January 2008 Issue | Eleanor Rogan, PhD

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Welcome to *Functional Medicine Update* for January 2008. Yes, we are starting a new year, and what a year it is going to be. With many things on the horizon, I think this field of functional medicine is going to continue to wake up and move into its young adulthood in 2008.

The Women's Health Initiative (WHI): Five Years Later

In this issue I want to focus on what has been one of the more controversial areas within medicine over the past several years: hormone replacement therapy and the Women's Health Initiative. The reason I have chosen this topic is because I think it is a model for the controversy that exists about how you prove things in medicine. What are safe and effective therapeutic agents, are we asking the right questions, and is the formalism by which we go about diagnosing and treating conditions really consistent with the emerging understanding of biology and human physiology? We have come a long way in understanding more about systems biology approaches towards the function of the organism rather than just looking at pathology as a single entity that we call a disease.

I'd like to take us back to July 2002, when the National Heart, Lung, and Blood Institute of the NIH initiated a firestorm in women's health by announcing the termination of the estrogen and progestin arm of the Women's Health Initiative (WHI). The announcement was followed by a number of publications in the *Journal of the American Medical Association*. One paper was titled "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the WHI Randomized Control Trial" in which it was suggested that overall health risk exceeded benefits from use of combined estrogen plus progestin for an average of 5.2 year follow-up among healthy, postmenopausal, US women.[1] All-cause mortality was not affected during the trial. "The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen of hormone replacement therapy should not be initiated or continued for primary prevention of coronary heart disease," according to this *JAMA* article that really started this firestorm.

An Expert Criticizes the WHI and Calls for Transparency

Within the field of obstetrics and gynecology, the question was raised: How did we jump on the bandwagon and supplement women with estrogen and progestins if the follow-up work demonstrated they weren't able to deliver the proposed clinical outcome (reduce the risk of the major cause of death in postmenopausal women-- cardiovascular disease)? A very interesting article appeared recently in the

journal *Menopause Management*, in September/October 2007, authored by Dr. Wulf Utian.[2] Some of you know that name. He is the Executive Director of the National Association of Menopausal Management and a consultant in women's health at the Cleveland Clinic, and he is pulled out often as a resident expert in this area of hormone replacement therapy. He authored this editorial about the WHI that was quite scathing-its format, structure, the way the data was released, the conclusions drawn, and the integrity of the investigators.

The editorial was a pretty broad-brush indictment of the way the whole study was done and the results publicized. In reading this piece, you come away with the opinion (I think) that there was collusion, and there was a political agenda of the WHI that was anti-hormone replacement therapy and that is why the results were reported the way that they were. In fact, at the conclusion of his article, Dr. Utian says-and I'll quote-"For these [data] to be accepted with confidence, it is well time for the NIH to bring all their WHI investigators together to develop a transparent and comprehensive summary of their results. It is also time for the WHI investigators to cease their stubborn defense and misrepresentation of their 2002 data, and to return to scientific integrity. Do they owe a mea culpa? In my opinion, 'yes.' But there are important and relevant data in the WHI study that need to be clearly and honestly placed in perspective..."

The reason I'm going into this in such great detail is that by cohort analysis of this data, you'll find that some women were at much higher risk to problems with regard to cardiovascular outcome than others, and it appeared as if those women who took ERT in the perimenopausal period (at younger age) didn't have the risk that women who took it postmenopausally did. The question is taking the right compounds at the right time. Of course, that wasn't really what was told to be either safe or effective to a generation or two of obstetricians and gynecologists. It was said that HRT was highly studied and safe and effective for ranges of intervention for prevention of bone loss, menopausal symptoms of sweating, vaginal dryness, and dysphoria, and also for reducing the risk of cardiovascular disease (a major risk in postmenopause).

I think we can always use 20/20 hindsight, but the bottom line is that there were a couple of generations of women who got estrogen replacement therapy since it was heavily promoted by Robert Wood Wilson in his book, *Feminine Forever*, back in the 1960s. Since then, we have had this general thought that the research was secure, that there was a strong body of literature that ERT was both safe and effective, and that we wouldn't do anything in medicine other than scientific medicine. Now that there are some doubts cast on this, we are doing post hoc kind of microanalysis, placing the blame on the WHI investigators rather than on assumptions made for almost 40 years about what is safe and effective without really having data from which we can prove it. This is kind of turning around the tables and going from being the accused to being the accuser, which I find a very fascinating chapter in the way that we deal with new information. Rather than accept that it is important to recognize that maybe we didn't have all the answers and were making inappropriate conclusions, what we do is shift the blame over to somebody else; it's like Pin-the-Tail-on-the-Donkey.

Decision-Making in Medicine: Cautionary Tales from Epidemiology

There is a very interesting editorial that was written by Gary Taubes and published in *The New York Times* that I thought was an eloquent review of this controversy, without a lot of value judgment built in.[3] It is kind an overview of the whole process of decision making in medicine, using the WHI and hormone replacement therapy as a specific example (a case in point). Mr. Taubes says that originally

women took estrogen only to relieve hot flashes, sweating, and vaginal dryness thanks to the best-seller I have already mentioned, *Feminine Forever*. In the mid-1990s, the American Heart Association, the American College of Physicians, and the American College of Obstetricians and Gynecologists had all conducted what they considered reasonable review of the literature, and they concluded that the beneficial effects of HRT were sufficiently well established and it could be recommended to older women as a means of warding off both heart disease and osteoporosis. By 2001, 15 million women were filling HRT prescriptions annually. Of these, perhaps 5 million were older women taking the drug solely with the expectation that it would allow them to lead a longer and healthier life by preventing heart disease and osteoporosis. A year later, the tide turned.

In the summer of 2002, estrogen therapy was exposed. Dr. Jerry Avorn, a Harvard epidemiologist, has called it the "estrogen debacle" and a "case study waiting to written" on the elusive search for truth in medicine. Many explanations have been offered to make sense of this here-today-gone-tomorrow nature of medical wisdom that we were advised with confidence one year that becomes reversed the next. It calls into question the whole nature of whether we are truly practicing "scientific medicine" or medicine of lore. The simplest explanation, according to Mr. Taubes, is that the natural rhythm of science has ebbs and flows. An observation leads to hypothesis, the hypothesis is tested, and if it fails this year's test, which is always the most likely outcome in any scientific endeavor, then we change our opinion. This concept of locking in stone an idea without really understanding what you are talking about without qualification, to me, is emerging to be problematic and it is certainly a case in point with HRT.

