June 2007 Issue | Jeffrey Blumberg, PhD, FACN, CNS Director, Antioxidants Research Laboratory

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This is the 25 th anniversary edition of *Functional Medicine Update* for June 2007, volume 27, number 6. Here is Dr. Jeffrey Bland.

Jeff, after a quarter of a century, from June of 1982, we are still putting this out every month.

Jay, I can't tell you what this means. Twenty-five years and it seems like a lot has happened in our world-certainly our world individually, collectively, and globally. It has been a privilege to share this mic with you over these 25 years. Thank you so much. My voice has become synonymous with yours, so I guess we are linked.

At the birthing of this audio magazine, we were in the halcyon days of what was called the "blockbuster era" of pharmacology. I find it to be very interesting that now-in the 25 thanniversary June 2007 issue-that we are now looking at what the *New England Journalof Medicine* says in a recent editorial is the "Demise of the blockbuster?"[1]

In the last 25 years, we have seen the rising tide of the most profitable industry in America-the pharmaceutical industry. It has taken over much of our economy, and now we are starting to witness what appears to be the waning tide of a dominant theme of that industry: the development of the one billion dollar-per-year product called the "blockbuster."

This *New England Journal of Medicine* article, authored by David Cutler, says that the stoppage of the clinical trials of the cholesterol drug, Torceptrapib, by Pfizer in March 2007 resulted in Pfizer's stock market value falling by 21 billion dollars overnight. Similarly, when Merck removed Vioxx from the shelves, their market value fell 25 billion dollars. These pharmaceuticals were both (supposedly one was and one was to become) blockbuster drugs.

As you probably know, blockbusters have become increasingly important over the last 25 years for the profitability of the pharmaceutical industry. In the year 2000, 17 drugs brought in more than one billion dollars each in global sales. And in 2005, 94 drugs met this threshold. This increase over five years was very significant.

Lipitor (atorvastatin), obviously, heads the list of blockbuster drugs with 13 billion dollars of annual sales, but there are many other medications that you probably recognize that fall into this category. These include Zoloft, Norvasc, Nexium, Singulair, Zocor, Advair, Plavix, and Effexsor.

You'll notice that these blockbuster drugs fall into interesting categories. We have SSRIs for depression. We have cholesterol-lowering drugs. We have drugs that relate to the management of vascular endothelial function, calcium channel blockers, anti-inflammatories, and anti-platelet agents. It is a very interesting family of drugs that you might even suggest would be called lifestyle drugs to some extent because they are all managing disorders of lifestyle in our population, as well as things that relate to either physiological or emotional dysfunctions that occur from the environment-gene connection.

Factors Contributing to the Demise of the Blockbuster Drug

We are starting to (as Dr. Cutler says) witness the demise of the blockbuster as a consequence of what he thinks are three factors. One factor is economic-companies becoming better at discovering and producing medications that fall into a class (so no one owns a class anymore). This tends to dilute the class, so a company may have the first statin (like Merck did with Nevacor), but then quickly it is filled in with many other companies, diluting the overall market size for each of the individual companies.

The second issue is equity and access. The article states that even Medicare's prescription drug benefit cannot be afforded by all people, and with the current cost trends (if they continue), Americans are likely to lose their tolerance for paying substantially more for drugs. As a consequence, we are starting to see a lowered use of drugs, and people starting to make decisions. "Do I really want to pay that large co-pay or pay for that drug entirely out of my pocket?"

The third factor, of course, is what we call biochemical individuality-the recognition that pharmacogenomics and genetics are playing a role. Not all people respond to a one-size-fits-all type of drug as the blockbuster concept assumes. Different adverse side effects are produced in people with different cytochrome P450 polymorphisms. This realization changes prescribing patterns relative to potential adverse risk.

If you look at the most significant singular cause of death-cardiovascular disease-you might say that these blockbusters have certainly helped to lower the incidence of major killer diseases as it relates to benefit-to-risk trade-off. I was very intrigued when I saw an editorial in the *Journal of the American Medical Association* titled, "The International Pandemic of Chronic Cardiovascular Disease."[2] It stated some things that I was unfamiliar with.

I wasn't aware of the fact that during the final decades of the 20 th century, even with the major medical advances made in the prevention of cardiovascular disease by the increasing application of statin drugs, that while there have been reductions in overall cardiovascular death rates, the overall incidence of acute myocardial infarction (or heart attack) has not declined and has actually increased over this period of time among women.

If we take that global, we see there is an ever-increasing epidemic of cardiovascular disease in cultures like China, which was not genetically protected against cardiovascular disease (they were protected by the fact that their diets were cardioprotective relative to now transitioning to the Western diet and lifestyle which is cardio-risk). The construct that we are winning huge battles against the war of cardiovascular disease by the application of these drugs like statins doesn't bear out when we look at the data.

There is another paper that was recently published in *JAMA* that supports this, I think quite dramatically. The authors of this article looked at atherosclerotic arterial disease mortality rates after one-year follow-

up in both primary and secondary prevention-type studies. Their findings also indicate that the incidence of MI continues to increase while the number of sudden cardiovascular death cases goes down.[3]

What we end up with is an increase in the number of chronically diseased people who have had a first heart attack. We have to learn how to manage these people. Whereas before they may have expired with their cardiovascular event, now they are able to be kept alive. And so they are not a mortality statistic, but they are a chronic disease statistic, and now we have to learn how to manage that condition as a chronic disease after a heart attack. Secondary prevention becomes a very big part of the new medicine.

Of course, statins have been used both for primary and secondary prevention, as have many other of the vascular-related drugs-the ACE inhibitors, the calcium channel blockers, the beta-blockers. One might ask about the data supporting the efficacy of these drugs over the long term versus lifestyle/diet intervention. Those questions have led to the National Institutes of Health making its proclamation that we should be engaging in first-line therapy, which is to intervene with lifestyle, diet, and exercise before intervening with drugs. If we can get a patient to comply with lifestyle and diet intervention, these are safe and effective ways of ameliorating both first potential risk to heart attack and subsequent secondary events.

Common Adverse Effects of Statin Use

What are some of the adverse risks associated with things like statin therapies? We have all heard (at least anecdotally) that patients often get these diffuse neuromuscular symptoms-tingling and twitches, zips and zaps, and pains like a myalgia. In extreme cases, which, fortunately, are infrequent, we get rhabdomyolysis and loss of muscle; this is very serious and could even be life-threatening.

For most patients, the symptoms are more subtle. They are musculoskeletal and neuromuscular issues. But there is another series of potential adverse side effects that I think are on the horizon for a population employing statins on a routine basis. In Britain, you can get statins over-the-counter without prescription at lower dose. There are even some who are advocating that young adolescents start taking statins to lower their cholesterol. This has become a family of medications with very wide use. What are the effects of lowering cholesterol?

