October 2008 Issue | Edward J. Calabrese, PhD Department of Public Health

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Welcome to *Functional Medicine Update* for October 2008. Small is beautiful. A classic book of that title told us how great things can often happen with small events. Sometimes we over emphasize the importance of big events in shaping our destiny, when we really should be looking at how small, very important, catalytic events create great institutional changes, cultural changes, and changes in the shifting sands of technology. That's the theme of this month's *Functional Medicine Update*: How the concept of small is beautiful applies to health care. I am going to look at this concept within the cell, within the tissue, within the organ, within the organ system, and within the whole organism. How does small translate into beautiful? How does small translate into dysfunction? How does small translate into disease?

I think these are interesting questions. You are probably asking, "What does Jeff mean by small?" Over the course of the next 90 minutes, we'll be looking at how small translates into what we call hormesis. Hormesis is an interesting term. You probably are familiar with it from previous issues of *Functional Medicine Update*. In this issue, we have the fortune of hearing from someone who is arguably the most well-known person in the field of hormesis. He has published in excess of 400 articles in the peer-reviewed literature in this area, and lives, breathes, and conceives how hormesis plays a role in shaping systems. I'll save his name for awhile as a carrot to keep us going through this issue, but I think you are going to be fascinated to hear this interview with a world leader in the areas of hormesis and nutritional hormesis.

Hormesis, as a term, refers to small things having large effects (unexpected large effects) on the outcome of a system. Just for context, if we look at hormesis in social terms, we could look at India in the period where there was unrest between the British and the Indian population and there was an emerging potential civil war. Ghandi argued for non-violence and he used as his symbol for cultural change in creating independence for India a very small idea: the spinning wheel. The spinning wheel: let's gain economic independence and weave our own cloth. The spinning wheel became the small icon for a great cultural movement that transformed India. If I could stretch the definition of hormesis slightly into social systems, that would be an example of small is beautiful. A small idea, even a small implement (the personal, peddle-pushed sewing machine), became the increment of change that ultimately created what we see as the independence of India

I think there are many, many examples one can think of throughout history-social, technological, and scientific history-that would exemplify this concept of a small factor having an unexpected large effect on

outcome. The first question we are going to raise this month in *Functional Medicine Update*: how do small levels of specific agents have unexpectedly significant effects on health? That is question number one. A corollary to that question is: if these substances can have an unexpectedly large effect on health, do those effects always hit directly where you see the histopathology, or are they removed from the histopathology, then radiating back an effect that lowers the disease?

Let me say it a different way. We could reframe this to say: is the origin of a certain disease a result of action at a distance to the diagnosis of the histopathology, which is created by some hormetic alteration in the system of biological function of that organism? This probably sounds very esoteric and highbrow, and so let me kind of distill it down to ground here and try to get it into a clinically meaningful package.

The system of differential diagnosis is the basis of the international classification of diseases (or ICD9 code) and the CPT code used for reimbursement for those therapeutics is built around the construct that histopathology defines disease. If you can see it, taste it, and feel it, then that is where the disease resides and that is what you are treating (what you see under the microscope, or under the CAT scan, or what you see visually), and that these particular associations between a disease and its treatment are intimately linked in cause-and-effect-type relationships. So a person who has a heart attack has a heart disease. A person who has a stroke has a brain disease. A person who has inflammatory bowel disease has an intestinal disease. You go to the site of histopathology and when you treat that disease, you are treating that histopathology, so that's a one-to-one kind of construct (cause and effect).

Here is the question I am raising: if there are hormetic influences in physiology (meaning a small agent has an unexpected large effect on outcome), could that effect then influence far distant from where you might expect it (the outcome that we call a disease)? Rather than treat "the" disease, you move back to the hormetic event. We might call this the physiological acupuncture point, to use a metaphor.

This thinking I'm delivering to you is dependent on the underpinning of a mechanism by which something at a distance could weave its way through the wires of living, or the tendrils of life, or the web of function, to influence the disease at a distance. As an example, we might say dementia is the result of a brain disease; or we could say dementia is tied to a physiological acupuncture point of the immune system that is distantly related to how the gastrointestinal lymphoid tissue (or the immune system of the gut) is functioning. So, ipso facto; the gut is connected to the brain. By properly treating the gut-immune system to normalize its functional integrity, the outcome at a distance through this hormetic effect would be a lower risk of dementia. You are not treating the dementia, rather you are treating the underlying factors that connect to it through what we call a systems biology matrix, or network.

Could it be by understanding where the critical switching points are in that complex web, and by putting what you might call aikido-type attention to those web hubs, that you would then be able to produce an unexpected and large effect in the patient's outcome? Rather than saying more is better in therapy, we are saying less is better as long as attention is focused on the appropriate regulatory center that connects to that ultimate disease or condition that we are trying to manage.

I hope I'm not losing you in the course of this discussion. I know it is kind of complex and maybe esoteric, but I believe you'll see how I'm going to develop this in connection with our clinician/researcher of the month, and how this plays out in clinical practice. Hopefully the concept will gain more clinical utility as we continue.

Just as a review, the two questions that I believe are very important to think about when you see a patient with chronic, complex disease and are then developing the management plan and therapeutic armamentarium for intervention are: (1) How do small levels of various agents have unexpectedly large effects on health outcome? And, (2) Could the origin of certain diseases be a result of action distant to the diagnosis of the histopathology that we see of that disease itself (meaning by managing the alterations at regulatory centers that are tied through this web of function, of which hormesis plays a role in the regulatory network)?

With that as the construct, let's now get to the topic. Let's go right down a clinical path for this debate and talk about something that probably, for most people, is in the back of their minds as a connection, but maybe not to the extent that it deserves as we are doing assessment and diagnosis of patients who present with complex, chronic diseases. I'm now talking about the oral cavity and its connection to the cardiovascular system, it's connection to the immune system, and it's connection to the systemic inflammatory system. We have spoken in *Functional Medicine Update* for years about the relationship of the gastrointestinal system to the inflammatory immune system, but we haven't spent as much time (I've only alluded periodically) on the relationship between oral health and the oral cavity to the gastrointestinal and hepatic and systemic and neuronal-related immune system.

The oral cavity is an area where the outside world touches the inside physiology. It is like the nose in its connection to the dendrites of the brain. The oral cavity is rich in organisms; it is moist; it is warm; it's got all sorts of food available; and, therefore, there is a lot of metabolic activity going on within the gingiva and the connective tissues associated with teeth and jaw. Periodontal disease is one of the most significant causes of loss of teeth in the adult population, even in the developed world. We might ask the question, is periodontal disease isolated as an oral health problem, disconnected from any kind of other subspecialty in health care? As if, somehow, the head (or the oral cavity) was cut off at the neck and had no connection, systemically, to the rest of the body? What has been emerging over the last five years with greater and greater degrees of understanding at the basic science and clinical levels is that there is a very distinct connection between the status of immunological function in the oral cavity and immunological and inflammatory status systemically.