With most issues of diet, lifestyle, and disease, hypotheses begin to transform into the public health recommendations only after receiving the requisite support from a field of research known as epidemiology. This science evolved over the last 250 years to make sense of epidemics (hence the name "epidemiology" and its relationship to infectious disease). Since the 1950s, epidemiology has been used to identify (or at least to try to identify) the causes of common chronic diseases that befall us, particularly heart disease and cancer. In this process, the perception of what epidemiological research can legitimately accomplish, at least by the public and the press, is maybe actually far in excess of what is reality.

The case of hormone replacement therapy for postmenopausal women is just one of the cautionary tales in the annals of epidemiology. Until there are case-intervention, controlled studies, much is unknown. Many of the conclusions that we derive about benefit are built around a presumption from epidemiology, which is a statistical analysis that has many confounding variables for which you really can't control, even if you try to use proper statistical methods.

I think what we have learned through this whole process of HRT and the WHI is to be very sober about drawing conclusions from short-term studies or from epidemiological research and moving into long-term decision making, particularly for things that people may be taking for years or maybe even decades. Unfortunately, this flip-flop rhythm of science has historically been seen in many areas, not just in the area of HRT, and we have had reverse decision making later on-better information that came through longer-term intervention trials. The difficulty is that a lot medical decision-making today is built on short-term intervention studies and epidemiological research, which doesn't necessarily then lead us into an understanding of long-term intervention outcome, both from a benefit and a risk relationship.

Natural versus Synthetic Molecules

I think that this particular discussion has a lot of below-the-water-line implication. It doesn't even really

address a more critical issue: using compounds in hormone replacement therapy that are not natural to human physiology because they have "super" hormone characteristics built on certain biological endpoints that are measured in absence of looking at the full effect on the interconnectedness of our physiology. I'm talking about progestins, which have a very strong effect on reproductive biology, but have a different effect on neurochemistry and immunology than natural-source progesterone. We might say we are looking at trying to examine an elephant with a microscope-we're not looking at the whole organism; we're not looking at the interaction of all of these things in the system called the "human being."

You might ask why we aren't doing studies of long-term intervention, comparing synthetic molecules to that of the natural-source molecules or bioidentical hormones to see if, in fact, there is different outcome, safety, and benefit from the substitution of one family of molecules for another. I think you all know the reasons. First of all, the cost of long-term intervention trials is astronomical. Second, there is really not a lot of motivation for intervening with bioidentical hormones in a controlled trial over a long period of time because the assumption has been made that the synthetically manipulated molecules have a higher biological activity and therefore are "better" than the bioidentical hormones. This notion is built around the presumption that comes from looking at a few variables that we call the biological indicators of the overall function of these hormones. Now we know that these hormones have pleotrophic effects across many organ systems and we have been isolating the effects of the hormones on just a few of their pleotrophic influences.

There is a little bit of similarity here to the situation with vitamin E. I know this may appear a very oblique analogy, but let me give it to you. How is the recommended dietary allowance for vitamin E established? It is a difficult standard to establish because there is no deficiency disease associated with vitamin E loss in the diet (it doesn't produce conditions like scurvy, beri beri, or pellagra); its influences on function are much more subtle and take place over a longer time. How would individuals establish an appropriate amount that was required for function, or a biological potency?

It was decided that an animal model would be used, because in the rodent (e.g., the rat) vitamin E is required during pregnancy to lead to patency of the pregnancy. In the absence of proper vitamin E, what happens is you get fetal resorption, and that's a measurable outcome (to look at resorption in the absence of proper vitamin E in the diet). The question was: How much vitamin E does it take in the diet to prevent rat fetal resorption? By quantifying this through animal studies, investigators were able to find a certain level of activity of vitamin E that was requisite for prevention of rat fetal resorption, and they called that the International Unit Scale, or an IU.

What about the synthetic forms of vitamin E that came out after the IU was determined, such as the racemic DL--tocopherols, which were less expensive? When studied in these bioassays for rat fetal resorption, they actually had higher potency (1.39 IUs per milligram versus 1 unit per milligram for the naturally-source vitamin E). People started saying that the synthetic vitamin E looked like it may be as active or very active and would be preferable because it was less expensive. Recall, though, that the way that vitamin E was assessed in its potency was to look at its ability to prevent rat fetal resorption, which is not the reason that most people are concerned about vitamin E in their own diet. Are there other roles that vitamin E has? Does it have pleotrophic effects on human physiology other than what is seen in a rat in terms of its reproductive biology? Of course the answer is yes.

The more vitamin E is studied, the more influence it is found to have on cellular function. One would ask, then, is the way that we asses its biological potency (of the synthetic vitamin E) really adequate to be realistic about how to compare it to the natural-source vitamin E in humans? This is a similar example (or at least an analogy to) the situation with estrogenic and progestrogenic hormones. If we measure biological potency based on one biomarker of a family of pleotrophic effects and we establish that as being higher potency (meaning "better"), then in our minds we say these other effects must be unimportant and therefore the best products to use are standardized, potentized derivatives of natural source estrogens and progestins that we call these synthetic molecules. I think that is another reason why there hasn't been an inclination or enthusiasm about doing long-term intervention trials with bioidentical hormones. I haven't even mentioned the patent issue or return on investment to companies that sell these products.

Bioidentical Hormones: The State of the Science

What is the state of science of the bioidentical hormones in supplementation or in replacement therapy? That is an interesting and controversial topic that has lots of heat on both sides. We need to really go down to ground zero and start looking at the state of science in order to get some type of intelligent answer to that question about the comparison between a bioidentical hormone replacement (that would be natural estrogens and progesterone) versus synthetic estrogen derivatives and progestins.

On this subject, the literature is a little confusing because there is a limited amount of comparative data doing head-to-head intervention trials of medroxyprogesterone acetate versus, say, bioidentical progesterone, or estradiol versus some of the estrogen derivatives. But that research that has been published to date-and I want to emphasize "seems to indicate" because we don't have the long-term, large-study-subject trials that we'd like to make definitive answers-suggests that there is a difference in biological activity of the bioidentical versus the synthetic estrogens and progestins. I believe this is a result of the fact that these bioidentical hormones have pleotrophic effects across many different organs because we find receptor sites for these hormones on so many different tissues and organs that then are beyond that of reproductive biology and influence, then, the neuro-endocrine-immune system in very complex ways beyond that of maybe what these synthetic molecules were engineered to be optimal to do, which was just a few of the myriad effects that the bioidentical hormones have.

When we talk bioidentical, we are really talking about a term that describes specific hormones that are identical in molecular structure to hormones made in the human body. With estrogens, we are talking about things like estradiol, estrone, and estriol. Are conjugated equine estrogens bioidentical? The answer is no because pregnant mares produce a different series of estrogen derivatives. They are natural to the horse, but they are not natural to the woman. These are things like equaline and equalinin; these are the so-called B-ring unsaturated estrogens, which are different than the bioidentical estrogens that a woman's body produces.