Decreased Libido in Males Associated with the Use of Statins

One effect that has emerged that I find interesting. This was published in the *British Journal of ClinicalPharmacology* recently-a report on decreased libido in males associated with the use of HMG-CoA-reductase inhibitors (or statins).[4] The reason for it (presumably) is that by lowering the pool of cholesterol, which is the precursor for the formation of steroid hormones, you induce an endocrine dysfunction by lowering androgens and producing hypotestosterone. In this particular paper, the authors said that in looking at two of the eight patients who had decreased libido during the use of HMG-CoA-reductase statin drugs, they found low testosterone levels. Again, I think we ought to be looking beyond just vascular effects into the other dynamics of cholesterol.

Cholesterol has some principally important roles to play beyond as a precursor to hormones (the steroid hormone family). Cholesterol also serves as a very important precursor to bile acids (the deoxycholic acid), necessary for proper fat digestion, metabolism, and as a critical component of membranes (to lead to proper membrane morphology and therefore intercellular signaling).

Biochemistry Review: Cerebrosterols

What are some of the downstream metabolites of cholesterol in the body? They are not just solely related to the steroid hormones that we are familiar with (like testosterone and estrogen), but they also get metabolized into things like cerebrosterols. I think this is a very interesting part of the story. In a recent review of cholesterol biochemistry that appeared in the journal, *Lipids*, in 2007, there was a review of cerebrosterol, which is a 24S-hydroxycholesterol.[5] It was identified more than a half century ago, and it was given the name cerebrosterol due to the fact that it was abundant in the brain. It was shown that the mechanism by which cholesterol is eliminated from the mammalian brain involves a hydroxylation into the cerebrosterol, followed by diffusion of the steroid over the blood-brain barrier.

Cerebrosterol actually has some structure-function relationships with brain chemistry. Because of this, could we be modifying active intercellular signal communication agents by lowering cholesterol beyond that which would be considered optimal for that individual? If so, we might, then, induce alterations in some secondary metabolites of cholesterol that could produce action at a distance (in this case, maybe functional changes in brain chemistry).

We have known for some time that people with very low cholesterol (lower than optimal) are individuals who have higher suicide rates. There has never been a direct cause-and-effect link that has been established-it has more been an association-but it does call forth some suggestions as to how we could modify bioactive mediator substances that are derived from cholesterol by lowering overall body cholesterol to too low a level. This suggests that there may be a U-shaped cholesterol-optimal function association-too low a level of cholesterol maybe putting a patient at risk to a variety of different issues related to cardiovascular secondary effects. This would be things like mood, and memory, and affect, and also things that are related to steroid hormones (as I was mentioning earlier, androgen deficiencies). And then too high a level of cholesterol, particularly in the atherogenic lipoproteins, obviously is associated with primary risk to vascular injury and vascular disease. There is this kind of bell-shaped relationship between cholesterol levels and function, with too low a level not being possibly good, and too high a level not being good. What is optimal? That would come back (obviously) to the individual and their own physiology.

Cholesterol dynamics plays an important role; it determines how fast cholesterol turns over and gets excreted. Whether cholesterol is taken in from the diet or it is biosynthesized (with a majority of the cholesterol in our blood coming from that biosynthesized in the intestine and liver, de novo), the way it is eliminated principally from the body is by conversion into biosalts and then excretion in the feces as bile.

Phytosterols and Cholesterol Absorption

How do you facilitate improved GI turnover of cholesterol? You get into things like phytosterols (found in plants) that are cholesterol mimetics and bind cholesterol and help eliminate it from the GI tract (and bind bile acids, as well). A complex diet contains phytosterols, beta-sitosterol, and coumesterol. These have been identified with lowered LDL cholesterol levels and improved digestive function and reduced lipidemia.

A recent article about phytosterols, cholesterol absorption, and healthy diets in the journal, *Lipids*, describes how important plant foods that contain these phytosterols are.[6] Soy is known to have a very high level of phytosterols; flax has a reasonable amount of phytosterols in the whole form; oats have a reasonable amount of both beta glucan and phytosterols. With the use of phytosterols, we start seeing

improved turnover of cholesterol and the favorable dynamics it has.

There are ways our body has developed a relationship with our natural environment and our food supply system over millennia to regulate these dynamics, and we have altered this relationship by changing our diet and our lifestyle. And then we step in with drugs that lower a variable (that is, cholesterol) by blocking an enzyme (HMG-CoA-reductase). We may, then, be on the other side of the bell-shaped curve, and we may actually get some disadvantageous effects of that.

I haven't even spoken yet about the effects cholesterol has on co-enzyme Q10. Co-enzyme Q10 is derived from biosynthesis from mevalonate, which is the pathway that is blocked by statins. A lowered co-enzyme Q10 level may have effects on antioxidant defense systems and cardiovascular function.

The cholesterol story is a much more complex story than it was made out to be in 1982 when we started to see Nevacor become the molecule of choice for saving people against the risk of cardiovascular disease. I think we have evolved and have come a long way in understanding this story.

The theme of this month's *Functional MedicineUpdate* is to look at a broader functional perspective. The functional medicine model has, in the last 25 years, had richness in its own evolution. It is now understood that things are connected, one-to-the-other, in a web-like pattern, and that we can't really pull apart and tease out one variable in human physiology and look at it in isolation. We now recognize that diseases are interconnected through mechanisms, and that the concept of disease is losing some of its formality and some of its specificity because we recognize there is no such thing as an independent, "clean" disease that is uniquely the same in all patients that have that label attached to them (that diagnosis).

What have we learned in 25 years about the role diet plays in modulating these functions? As blockbuster drugs have been developed to regulate, or control, or fix certain aspects of our broken physiology, what is the alternative view as biosciences have evolved over 25 years and as the systems biology approach to physiology has stared to become more clear?

Through this work, we have learned that our diet plays a very important role (as does our lifestyle) in signaling to our genes how they are expressed. Our genes are the templates that have pluripotentiality (meaning they can be expressed in multiple ways) to give different outcomes based upon the environmental messages that the genes are receiving. Although we can't change (as an individual) our genes, we can change the messages that are received by our genes and how that signals alternative function, in terms of what we call the phenotype (the outcome of the individual).

Diet plays an interesting role because it is not just the foods that we eat in the moment. The information from our diet washes over our genes and creates a phenotype that reshapes us-our physiognomy and our physiology-and this occurs over decades of living. People generally tend to eat diets that are consistent for many years, and so the shaping of gene expression patterns occurs as an outcome from that information that those foods are bringing. The information molecules in food are macronutrients. They are vitamins and minerals. They are accessory nutrients. They are phytochemicals. And they are all this rich tapestry of information sent to our genes over time.