Let's cut to the chase here. Recall, if you would, that the bacteria in the oral cavity, as contrasted in mass to the bacteria in the gastrointestinal tract are but very, very small. The mass of bacteria in the intestinal tract, for an average human being, is around a kilogram (over 2 pounds). You can imagine if your oral cavity was laden with 2 pounds of bacteria you'd be a mess, so, the number of bacteria is very, very small. Therefore, you might say, "Well, except for regional effects, the small number of bacteria could have very little effect upon systemic health." But using the hormetic model that I was describing earlier, could it be possible that this small number of bacteria in the right place at the right time and the right species could activate the immune system in such a way that it sends signals (action at a distance, so to speak) to other immune regulatory tissues that then sets the stage or poises those tissues to have their own altered physiological status that leads them into a state of alarm and ultimately into chronic disease? Could the oral cavity, through alteration in its inflammatory-mediated function, produce a chronic state of inflammatory stress on other organs at a distance, for which maybe the patient doesn't even have severe periodontal disease, but they have other diseases that then we try to treat as if they were localized diseases?

Oral Data from the Physician's Health Study

A recent paper in *The Lancet*, certainly raises that question very nicely. It was a 2008 paper titled "Periodontal Disease, Tooth Loss, and Cancer Risk in Male Health Professionals: A Prospective Cohort Study."[1] This was a fairly large and well done study started back in 1986 when US male health professionals, aged 40-75 years, were responding to questionnaires posted by the Department of Nutrition (the Walter Willett Physician's Health Study). In addition to the baseline questionnaire, follow-up questionnaires were posted to all living participants every two years and dietary questionnaires every four years in the study. At baseline, the participants were asked whether they had a history of periodontal disease with bone loss. Participants also reported the number of natural teeth at baseline and any tooth loss during the previous two years was reported on the follow-up questionnaire, so we got kind of a serial prospective history. Smoking status and history of smoking were obtained. Other kinds of parameters related to food frequency. Questionnaire data were assembled with a 131-item, semi-quantitative, food frequency questionnaire. Any disease indices were all recorded over this period of time as well, with participants reporting on any new cancer diagnosis on follow-up questionnaires.

This study enrolled 48,375 men with median follow-up of 17.7 years from, as I said, 1986 to January 31, 2004. Participants diagnosed with cancer before 1986 and those with missing data on periodontal disease were excluded. There were 5720 incident cancer cases that were documented during that period, excluding non-melanoma skin cancer and non-aggressive prostate cancer. The five most common cancers were colorectal cancer, melanoma of the skin, lung, bladder, and advanced prostate. After adjusting for known risk factors, including detailed smoking history and dietary factors, participants with a history of periodontal disease had an increased risk of total cancer compared with those with no history of periodontal disease. By cancer sites, significant associations for those with a history of periodontal disease were noted for lung, kidney, pancreas, with relative rates of increase for pancreas about one-and-a-half fold over controls with no periodontal disease, kidney about one-and-a-half fold, and lung about 1.36 fold.

This is not insignificant. In fact, it reaches a level of high significance. The interpretation of the study was that periodontal disease was associated with a small but significant increase in overall cancer risk which persisted in people that never even smoked. The associations recorded for lung cancer are probably because of residual confounded by smoking, but with the other cancers, it appears as if there is a very strong link to action at a distance.

You have to ask questions: What role would oral infection have on systemic risk to cancer? How is there an inflammation risk? What has to do with genomic stability when you have high inflammatory burden or high bacterial debris burden? We go back to the interview that we had with Dr. Michael Fenech, which was a very, very powerful interview about one of the most important biomarkers for age-related dysfunction in all animals, including humans: genomic instability. Genomic instability can occur through many different mechanisms, as you heard from the eloquent discussion with Dr. Fenech.

Is this chronic state of inflammation occurring as a result of the oral cavity having bacterial action and debris that incites a systemic immune inflammatory response? Is this one of the additional layers of risk in this systems biology web of living in which we all live that then increases the relative risk in people that may have certain genetic susceptibilities to specific cancers? This kind of thing I'm describing takes us away from looking at the origin of the disease as being its histopathology and where the site and locus of that disease resides, to moving to distant sites to look at where regulatory mechanisms may influence, through a cause-and-effect relationship, the signaling to that disease (the alteration in function at that

tissue, ultimately, that is not obvious at first look, but rather is only obvious when you start backing up and looking at these interrelationships).

Gingival Health an Indicator of Overall Systemic Tissue Health

The same type of theme I am talking about with periodontal disease is also seen as it relates to gingivitis in a slightly different model related to atherosclerosis. I want to take us beyond just looking at the cancer connection to periodontal disease to also looking at gingival health, which is the soft tissue around the teeth (the tissue of the gums). This tissue is an indicator not solely of poor oral hygiene, but it is also an indicator of overall systemic tissue health. In a paper that was in the *International Journal of Clinical Practice* in April of 2007, investigators were looking at the relationship between gingival health status in renal transplant recipients and whether there was a relationship between gingival health, systemic inflammation, and atherosclerosis.[2] They used carotid intima-media thickness (CIMT) as a surrogate marker for looking at relative risk to atherosclerotic disease (this is the thickening of the carotid artery intima-media boundary), which is indirectly related to the atherosclerotic process.

What these investigators found was a very close correlation between increased CIMT values in those individuals who had gingivitis and poor gingival health. One might raise the question: is poor gingival health a cause or an effect of an overall relationship then to cardiovascular disease risk? Could it be that other factors lower systemic health in such a way that the radiating effect of that (the halo effect, so to speak, or the shadow) is to alter all soft tissue functional health because you have induced a state of poor tissue performance?

With gingivitis, what you see clinically if you look in the oral cavity (even with people who might be brushing and flossing and getting regular preventive care) is that they've got bleeding gums and they've got all sorts of issues related to tissue integrity. Could, therefore, the gingival and gingival health be a reflection (kind of a surrogate marker) of overall tissue health? Gingival tissue, just like mucosal tissue of the body elsewhere, is a rapidly turning over tissue that reflects the changes that are occurring within the environment of that person-their nutritional status, their stress, their sleep patterns. When we look at gingival tissue, we need to look at more than just whether they brush and floss. We are looking at a whole environment of that person that constructs their tissue integrity.

I think this is another interesting example of how a disease (cardiovascular disease) is connected to a distant sign which may be ultimately reflective of a systemic shift in the web of physiology. Predispositions are based upon the genetic uniqueness of that patient, and what we see later as diseases come downstream as a consequence of these outcomes. So asking the right questions, making the right assessments, moving upstream becomes very important. Do we look in the mouth? Do we ask questions about tooth loss? Do we connect with the dental community or oral health community to recognize these things are all interrelated? Does oral health connect to the gastrointestinal health? Are we looking at all these various focal points (or let's call them balance points) upon which immune system integrity can be seen? I think these are very, very interesting things.

