractable, genetically,

and showed in screens that you could find specific genes where you (if you increase their activity) were able to increase lifespan in yeast-those were the sirtuins. And then they went on to show that downstream of calorie restriction you found the sirtuins were turned on and could, in fact, substitute for calorie restriction (so bringing the world of physiology together with the sirtuins in a way that no one had expected but one might have been able to predict, given the findings).

The next step, then, was finding that the sirtuins were dependent on NAD, the intermediate in metabolism, which again made an enormous amount of sense: that the metabolic state of humans (or any organism) really does correlate in a great way with the aging of that organism. And then that next step, which you questioned and was really quite exciting, was when David said, "Well let me take an unbiased approach and screen the Harvard library of small molecules and see which small molecules could, on their own, activate SIRT1." So he took an unbiased approach and went into screening mode, found resveratrol, and then we at Sirtris have found molecules that are about a thousand times more potent than resveratrol, completely distinct in terms of their structure, and are moving into human clinical trials in the first half of this coming year, so arguing that we should be able to have lower dose levels needed for these synthetic resveratrol equivalents.
JB: That's really, really an exciting process. I mean, just the whole method of getting to an answer is a whole new model for the pharmaceutical industry. Dr. Sinclair talked about-kind of on a more philosophical plane-how these interesting events might occur. It seems (probably to the first-time listener) that the connection between calorie restriction and small molecules (in this case, in food, which share a similar pathway) sounds very-probably-unusual, but he advanced the concept of xenohormesis, which I think is a very interesting concept as it relates to our whole evolutionary history coming up through lower animals and then ultimately to humans/mammals. Could you describe a little bit this xenohormesis concept? I think it is very interesting.

CW: Yes, it goes again to this idea that we think we are mimicking a natural process, and so the belief is when we face periods of adversity or lack of food stuff, it should be evolutionarily preferred, and conserved, and, in fact, favored if we would be able to respond to signaling molecules in our environment. The theory is that over evolutionary time, billions of years ago when the sirtuins evolved, they evolved to be able to sense periods of adversity and periods of lack of food. When our forebearers (or, perhaps, yeast, which, of course, are a couple of billion years older than humans) evolved, they evolved to be able to overcome a period of lack of food by being able to sense in the environment signaling molecules such as resveratrol, which is actually expressed at higher levels in stressed plants. To make it even more clear (hopefully), for example, resveratrol found in the skin of grapes is actually increased in content when those grapes find a harsh climate (a climate without enough water or nutrients). The thought would be that the organisms that depend on food stuffs, such as us or yeast, when they are exposed to stressed plants, would then turn on a system that would allow them to overcome that period of lack of food. That being evolutionarily conserved, once you survive that period you could still have offspring. So it is very complicated and it's a pretty big idea, but when you think it through it does actually make sense.

JB: Well, we're on the horns of big ideas. Obviously there is another very big idea implied in your work that I think is very fascinating because it relates to medicine as a whole, and the whole concept of the primacy of diagnosis: the concept that a substance (let's use resveratrol as an example) could modulate processes that cut across so many ICD-9 codes (diabetes, cancer, neurodegenerative diseases), and this kind of flies in the face of the way that many of us learn differential diagnosis and histopathology and the

fundamental underpinning of medicine. Could you give us your insight as to where you think this work is taking us in terms of our medical paradigm?

CW: Yes, Dr. Bland, it's a great question and it is really something that we think about everyday at Sirtris because it has pretty profound implications, not only for our small company, but if we are right about this idea, it may have pretty interesting and far-reaching implications for medical care. Perhaps the best way to answer that is with a question I will ask you-a rhetorical question-and then I'll answer your question. When folks ask me, "Well, if you are right, this might apply to many diseases," I say to them, "Could you name to me the diseases that, strictly speaking, are not associated with aging?" In fact, when we think about it, diabetes is, of course, associated with aging; it used to be called "age-associated" diabetes for type 2 diabetes, Alzheimer's, Huntington's, ALS, inflammation, cancer. And really it makes sense, when you take a step back, to think if we are targeting the genes that control the aging process, not to stop aging, but to modulate aging and to perhaps slow aging, it would make a lot of sense that we should be able to develop therapeutics based on that approach for a variety of very important chronic diseases of aging. That is why at Sirtris Pharmaceuticals we actually believe our drugs should have applications not only for type 2 diabetes, which has an age association, but also for severe neurological illnesses, for inflammation, for cancer, for many of the mitochondrial illnesses. When you ponder that, of course, it is an enormous opportunity. We need, as a small company, to focus on the straightest shot from animal models into human studies, but certainly our hope, ultimately, is to be able to affect many of the major killers of Western society.