We know diets today are very luxurious in calories. We have super-sized our diets. We also know that the

information we are super-sizing is information that often is received by our genes as disinformation, or incoherent information. This disinformation can produce an alarm reaction in the way our genes respond. There is some question as to whether the best way of managing the risk to chronic disease is maybe to stop eating so much. This question leadsto the calorie restriction concept.

More than 60 years ago, Clive McKay at Cornell University made the observation that when he put animals on a calorie restricted diet (about 30{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of their calories restricted), it increased their lifespan and compressed the diseases of age so they also had an improved health span. Based on his observations, he suggested that calorie restriction might be a way of extending lifespan. The calorie restriction concept has become well-respected in physiology as being the only demonstrable and reproducible way of extending lifespan in animals. It hasn't been proven entirely in humans, but it certainly has been shown that calorie restriction in primates (monkeys) results in increased lifespan and a reduction in the diseases of aging, including cardiovascular disease, arthritis, and other things of that nature. Calorie restriction is not micronutrient restriction. It is not under nutrition relative to the quality of the diet, but rather it relates to the quantity of the diet.

Could you introduce a calorie restricted diet to a population that is used to a luxurious diet (sometimes a smorgasbord-type of diet) and achieve the same benefits that have been seen in animals? In our world where food is part of our recreation, most people have a tough time complying with a calorie restricted diet and becoming part of a study of this type.

Alternative Day Calorie Restriction Could Increase Compliance

Could we, then, rather than go to a total calorie restriction, go to some kind of alternative day calorie restriction? Could that be more modifiable (every other day, or twice a week), and would you see any benefit? Recently, an interesting paper was published in *Free Radical Biology and Medicine*, in which researchers looked at patients with asthma.[7] These were individuals who were overweight, had asthma, and obviously had an inflammatory condition with increased oxidative stress, as measured by different markers.

The researchers measured peak expiratory flow, and they correlated that with quality of life questionnaires and the asthma rating scale. They also correlated the data with oxidative stress indicators. The patients were put on an alternative-day calorie restriction program (meaning one day they would eat an adlib diet, and the next day they would be on a calorie restricted program, and it would alternate one day after the other). The results were very interesting. A rapid and sustained beneficial effect of the alternative-day calorie restricted diet on the underlying disease processes was demonstrated. Oxidative stress markers went down, clinical symptoms improved, quality of life improved, and FEV1 (forced expiratory volume at 1 second) improved dramatically. These results suggest that this might be a novel approach for therapeutic intervention in this disorder. You could conceive all sorts of interesting ways of packaging a clinical program (a dietary and lifestyle program) that would be an alternative-day, calorie restriction program.

Why calorie restriction? What is going on? This, of course, is a very interesting topic of investigation right now. In the March 7, 2007 issue of the *Journal of theAmerican Medical Association*, there was an editorial titled, "Aging Adiposity and Calorie Restriction."[8] In this particular paper, the authors did a kind of meta-analysis of PubMed from 1966 to 2006, using search terms that included calorie restriction,

dietary restriction, aging, longevity, lifespan, adiposity, and obesity. They then reviewed all the reports that have been published under those topics, correlated the information, and tried to come up with an understanding as to what the trajectory of the literature is. Is it heading us down the road to say there is something here-there's some gold in them thar' hills? Or is this just an interesting intellectual observation?

What they came to as a conclusion in this evaluation of the literature was that calorie restriction in adult men and women does seem to result in beneficial metabolic, hormonal, and functional changes. But we are not yet sure about the precise amount of calorie restriction that has to be achieved, or how much body fat mass has to be lost, to enhance the optimal outcome and to improve longevity. But it does appear, from the weight of the evidence at this point, that there is something there. There is gold in them thar' hills, but we just may not know yet where the mother lode is: exactly how to package this in a clinical program that will lead to high compliance with optimal benefits.

The information that is brought forth in the diet modifies all sorts of gene expression patterns and we get a whole series of altered postprandial messenger molecules: insulin, glucagon, insulin-like growth factor, somatostatin, cholecytostokinin... the list goes one and on and on. All these regulators connect the brain to the gut, to the pancreas, to the muscles, to the liver, to the adipocytes, to our endocrine system, and ultimately even to our central nervous and peripheral nervous system. There is this wonderful kind of orchestration that occurs after eating. In a postprandial state, these messenger molecules tickle specific receptors that modulate, then, gene expression patterns through a family of enzymes that we have talked about in previous editions of *FunctionalMedicine Update*: the kinase families that are kind of the translators of this outside information to inside gene expression alteration. Diet has a very, very big role to play. Diet, exercise, and stress management all trigger and signal through these pathways altered or modulated gene expression that then (over years) regulates the physiognomy and the physiology of the individual.

SIR2 Gene Expression and Calorie Restriction

Dr. David Sinclair at Harvard University has been involved with some interesting studies looking at specific phytochemicals. Out of the tens of thousands phytochemicals that are in food, he is looking at one-resveratrol-which we have heard about in red wine and peanut skin. What Dr. Sinclair's group has been looking at is the effect that resveratrol has on the gene family expression of the SIR2 genes. SIR2 gene expression has been associated with the beneficial effects of calorie restriction. By restricting calories, resveratrol sends a signal to the SIR2 family of genes that are engaged in regulating aspects of metabolic control associated with longevity.

Dr. Sinclair has been asking the question, can you modulate SIR2 not just by calorie restriction alone, but by also signaling with specific phytochemicals? Resveratrol, given at high dose to animals, has been found to produce a similar effect in terms of SIR2 gene expression as that of calorie restriction. So now the question is, could we then add supplemental levels of specific phytochemicals to our diet that would give them a mimicking effect to that of calorie restriction to make the compliance with this program both convenient and higher?

There is a nice review of this potential target for calorie restriction mimetics, the SIR2 gene, that in *Trends in Molecular Medicine*.[9] The article talks at length about how studies (starting with *Sacromyses cerevisiae* [yeast], from there moving to the flatworm [*Caenorhabditis elegans*], and now moving into animal studies) have shown that a specific phytochemical (in this case, resveratrol) can modulate SIR2 in

the same manner as calorie restriction. The SIR2 gene is the so-called Silent Information Regulator 2 gene and it is known to help regulate lifespan and mediate the effects of calorie restriction, and it seems to have a mimetic (as I mentioned) of a phytochemical when given in high doses.