Then, of course, we go to the skin and the eyes, right? These are other tissues that are very related to quick changes in status with an altered environment. We had a very wonderful interview with Dr. Valori Treloar this year on the dermatological connections to insulin resistance and dysglycemia, again showing how this is a radiating effect. You might say, "Well, the skin is the skin, so we'll treat the skin." But the skin is a reflection of this web, which then may go back to specific regulatory nodes in this complex web,

and these regulatory nodes are where hormetic effects might have a great unexpected impact on outcome, either

positive or negative. The regulatory nodes are the places where you have the greatest amount of potential leverage to create gene expression changes, to create outcome at cell physiological levels. So often we use the kind of karate mechanism in medicine: let's break the brick by using the biggest arsenal of weapons we have, versus maybe a different philosophy which is the aikido concept of moving to the regulatory network and using the right energy, or right kind of therapeutic at the right dose, under the right conditions to radiate this influence to influence the whole system

Let me, if I can, take the construct I have just talked about (oral health and its effects on systemic outcome in multiple diseases) and look at things that we might say at first blush are seemingly very hard to understand. For example, how could omega-3 fatty acids influence so many different factors, from cardiovascular health, to ocular health, to brain health, to immunological function and inflammation when the amount that has been found in clinical studies to influence these functions in an adult human is about 3 to 6 grams a day?

Let's put this in context. What does 3 to 6 grams a day of omega-3 fatty acids (usually referring to eicosopentaenoic and/or docosahexaenoic (EPA or DHA)) really mean? If you look at the amount of fat in the whole body, we would say that these are forms of fat. These are fatty acids that become part of triglycerides that are part of our fat storage. If we have an average 70 kilogram person (~150 to 160 lb person) and they are reasonably fit, they carry about 20 percent of their body mass as fat. Let's say that's 20 percent of 70 kilograms. What is that? That's 14 kilograms, would you agree? Fourteen kilograms is how many grams? That is 14,000 grams? Fourteen thousand grams. And what did we just say was the dose per day of a fatty acid that would have influence on function? We said it was 3 to 6 grams. Now, what percentage of 14,000 grams is 3 to 6 grams of fatty acids? It is so small it is a rounding error to the right of the decimal point.

If you were to look at this from a straight physiological (kind of mass action) effect, you might say, "Well hold it, in the face of the fat reading everyday and the amount of fat in our body, 3 to 6 grams of additional fat will have no effect. It will just be lost in the sea of other fats." But we know that it does have an effect. And how does it have an effect? Just asking that question opens the door to a new possible discovery because maybe it has its effect because its effect is small in amount but big in outcome. It is like Schumacher's *Small is Beautiful*. It is like the spinning wheel of Ghandi. A small effect on a regulatory network produces a big effect by recruitment of what goes on downstream.

That's a very interesting concept, isn't it? You might say it prompts many questions about how various constituents of foods could influence function, and not just fatty acids. In a complex minimally processed diet, aren't we eating literally tens of thousand of different small molecules that in amount are small, but could have a big effect on regulatory networks, and therefore the potential for hormesis could be large? Do you see where we are going with this discussion? In other words, for years we have discounted the amount of these secondary phytochemicals and other stuff that wasn't vitamins or minerals, that weren't part of the essential family of nutrients, as having irrelevance in human physiology. But what we are now saying is by a different way of sieving or a different way of focusing this information, maybe some of these molecules that were excluded as of being of value could have much broader effects when we look at them as potential modulators of regulatory nodes within the complex physiological matrix (small is

beautiful) because there are new mechanisms of understanding that have emerged that are related to systems biology

There are many, many places we could apply this thinking, but I'm just choosing a few examples to try to illustrate clinically how this could play out. Let's look at the July issue of *Nature Reviews of Neuroscience*. There is a wonderful review paper in that issue titled "Brain Foods: The Effects of Nutrients on Brain Function."[3] This is a nice review paper authored by Fernando Gomez-Pinilla, and he says it has been suspected that the relative abundance of specific nutrients can affect cognitive processes and emotions, however, newly described influences of dietary factors now looking at their influence on neuronal function and synaptic plasticity have revealed some of the vital mechanisms that are responsible for the action of the low level of these substances on brain health and mental functions. They also--he says--influence indirectly through the modulation of gut hormones. These gut hormones can serve as putative neurotransmitters, entering the brain and then altering brain function itself, which influences cognitive ability. So it is not just the direct effect, but it is also the secondary effect, where you modulate at the gut level (with specific phytochemicals) the gut function, which then sends a signal through a neurohormone (a gut hormone). Remember that the gut is the second brain, which then influences brain function. It is a much more complex construct than we may have laid it out to be in the past.

Dr. Gomez-Pinilla goes on to say that using this molecular basis the effects of food and nutrients on cognition helps us to determine how best to manipulate diet and the constituents of it in order to increase the resistance of neurons to insults and promote mental fitness. This clearly takes us to things like type 3 diabetes, doesn't it? This has been in the news recently. Type 3 diabetes is the diabetes associated with Alzheimer's disease and cognitive decline, where insulin becomes toxic to the brain and is associated with the production of neurofibrillary tangles and tau proteins, which then is associated with the pathophysiology of hippocampal functional loss and Alzheimer's disease. We now even give a name to it--as I said, it is not just insulin resistance, it is "type 3" diabetes. Someone can own part of that in the neurology field, but these functional states know no disciplines and boundaries among subspecialties of medicine. They can influence the whole of the biological web, and they can do so hormetically, by small levels producing big effects on function across distance.

It may seem to you that what I am saying is fairly simple and very obvious. But I would suggest that maybe this is a much more profound, altered way of thinking about health and disease than most of us learned in school when we came up through the international classification of disease (ICD9) and its companion, CPT coding, for treatment. We are now really taking a bigger picture, a bigger snapshot, of the interconnectedness of these systems, and we are asking, where, in this interconnectedness, might small effects of specific things have big influence on outcome? It is in these regulatory nodes that I talked about earlier.

Food has classically been perceived as a means to provide energy and building material to the body. We learned from Casimir Funk, the Goldbergers, Albert Szent-Gyorgyi, and others, that there are these small molecules that we call "vitamines," or vitamins. These are life-giving amines that are necessary to prevent deficiency of diseases like scurvy, beriberi, pellagra, xerophthalmia, and rickets; protein for kwashiorkor and and marasmus. Food is relegated to energy and material construction of our connective tissue and bones, and these small regulatory micronutrients are there along with trace minerals to activate enzymes and produce our function. But research over the past years has provided exciting evidence that there are other mechanisms by which nutrients and the array of phytochemicals (thousands of them) can influence

molecular systems and mechanisms that maintain things like mental function.