JB: That was really beautifully stated. It sounds to me, as I just listened to you, that you are really painting a wonderful verbal picture of what might be called a systems biology approach to medicine, which is a very different way than most of us learned about anatomy and physiology and ultimate translation into disease.

CW: That's very kind. Yes, it is a very exciting time for Sirtris. I do always want to make sure when we talk to the media we do always want to emphasize that this is, of course, several years from approval by the FDA, and as you understand there are, of course, enormous risks still ahead of us on the clinical development path.

JB: So one of the things that you have alluded to, which I find really fascinating, is this redox connection to the SIRT1 gene and its control of all these various interesting functions. When we think of redox, in the parlance of Helmut Sies (his concepts from a number of years ago of oxidative stress), we often think of the oxidative stress relationship to redox gone array. And then that leads us to think about DNA strand breaks and repair of DNA and ties into things like polyadenyl ribosomal polymerase, or PARP and I know that there is a connection here between SIRT1 and PARP. So, it seems like we are also talking about protection of DNA, as well, against oxidative injury.

CW: Yes, the way we agglomerate and sort of interpret our data, which has mainly been published in the academic literature and we continue to do so, it's a reasonably parsimonious (we think) explanation. When you have type 2 diabetes you go to your doctor and your doctor, of course, suggests, first of all, calorie restriction (in other words, reduce your calorie intake) or exercise. When you are doing those two things, as far as we can tell, and consistent with the field that you are alluding to, you drive mitochondrial biogenesis. In fact, you appear to be increasing the coupling of mitochondria, such that the mitochondria are more efficient, with less oxidative damage. When we turn on the sirtuins, via resveratrol or our much

more potent and novel small molecules that do the same, even in the absence of exercise and calorie restriction, in our animal models we increase the number and function and affect the coupling of the mitochondria such that there is less leakage (proton leakage) through the mitochondria and less oxidative damage.

I think that's how you can really bring these different fields of insight together such that we understand what people have always been telling us (reduce your calorie intake and try and exercise) and put that together with the other insight, which has always been to try and prevent oxidative damage to your DNA. The way we think that is happening is really via SIRT1 turning on PGC-1a, increasing the number and coupling and functioning of mitochondria in a way that is intuitively obvious, the same way that you do with exercise or calorie restriction.

JB: So from that I take away that we are moving into an era to redefine the term "antioxidant." It has always kind of been problematic for me that "antioxidants" is like a generic term-it is like the term "love"-in that has many meanings to different people in different concepts, whether it's agape or amore, and by a similar token, "antioxidants" is a fairly broad-based term that doesn't have much specificity related to tissues, or organelles, or even function. It sounds like what we are starting to say is that these processes that you are describing have very specific influence on cellular redox within certain tissues and how that influences ultimate outcome in the phenotype of that tissue, which is much more specific than just the broad-based concept of antioxidants.

CW: Yes, our perspective-and, of course, it continues to evolve and it is certainly not 100 percent confidence at this time-but our perspective is if you can reduce the number and amount of oxidative units by having your mitochondria be more coupled, that may be a better way to treat diseases, or to prevent diseases, versus trying to soak up the oxidants that are already there. Our view is we appear-as with calorie restriction or exercise-to be reducing the damage to end organs and reducing disease by preventing the disease from taking place in the first place.

JB: That's beautiful. That's very, very interesting. I'm going to ask you-if it is not too uncomfortable for you-you know food is a very complex matrix that has, literally (now, we are learning), tens of thousands of different potentially bioactive molecules in it, some of which were not considered very interesting until recently. Do you think that there are other things in the complex matrix of foods that have influence on sirtuins other than just resveratrol, itself?

CW: We've found, of course, much more potent and totally unrelated molecules to resveratrol that also turn on the sirtuins and we think are probably even better suited to be drugs for diabetes. We believe that there will be multiple molecules in foodstuffs, not only resveratrol, that have a similar effect. I do need to emphasize, however, that ultimately our point of view is that you either need to turn on the sirtuins with a small molecule such as resveratrol or our new chemical entities, or you need to turn on the sirtuins by reduction of calorie intake. So I would caution the view that significant calorie intake plus some good food additives, that being very good for your health, I don't know that I'd support that.