B-ring unsaturated estrogens have different metabolisms, different cell receptor activities, and different functional outcomes than human-nature-identical estrogens. I think the chemistry becomes a little complicated here because we often don't think about trace constituents in equine conjugated estrogens, but these-even in small amount-could have significant influence on modulating effects. They may even be metabolized in different ways and they are more likely to be converted into the 4-hydroxy estrogen derivatives, which may have some problematic risk related to breast and other types of reproductive

cancers.

The story is always greater than it might seem. That is what we learn in life in general, but certainly in medicine also. We can take things at a superficial level or we can start deeper drilling, and the more deeply we drill the more we learn about differences that we were unaware of.

Going beyond estrogens, we can move into the androgens and progesterone. These are also relevant to this bioidentical category because nature-identical, or bioidentical, progesterone is different than the progestins or the progestegens (the synthetic derivatives) which have been found to have very high biological activity. As I mentioned, that biological activity has really been focused on its effects on reproductive biology, not on many of the other effects that progesterone has in the nervous system and the immune system at receptor sites outside of the reproductive system.

It would be wonderful if we could sit down and we could absolutely define unequivocally the differences between bioidentical hormones and synthetic hormones and resolve this discussion once and for all, but it is not likely that that is going to ever occur. I don't think the studies that would be required to give us complete comfort with this discussion will ever be funded or accomplished. We have to use information that is suggested (that is inferential) and follows what I call "rules of reasonableness." Within the context of experts in the field, there are rules of reasonableness-things that make some biological sense, that have a history of greater potential for safety and effectiveness.

How does this relate to the WHI trial and the recent disillusionment that maybe cardiovascular protection was not afforded by giving conjugated equine estrogens and synthetic progestins? It is very possible that rather than throwing the baby out with the bathwater and just saying hormone replacement therapy doesn't work, we might try defining the right partners and the right players and those that have the right communication across multiple organ systems. That leads us, obviously, into a very interesting question: Do we really have to engage in hormone replacement therapy in order to get these beneficial effects?

A woman who is suffering from very severe dysphoria as a consequence of excurgencies in her hormone levels during perimenopause, or has night sweats and is suffering from insomnia, and her days are very blue, and she has hot flushes...these are very complicated symptoms. As many women would point out, this period of their lives may be associated with a kind of "living hell," and that's what Robert Wood Wilson talked about in his book *Feminine Forever*.

This is a transient period, but it may seem that it goes on forever for the woman who is suffering, so she is looking for relief of symptoms. Of course, some dysphoric symptoms have been modified by using various types of antidepressant medication in lower dose to try to modulate the depressive effects, and also to influence thermal regulation and lower sweating (to some degree) and hot flushing. There are some alternative medications that have been used in place of hormone replacement therapy, but then there is also the diet and lifestyle intervention component and how that relates not only to severe menopause symptoms that a woman is having, but also to the health outcomes (postmenopausally) for cardiovascular disease, osteoporosis, and even cancer. What are the strategic approaches that may provide alternatives to hormone replacement therapy, be it either bioidentical hormone replacement therapy or synthetic hormones?

Diet, Exercise, and Lifestyle Intervention during Perimenopause

When I think of this question, I am always reminded of the extraordinary work that has been developed that doesn't get much shrift in these discussions. This is work focused on diet, lifestyle, and exercise intervention for women who have these complicated highs and lows associated with altering hormones during the perimenopausal period, as well as how the benefits of those diet and lifestyle and exercise interventions stay with a woman throughout the postmenopausal period and as long as she continues to maintain those lifestyle commitments. These interventions can greatly lower a woman's relative risk to all of the major postmenopausal diseases.

Literature-many different studies-has been published on this with no evidence of toxicity or adverse effects. I wonder why we never see much discussion about diet, exercise, and lifestyle interventions. The discussion is always, seemingly, about bioidentical hormones versus synthetic hormones. Maybe the voice should be louder about not taking hormones as a first choice at all, but rather looking at how we modulate stress, activity patterns, and diet in women who are going through the dramatic changes in hormone levels in perimenopause, and how these choices could be used to hopefully modulate these excurgencies of hormones and affect positively mood serum lipids, and neuroendocrine function associated with hot flushing and night sweats.

Are there trials that have been done and published that illustrate the positive benefit of diet, and lifestyle, and exercise modulation during perimenopause and menopause? The answer is absolutely yes-even studies throughout the postmenopausal period. Some interesting work appeared even before the 1977 paper in *The New England Journal of Medicine* by Dr. George Mann called "Diet-Heart: End of and Era."[4] He actually discussed the work of Ansel Keys back in the 1950s on the management of heart disease risk by dietary intervention. This was basically to modulate dietary fat intake and to improve the P-to-S ratio (the polyunsaturated-to-saturated fat ratio) as a primary intervention for the control of heart disease risk factors.

We can go back to the work of E.H. Ahrens, Jr. in 1969, or back to the 50s with Ansel Keys' work, to examine this dominant theme about how to prevent heart disease by dietary fat modulation. The difficulty with this intervention, when it was employed within the food industry, was it really meant doing partially hydrogenated vegetable oils, and it meant getting people on high linolenic-acid containing diets from corn oil. As a consequence of this we started to see a declining intake of omega-3 fatty acids, and we started to recognize in the last 10 years that these omega-3 fatty acids are very important for neuro-endocrine-immune function. Omega-3 fatty acids help to establish mood. They help to establish immune function. And they even help to establish insulin sensitivity and lipid levels in the serum (lowering triglycerides and having a salutary effect upon lipoproteinemias).

When we started to introduce a concept of lowering fat and increasing the P-to-S ratio in the diet, and then modulating this by increasing animal protein, we now recognize that we may have started to shift people over (specifically women) into more and more endocrinological imbalances (neuro-endocrine-immune imbalances). That is really part of what Dr. Mann was speaking to back in his 1977 article. His advocacy was that we need to take a better snapshot of which diets are important for lowering cardiovascular disease risk, modifying cholesterol biosynthesis, and improving cholesterol conversion to cholic acid (one of the bile acids) to help in proper digestive process, increase hormonal metabolism, and excrete hormones by binding with bile acids and eliminating these hormones that had been metabolized in the feces so they wouldn't have long residence in the body. It all fits together with a different model.