We talked about omega-3 fatty acids. Certainly our level of understanding about these nutrients has increased. As we have reduced our intake of omega-3 fats, we have seen adverse effects (maladaptive effects) on our physiology. In fact, if you look just at major depression on an age- and country-adjusted type of format, there are some very interesting studies published showing that those countries that have the highest level of fish consumption (meaning the highest level of omega-3 fats and other nutrients in fish) have a logarithmically decreased incidence of depression versus those countries that receive or consume the lowest amount of fish. An association like that doesn't prove causality, but it is certainly worthy of some attention, isn't it?

You start asking, "What are these things?" Maybe it is just different in diagnosis, or maybe it is just a different way people manage depression in the Orient versus Germany. Maybe it is Seasonal Affective Disorder. There are myriad variables, here, but I just want to throw out one variable: omega-3 fatty acids. There are studies in animals that show if you remove omega-3 fatty acids from the diet, cognitive ability goes down, memory goes down, and depression (staying unresponsive to the environment) goes up. If you supplement these animals with omega-3 fatty acids, you get improvement in all those functions. The association of animal models with an epidemiological association in humans doesn't prove causality, but these are certainly very strong connections, particularly with new mechanistic understandings of how omega-3 fatty acids alter brain-derived neurotrophic factor (or BDNF) and improve, then, things that are associated with mood, mind, memory and behavior in animal-controlled studies. It mimics the effects that SSRIs have anti-depressants. In other words, the natural way our brain regulates affect and mood is through the regulation of BDNF and adrenaline receptors and activity.

I think there is a strong argument for connection of mechanism to epidemiology to animal studies. What about gut hormones? Certainly we see with gut hormones the relationship of cognition and things like insulin-like growth factor and glucogon-like peptide 1 (or GLP-1), which then have effects on brain function, not just solely on gut function, or pancreas, or liver function. What nutrients then influence GLP-1 release? That's starting to be understood now and research is being published.

I could go on and on and on. This is a very nice review paper for those of you who might wonder how this field of nutritional hormesis is emerging in the relationship to brain function and how that ties to brain food. It is certainly, again, another step in understanding this. The gut connection really takes us into this whole issue of nutrigenomics and gut health and how they are connected together. The gastrointestinal associated immune system has kind of this regulatory node effect upon other portions of the body; it is not just the sole purview of the gastroenterologist, but a part of the overall functioning of the whole body as it relates to the immune system. A very nice paper was just published in *Mutation Research* titled "Nutrigenomics and Gut Health"[4] This article is about this whole concept of single nucleotide polymorphisms and the human variability in response to signaling from the diet and how that influences, then, gut immune function, which influences not only localized inflammatory conditions of the gut, but systemic problems that relate to altering the web of function.

This takes us, lastly, to this question of nutritional hormesis and plant phytochemicals. There is a very nice paper that appeared in *Science* magazine in 2008 titled "Plant Stress Profiles."[5] In this article the authors mirror the construct that we've been developing for you in *Functional Medicine Update* for the last year: when a plant is under stress, it upregulates the activity of certain genes that are involved with its

stress response. These genes then regulate the production of secondary metabolites that we call phytochemicals. A plant that is more stressed has a higher phytochemical production, which then helps it to defend itself against things like high solar intensity of the summer, or stress like drought, or stress like mold, or insect predation. The plant will upregulate the synthesis of agents that come off the anti-stress genes, and these agents are things like flavonoids and epigallocatechin gallate (ECGC), or things like theaflavins, or things like various families of isoflavones. These molecules, when consumed by humans, have interesting hormetic effects on regulating stress response at different organ systems or tissues.

This is a whole different way, obviously, of looking at nutrition, because now we are talking about almost a kind of a co-evolution relationship between plants and humans in which plants under stress produce agents that humans (when consumed) use as anti-stress compounds for improving functional integrity of their outcome. You might say, "Well aren't those just antioxidants, all those things you talked about?" To me, "antioxidants" is just a generic term for lack of explanation of mechanism. The ability to trap oxidants is really more related to how they are regulating those processes at the cellular physiological level that are correlated with reactive oxygen species, which has to do with mitochondrial function, electron transport function, the proteome, and how the cells, tissues and organs are functioning at a level of regulatory control (bioenergetics). So I think that we are more than just trapping oxidant radicals. That's a fairly simple-minded explanation for what's really going on with these phytochemicals

Our research group recently published a paper that appeared in the *Canadian Journal of Physiology and Pharmacology*.[6] We looked at the combination of various phytochemicals for the modulation of inflammatory condition from in vitro to animals and finally into humans, kind of a three-level series of studies. We were able to demonstrate that specific ratios of various phytochemicals modulated at the proteomic level the appearance of inflammatory markers. We went through the in vitro work with cell lines, and then into the animal model, and finally into the humans, and these phytochemicals mapped right into the human with the same effect: these plant-derived materials that were specific ratios of ingredients from olive leaves, and from rosemary spice, and from hops were capable of actually eliminating some of these inflammatory signals at a distance in humans. So I think you are seeing the emergence of a whole new construct. This construct has been reviewed in a nice review paper that Dr. Deanna Minich and I coauthored that recently appeared in *Nutrition Reviews* in the August issue, 2008, titled "Dietary Management of the Metabolic Syndrome: Beyond Macronutrients."[7] In this paper we look at how these various phytochemicals serve as hormetic agents to modulate insulin signaling and signal transduction.

I hope I have tee'd you up for the opportunity to meet the person who, as I said, is arguably the father of modern nutritional hormesis, Dr. Edward Calabrese, Dr. Calabrese is with the Department of Public Health, Environmental Health Sciences, at the University of Massachusetts, and has just authored a fascinating review titled "Hormesis: Why it is Important to Toxicology and Toxicologists" that appears in *Environmental Toxicology and Chemistry* in 2008.[8] You will hear from him how important this construct is for all of us to understand as we are developing both the assessment and therapeutics of patients who have distortions of their systems biology that appears as chronic disease. With that, here is Dr. Calabrese.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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As you know, we look forward to this section, the clinician / researcher of the month, in each issue of Functional Medicine Update. For the last 27 years, we to have some of the world's leading pioneers and innovators discussing things that really are changing our view of medicine and physiology. In this issue, we have a person who I believe is really an icon in the field. I have had the privilege of following his published work for more than 25 years; he has been publishing since 1976. I am talking about Dr. Edward Calabrese, who is a board-certified toxicologist, a professor of toxicology, and the chair of the environmental health sciences program at the University of Massachusetts School of Public Health. Anybody who has been in the field of environmental toxicology knows Dr. Calabrese's work. He is, as I said, an icon. He has researched extensively in the area of host factors affecting susceptibility to pollutants, and is the author of more than 600 papers in scholarly journals, and actually has had funding for his research exceeding 30 million dollars over the past 30 years.