JB: Yes, I think we would completely support that concept as well. Lastly-I know you've got to run-I just have two quick questions, one of which is these effects that you are describing have a different influence, mechanistically, than the way that often people have learned about nutrients. They have learned about nutrients having an effect more on the metabolome, directly, by vitamins activating a cofactor which then

controls a metabolic pathway, or (as you discussed earlier) an antioxidant such as ascorbate or tocopherol trapping a free radical at a certain cellular site. What you are describing is the influence of substance (in this case resveratrol) way upstream of that at the initiation of cellular signaling, which really occurs epigenetically. I think this concept of response to our environment due to epigenetic, kind of histone-related effects is a pretty dramatic change from the way that we have traditionally thought about nutrition and its effect on cellular physiology. Could you just quickly summarize your view of this epigenetic-nutrient connection?

CW: Yes. At this point I will move into pure speculation and hypothesis versus very strong data. Our point of view is that either exercise or calorie restriction probably has very broad and very pleotrophic effects on your gene expression and the status of your chromatin. I think you have alluded to probably having a similar view. We think that there are a couple of switches that the body flips from off to on in that setting. We know in humans, of course, that calorie restriction or exercise turns on SIRT1 and we can mimic that with small molecule activators quite dramatically. So we think you are absolutely right. We think this is going to be a whole host of changes-a wide-ranging beneficial change that is really sort of triggered by a few key cellular switches such as the sirtuins.

JB: I can't tell you how much we have enjoyed this discussion and just watching your work evolve. It is really reframing so many of the fundamental things that we thought were facts that now have to be modified. One last quick question, just from a commercial perspective as the CEO of Sirtris Pharmaceuticals: How do you protect these amazing discoveries in IP that come out of the natural world?

CW: At Sirtris, (the ticker on that is S-I-R-T), we've raised about 170 million dollars to date. Most of that we continue to have on our balance sheet so that we can invest very significantly in our intellectual property. We have over 120 patent applications, and several of those patents have been issued. There is a very broad set of claims related to activating SIRT1 to treat diseases of aging which we believe covers any molecule that will do so. We also, of course, have the specific formulation of resveratrol that we believe is able to reach therapeutic blood levels in man. And, finally, we have composition of matter for our completely novel synthetic molecules. We are very focused (if we are really right about this area) to try and get these medicines to man as quickly as we can, and we believe that the earliest that that can be is probably about 2012 in terms of FDA approval. We are also very actively speaking with a broad set of companies. Really our goal is to enable the field because if we are right we really think it could be quite important for human health and there is no reason for us to want to stand in the way of that.

JB: Well, Dr. Westphal, this has been very inspiring and I want to compliment you and your colleagues and obviously also Dr. Sinclair for this pioneering work. I think it is going to reset a lot of our views and premises about the way that discovery is made in the field of pharmaceuticals and also the role that natural products may play in human health.

CW: Thank you so much, Dr. Bland. I really appreciate the great work you do as well.

The discussion that we have had with Dr. Westphal also raises another very interesting question: what are the number of environmental factors that could influence these important gene response elements that ultimately regulate cellular function and modulate stress response and various functions that go downstream to induce insulin resistance, dyslipidemia, alarm, inflammation, and associate with accelerated cytological aging? Of course, one of those factors is what we consider physiological stress.

This takes me back to an interesting observation. You probably know that more than a century ago Robert Koch established that infectious diseases were caused by microbes-it won him, actually the Nobel Prize in physiology and medicine in 1905-which was a major, kind of fundamental discovery in medicine. About that same time Dr. Elie Metchnikoff, who was (I think, at that point) the actual chairman of the Pasteur Institute in France and was one of the pioneers of cellular immunology and also won a Nobel Prize in medicine and physiology, was the first to recognize that microbes might also have beneficial effects on human health. The concept of lactic-acid-producing bacteria prolonging life was actually part of his book that was a best-seller, first in French and then later translated into English, called Prolongation, and that particular book advanced the concept that the consumption and even the use of enemas containing Lactobacillus acidophilus would be valuable for improving health and improving immune function.