Are there other phytochemicals in foods that help regulate specific gene expression patterns associated with longevity, lower oxidative injury, improve hormonal regulation, and may actually help fight the epidemic we are seeing in insulin resistance and type 2 diabetes? I just recently authored a paper titled, "Type 2 Diabetes and Heart Disease: All Roads Lead Through Altered Insulin Signaling."[10] This paper appeared in the *Townsend Letter* in the May 2007 issue.

In this article, I try to describe what is happening right now. Information is exploding concerning how dietary variables and principles can modulate these signaling pathways that affect insulin signaling and ultimately modify gene expression through things like the insulin receptor substrate 1, and through various kinases like glycogen synthase kinase 3, phosphatidylinositol kinase gamma and delta, and ultimately protein kinase C beta 2 epsilon. All of these regulators of various functional materials within our diet can have the ultimate outcome on insulin signaling.

What does this all mean? What it might mean is that it is not just a case of eating too much. It is a case of eating too much of the wrong thing. We are sending the wrong signals to these gene response modulating pathways-these receptors that are facilitated through kinases, that ultimately then signal into the gene a phenotype that is associated with lowered longevity and increased risk to age-related chronic illness.

Let me give you a specific example that I think is interesting. The example is soy in its full state. Soy is a very complex plant food. It has many, many different constituents, including the protein, carbohydrates, and fatty acids, but it also has a rich array of phytochemicals like isoflavones and lignans, and these all play very important roles in regulating aspects of cell signaling. I already previously mentioned phytosterols like beta-sitosterol within soy that have these effects as well.

With metabolic syndrome, there are a couple of things you should be aware of clinically that may not be well understood. Metabolic syndrome has a connection to many different clinical presentations, but one that is emerging (and seems almost epidemic in its increase) is obstructive sleep apnea. As you probably know, people with sleep apnea have to be on breathing assistance machines (or CPAP machines) at night.

It has often been said that sleep apnea is a very strong risk factor to cardiovascular disease. If you think about what is going on at night when a person is going through apneic events, they are actually in a state of brain ischemia. It is like they are starving from a lack of a critical nutrient (oxygen) in their brain, and that is the time that produces the highest degree of cerebral oxidative stress. It is a paradox that low oxygen produces increased oxidative stress. We spoke years ago about the mechanism by which that occurs, but just suffice it to say that whereas our body doesn't need to eat for weeks sometimes, and we don't need to drink for days, if we don't have oxygen or air for minutes, we are in trouble and it produces very serious brain ischemic events leading to oxidative injury. With obstructive sleep apnea, you get left ventricular hypertrophy as the heart tries to compensate for this oxidative problem.

Obstructive sleep apnea is independently associated with metabolic syndrome, even in the absence of obesity. Often we think this is just an obesity-related problem, but there can be people with metabolic syndrome with sleep apnea who do not have high BMIs. I am quoting from a recent paper

in *CardiovascularDiabetology*.[12] Obesity, metabolic syndrome, and sleep apnea are all pro-inflammatory states. We don't necessarily have to be obese in order to get some of these pro-inflammatory problems, but there is a high correlation, obviously, between metabolic syndrome and obesity. This correlation is discussed in an issue of *ObesityReviews*.[13] In a group of Chinese adults in Hong Kong, treatment of metabolic syndrome led to improved sleep patterns and lowered apnea (this study was published in*Respiratory Medicine*).[14] Alterations in brain chemistry brought about by metabolic syndrome seem to account for the connection with obstructive sleep apnea.

Just as there are very important connections between metabolic syndrome and sleep disorders, so too is metabolic syndrome also connected to problems of erectile dysfunction in males. There is more and more evidence demonstrating that metabolic syndrome/insulin resistance connects with vascular endothelial dysfunction, which is connected to problems of erectile function in males, and so a lot of men are treating their metabolic syndrome with sildenafil. These men think they need assistance from a drug (Viagra), when really the surrogate problem that underlies this real problem is that of vascular endothelial dysfunction associated with metabolic syndrome. If you treat the metabolic syndrome effectively, erectile function improves and vascular endothelial function also improves.

Metabolic syndrome and hyperinsulinemia is also associated with nonalcoholic steatohepatitis. By properly managing blood sugar and insulin through dietary and lifestyle intervention, we can also lower the potential risk to fatty liver, which (as you probably know) is the major cause of liver failure and the need for liver transplant. And there is another variable beyond just stabilizing insulin sensitivity. There is also the food toxicity connection through what we might call allergic-like responses and autoimmune complexed disorder. This is seen in patients who have severe liver disease and fatty infiltration. In one study, a gluten-free diet was found to reverse elevated liver enzymes in these patients. This study is described in a very interesting paper in *Gastroenterology* that suggests that if a patient has elevated liver enzymes of unknown origin, you might put them on a gluten-exclusion diet and that might have beneficial effects on their liver function.[15]

So we are starting to see a tremendously interesting evolution of this whole field and recognizing that what we eat connects so much to our signaling mechanisms. Here is an interesting example of why we should be looking at the enteric bacteria in our gut that connects signals to the rest of our body. I found this paper in *Brain Behavior and Immunity* in 2007 titled, "Infection-induced Viscerosensory Signals from the Gut Enhance Anxiety: Implications for Psychoneuroimmunology."[16]The article indicates that infection in the gut may have an adverse effect on signals that go out systemically and affect brain chemistry, producing an altered sense of mood. In fact, there is now evidence that bioactive components from various hydrolysates of protein, like tryptic hydrolysates from bovine milk alpha S1 casein, have a positive effect on mood in individuals and reduces stress-related responses. What an unbelievable thing we are learning: that diet contains all these potential signaling substances. To think that a tryptic hydrolysate from a milk protein (a bovine milk protein) could, in fact, help us to manage stress and lower anxiety (be an anxiolytic) is just a truly remarkable step forward in our understanding of the role that diet plays on function.

With all of this in mind, we are very pleased to have a world expert to share with us his almost 30 years of experience in this field of how nutrients within the diet and various active principals play roles in modulating function.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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What better way is there to celebrate a 25 th anniversary than to have one of the pioneers and true icons in the area of antioxidant research, Dr. Jeffrey Blumberg, as our researcher of the month? Many of you are well aware of Dr. Blumberg's contributions to the field, going back many, many years.

Just quickly, for those of you not familiar with his background, Dr. Blumberg received his bachelor's in pharmacy and a BS in psychology from Washington State University (WSU) back in the late 60s, and then went on to get a PhD in pharmacology from Vanderbilt University School of Medicine. He did postdoc training in the areas of nucleic acid, biochemistry, and nutrition, and ended up working at the Jean Mayer USDA Human Nutrition Center and Aging at Tufts. He is a professor in the Friedman School of Nutrition Science and Policy, at Tufts University and is the director of the antioxidant area of research at Tufts.