Dr. Calabrese is an author of 26 books, 40 monographs and conference proceedings, and has given 500 invited presentations at major conferences and university seminars. I think you get the drift that we are talking about a person who is an expert in this field. He has been actively involved in helping us understand the role that environmental agents and various types of pharmacoactive substances have on physiology through this process that he is going to be describing. You have heard me review this subject in past Functional Medicine Update, but certainly not at the depth nor understanding of Dr. Calabrese; it is the concept of hormesis.

Dr. Calabrese, we really would like to welcome you to Functional Medicine Update. I think, right out of the box, probably the first thing is just to ask you the simple question: could you define for us what hormesis means, so we'll all have a similar point of reference?

Hormesis: Low-Dose Stimulation/High-Dose Inhibition
EC: Thank you very much and it's my pleasure to be here. I define hormesis as a dose-response phenomenon, characterized by a low-dose stimulation and a high-dose inhibition. This dose-response relationship has specific quantitative characteristics. The low-dose stimulation is very modest, usually at maximum it does not exceed about 30 to 60 percent greater than the controls. The width of the stimulation is a bit more variable, but typically is about 10- to 20-fold below what I would call the traditional pharmacological or toxicological threshold. The hormetic response is one that has been observed for a long time and derived its name from researchers at the University of Idaho in 1943 who were studying the effects of extracts from the red cedar plant on the growth of fungi (they were concerned with the rotting of the wood). Both of these individuals went on to biomedical fame. One, John Ehrlich, became the co-discover, later on, of chloramphenicol, and the other, Chester Southam, became very well known after he got his MD from Columbia in the area of immune responses, immune antigens, and tumors. So there is a medical linkage to its origin.

JB: I think this concept is so dramatically important because it shifts our frame of reference away from that which most of us learned in our pharmacology courses about the nature of a dose-response relationship. We all kind of got the sense that there was this linear relationship (or nearly linear relationship) between the dose of a substance and its response. In terms of most views this was kind of a straight line or maybe even a slightly curved relationship (a sigmoidal relationship), but not a relationship that at some lower concentration might shift its whole personality, going from either an antagonist or an agonist to the opposite (to become an agonist or antagonist). This concept of hormesis seems like it flies right in the face of what virtually everyone has learned as their traditional pharmacology.

Early Dispute between Traditional Medicine and Homeopathy

EC: Yes, it is hard to believe that the field of biomedical science could actually get the most fundamental pillar of the discipline wrong, and it is upon which our pharmaceutical and governmental regulations on the environmental side are based. Yet, actually, I believe this is true. The reason for this is a complicated set of factors. Back in the early part of the 20th century there were several things going on. One was a phenomenal dispute between traditional medicine (what we call traditional medicine) and homeopathy.

A fellow by the name of Dr. Hugo Schultz in northern Germany in the late 1880s had discovered, while studying the effects of disinfectants on yeast, that at low doses they seemed to have stimulated the metabolism of the yeast, but at higher doses they inhibited it. Schultz believed that he had uncovered the explanatory principle of homeopathy and he became very--you might say--active in advocating this. I would say he became a lead spokesman for the homeopathic community, even though Schultz was very traditionally trained. In this (really) war of two medical titans (traditional medicine and homeopathy), we know how the battle came out: traditional medicine actually won.

Schultz, because he took sides in this matter, became the object of a lot of criticism. The criticism that was leveled at him really came in its most poignant form out of leading intelligentsia of the British pharmacologists of the 1920s and 1930s, led by a really great pharmacologist by the name of Alfred Joseph Clark. He viciously attacked Schultz in his writings and, unfortunately and unfairly, linked him to the high delusionist wing of homeopathy, and in many other ways associated him with extremism and quackery, which was really, for the most part, totally unfair. I believe the reason why this went on was that ultimately homeopathy had to be defeated in this economic battle.

Development of the Threshold Dose Response Model

Once the attack went on Schultz, I believe that Clark and his other associates had to come up with an alternative dose-response model which actually seemed to fit the data, and that was the threshold dose-response data. In fact, Clark and some other colleagues helped to develop the probic dose-response model and then they biomathematically forced the modeling to always be constrained to be above the control and to approach the control, in effect denying the possibility that hormesis or biphasic dose could exist.

This perspective became institutionalized and within a developing governmental apparatus at the time (within the US FDA and over in Europe), and appeared in the major textbooks. The next thing you know, the threshold model was then the biphasic hormesis model. All our testing schemes were based upon a threshold model, which required essentially just a few doses (high doses) in an assumption that a threshold would be easily extrapolated to. If you only have two or three doses when you do hazard assessment and risk assessment, it is always going to be next to impossible to see the hormetic stimulation.

Development of the Biphasic Dose Response Model
What that meant was out of sight, out of mind, and that is essentially what was perpetuated all throughout the remainder of the 20th century. And so all of our-essentially-national toxicology program testing, the prior work before that, was all based upon an assumption of a dose-response that I believe was incorrect. When individuals (either because of their own interests or because of other reasons) studied many doses, and doses in lower-dose arms, they began to see that there was this biphasic dose response that was developing. It is very difficult to prove because this low-dose stimulation is actually a very modest stimulation, whereas I mentioned before the maximum stimulatory response is only about 30 to 60 percent above the control. If you have a high background variability in your control animals you can easily ascribe that to chance or it maybe chance itself, but if you only have one dose that happens to fall into that below-threshold zone, you'd most likely just discount it.

I got into this because (just to add a little personal aspect) many years ago, as an undergraduate taking a course in plant physiology, I was conducting an experiment in which I was to evaluate the dose-response relationship of a growth inhibitor in the plant (we were studying peppermint plants). It was just to evaluate a dose-dependent response. In our experiments, the professor came in one day and said, "Something unusual is happening, there is a growth stimulation taking place which is not suppose to happen (it is just suppose to be an inhibition)." He wanted to know if somebody would come back at the end of the semester to do the study over again and of course I was the only one who had the interest and went back. This time we did it exactly the way he said we should, and from looking at my notebook it appeared to be that we actually made a dilution error when making up stock solutions, and so we actually gave our plants about 10-fold less than they should have received. When we combined our low doses with his high doses we got this nice inverted, U-shaped dose-response of a low-dose stimulation high-dose inhibition. He made me extend that study and replicate it probably eight different times, in soil, getting the same results all the time, then extending it over into the world of hydroponics, where we got the same low-dose stimulation high-dose inhibition. And even though I had never heard of the term "hormesis" we published the work calling it a low-dose stimulation/high-dose inhibition. That is really where I got my initial insights, and then ultimately have built upon this in a much more extensive way looking at lots of other peoples' research experience, in which they surprisingly showed the same phenomenon. It wasn't just occurring in plants with growth inhibitors, it was occurring in all cell types (with microbes, with viruses, all kinds of nerve cells, and any kind of tissue that you might want to consider).