Do vegetarian women who consume more omega-3 fatty acids as a natural consequence of their diet and have lower animal protein and higher fiber (and also, by the way, higher phytochemicals as part of their vegetarian diet) have altered estrogen metabolism, estrogen levels, sex-hormone-binding globulin levels, different insulin sensitivity, different lipoproteins in their blood, and different serum lipids? The answer is yes to all of those questions. By just changing the diet to a more vegetable-based diet with higher fiber, higher phytochemicals, lower animal fats, and lower partially hydrogenated vegetable oils, you end up with a different endocrinological response that modulates many of these hormones that we see in excurgency during perimenopause. I think this is an interesting context to use in looking at this debate between hormone replacement therapy and always assuming that the debate is only between synthetic hormones and bioidentical hormones.

Let me give you another part of the story that I think is quite fascinating. This has to do with the composition of the lipoproteins that are associated with atherogenic risk and how they really reflect a more dramatic change in endocrinology and immunology than just that of the serum lipids that we measure. Recall that fats that are transported around your blood (be it cholesterol or triglycerides) have to ride on the back of a carrier because fats don't dissolve well in blood. They have to be carried around by a detergent-like molecule that has an ability to look both like water (which is principally what the blood is made of) and like fat. These are called the apolipoproteins and they have the names A, B, C, D, and E.

We talked at length with Dr. Roger Newton in a 2007 edition of *Functional Medicine Update*, about one of those apolipoproteins-apolipoprotein E-and also about one of the packages of apolipoproteins with lipid to form what are called serum lipoproteins (that was the HDL lipoprotein). To quickly summarize Dr. Newton's beautiful discussion with us, the HDL particles really break down into different sub-families of HDLs that have different physiological effects, and the different sub-particles are a consequence of the fact that there are different proteins found within the HDL particle. These proteins (these apolipoproteins) are manufactured in the liver as a consequence of messages that the liver gets from the outside environment. These messages could be stress messages. They could be hormone messages. They could be nutritional messages, phytochemical messages, toxins, or allergens-all of these things influence the endocrine and immune system in such a way to then send signals to the liver to modulate the gene expression and change the pattern of lipoprotein synthesis. That, then, binds fats in different packages, which we see in our blood as a simple elevated blood fat level (or an altered blood fat level) with different HDL levels or different HDL type.

If you look at a patient who, for instance, has insulin resistance/metabolic syndrome and they are on their way to getting type 2 diabetes, you'll find that their blood fats change composition. Triglycerides tend to go up and HDL tends to go down, so the triglyceride-to-HDL ratio tends to be elevated. This is one of the surrogate markers for metabolic syndrome. As you get above 4-to-1 (ratio of fasting triglycerides to HDL), it indicates increasing relative risk to metabolic syndrome and its severity moving on into type 2 diabetes.

Why is that? It is because the signaling that occurs in a hyperinsulinemic state induces a whole series of changes relative to lipoprotein synthesis and lipid biosynthesis (hepatic biolipid synthesis), so what we get is an alteration in the type and family of lipoproteins that are floating around in our blood. The LDLs, intermediate LDLs, and HDLs change in their composition and magnitude.

If we were to really start asking questions about how would we properly modulate the hormones of

postmenopausal or perimenopausal women through diet and lifestyle intervention, we might start looking not just at the hormones themselves, but also at the outcome that these hormones have on things like lipoproteins as a surrogate marker because we know that changes in hormone levels alter inflammatory markers, alter insulin signaling, and have pleotrophic effects on gene expression, some of which are reflected in altering levels of HDL, LDL, and ultimately the apolipoproteins themselves.

A paper was just published describing what happens to individuals as they drift into atherogenesis (to the apolipoproteins that are found in HDL as part of the HDL particle). This article was published in the *Journal of Clinical Investigation* in 2007, and what the authors did is examine the proteins that make up the HDL particle and how these proteins can change in composition under conditions of inflammation or hormonal modulation.[5] Surprisingly (to some of us maybe), they found that the HDL particle is actually made up of more than 20 different proteins, and those proteins that bind the fat to make up HDL can change in composition based upon the state of the individual. For example, if the person is in an inflammatory situation, there is a different composition of the HDL protein particles than there is in a person without inflammation.

The point I am trying to bring attention to is that when we look at diet, lifestyle, and exercise intervention and estrogen modulation, we see a whole series of physiological variables, including serum lipids, apolipoprotein levels, or apolipoprotein B or A-1 ratios. Things like oxidative stress and inflammatory markers can be used to identify a trajectory towards problems not solely related just to estrogen or progesterone levels. How the signaling occurs in the context of that web of that individual woman's physiology is important.

We are going to talk more with our researcher of the month in a moment about estrogen metabolism and its effects on the body. We know that estrogen metabolism, (producing these hydroxylated estrogens) can influence inflammatory markers and oxidative stress, and that ties together with potential bone loss risk. By lowering inflammation and improving estrogen metabolism, you can also lower bone loss risk in the face of the same estrogen levels; it is not just simply estradiol, estrone, and estriol. I'm now quoting from a recent paper that appeared in the *Proceedings of the National Academy of Science* in 2007 looking at oxidative stress and its relationship to bone loss in estrogen-deficient animals and how this relates to dendritic cell activation and ultimately resorption of bone.[6]

This story is much more complex than we have given credit for. We know that other hormones like thyroid hormone play a role. As estrogen levels change, the thyroid hormone receptivity changes, and so women on thyroid hormone replacement therapy may have different effects on their estrogen levels. These women may have to balance their thyroid hormone if they are taking estrogen or they may have to balance their estrogen if they are taking thyroid. This was published in the journal *Thyroid* in 2004.[7]

The Role of Diet in Modulating Estrogen Metabolism

We also know that diet plays a role in modulating estrogen metabolism. Soy isoflavones with soy protein has an effect on upregulating estrogen metabolism into the 2-hydroxy estrogens. It is also known believed soy isoflavones do not have a significant effect on suppressing iodine, nor thyroid function. This is-I think-in contrast to what some people are saying recently: that soy supplements suppress thyroid. An article in the *Journal of Medicinal Food*that appeared in 2003 showed that isoflavone supplements from soy do not affect thyroid function in iodine-replete postmenopausal women.[8] In fact, in a nice review of soy protein

and soy bean isoflavones on thyroid function in healthy adults, it was found that only in the hypothyroid person and those with iodine deficiency that soy isoflavones have an adverse effect on thyroid function. I'm quoting from *Thyroid*, volume 16, page 249 in 2006.[9] Another interesting review paper appeared in the *American Journal of Clinical Nutrition* in 2002 that is a collaborative study among a number of investigators looking at the effect of soy protein on endogenous hormones in postmenopausal women and finding that soy protein had a salutary and beneficial effect on estrogen and progesterone hormones without an adverse effect on thyroid hormone except (again) in those women who were iodine deficient and had suppressed thyroid function.[10]

Again, my point is that before we jump to the conclusion that we need to replace hormones (be it either bioidentical or synthetic, and get engaged in this whole question of what is better and what is safer, knowing that the bioidentical certainly speaks more to the evolutionary history) we ought to look at lifestyle intervention. Diet plays a very important role. Cruciferous vegetables, soy proteins, complex carbohydrates (unrefined, rich in fibers), a more vegetarian shift, staying away from partially hydrogenated vegetable oils, saturated fats, and even too much of linoleic acid-rich corn oils. Moving back into a centric position relative to diet, lifestyle, and exercise may be the principal way of modulating both the symptoms of perimenopause and even later-stage postmenopausal disease risk.