Dr. Blumberg has a rich portfolio of publications in top-level journals. One article that influenced medical world opinions and perspectives about antioxidants was an article that he principally authored that appeared in the Journal of the American Medical Association in 1997 titled, "Vitamin E Supplementation and in vivo Immune Responses in Healthy, Elderly Subjects."17 This was a randomized, controlled trial that we actually reviewed on Preventive Medicine Update back in those days. The conclusions of that particular paper indicated that vitamin E supplementation could enhance certain clinically relevant in vivo indices of T-cell-mediated function in healthy, elderly people, and that there were no adverse effects observed at that level of vitamin E supplementation. That is just one of many, many papers-in fact, over 100 publications according to my counting-that Dr. Blumberg has authored. One of his recent papers that I hope we'll get a chance to talk briefly about is in the Journal of the Society for Integrative Oncology this year. Dr. Blumberg and his investigating group are looking at a question we have all asked: Do antioxidants supplements during radiotherapy (or chemotherapy) have any effect on the outcome?18 An animal trial that was just published is part of the answer to that story.

Dr. Blumberg, thanks so much for joining us on Functional Medicine Update.

JBlumberg: It's my pleasure to be with you.

JBland: To set the context for our listeners, who are principally practicing healthcare providers around the world, it might be interesting for them to hear a little bit of a thumbnail from you about what got you into this field and how you got started down this road of looking at and then becoming a world expert in the area of antioxidant physiology.

JBlumberg: Well, it's a long story and has a lot to do with serendipity. I actually had been doing research in environmental toxicology and was looking at some common pathways for a number of different pollutants, which was lipid peroxidation. When the opportunity came to move to the Tufts Human Nutrition Research Center on Aging and I had to start doing more nutrition research, I was asked by the founding director of the Tufts Center what I was feeding my experimental animals when exposing them to these toxicants. I asked, "What difference does it make what's in their diet?" And that was my first real lesson in nutrition, and then I learned all about the power of antioxidants to protect us not only from exogenous free radical peroxidant sources, but from endogenous production of these toxic compounds as well. Now, about 27 years later, I know just a bit more about it.

JBland: To say the least. If you could let people kind of have an insight as to what goes on at the Tufts and Human USDA Nutrition Center on Aging it might be interesting for them to understand the collaborative group you have there, which is quite impressive.

Tufts Human Nutrition Research Center on Aging

JBlumberg: We have about 200 faculty and staff here. As you may recall, from ancient history, when the recommended dietary allowances were established for different age groups, there were RDAs for pregnant women and for toddlers and for adolescents and adults, and then there was a group of RDAs called "51-plus years," as though the nutrient requirements for people over the age of 51 (61, 71, 91, 101) were all the same, and although I don't think anybody believed that was the case, there was simply no data available to indicate how nutrient requirements changed as we got older. The institute here at Tufts was established back in 1981 to ask the question, "Using people who are older, what are your requirements for essential nutrients? And now that we are increasingly looking at a variety of phytochemicals as well, what are the requirements to promote health and reduce the risk for chronic disease in people who are 70, or 80, or 90 already?

In those early days (before 1980), the assumption was that as you grow older, obviously your requirements for a nutrient goes down because you are more sedentary, you lose weight, you don't eat as much, and you just don't need as much. What we have found, of course, is that exactly the opposite is the case for a variety of reasons, some being age-related impairments in the ability to absorb nutrients or metabolize nutrients. The requirements for nutrients for older people oftentimes go up and go up substantially as we get older.

JBland: For the sake of, again, our listeners who may be unfamiliar with the range of things that you have been involved with, I'd just like to highlight a couple of the many-180 or so-publications that you have authored. You have been recently in the European Journal of Clinical Nutrition with an article on the effect oat beta-glucan on blood pressure, carbohydrate metabolism, and biomarkers of oxidative stress. You published a review of South African herbal teas, and also a review of the bioactivity and potential health benefit of peppermint tea, and yet another review on the health benefits of chamomile tea. You have also looked at age-related associations between acute exercise-induced interleukin-6 and oxidative stress in humans. The work that you have done and published on cocoa and how it affects blood pressure and endothelial function and insulin resistance (collaborative work with a group in Italy) is (I think) fascinating. Flavonoids from almond skins and the effects they have with vitamins C and E is another topic you have written about. Lutein and zeaxanthin and their roles in disease prevention, and on and on and on... I just want people to recognize the breadth of experience that you bring from the many different collaborative research projects and individual research projects you have pioneered.

Phytochemicals and Zoochemicals: The Forefront of Nutrition Science

JBlumberg: Thank you. I would tell you that part of this has to do with just staying at the forefront of where nutrition science is going. We are entering a new era, where we are beginning to recognize that there is so much potential from the so-called non-essential nutrients. Vitamins and minerals clearly are very important and we are learning so much about how fatty acids can affect health as well, particularly some of the omega-3 fatty acids (for example, in ratios with the omega-6 fatty acids and so on). There is this enormous area with virtually tens of thousands of phytochemicals (and I would add even zoochemicals) that we are now learning that are part of our diet and can have a huge impact in the promotion of health and the prevention of chronic diseases. Whether they are carotenoids, flavonoids, or stilbenes, we have all of these tantalizing studies that tell us how important these molecules are. It is very interesting, then, to look at what some people like to call complementary or alternative medicine and find that some of these very nutrients that we find in herbal teas and some fruits and vegetables and whole grains, in fact are important components in the practice of Ayurvedic medicine, traditional Chinese medicine, and Native American medicine. We are actually at the cutting edge, while also going back a millennia or two in traditional medical practices to find out what the bioactive ingredients are in all of these plant components that are used.

Controversial Study Linking Antioxidants and Mortality in JAMA

JBland: With that great context, now we go to the thorny side of this discussion, and that has to do with what appears to be an ever increasing body of literature that has been published in first-tier journals that suggests that antioxidants (at least as they have been used in these trials) may not have beneficial effects and may even have deleterious effects. This controversy dates back to the beta carotene smokers study in Finland -- that we had the chance to discuss some years ago on Functional Medicine Update -- right up to the recent and highly publicized discussion concerning the JAMA paper that appeared February 28, 2007 titled, "Mortality and Randomized Trials of Antioxidants Supplements for Primary and Secondary Prevention."19 The authors of this paper stated that treatment with beta carotene, vitamin A, and vitamin E may increase mortality, and the potential roles of vitamin C and selenium on mortality need further study. This has raised a pretty large flag for many people within the healthcare community about the safety and relative risk of antioxidants. Could you help us to kind of understand the origin of this meta-analysis/systematic review? When you talk about reviews and meta-analyses, we know there are always different ways of interpreting data, so maybe you can help guide us in this area?