When you really look at the broad spectrum of the responsiveness (looking at a broad range of concentrations or doses), you typically will find that low-dose stimulation and high-dose inhibition, and it has a lot of implications for the medical world because the medical world is dealing with the pharmaceutical industry and the chemical industry-we've built industries upon killing things. It could be using insecticides, or antibiotics, or disinfectants, anti-tumor drugs-these all act at the high end of the dose-response spectrum. They are effective because they kill things. However, hormetic stimulation is really below that toxic threshold, and what I think the hormetic stimulation is actually measuring is biological performance, which is really very different than measuring toxicity at the higher level. By performance I mean you could take a look at extensions for longevity, for growing hair, it could be for increasing memory, increasing cognition, strengthening bones-many different types of biological activities, which all fall, for me, under the broader rubric of biological performance. And it is in that area of biological performance where there are many, many different kinds of opportunities that certainly the pharmaceutical world, but also many other aspects of society, are interested in.

Cap on Capacity to Increase Biological Performance

And the interesting thing here is that when you look at the thousands and thousands of cases that we have found of hormesis that are in our hormesis database (we have probably close to 9000 now), the one thing you find that is a real constant here is the modest increase that you have in that low-dose stimulation. What that really means is that our capacity to increase biological performance on just about every parameter that I know can only be modestly increased, and that is by 30 to 60 percent. And so when people talk about a drug to improve memory, the most you are going to get out of a drug is an increase of 30 to 60 percent. In bone strength by about the same, increase in hair growth, the same, increase in whatever parameter that you want to look at, even if you have two drugs that interact synergistically, they will still be capped, they will not be able to exceed that amount. They may be able to get there by lesser doses, but I believe that there is a cap, and I believe that that is imposed by constraints imposed by biological plasticity across all biological tissue, from plants, to microbes, to invertebrates and vertebrates. This puts many constraints on what pharmaceutical companies can achieve. You might like to think, "Oh, gee, I can make it more difficult to have a seizure occur by giving a drug that increases the threshold by which a seizure could occur," but the most you can increase a threshold is in the modest 30 to 60 percent, and the same for all these other parameters. This creates numerous opportunities for us, but we are also working within the constraints of biological plasticity.

JB: Oh boy, there are so many incredible things you just left us with. Talk about high-density information. Let me go back and pick up just a few of the pearls you laid before us. Let's go back to this homeopathy question. When you look at the data in this really beautiful review paper that you just had published in Environmental Toxicology and Chemistry in 2008 titled "Homesis: Why it is Important to Toxicology and Toxicologists," you present quite an array of data from different types of studies showing this low-dose stimulatory effect and then a high-dose inhibitory effect with things like mercury, cadmium, various pharmaceutical compounds. I notice that at the low dose, often the doses extrapolate back to, say, 10-7 molar, or something like that, but in homeopathy, often the doses have much higher dilution than that. In fact, even mathematically they might exceed Avogadro's numbers, so it seems like there must be a range in which you still have to have active enough molecules in order to do this, or can we extrapolate this all the way back to zero?

EC: Well, you certain can extrapolate it back to zero, and this would be really incompatible with what I would call the high dilutionist wing, so to speak, of homeopathy. I would have to say that there are many homeopathic medications that are in the measurable zone, so to speak. I'm not saying that these would show hormetic effects in those treatments or not, one would have to look at it, but you do have to have enough of a concentration to, let's say, activate receptors on different cells to initiate a process of activation. Generally speaking, there would be a threshold, for the most part, that has to be exceeded before you could initiate the hormetic response.

JB: That really answers that question very nicely. It seems that there is an analogy here-and maybe I am overly extrapolating-but knowing a little bit about immunology... in the area of immunization, there is this thing called low-zone tolerance versus high-dose energy. This is the whole theory of immunopotentiation, or developing an immunization, that you get this low-zone tolerance. That seems like it is very much a diluted dose, generally, of the hapten or the antigenic substance that at a higher dose would produce an inflammatory or energenic response. Is there an analogy here somehow between what we see in the immune area and what we are seeing in the hormetic area?

Hormetic Effects on the Immune System

EC: In the immune area-and I have looked at that, not so much with vaccines, but I have looked at it within the context of agents that could modulate immune response-this is looking at a wide range of chemical agents, therapeutic agents, as well as physical agents, including various types of radiation. In this area there is an amazing capacity to enhance immune function for almost any kind of immune endpoint that you could imagine. Studies have demonstrated that in the biomedical literature, and I published, actually, a very comprehensive review of that in 2005 in Critical Reviews in Toxicology.9 But the important thing here is when you activate the immune system within an hormetic context, it still actually conforms to the constraints that I mentioned, and that is that the maximum stimulatory response is still only modest, and is about 30 to 60 percent greater than the control background. I have to say, in the literature that I have looked at, about 80 percent of the cases where the people who commented on the clinical implications of their findings argued that these would be consistent with enhancing health. In about 20 percent of the cases, the activation of the immune system within an hormetic sense was thought to actually have some adverse health implications. It could be any of a variety of potential endpoints, such as enhancing an autoimmune response. However, for four out of five, the response was to be supportive of health, but that depends, obviously, on what system you are trying to study and the endpoint that you are interested in. But there is no question that the immune system is one in which hormetic effects have been extensively studied.

JB: Another interesting pearl you left us with was this concept about biological performance and the takeaway, and you describe this in several of your papers, that there is some advantage to modest stress of physiological systems to produce plasticity or to produce functional performance. That would include things like exercise, or calorie restriction, or all these variables that we are describing that maybe even a low level of what might be considered xenobiotics in the environment that induce, then, this plasticity through this hormetic effect. Is that a logical takeaway from this discussion?

EC: Yes, it is. It seems as though biological systems, to be optimized, need to be stressed. This stress can come in many different forms. It can come in the form of low-level exercise, it can come in the form of oxidant stress, it can come as a result of even hypoxic stress, and dietary restriction is another. There are many different ways to achieve this enhancement in different systems. The bottom line is that in essentially all of those cases, what happens is that it makes the cell system or the individual much more resistant to any subsequent follow-up stress.

JB: So this obviously begs a question which I know you have been looking at for many years, and from your writings it appears as if we are still in search of a definitive answer. That is related to mechanism. How-at low dose-do we shift over to what appears to be an entirely different mechanism from the same substance that produced, at a higher dose, say, an inhibitory effect? So it becomes an agonist at a very low dose and an antagonist at a high dose?