This raises a question whether our enteric bacteria might also influence our stress response in gene regulation, and of course that then leads to a more recent discovery. When I say "more recent," it is really more recent but is built on some initial discoveries made by William James back in the 1800s, who was a psychologist at Harvard given some of the early credit for developing psychological theory. He had published a provocative theory of emotion: that the perception of emotions follows from the perception of our physical responses to cognitive apprehension of external threats or even pleasant stimuli. That is, I guess we could say, the experience of emotion is integrated with the somato- and viscero-sensory signals that result from cognitively driven motor, neuroendocrine, and autonomic responses (in kind of this brain-body-brain loop of communication/integration), which is really one of the fundamental themes that functional medicine talks about. It is more of a systems biology approach to looking at how we respond to our environment and how the stress response can be modulated.

Dr. James further proposed that when emotions are mapped in the brain, rather than existing in separate centers (like an anxiety center or a happiness center) that the neural substrates of emotion would be integrated with the somato/ viscerosensory representation and that we would see this kind of integrated holograph of how the immune system, the endocrine system, and the nervous system interrelated with one another. So we would have neuro-endocrine-immunology connection. This goes way back to the 1800s, and, of course, one of the agents that could trigger this function (we have discovered since) could be the enteric bacteria and their functional effects on the gut-associated lymphoid tissue or the gut-immune system. So that leads into this host-microbe interaction, and is there any relationship between bacterial activity and viscerosensory signals from the gut that enhance anxiety? What are the implications of such for the field of psycho-neuro-immunology? These are kind of interesting modulators of gene expression and the stress response that may not be on top of mind for most people who are thinking about immune modulation.

Infection-induced Viscerosensory Signals

Recently a paper was published by a group of researchers out of the Department of Psychology, University of Virginia, Charlottesburg and the School of Pharmacy at Texas Tech, Hill Sciences Center. This appeared in *Brain Behavior andImmunity* in 2007, in the November issue.[12] In this particular paper the researchers looked at the effect of infection-induced viscerosensory signals that came from gut bacterial activation (these would be considered parasitic bacteria, or what we have often called "dysbiosis"). What they found is that the signals from these bacteria in the gut (the molecules they produce and the interaction they have with the gut-associated immune system) actually induced or enhanced responses through the immune system of anxiety in these animal studies. It goes through the

vagal sensory neurons and occurs as a consequence of the response to various chemical mediators that are produced as a consequence of these bacterium.

At the clinical level we could say that gut infection or dysbiosis may have impact upon brain chemical function and induce stress response, but it occurs through a very interesting web of interaction of the immune and nervous systems that then induces changes in behavior. When we talk about events that trigger different gene response elements inducing different phenotypic changes in the individual, we have to look at the whole organism. We have to look at the interaction of that stimuli with the whole of the body, and it takes us back, actually, to the early days of trying to look at the origin of disease (as I said, going back to Robert Koch and infectious disease, or Elie Metchnikoff and the role that bacteria have [friendly bacteria-symbiotes] on improving the immune system function, or even the psychological theory of William James that really talks about these viscerosensory signals that then translate into mood and behavior changes). So it certainly redefines psychology in a different way. I believe it is part of this whole emerging model that we are starting to see that Dr. Westphal alluded to of agents in our environment and the case of small molecules in our food like resveratrol, but also psychological or chemical events that occur from the result of bacterial enteric activity can all influence, similarly, the stress response.

Vitamin D Takeaways

Well I know that you enjoyed listening to Dr. Holick's extraordinary presentation as much as I did. There is so much news-to-use as a takeaway from his words and his wisdom and experience in the field. And of course it begs a very important question, doesn't it? That is, are you supplementing every one of your patients with 1000-2000 IUs of vitamin D a day? If you are not used to giving supplements of nutrients to patients you might still have some reservation about the potential toxicity of vitamin D. Should you do testing prior to the supplementation by measuring the 25-hydroxy and the serum calcium as Dr. Holick was speaking to? The answer I think we can takeaway from his presentation is that if you are dealing with a patient who doesn't have sarcoidosis and doing this enhanced conversion of 25-hydroxy to 1,25 through their macrophage conversion, then you have a patient who, at worst, is going to do no harm, and at best is going to be of great benefit in raising their 25-hydroxy at or above 30 nanograms per mL, which is the level of serum 25-hydroxy that he was speaking to where you get this threshold effect. As he has indicated, levels in the serum up above 100 nanograms per mL have not been associated with vitamin D toxicity.