JBlumberg: Vitamin studies always seem to stir controversy, particularly in JAMA or the New England Journal of Medicine. In part this is because these publications like to choose controversial studies when they publish anything about nutrition.

While there has been controversy about some of these vitamins, they certainly have never stimulated visions of death like this study by Bjelakovic and his colleagues in Denmark. I would tell you that this is such a fundamentally flawed study that the conclusions are of no value at all, but I have to place it first in a somewhat larger context because you talked about how many of these antioxidant clinical trials have been-at best-disappointing in having null outcomes, and in some cases in a meta-analysis like this particular one in JAMA, suggesting terrific harm is being done. I would like to tell you that it is my viewpoint that with many of these null outcomes of antioxidants, you really have to understand that these were secondary prevention trials. That is, these trials were conducted using people who already had a disease, most commonly either some form of cancer or heart disease, and then they were given the antioxidant supplements, which might have been a single compound like vitamin E, or sometimes just a

few antioxidants like beta carotene plus vitamin C plus vitamin E, and even those. There have been few trials where they tried to look at more than one antioxidant at a time.

The promise of antioxidants has always been in the prevention of chronic disease, as opposed to the therapeutic treatment and the reversal of established lesions like in atherosclerosis or in tumorogenesis. So, in some respects, it is not too surprising that even with all of the many, many, many observational studies that show that healthy people who take antioxidant supplements are at a lower risk for many chronic diseases, including Alzheimer's disease and other age-related dementias, that when you do a study in people with cancer or heart disease, the compounds (these antioxidants) are not so successful in reversing the disease. They never really were established to reverse disease; they have always been about preventing them.

Moreover, there is another confounding factor that I think most people fail to realize about these studies. As an example, in several studies of patients with heart disease who were given vitamin E, the results showed (in most all of these studies) that vitamin E didn't prevent a secondary cardiac event like a myocardial infact, but people think these are studies about vitamin E. The real question being asked in these studies is: Does the antioxidant supplement, like vitamin E, when given with anti-platelet drugs, beta blockers, calcium channel blockers, ACE inhibitors, anti-coagulants, diuretics, statins, and other drugs significantly reduce the risk for reoccurrence of an event in the presence of this polypharmacy regimen? Frankly, in my view, that is asking an awful lot of any vitamin-to prove that it is substantially more efficacious than six or seven well-established drugs.

JBland: I think that is really insightful. It always strikes me as interesting when I look at these papers-there are a couple of things that you have alluded to that are very interesting-that first of all, given the flaws in the way that these studies are done, how do they end up in a tier one journal? One expects, with a very high rejection rate, that you'd only get the crème de la crème of papers. That's question number one. Question number two is: Why is there not a contextualization of these types of studies in the broad array of research with many of these papers that have been done by you and your groups that show very positive roles of intervention in human trials? It seems like there is never a balance in this discussion.

JBlumberg: I agree. I think if you really want to find a number of very high quality research studies that deal with the efficacy and the safety of dietary patterns and specific nutrients and dietary supplements and so on, there are a number of wonderful, peer-reviewed, scientific journals in the nutrition field that do publish them on a regular basis. But when you get to some other journals, such as JAMA or the New England Journal of Medicine, and you do a survey of those nutrition articles they publish, you'll come to a quick conclusion that they seem almost always to publish only very controversial and very negative results. They tend to reject studies that are published elsewhere that show the benefits of nutrition.

But let me further address this recent JAMA article by Bjelakovic and his colleagues in Denmark that looked at all-cause mortality in people taking antioxidant supplements.I want to clarify something. I would just remind you that almost every single one of those clinical trials of antioxidant supplements was, in fact, a secondary prevention clinical trial. I'll summarize it briefly. What they did originally was to identify 1663 clinical trials of antioxidant supplements. Then they excluded 848 of those trials that were looking at more acute outcomes like infectious disease or some cancer outcomes that they decided they didn't want to consider. So then they had 1815 trials to review, but then they excluded 747 of those trials because they had no deaths. So they had 747 trials of antioxidant supplements that showed antioxidant

supplements are not associated with any mortality, but because they were interested in mortality, they didn't look at any studies that had no deaths, which is a very interesting bias in approaching this. Then they ended up with 68 trials that they decided to actually put into their meta-analysis, but when they came to reaching their conclusions, they excluded 21 trials that they felt didn't meet their high standards for methodological protocol, and therefore they called studies with "high bias," so they excluded those from their analysis. So they really only looked at 47 trials, but 21 of those trials looked at selenium, which actually was associated with reduction in all-cause mortality, so they excluded those from their final analysis. So in the end, of the 1663 trials that they had identified (looking at antioxidant supplements), they based their conclusions on 26 clinical trials. Well, that is cherry picking the data. You can draw any conclusion you want if you only pick studies that already show the conclusion that you would like to reach.

I suspect this might be the case because this very group published an article in Lancet three years ago that looked at antioxidant supplement studies in cancer trials and they came to exactly the same conclusion that antioxidants actually kill you instead of help you, but they did that by eliminating what they considered to be any study that showed a benefit and had no harm because those studies were of low methodologic quality. I think it is a deeply flawed meta-analysis that is allowed because of the esteem-the gold standard-that randomized clinical trials are considered to be. The fact that they reached this conclusion and said it was based on randomized clinical trials is, I think, totally fallacious. They managed to ignore most of the clinical trials that have been published, and they did not consider this in the context of what we know from experimental studies, from observational studies, which have established the safety of these compounds. They had to ignore that to come up with a conclusion that simply had no coherence with any other published studies and what we know.

It was certainly controversial. It got a lot of headlines. It was covered in most every newspaper in the world, even though it was completely inconsistent with all known studies about antioxidants. And nobody asked the question, what is the importance of all-cause mortality? What were people actually dying of, that you say that antioxidants now kill you? Well, they didn't bother to tell us. In fact, if you go back to the individual studies, all-cause mortality, of course, means death for any reason-death from heart disease, hip fracture, infectious disease, cancer, suicide, homicide, drowning, automobile accidents-all of those causes and others were included in this analysis. I would suggest that there is no biological plausibility that if you take an antioxidant supplement you are more likely to be in an automobile accident and die, and yet this paper did exactly that. And so I find a difficulty in drawing any meaningful conclusions from such a highly biased and flawed study.