EC: This has been looked at and documented with a lot of detail in actually a good number of receptor systems, and that is that the same agonist that is able to activate, let's say, pathway one will, at a higher concentration, actually activate the opposite pathway. In so doing, it provides a regulatory framework to, in effect, keep the system properly functioning, but also to give it the flexibility to operate within a zone of performance. What you would have on a cell, is two receptor sub-types that that agonist can bind to. One may have much greater affinity to it, and the other has much less affinity by having many more receptors. So one pathway gets activated at low doses, and the other pathway takes over at higher doses. In so doing, you end up (if you plot it out by doing an experiment) having a beautiful biphasic dose

response. Actually, that would happen very much so in toxicology experiments where you might give a very broad range of lead, or cadmium, or mercury, or something else. What they are going to do is change very widely the concentrations of different types of agonists and what that is going to do. Is it just going to create a whole series of biphasic dose-response relationships? That is why I think these hormetic dose responses are so common when one actually looks at a broad range of doses within well-designed studies.

JB: So that then leads us to a very interesting example of the potential clinical application of what you are describing. I notice that you have authored a number of very interesting papers recently about the potential application of this hormesis concept in functional neurology and improving neurologic function. Could you describe a little bit about your thoughts in that area?

Neuroscience and Hormesis

EC: The area of neuroscience and hormesis is one that I have just spent three years looking at. I have fourteen papers that are now being published in the journal Critical Reviews in Toxicology. By the end of the summer all fourteen will be officially out. For example, if you take a look at the field of, let's say, anxiolytic drugs and you look at the animal models that are being used in these studies (for example, mice and rats), they tend to be very much liking to be where it is dark and not liking to be where it is light, probably because they are afraid of being (in their evolutionary history) essentially gobbled up by a hawk or something like this. And so the pharmaceutical researchers, what they try to do is they see that (from an anxiety point of view) trying to get a rat to go into the light is actually like getting me to drive to New York City (I would have great anxiety). You don't want to do it. The animal doesn't want to go out into the light. But if you can get the animal to do what it doesn't want to do-what is very, very stressful for him-that's what you are trying to achieve with an anxiolytic drug. What you would do is take the drug and you give the animal a choice to go into a darkened alley or a lightened alley, and with the anti-anxiety drugs, you can see that you can actually get the animal to spend more time in the lighted zone at low doses than at higher doses, when it actually drops down and spends more time in the dark zone. When it goes into the lighted zone it is a measure of a reduction in anxiety, but when it goes and spends more time in a dark zone, it is actually a sign of increased anxiety.

That is how these dose-response relationships actually follow the quantitative features of the hormetic dose response. In fact, the anti-anxiety response in the animal model is exactly a hormetic dose response, and the pharmaceutical companies, themselves, actually choose the dose for the therapeutic zone based upon that low-dose stimulation, and without them even knowing what they are doing (with respect to hormesis), they are actually using hormesis to pick the right chemical and then to use a hormetic zone for their therapeutic range.

One could then look at the whole spectrum of anti-anxiety drugs as being a clear example of how major pharmaceuticals are making billions and billions of dollars by applying the hormesis principles to a main core of their business. And the same actually is true for anti-seizure drugs. If you take an anti-seizure drug, what it is really supposed to do is make it harder for seizures to occur. You can induce seizures in animal models with certain chemicals, and then when you come in with your treatment modality, that treatment chemical, if it can increase the threshold by which a normal seizure inducer causes seizures, then you basically have a good chemical. What you find is that it causes an increase in the threshold at low doses, but then decreases the threshold for the induction of seizures at higher doses, again very much within the context of a hormetic dose response with the same quantitative features, and this gets replicated to just about every other effect within the pharmaceutical realm in which the industry is

interested in performance rather than toxicity. Essentially, the hormetic concept is actually well integrated within this, but without it actually being recognized that this is the same... this dose-response, which is occurring for anti-anxiolytic drugs, is occurring for seizures, is occurring with respect to stroke, is occurring with respect to pain, is occurring with respect to neuroprotection, growing neurons, and also with regards to many other aspects that we see in the biomedical world. It is actually, I believe a dose-response principle that has never been recognized before and has been missed because of the hyperspecialization to which biomedical science has had to drift into.

JB: So that leads to a very nice segue. I don't want to lead you into an area that you are uncomfortable with, but that's the whole concept of nutritional hormesis. We know that nutrients have interesting biological response-modifying capabilities. They can serve as intercellular signal transduction agents but yet we are told they are very low dose compared to new-to-nature molecules that come off the benchtop of medicinal chemists. So people would say, "Well, nutrition is really not a medicine as such, it is really dealing with other factors that are preventing anemia or preventing scurvy, beriberi, pellagra, xerophthalmia, rickets, kwashiorkor, marasmus, and that's a whole different field from that of pharmacology. But yet it would seem, from what you've said, that these nutrients, which may be considered low dose in a pharmacological model of toxicity may have a performance-related function at hormesis that might be very different. Am I saying something that has any credence?

EC: Yes, I think you are, and that is-I believe-there is being shown in a lot of ongoing research that, in fact, various types of nutrients have hormetic effects that go beyond what I am going to call the normal features upon which they were described as being an essential nutrient. This could relate to activation of different types of biological systems that they may have. It could be neurological. It could be any kind of factor. You can also have certain nutrients that could actually inhibit what I call hormetic effects. For example, people used to be afraid of oxidant stress because of it, perhaps, affecting mutagenicity and other end points, but, in fact, low levels of oxidant stress provide the messaging that goes on in every single cell that we have in the body. It could be that with a desire to expose oneself to massive amounts of antioxidants actually could shut down an hormetic response if, in fact, the level of oxidant intake was too great. So I think there is going to be some balancing of intake to result in an optimized type of response. This is a bit avant garde, but that is emerging, and every time it is seen it is a surprise. It is not really a surprise if you have been following the hormetic literature.

JB: Dr. Calabrese, let's go back, say, to 1967, to an article that Linus Pauling authored in Science magazine titled "Orthomolecular Psychiatry" in which he talks a little bit about this concept of molecular medicine from a nutritional perspective. And later Bruce Ames picked this up in a very nice review article that he authored in the American Journal of Clinical Nutrition in which it was discussed that high doses of specific nutrients can modulate cofactors in intermediary metabolism by mass action that then pushes sloppy equilibrium towards completion and improved function.10 That's one role that nutrients might have as cofactors that stimulate enzyme activity at a higher dose. I think what you are suggesting (and I think the literature supports this) is that there may be other phytochemicals and other nutrients in foods that work by a different mechanism than just apo enzyme-halo enzyme relationships, that work through these hormetic receptor transduction processes that may be better at lower dose than higher dose.