I hope this has been helpful as a context we have set for our discussion with our researcher of the month.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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Once again we are at that place in Functional Medicine Update that I know you all look forward to. I say that every issue because I do look forward to it so much, and that is our discussion with someone who is making news on the frontier of medicine.

We are very fortunate to come back and revisit one of our researchers of the month from 2006. I said we would come back for a second chance to talk to with her because the ongoing work in her laboratory is absolutely fascinating and is opening up a whole new era as it relates to cancer prevention and possibly even cancer management.

In a recent personal communication she commented to me (and I'm quoting), "An estimated 1,444,920 men and women will be diagnosed with cancer in 2007, and of those, it is estimated that 559,650 will die from the disease."11 The goal of the work of she and her colleagues is to reduce this incidence of cancer, both the initiation and obviously mortality. They think they have identified the initiating step in the induction of breast and other human cancers and know how to prevent its occurrence.

That's a very strong statement. The research that you will be hearing about introduces a new approach to

cancer prevention that could be adopted widely, and new diagnostic technology could be available to determine risk of developing cancer long before a tumor is detectable, which is really at the functional biochemical or cell level. These outcomes could result in advancements in reducing the incidence of cancer across the population within the next decade.

Our discussion this month is with Dr. Eleanor Rogan. Just to remind you all of Dr. Rogan's extraordinary background: she is a professor at the Eppley Institute for Research in Cancer and Department Pharmaceutical Sciences from 1990 to the present in biochemistry and molecular biology. She also became the Chair of the Department of Environmental Agriculture and Occupational Health at the College of Public Health in 2007, so congratulations, Dr. Rogan, for that nice advancement and promotion. She has 200-plus publications in very highly esteemed journals. In April of 2006, she was a researcher of the month in Functional Medicine Update, and also was awarded (in May 2006) what I consider a very prestigious award, the Institute for Functional Medicine Linus Pauling Award.

With all of that fanfare, Dr. Rogan, we welcome you once again to Functional Medicine Update. We are sitting on the edge of our seats with excited anticipation of the discussion about how things have gone in your laboratories and your work over the last year.

ER: Thank you.

JB: Let me start, if I can, for those people who may not have had the privilege of hearing you previously talk, with the discovery of the catechol estrogens and DNA adducts and how that interrelates with the potential initiation of cancer. Maybe you could give a brief summary as to how you made these discoveries initially and got into what really is some exquisite and difficult chemistry to evolve this field that most people would say you and your group have created?

Background Research on Polycyclic Hydrocarbons and DNA Adducts
ER: My long-time collaborator and I spent a lot of years studying chemical carcinogenesis by a different group of compounds called polycyclic hydrocarbons that are present in smoke whenever you burn anything organic. We studied those because we had the technology to do so, but also because we recognized early on that they shared some chemical properties with estrogens, and we were really interested in the estrogens.

This approach enabled us (when we finally had the technical ability to work with estrogens) to make rapid progress because we could apply the knowledge we had learned from working with the polycyclic hydrocarbons. Our approach all along has been that estrogens, in addition to the whole variety of processes that they mediate through estrogen receptors, also can be metabolized incorrectly and form metabolites that are reactive and, in fact, react with DNA.

One part of our hypothesis was that it could be the endogenous estrogens (the ones that all of us-both men and women-have in our bodies) that could be metabolized to forms that react with DNA. We started out, naturally, studying in test tube reactions, and then in laboratory animals, and then finally we got to cultured cells, studying these reactions and finding that indeed the estrogens are metabolized. Normally estrogens are metabolized to another form called catechol estrogens. These are important and they have functions in the body and they are okay, but then they can occasionally be further metabolized to something called catechol estrogen quinones, and these are the forms that actually react with DNA.

The problem is that when they react with DNA, they overwhelmingly (more than 99.9{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}) form what is called a DNA adduct, where the estrogen has actually attached itself to a DNA base. When they do that (form these adducts), the bond is broken between the DNA base (the adenine or the guanine) and the deoxyribo sugar that makes up the backbone of DNA. So the estrogen (let's say, adenine) adduct is released from the DNA and that leaves a little gap known as apurinic site, and these can be mutagenic. Our lab has also developed a lot of evidence on that, and we think it is the mutations coming from these lost adducts that can (if they are in the critical genes) end up starting the process that leads to cancer. The last time I talked on this program, we had developed a lot of evidence that showed that, both in test tube and in laboratory animals, and now we have gone on from there.

JB: Before we jump into that exciting new work I just want to go back and make sure that some of our clinicians who are not biochemists understand the real significance of what you just said. I'd like to review this concept of estrogen metabolism because I think there is still an idea in the minds of many clinicians that estrogen really is estradiol, estrone, and estriol, and perhaps they are not so aware of these estrogen metabolites that come by way of cytochrome P450 oxidation of the estrogens that are common and into these secondary metabolites-the 2-hydroxylated, 16-hydroxylated, and 4-hydroxylated estrogens.

I think just for the sake of review you might want to let people know that there is a lot of activity of these metabolites that has come from your research, and that environmental factors influence the metabolism of estrogen into these active metabolites. So I'd like you to kind of focus on that for a second.

ER: Okay. Absolutely, agents in the environment certainly affect how estrogens are metabolized. There are environmental compounds that, in particular, induce forms of cytochrome P450 (CYP), specifically there is one called cytochrome P450 1B1 (CYP1B1) that gets induced by a lot of environmental contaminants. When the P450s are induced, that leads to higher levels of the catechol estrogens (the 4-catechol estrogens and the 2-catechol estrogens). This can set up a dangerous situation because these catechol estrogens then can be further oxidized either by other cytochrome P450s or peroxidase enzymes to the catechol estrogen quinones that are reactive.

JB: Great. There's a little bit of chemistry here that I want people to understand: the difference between the adducts that might derive from the 2-hydroxy estrogens or the 2,3 catechol quinones versus those that derive from the 3,4 catechol estrogens, which are the 4-hydroxy compounds. You talked about these apurinic adducts. For a lot of people, when they think of injuries to DNA, they think there are repair enzymes. Aren't there ligases that cut out the damaged DNA nucleotides and insert new ones? I'd like you to tell us a little bit about the difference between those adducts that are more easily repaired versus those that are not.