JBland: Thank you very much. Very eloquent interpretation and evaluation of the work. The two questions that I commonly have asked to me by clinicians that have been confronted with patients who have asked about this study are: Number 1, what do I tell my patients when they ask me about the safety of vitamin C, E, A, or carotenoid supplements?; and 2, should I be telling them to take these supplements really as a mixture of complex phytochemicals in food or is it still adequate to say good diet plus taking these individual nutrients as supplements?

JBlumberg: Well, as I indicated, this study is not coherent with everything we know. The Institute of Medicine has established tolerable upper levels for most all of the essential vitamins, including vitamin C and vitamin E and the mineral, selenium. And those numbers are much higher than this particular article suggests. I guess I would like to make one other point, and that is that this meta-analysis violated some of the basic statistical principles of meta-analysis, which is that you are supposed to compare comparable

things. But, they included in their studies clinical trials that lasted 28 days, some lasted 12 years. Some were studies of doses as low as 10 IU of vitamin E, others as high as 5000 IU of vitamin E. But they put them all together and compared them. Some were studies of vitamin E (where they attributed deaths to vitamin E) that they didn't mention actually had 5, 6, or 7 other nutrients also given in the supplement. It just makes no sense. I think when clinicians are faced with highly controversial studies like this, that the first response-and I think it should always be the first response-is that you should not make either a medical decision or a lifestyle change based on one, single study.

And of course, this study by Bjelakovic wasn't even a new study; it is a meta-analysis of old studies. One study can always be misleading, and certainly this one study is, but what we do know from the totality of evidence that has been collected over many decades from many different research approaches, including clinical experience, is that antioxidants in our diet, antioxidants in dietary supplements or in functional or fortified foods, are quite safe, even at doses that I don't happen to think one needs to go to (really very high doses I don't think are necessary to achieve their benefits). But they are beneficial, and they have been shown to be safe.

The Institute of Medicine says that you can consume 2000 milligrams of vitamin C a day and it is perfectly safe, although if you go over, you may actually develop loose stools, which I'm not quite sure is a very serious toxic side effect, but there is a consensus about how safe vitamin C is. There is a consensus from The Institute of Medicine that doses up to 1500 IU of vitamin E a day are completely without harm, even though we actually have long-term (five-year-long studies-randomized clinical trials) using 2000 IU of vitamin E where there were no adverse events and no effect on all-cause mortality, either.

JBland: So when we look at the relative benefit-we've been talking about risk, but now I go to many of your studies and that of your colleagues looking at the benefit, particularly in older-age individuals and individuals on various exercise programs-there seems to be (now that we are focused so much on risk) the loss of understanding that there is a lot of work out there that suggests benefit at doses that would not be extraordinary, but intakes that are within the 400 IU range.

Many Trials Have Shown Benefits of Antioxidant Use

JBlumberg: Oh, absolutely. Again, if you want to stick to randomized clinical trials, the age-related eye disease study showed that an antioxidant combination of vitamin E at 400 IU, vitamin C at 500 IU, plus selenium, zinc, and copper reduced the risk of age-related macular degeneration-an untreatable form of blindness in older people-by 30{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}.

We know from studies that my colleagues and I have done that vitamin E supplements at 200 IU in older people can reduce significantly the incidence of upper respiratory tract infections, which (by the way) just happen to be the fourth leading cause of death in older people. We know from the recent Women's Health Study that older women (over the age of 60) had a 25{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduction in the risk of cardiovascular mortality from taking 300 IU of vitamin E every other day for 10 years.

And this doesn't even get to the greater number of observational studies that really have been looking at healthy younger adults who take these supplements for a long period of time and then seem to be at lower risk for a variety of chronic diseases, although most of the emphasis has been on cancer, cardiovascular

disease, and some eye diseases like cataracts and AMD. There are lots of studies showing benefit and safety, including some randomized clinical trials, but the most positive data comes from observational studies because they are looking really at the role of these antioxidants in primary prevention, whereas the randomized clinical trials (and I do want to be candid that many of those randomized clinical trials have failed to find a benefit, although none have really found harm, and when harm has been found... for example, there was one study that showed vitamin E was associated with an increased risk of congestive heart failure, and I do believe that study found that, but if you look at every other randomized clinical trial of vitamin E supplements, there is no evidence of that happening, so I just think it was a fluke). Some of the time, these kinds of events can happen, but they only happen in one study. As you know, when you can repeat a study, or when no other study has come up with that same observation, then it is really not credible to say, "Aha, vitamin E causes congestive heart failure." It doesn't. One study, one time, and no other studies ever have shown that effect. But when people want to write articles and talk about the harm of these compounds, they will cite the one study that supports their contention.

Synthetic Tocopherols vs. Natural Source Tocopherols

JBland: One of the things that we often hear, and I'm sure you've heard this question many times, is that studies not only have differing lengths of time and different patient intake criteria, but they also use different levels and different amounts and different types of the nutrients, and I have often heard the question, is there a difference between the all-racemic synthetic tocopherols and the RRR natural source vitamin E? I guess the question is, do you feel that some of these studies have confounding variables as it relates to the source of these ingredients?

JBlumberg: I think many of these studies have a large number of confounding variables, but I wouldn't overstate the difference between the synthetic and the natural source forms of vitamin E. There is a difference. The natural source form is much more bioavailable and much more potent than the synthetic form. But we know from trials that have used the synthetic form, and from observational studies that have looked at people using that synthetic form, that the synthetic form works. It doesn't work-perhaps-as well, or it requires higher doses to get the same efficacy, but I think the things that confound some of these studies much more are other variables that have not been looked at.

There is a very interesting recent paper that has just come out trying to identify the effective dose of vitamin E to lower levels of isoprostanes. This is a validated biomarker of damage to lipids and lipid peroxidation. Because many of the studies that have been done (the randomized clinical trials that have failed to find an effect) said, "Well, we're testing vitamin E as an antioxidant," and then they didn't find a beneficial effect, but they actually never tested whether, in fact, they got an antioxidant effect, particularly in patients who had very high levels of oxidative stress because of their diabetes, their smoking addiction, the presence of heart disease, and so on. But we are finding, in fact, that in these patients, we may need much higher doses than the 200-400 IU that are used in many studies of vitamin E. If we are looking at sick patient populations, this study was suggesting that we'd need over 1000 IU to achieve a reduction in the plasma levels of isoprostanes.

JBland: That's fascinating. I'm reminded of the work that Maret Traber at the Pauling Institute and Bruce Ames have done down in Northern California that have at least suggested that with vitamin E the inclusion of some of these other forms (other than the alpha form, specifically I'm speaking of the gamma form here) may have some additional benefit. Plants make mostly gamma and yet we supplement mostly with alpha. Do you have any thoughts about how that field is evolving?