EC: I believe that's true, and these are going to be found for trace elements, even things such as cerium, lanthanum, neodynium, agents that we normally, you know, rare herbs that we normally wouldn't study because we have the impression that they are so low in concentration that they are not biologically

important. Or other factors like that. And it depends on the system. Even toxic metals, for example, such as mercury and lead, even though they are not considered essential nutrients, you can find in many different systems that these actually can be used to have a positive impact on the biological response going way back to-I would say-the early decades of the 20th century where investigators have shown that low levels of such stressor agents could enhance plant growth at low dose and inhibit it at higher. The same with microbes as well. I think that it is expansive in terms of the intellectual breadth that it offers us because we have oftentimes had biases against either a certain chemical, or against a certain process, but really when you open your mind and actually follow the data rather than your own ideas, it actually creates a whole set of new opportunities for you, research-wise. I think that is what this low-dose domain is doing.

JB: This has just been a fascinating discussion with you. Obviously we could go on for hours and hours, this is just amazing. But in the last few minutes, I would like to just get maybe a summary from you, as you look at the horizon-I know this is asking for a level of clairvoyance that is not very fair-what this is doing as changing the perspective, the frame-shift that interfaces with network biology (or systems biology) in a unique way, this whole view that we don't really see the body as a collection of pathways, but we are really a part of a network and applying stress to the network then modulates its functional integrity. If we take that model and then we look at how your discoveries influence environmental toxicology, pharmacology, and clinical therapeutics, what would you say is going to happen here in the next period of time, looking out at the horizon?

The Future: Looking for Patterns of Dose Response

EC: I think what is going to happen-what I hope happens, anyway-is that somehow our highly specialized trend in medicine (and science, in general) is able to stand back and to take a look at general strategies which have been selected for that help us in adapting to all sorts of environmental stresses that we have. In fact, we have a dose response that is, in many ways, truncated into a high zone and a low zone, and the low zone actually deals with performance. How do we maximize that and what are the constraints? I think if we begin to see this from the plant world, to the microbe world, all the way to the human behaviors, we begin to see such integrative simplicities, even, for example, when you take a look at male sexual performance drugs that are advertised on television, or the memory drugs, or anything that we see. They all actually conform to an inverted U-shaped dose response, and the dose response actually has the same quantitative features. You have to sit back and ask yourself, could all of this have happened by chance that all these end points, that all these organisms, and all these chemicals, that they somehow have adopted the same quantitative features of the dose response? In my opinion, they obviously couldn't have. This must be something that has been highly selected for over time, that it is placed to our species (and all species') advantage, and you have to ask yourself, how did we miss it? Why do we continue to miss it? How is it serving us (as a society) to continue to miss it? And how do we overcome this to our collective advantage? My greatest fear was that this trend that I have been working on would actually be totally missed because the system rewards hyper-specialization, where the person in microbiology actually doesn't talk to the person who does animal physiology, who doesn't talk to the person who does behavioral pharmacology, who doesn't talk to the geneticist, and yet if you look at all these patterns of dose response, they actually are highly consistent and follow the same basic framework. It is like missing a fundamental biological principle. We would never think that that was possible. But I actually think that this is the big issue. Modern science doesn't have a built-in failsafe to protect it from missing a basic scientific principle.

JB: I can't tell you, Dr. Calabrese, how we have appreciated this. Your articulate summary of a huge body of work has just been overwhelming. I think you have left every listener of this reeling with some of their past preconceptions and reflections on what this all means. Thank you very much. We have started into the age of hormesis thanks to you and I really appreciate it.

EC: Thank you very much.

I certainly hope you found the discussion with Dr. Calabrese to be as innovative, provocative, and stimulating as I did. I think it encapsulates a tremendous amount of both good science and rich history that we can leverage in how we see patients with chronic disease and how we manage them. As I mentioned to you earlier, Dr. Minich and I authored a review paper on metabolic syndrome that incorporates many of these principals that just appeared in Nutrition Reviews, August 2008 issue, titled "Dietary Management of the Metabolic Syndrome: Beyond Macronutrients." In this particular article, which I think is reasonably well referenced (about 183 references, I believe), we talk about the work that is both ongoing in our nutrigenomics MetaProteomics research lab and the papers that we published out of that research the last few years, but also the body at large of work that is going on related to signaling effects and how nutrients serve as signaling agents, as if they are speaking to the genes through these regulatory intercellular signal transduction networks. I think this construct (that a little amount of something can have a large effect on function) traces all the way back to the rich origins of homeopathy. But you still need to look at this in the construct that these regulatory nodes are the places that you have the highest sensitivity to functional changes, so a little can be a lot, and a lot can be less, because you can actually start having altered function. So it is the right amount. Maybe the body has been getting the right amount by eating a complex diet rich in these substances that are coming from stressed plants, and so we are starting to emerge, maybe, a different construct, that for chronic disease, the best therapeutics are utilizing nutritional hormesis with foods of variety and foods of complexity.

Bibliography

1 Michaud DS, Liu Y, Meyer M, Giovannucci E, Joshipura K. Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. *Lancet Oncol*.2008;9(6):550-558.

2 Genctoy G, Ozbek M, Avcu N, Kahraman S, Kirkpantur A, et al. Gingival health status in renal transplant recipients: relationship between systemic inflammation and atherosclerosis. *Int J Clin Pract*. 2007;61(4):577-582.

3 Gomez-Pinilla F. Brain foods: the effects of nutrients on brain function. *Nat Rev Neurosci*. 2008;9(7):568-578.

4 Ferguson LR, Shelling AN, Lauren D, Heyes JA, McNabb WC. Nutrigenomics and gut health. *Mutat Res*. 2007;622(1-2):1-6.

5 Voesenek LACJ, Pierik R. Plant Stress Profiles. *Science*. 2008;320:880-881.

6 Minich DM, Bland JS, Katke J, Darland G, Hall A, et al. Clinical safety and efficacy of NG440: a novel combination of rho iso-alpha acids from hops, rosemary, and oleanolic acid for inflammatory conditions. 2007. *Can J Physiol Pharmacol*. 2007;85:872-883.

7 Minich DM, Bland JS. Dietary management of the metabolic syndrome beyond macronutrients. *Nutr Rev*. 2008;66(8):429-444.

8 Calabrese EJ. Hormesis: why it is important to toxicology and toxicologists. *Environ Toxicol Chem*. 2008;27(7):1451-1474.

9 Calabrese EJ. Hormetic dose-response relationships in immunology: occurrence, quantitative features of the dose response, mechanistic foundations, and clinical implications. *Crit Rev Toxicol*. 2005;35(2-3):89-295.

10 Ames BN, Elson-Schwab I, Silver EA. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K(m)): relevance to genetic disease and polymorphisms. *Am J Clin Nutr*. 2002;75(4):616-658.

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