ER: Okay. The apurinic sites that are left in the DNA-these little gaps because the adduct left-they are typically repaired by a process called base excision repair. For many years everyone thought that this process of DNA repair was error-free; it never made a mistake. More recently, our lab demonstrated, and now other labs have started concurring, that this process does make mistakes and you can get so-called "error-prone" repair. We think this happens when a cell gets overwhelmed because it's got too many apurinic sites to repair, and so it ends up making mistakes because there is such pressure on the system. These mistakes, then, get fixed in the DNA and then inherited by all the daughter cells when the cell divides. This is how you end up with errors-these mutations-that can begin the process leading to cancer.

JB: Is there a difference if the woman or man were to metabolize their estrogens in such a way that they predominantly produce the 2-hydroxylated estrogens versus those that produce the 4-hydroxylated estrogens in terms of their carcinogenicity?

ER: Yes. There clearly is a difference. For a long time the 2-catechol estrogens were considered not to be carcinogenic while the 4-catechol estrogens did induce tumors in laboratory experiments (in animals). More recently it was found that the 2-catechol estrogens are very slightly carcinogenic, but the 4-catechol estrogens are more carcinogenic. Interestingly, we have found that when the 2-catechol estrogens and 4-catechol estrogens...if you mix them together and you oxidize them to the quinones and have them react with DNA, the 2-catechol estrogens compete very poorly. In fact, if you want to get as many adducts that have 2-catechol estrogens in them as 4-catechol estrogens in them, you have to have a ratio of 95{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} 2-catechol estrogen there and only 5{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} 4-catechol estrogen. Otherwise, the 2-catechol estrogen just doesn't seem to be able to compete to make any adducts. We think this is probably why the 4-catechol estrogens are so much stronger carcinogens than the 2-catechol estrogens.

JB: That's fascinating. I just read a recent paper from an investigator by the name of Devra Davis-you are probably familiar with her work-and she was talking about xenoestrogens and how they have a higher carcinogenicity. She was actually quoting your work, saying that the xenoestrogens (like some of these plasticizer molecules) induce more 4-hydroxylated estrogens and more of the 3,4 catechol quinones. Is that what you have found or is that similar to what you understand?12

ER: We have not directly studied the xenoestrogens, but I know that others have and indeed that is exactly what we think the xenoestrogens and some other environmental contaminants are doing-that they induce the enzymes, particularly this cytochrome P450 1B1, so that you get higher levels of the catechol estrogen quinones that make the adducts that lead to the mutations.

JB: Great. I think you have done a superb job of giving us all the background, so now we are going to go on to the point that you were leading into-the more recent work. I have been to a number of OB/GYN meetings over the last couple of years and it is very interesting when you talk to that community. I raise your extraordinary work to some of these individuals and say, "What do you think of this work? It really sounds groundbreaking and it opens up all sorts of new doors towards chemoprevention and even maybe management of the disease?" I often hear the response, "Well, it is very interesting intellectually, but there is no real clinical relevance that has been proven for this." How would you respond because I'm sure you've had that point brought to you?

New Methodology for Examining DNA Adducts in Urine has been Developed
ER: I'm happy to say that that is now an incorrect statement because we now have one very small study published, and another one in press, and we are writing up a third study, and finishing a fourth study. I should really backtrack and say that in 2003 we published a study looking at breast tissues from either women who didn't have breast cancer or women who did have breast cancer (but we didn't look at the tumor tissue, we looked what we'll call "normal" tissue from the same breast).13 What we found was that the biochemistry had changed. In the women with breast tumors we saw higher levels of the 4-catechol estrogens and also some conjugates from them (at that time we couldn't measure DNA adducts but we could do it with the conjugates), so it was clear that these quinones were forming in greater amount in

women who had breast cancer; that is the first study that we did.

Now we have developed the methodology to look at urine samples (and that's what we have published and I'll just say, parenthetically, we can do the same thing in serum) where we've taken urine samples, in one case, from three different groups of women. One group was the control group of women who were healthy and had a low normal risk of breast cancer. A second group was women identified by oncologists, due to a variety of characteristics, as having high risk of breast cancer. And then there was a third group of women who had breast cancer. We are now able to look at their urine samples and look at 40 different estrogen metabolites, conjugates, and, most importantly, the DNA adducts that I have described as coming from the catechol estrogens.

What we find is that the level of the DNA adducts indicating that their DNA has been damaged by the catechol estrogen quinones are significantly higher in women at high risk of breast cancer and women with breast cancer compared to the normal women of low breast cancer risk. This is highly significantly different between these populations. What this suggests or tells us is really two things. One is that it appears the estrogen DNA adducts are biomarkers for risk of developing breast cancer, and it makes it clear for the first time that these adduct levels are high; that the DNA damage has already happened in women who don't have breast cancer yet, but they are at high risk of it. I think that is the groundbreaking, really paradigm-shifting research that has now been accepted for publication.

JB: Congratulations to you and your colleagues. That is a very big step forward and hopefully people who have had blinders on will get a little neuronal plasticity and be able to look at this work and its significance with a clean slate. One of the things that has been so extraordinary, I believe, for the field is the discovery that you have made that this not only applies to women, but now has application to men. I thought the recent publication from your group in Journal of the Prostate in 2006 on the potential biomarkers for early risk assessment of prostate cancer following the same model was groundbreaking.14 I think there are still many, many, many people in the medical profession treating patients (males) who have prostate cancer who don't understand this estrogen connection at all. Maybe you could help us to understand this a little bit better.

Relationship to Prostate Cancer

ER: Okay. Actually I have to give credit to another scientist named Martin Bosland, who, in the middle 90s, developed a model for prostate cancer in rats. He developed the hypothesis and found that if these rats were treated once with estradiol and then he implanted them with testosterone, all of his rats developed prostate cancer. He developed this idea that estradiol initiates prostate cancer and then testosterone promotes the tumors. That is really the fundamental hypothesis of the role that we think estrogens play in the development (the induction) of prostate cancer.

Following up on that idea, we had a small group of samples of men with prostate cancer or control men who were not diagnosed with prostate cancer. In that first paper we only measured one type of DNA adducts-the ones that are formed with adenine bases-but, indeed, in that (which we did with a colleague at Kansas State) we used three different independent analytical methods and saw exactly the same thing, which is that the men with prostate cancer had high levels of these adducts in their urine samples while the control men had background levels that were right at the level of our ability to detect anything by any of these methods.