I think the takeaway that I have-and I believe Dr. Holick's book actually speaks to this-is 1000 IUs of vitamin D supplementation a day would be considered safe and valuable. In people of northern latitude, or people who have reduced sun exposure, or people using high SPF sun-blocking formulas, the level might even be as high as 2000 IUs a day. But certainly a1000 IU a day supplement for all people would be considered safe and effective except for that outlier that he spoke to (the person with enhanced macrophage conversion of 25 to the 1,25 which is the sarcoidosis patient).

This also begs a question about bone loss and goes back and asks the question: is vitamin D really important beyond that of calcium supplementation and estrogen replacement therapy for women, and maybe even men, related to bone loss? In the August 25-31 issue (2007) of *The Lancet*, the cover featured a breakout that said calcium supplementation alone or in combination with vitamin D is effective in the prevention of osteoporotic fracture.[21] There has been a long-standing debate as to whether calcium and vitamin D are, in fact, truly preventive agents in patients at risk to osteoporotic fracture.

This was a study looking at people 50 years of age and older, a meta-analysis actually of many studies (29 randomized clinical trials) with total number of patients 63,897. The trials were evaluated based upon quality. Of those, 17 trials of the 29 were found to be of high quality and that constituted 52,625 patients. What the authors found was that by vitamin D and calcium supplementation at 1000-1200 milligrams of calcium a day and 800 IUs daily of vitamin D supplementation there was approximately a 12{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} risk reduction in fractures of all types across these trials with a p value of less than .004 (a highly significant reduction over those who did not supplement with calcium and vitamin D). This represents the largest meta-analysis of calcium/vitamin D intervention trials that has been published and certainly suggests strongly that vitamin D and calcium are beneficial at the level of 1000-1200 milligrams of calcium a day and 800-1000 of vitamin D daily.

Following this article, there is an editorial titled "Calcium and Vitamin D for Osteoporotic Fracture Risk" that says that osteoporotic fracture represents, indirectly, about the 12thleading cause of death in America, which is kind of hard to believe because we don't normally think of bone fracture as being a fatal event.[22] But for an older age person, if they have a hip fracture and they go to hospital, many of them don't leave the hospital-they get opportunistic infection, they get other metabolic problems, and it becomes a lethal event. By reducing bone fracture in the elderly, we have a significant reduction in mortality as well as morbidity.

This also pertains to males as well. We often focus our interest only on females, but older and older age men, 65 years of age or older, are also at significant risk to increased fracture as a consequence of osteoporosis. In the *Journal of the American Medical Association* just recently, there was a report on cost effectiveness of bone densitometry followed by calcium and vitamin E treatment with various types drugs to reduce osteoporotic fracture in men.[23]They showed it was cost effective and that increased quality of life years, as well as overall longevity, and that osteoporosis and osteoporotic fracture in males is clinically significant as well.

Of course, that begs the question, is it just calcium and vitamin D? And the answer is no. There are obviously anabolic therapies that are also used to build the protein in bone as well as the matrix of calcium and vitamin D. There is a nice paper that just appeared in the *New England Journal of Medicine* titled "Mechanisms of Anabolic Therapies of Osteoporosis."[24]This paper tries to get us to recognize that morphogenic-proteins are very important for forming the matrix upon which calcification can occur, and that this is stimulated by agents that activate protein synthesis (growth hormones and anabolic factors).

It is also recognized that agents that increase oxidative stress and agents that increase autoimmune reactions have untoward effects on the formation of the bone matrix and become risk factors. There is an interesting paper that appeared in the Proceedings of the National Academy of Science in the September 18 issue talking about oxidative stress causing bone loss in estrogen-deficient animals as a consequence of enhanced bone marrow dendritic activation, and it almost sounds like activation of an autoimmune process that is associated with this bone loss.[25]

Estrogen loss in female animals causes an imbalance of Th1 and Th2 macrophages (monocytes) and so what we get ultimately is a change in the immune vigilance leading to higher levels of inflammatory

cytokines and more oxidative stress and this contributes also to lowered protein synthesis. So when you are dealing with a patient with bone loss, certainly calcium and vitamin D is important but we ought to be looking at the anabolic factors, the insulin sensitivity, and we ought to be looking at the autoimmune profile as well to see if there is any evidence of inflammatory disorders.

I hope this gave you some news-to-use as it relates to this extraordinary evolving story of vitamin D. We'll talk to you next month.

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