JBlumberg: I think we certainly are finding that other forms of tocopherols and tocotrienols (closely related cousins to the tocopherols) do have bioactivity, including gamma tocopherol, which has a unique ability that alpha tocopherol does not have: to quench reactive nitrogen species. However, I think it is important to recognize that while we consume, in the American diet, about five times more gamma tocopherol, in part because we get a lot of that from soy beans and corn oil that are in our diets, that in fact if you look at our plasma, we have five times more alpha tocopherol than gamma tocopherol because our liver discriminates in the absorption of vitamin E against all forms of vitamin E and preferentially absorbs the alpha tocopherol form and packages that into lipoproteins for distribution throughout the body. This does not mean that non-alpha tocopherol forms of vitamin E have no bioactivity or that they are not important. We think they do play unique roles, but the human requirement for vitamin E is based on alpha tocopherol now because of the identification of very specific hepatic transfer proteins that deliver alpha tocopherol, specifically, in to our body. So that's really our highest requirement, but again, I don't want to suggest that there is not some very exciting research suggesting that some of the other forms of tocopherol might now play some very interesting and unique roles, independent of that of their antioxidant functions.

JBland: And when we look at carotene, I recall the paper that was published many years ago that kind of challenged us to look under double-blind, randomized, clinical-controlled trials as to whether beta carotene, in supplemental form, could be a cancer chemopreventive agent. And then more recently, the work of Walt Willett and his group at Harvard in a kind of epidemiological study, looking at the relationship of vitamin A, which is obviously the metabolite of carotenoids in humans, and its relationship to fracture (spontaneous bone fractures at high levels of vitamin A intake). Is there a different story, do you believe, that is emerging around the carotenoid and the retinoid family than we see in the vitamin E story?

JBlumberg: Yes, I do think it is a different story, but it is really important to understand the difference between beta carotene, or other pro-vitamin A carotenoids, and pre-formed vitamin A, or retinol. We've actually known for some long time that high doses of retinol (pre-formed vitamin A) can be quite toxic. The Institute of Medicine's tolerable upper level for vitamin A suggests it is one of the more toxic vitamins; that is, it is the difference between its required intake and the lowest observed adverse effects is a relatively small margin of only about 5-fold, whereas for many nutrients we have 20-, 100-, 1000-fold differences between requirements and adverse effects.

But what we do know is that pro-vitamin A compounds, like beta-carotene, are really remarkably safe because they are converted into vitamin A only to the extent that the body requires it, and then what you see is the accumulation of the carotenoid rather than accumulation of retinol, so it is very safe to meet your needs through as high a dose as you'd like of pro-vitamin A carotenoids like beta carotene or beta cryptoxanthin. But, as you mentioned a couple of times, studies have shown that high doses of beta carotene in heavy smokers does increase their risk for lung cancer, in contrast to the observational data that suggests that people who had high levels of dietary beta carotene intake for long periods actually had a reduced risk of lung cancer.

There is no doubt that the results of the alpha tocopherol/beta carotene study in Finland, or the carotenoid and retinol efficacy trial done in the United States, showed that high doses of beta carotene given to people who have extraordinarily high oxidative stress due to 30 years of smoking do have an increased risk, but even if you look the subgroup analyses of those studies, the increased risk for cancer was not just

in smokers, it was in the heaviest smokers (those smoking 2 packs or more a day) and who (by the way) were drinking at least 3-5 alcoholic beverages a day, so that toxicity of high doses of beta-carotene (these were doses that increased beta carotene levels up to 60-fold higher than you could ever achieve from diet or low-dose supplement). But this adverse effect of beta carotene is really an interaction with high levels of oxidative stress through heavy smoking, plus high levels of oxidative stress and liver damage due to alcoholism. And we know from experimental studies that have been done more recently, that this adverse effect doesn't occur when in the presence of additional levels of vitamin C and vitamin E.

The recycling of these compounds and the sparing of one on another to prevent the eccentric cleavage, that is, the abnormal breakdown of beta carotene, which is the actual toxic principal in these cases, does not happen when the antioxidant status of other compounds in this very complicated defense network are there as well. So, it is true that if you take this one beta carotene molecule outside of the antioxidant defense network, provide it at very high levels to people at extraordinary levels of oxidative stress, you do get an adverse effect that is real, I don't think that necessarily is a message that translates well to people who are otherwise healthy-not smokers, not alcoholics, and are eating pretty good diets or taking other antioxidant supplements that complement the carotenoids.

JBland: That was a brilliant answer. Thank you-very, very complete. We've just got a minute left, Dr. Blumberg, and maybe I could just close by asking you one last question. Given all that you have talked about, and our increasing sophistication and understanding, do you feel that we are witnessing the end of an era related to how nutrient supplements have been viewed and moving into a new era?

JBlumberg: Absolutely. I am very excited by the advances being made today in nutrition science. We are now looking at compounds that we didn't even know about-or barely knew about-in the past, like resveratrol, a stilbene that is found in grapes and red wine and peanuts. We are learning much more about the complex array of somewhere between five and ten thousand different flavonoids and their antioxidant effects. But even more importantly, what we are learning about-and I think this is very important for the design of new research studies-is that antioxidants are unusual in being classified by their putative mechanism of action. What we actually know is that antioxidants, like many other nutrients, are multifunctional molecules. And while it is true they have antioxidant actions, they have a number of other mechanisms for bioactivity that may, in fact, importantly underlie some of their health-promoting benefits.

JBland: Well I can't tell you how much we appreciate this. You have given us more time than I know you probably had available, but we appreciate your sacrifice of time. What a great way to celebrate our 25 th anniversary of Functional Medicine Update with your very lucid and global perspective. Thank you so much.

JBlumberg: You are very welcome.

Well, Jeff, this wraps of 25 years of doing the update every month. It has been a rewarding and fulfilling journey (at least it has for me). What do you see for the next 25?

Jay, I really share that extraordinary feeling about the future with you. I think what we have started to witness is what was just an apparition for us 25 years ago: the hope that we would ultimately start to understand the role that nutrients play in both prevention and management of complex chronic health

problems, the compression of morbidity, and the achievement of the benefit that we have been looking for: to allow people to live to the limits of their biologically determined lifespan so they could maybe have two or three careers in a life, and if they practiced the right things, they could actually achieve those kind of helpings that were given within their genes. I think that this concept of signaling, and kinases, and gene expression is witnessing the birth of a whole new view of the role that diet, nutrition, and lifestyle play in modulating our function. And we'll make this, over the next 25 years (if we can be so lucky as to continue), a voice for the new medicine that is emerging. It has really been a privilege to be a part of this with you over the past 25 years and I look forward to the next.

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