The study was a little funny (humorous) in our lab because we had gone to great lengths to try to improve the sensitivity of our analytical method and then when we actually measured the samples from the men with prostate cancer we had to go back and scale everything differently because the levels were so high. We published that, as you said, in 2006. We have now repeated that in a second set-a larger set-of men, with and without prostate cancer. This time we have done it the same way we have done with the women in which we analyze the 40 estrogen metabolites, conjugates, and DNA adducts, but we got the same result: a highly significant difference in that the men with prostate cancer had much higher levels of estrogen DNA adducts in their urine compared to the control men who don't have prostate cancer. How I think we can relate this to prostate cancer is by thinking about the estrogens men have in lower levels than women but that can (if metabolized wrong) start the process that ends up leading to prostate cancer.

I'd like to make a little point here that relates to this because men, obviously, have much lower levels of estrogens than women do. In our experience, our hypothesis, and our findings it is not the level of the estrogens, it is how their metabolism is balanced. There are two or three enzymes that we think of as activating enzymes (for example, cytochrome P450 1B1) that push the estrogens toward making these reactive forms, but then there are two or three enzymes that we consider protective enzymes and they tend to push this whole process back toward the catechol estrogens that are not reactive. We think that for each person there is a balance of this process (the activating against the protective, or deactivating enzyme activities), and hopefully a person is kind of in a homeostatic balance where you don't get large amounts of the adducts formed. We think this relates to genetic factors (the balance of enzyme activities), but also is influenced by diet and lifestyle and environment--those kinds of other issues.

JB: I am very fascinated. As you describe the more recent work in men with prostate cancer and DNA adduct formation--I'm going from memory here so I may be wrong--it sounds very reminiscent of the kind of results that you got under controlled conditions a number of years ago with animals where you actually treated male animals (as I recall) with 5DHT and with the estrogen metabolites. I think in the animal model you showed some very similar results, didn't you?

ER: We did. We do have a paper on that (we collaborated with Martin Bosland on that).15

JB: Yes, I thought so. So this all holds together-it sounds to me-very, very consistently.

ER: It does. One of the very satisfying things for us now is we are doing a lot of work in a cell culture system that has human breast epithelial cells and they have been immortalized so they continue to grow, but they are not transformed, and when we treat them with the estrogens (with estradiol, for example), we not only see the DNA adducts form, but we also can get the cells to transform to malignant cells. We can affect this process by modulating the levels of these different enzyme activities.

JB: So, now I am going to ask you what I think is a complicated question so I'll try to make it as clear as possible. I have heard in conversations with some people in the scientific community that this association that you've discovered with your colleagues is very good science and well done and irrefutable, but it doesn't necessarily demonstrate that the formation of the catechol estrogens is the limiting step in this process; it could be other factors that regulate adduct formation that are beyond the 3,4, the 2,3 catechol estrogen formation. What would be your response to that?

ER: My response would be that in a sense it is always hard to prove a negative. You know, to prove that

there is nothing else involved. I think the fact that we can now see that by changing these enzyme activities and getting more adducts formed or fewer adducts formed and then seeing that in concert with that the human breast epithelial cells either transform to malignancy or they don't, that that is very strong evidence that this is what is playing the key role in transformation. To our disappointment, we haven't been able to demonstrate this in animals because there isn't really a good animal model for this. There is this male prostate cancer model, but it is pretty complicated and it hasn't lent itself to really definitive studies, and there is no good animal model for this for breast cancer. So that is disappointing. I have to acknowledge that we could never say that at this point this is carved in stone, but I think there is a lot more evidence for this than there is for anything else.

JB: That leads us to how these things are modulated, both in a positive and a negative way. Let me first start with probably one of the more controversial areas-that is the WHI and the HRT studies. Do we know anything about HRT, at this point, in adduct formation, or is that still an area of research?

ER: No, we don't know anything about that. We actually had hoped to be able to do some analyses on samples from the Women's Health Initiative, which could have given us information on that, but it turned out that their sample sizes are too small (the size of the samples-the volume) for our level of technology at this point. So that hasn't worked out, and we have not yet secured funds to look at HRT.

JB: So let's move from there. You already alluded to some of the xenoestrogens and environmental polyaromatic nuclear hydrocarbons and other kinds of compounds. How about the nutrition area? Are there nutritional agents that both encourage and discourage the formation of the catechol estrogens?

ER: There are nutritional supplements that do discourage the formation of the adducts. I'd say one of the most widely used ones is N-Acetyl-Cysteine (NAC). There are a number of antioxidants. I haven't tested this, but I'm certain that sulfurophane, which you find in broccoli, would inhibit adduct formation because I know that it induces an enzyme called quinone reductase and that would take the catechol estrogen quinones back to catechols and they wouldn't be reactive then.

JB: And how about glutathione s-transferase and glutathione reductase? Are those enzymes involved with that process?

ER: Well, you know what has surprised us as we have looked at the samples (particularly in women because we have done more but also in men) is we expected that the level of glutathione conjugates in the urine would be a lot greater than the level of DNA adducts, and that hasn't turned out to be true. They are really pretty comparable. To our surprise, it doesn't look like glutathione is a big scavenger here-as big a protective agent in the cell-as we thought it probably would be. I would not look to the glutathione s-transferases as being tremendously helpful here. That is a tentative finding that surprised us.

JB: That's very interesting. It kind of points more towards other phytochemicals that might have influence on some of these detoxifying enzymes. That leads to a question. You have been at the University of Nebraska now, I think, since the middle 1970s (somewhere around 1976)? That's coming up over 30 years and you have been very diligent and really have done some very hard work in terms of this chemistry, which is not easy; these are very difficult metabolites and compounds to measure and to develop the procedures for. How has the University of Nebraska looked at your work, and do you feel like sometimes you have to be away from home with slides in order to really be seen as a leader? Are you

starting to be acknowledged within your own place of 30 years?

ER: To some extent. I would say that probably very typically a lot of the effort here in the cancer center is aimed at therapeutics and a lot of people focused on curing cancer and making therapies better. Prevention is not so much on the radar screen for a lot of people. However, among the physicians on campus (some of the physicians), there is a great deal of interest in this, and we have always had really great collaboration with various physicians here. In fact, my colleague gave us a translational research seminar about three weeks ago and we had a new clinician come up and make an appointment to come see us because he said he wants to try this out and he wants to give us urine samples from his patients and see what we see with them. In that regard, I think people are very much taking notice and beginning to think about what this could contribute in the future to developing something for the patient population.

JB: That's very exciting. I guess part of driving this will be the ability to assess biomarkers in patients. Often we don't think about that which we can't see. Where are we in the future, do you think, in developing a method for evaluating, clinically, these adduct biomarkers?

Anticipated Clinical Applications
ER: What we are doing now in the laboratory in analyzing these compounds could actually be done as special chemistry in a clinical lab. We know the guy in charge of that here and he's got a mass spectrometer that's basically just like ours. It would be fairly cumbersome, though. One of our goals in the near future is to probably work with a company that makes mass specs in order to develop this so it could be more routine for a clinical lab. The assay is there; it just would be a matter of how to make this so any hospital lab could do it and they get a good result. We also have a colleague-an analytical person-who has been working for several years now to try and make a chip-based assay. We have monoclonal antibodies to the DNA adducts, and to use that approach. So we are working in both of those directions.

JB: On behalf of all of our listeners I want to thank you. The diligence that you have put into this work and how it is evolving and your most recent, really exciting results in women with breast cancer and with prostate cancer in males is extraordinary and I think it just once again demonstrates (for all of us) the importance of committing ourselves to an idea and working through the barriers and the challenges and watching things evolve, knowing that the work is not always easy. I think you're really making an extraordinary contribution and I believe-you used the word "translational" science-we are going to see your work actually open doors for all sorts of translational science. It will, in fact, result in what you talked about in your introduction, that is, the reduction of risk and incidence of cancer. I want to thank you so much for making this information available to all of us.

ER: You're welcome and I have enjoyed discussing it with you.

JB: We'll check in again soon.

Connections: Nutritional Hormesis, Xenohormesis, and Neurohormesis

Dr. Rogan talked about translational science and I think it is a really interesting case in point to look at what translational science means in terms of her eloquent presentation and the extraordinary work that she and her group have done in this DNA adduct and breast and prostate cancer area. That takes us back to where we were in the December 2007 issue of *Functional Medicine Update*, talking about nutritional

hormesis and xenohormesis and how these interrelate to cellular function and protective effects of low-level stress compounds on inducing gene expression that encourages anti-stress response of the cell.

Is there a segue or a connection between what we heard in December 2007 and what you are learning from Dr. Rogan in her most recent work in January 2008? As an example of the connector between these two issues, I would like to cite a recent paper that appeared in*Trends in Neuroscience* that came out of the Laboratory of Neurosciences National Institute on Aging, the intramural research program in Baltimore, Maryland.[16] This is the work of Dr. Mark Mattson and his colleagues that I think is very insightful because it speaks into this whole topic that we were just discussing, which is the question of how you prevent these untoward events that lead to these DNA adducts that might initiate cancer of the breast or prostate or other tissues.

As Dr. Rogan pointed out, some of this relates to altering things like detoxification pathways through gene response elements like nuclear regulatory factor 2 (or NRF2), which is a regulatory factor that is very important for turning on and turning off the genes that are associated with detoxification. And that associates with the antioxidant response element genes that are associated with protection against oxidative stress and these are all woven together and they have loci on the genome that are in proximity to one another, and, in fact, they have similar regulators. Their regulatory elements (their response elements) share homology. Is this coincidental? Very little in nature, probably, is coincidental. These are interrelated patterns of metabolism and the relationship it has to antioxidant response element and to detoxification enzyme production as a consequence of upregulation of things like NRF2.

How does that relate to hormesis and various phytochemicals that can help to improve redox potential in cells, shift to greater levels of detoxification, and lower the levels of the secondary metabolites that are associated with carcinogenesis? That is what this article by Mattson talks about: low-level substances that induce adaptive stress responses (these hormetic phytochemicals). I think we have been talking about this at some length, but this is just another example of where this might apply.

Plant cells contain many different chemicals that exert biological effects on organisms that ingest them, and considerations from evolution suggest that many of these phytochemicals with biologic activities are beneficial for mammals. They evolved as toxins that protect the plant from insects and other damaging organisms and actually serve as anti-stress compounds by the humans that eat them. They have effects upon regulatory pathways associated with reducing chemical and various environmental stress factors.

As you probably know, there are thousands of such compounds that have been found within plants. These are secondary metabolites in plants we call phytochemicals and include such things as flavanoids, and terpenoids, and alkaloids, indole-related compounds like indole-3-carbinol, which we know upregulates the formation of the 2-hydroxy estrogens. Things like the monoterpenes, eugenol, the essential oils, for instance, have these properties of affecting the detox response elements, as well as the antioxidant response elements.

The question is, when you eat a diet that is rich in these compounds, how do they influence, then, the metabolism of carcinogens and/or the effects on cellular redox potential (the reduction oxidation potential) by lowering oxidative stress? We call those simply antioxidants in the parlance of commonality, but they are really not antioxidants; they are more regulators of gene expression that then control cellular metabolism, oxidoreductive capacity, mitochondrial function, and ultimately the

expression of various enzymes that are mono-oxygenases (like the cytochrome P450s) that are involved with detoxification phase I and phase II conjugases.

This concept of eating certain dietary factors, for instance, from grapes, we now know about and have talked about with people like Christoph Westphal from Sirtris (about the resveratrol effect upon specific gene induction through SIRT1 genes). We know from previous discussions with Dr, Johanna Lampe from the Fred Hutchinson Cancer Research Institute about the role that sulfurophane plays and other various types of glucosinolates in cruciferous vegetables (the broccoli, cauliflower, cabbage, Brussels sprout family). Two years ago on *Functional Medicine Update* we talked with an investigator who was looking at the anti-inflammatory effects in rheumatoid arthritis of tumeric's active ingredient (at least, one of them) called curcumin and how that influences the NRF (nuclear regulatory factors) and the redox elements in inflammation. We know about St. John's Wort and hypericin, which has effects upon these same regulatory factors. We know about allicin in garlic that affects these regulatory factors, and we know that catechins that are found in tea (both black and green tea) have these influences. These are dietary agents that all influence the processes that Dr. Rogan was talking about, that modulate, through enzymatic activity, the flux of these catechol estrogens into or out of the potential adduct formation.

So there is an extraordinary opportunity here to connect together the work that is going on in phytochemistry, in cellular physiology, and in detoxification and oxidative stress research and antioxidants with the relationship that we are talking about with metabolism of compounds like estrogen that can go into these secondary metabolites that can be potentially carcinogenic. I just wanted to make sure that you recognized that when Dr. Rogan was talking about agents in the diet that may defend against the formation of these potential carcinogenic adducts that we are talking about the same types of molecules that are chemoprotective, which we have discussed in many previous issues of *Functional Medicine Update*. I hope that that leads you into some clinical thoughts about diet modulation and selected formation of pharmacological activities from some of these bioactive compounds from food.

Thank you very much for being with us and we'll look forward to our February 2008 issue.

Bibliography

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