# November 2008 Issue | Jane Murray, MD Women in Balance

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Welcome to *Functional Medicine Update* for November 2008. In this issue, we are once again looking at the complex issue of modulating the neuroendocrineimmune system with therapy. In past editions, we have had several extraordinary leaders in the field talk about things like bio-identical hormone replacement therapy. We are going to have a chance to have an update on this topic. The reason I continue to revisit this subject is because it is an evolving field and it's a rapidly changing field in our understanding. I think the more opinions and the more leadership we get in this area the better off we are in being able to really manage this process and provide the patient with the best information.

This month we have had the privilege of visiting with Dr. Jane Murray who is going to be discussing a very remarkable monograph that the group Women in Balance has put together on this topic. Before we get to the interview, I want to say some things about women's health in general and the push towards hormone replacement therapy. I'd like to provide some context.

There is now evolving information indicating there is wide diversity at the genetic and metabolic level among both women and men. The concept of biochemical individuality that Roger Williams talked about all the way back in the late 1940s (and Linus Pauling, with his concept of orthomolecular medicine) is starting to really gain traction as we learn more about the transcription, translation, and the outcome of the human genome into the phenotype of the individual.

The Role of Single Nucleotide Polymorphisms in Women's Health
With regard to hormone replacement therapy and managing women as they go through perimenopause, and into menopausal and post-menopausal years, we start to recognize that women respond very differently based on the principles of epigenomics and genomics through the pre-menopausal and into the post-menopausal period. A lot of this has to do with SNPs (single nucleotide polymorphisms) that modulate the way that various compounds travel through the body and are biotransformed and excreted, and also how they interact with receptor sites and are engaged in intercellular signal transduction. They communicate through information as hormonal materials to change/regulate cellular function. So there is a wide diversity of responses.

Some of the most critical single nucleotide polymorphisms that relate to women's health are now starting to be identified. Of course, this is giving birth to a whole new field of molecular genetics as applied to the female reproductive system, particularly coming out of the area of breast cancer in which certain single nucleotide polymorphisms are being identified to have higher associations with breast cancer risk and responsiveness to certain chemotherapeutic drugs, particularly certain kinases within the kinase inhibition family of drugs, like Gleevec.

Conflicting Information from the Women's Health Initiative

We are starting to see a move from "medicine of the average" to "medicine of the individual." This shift might help us understand some of the apparent conflicting information around the Women's Health Initiative studies that were done with mixed equine estrogens and progestins in the management of women's health throughout the menopausal period. It appeared as if many women had no adverse side effects from intervention with mixed conjugated equine estrogens and progestins, whereas other women had increased risk. Overall, the weighted average (as if there was an average woman) was not good, but if you looked at certain cohorts within that full spectrum of women in these studies, you find that there were some who faired very poorly and others who faired reasonably well or even well.

How do we identify those who didn't respond so well? What is uniquely different about them? Various genes and their single polymorphisms that are unique to those who are more at risk are starting to be seen as part of the story, like possibly Leiden Factor V. In women with these specific SNPs (these polymorphisms), there is an increased risk of thrombolytic and thromboembolic risk. I think we want to stratify many of these data sets into looking at individual characteristics of groups of women who may be at differing relative risk. This moves us from the age of the blockbuster drugs (the class effect of "one-size-fits-all") to the new age of gene-targeted agents (which might be considered "microbusters"). Targeted agents are more focused on individual characteristics, and they allow clinicians to stay away from those at risk and only give them to those people who have appropriate need.

Hormone Replacement Therapy and Risk of Venous Thromboembolism

I think this links very directly to a whole variety of recent published studies, but one that I think exemplifies this that I want to share with you has the title "Hormone Replacement Therapy and Risk of Venous Thromboembolism in Postmenopausal Women."[1] This was a systematic review and meta-analysis of a variety of published studies on the role of hormone replacement therapy on the risk to venous thromboembolism. I think this article is very well done. It appeared in the *British Medical Journal* in 2008.

We recognize that hormone replacement therapy has been shown to improve the quality of life for some women who have hypoestrogenic symptoms (vaginal dryness, night sweats, even some of the cognition and depression dysphoria symptoms), but then we buttress that against (or juxtapose it against) the relative data that has come out of the Women's Health Initiative looking at mixed conjugated equine estrogen and progestins and their effect on cardiovascular outcome, which was not too good, on average. The authors of this article started to look at the meta-analysis and the randomized trials from a larger kind of study perspective. What they concluded was that estrogen replacement does increase the risk of venous thromboembolism when given as oral mixed conjugated equine estrogens, especially during the first year of treatment when averaged across all individuals. The women most highly at risk may be those who carry the Leiden Factor V polymorphism. That is the overarching view from summarizing eight observational studies and nine randomized controlled trials that have been published to date.

Research on Hormonal Delivery Systems

According to these researchers, transdermal estrogen was found to be much safer with respect to thrombotic risk. They go on to say that more data are required to investigate differences in risk across the wide variety of hormone regimes, looking at bioidentical versus synthetic progestins, using conjugated equine estrogens versus native estrogens to the human specie, and also how it relates to different types of progesterones, and progestogens, and progestins, as well, which play different roles.

I think the 2008 view is that there is still a lot of confusion. We still haven't nailed all this down, but what has emerged is that we need to look at the individual woman. We shouldn't be using a general "rules of the road" or "one-size-fits-all" mentality. We have to really look at how each woman responds. What are her unique genetic characteristics, and how do those, then, influence outcome when she is exposed to exogenous hormone replacement therapy? I think that is going to require a different level of knowledge. Many therapists have basically been just administering these agents on a standard dose regime without really recognizing the diversity of different ways that women respond: how they metabolize estrogens, producing more or less of the 4-, or 16-, or 2-hydroxyestrogens; how these estrogens travel through the detoxification process and get eliminated; how the progestins differ in their physiological response from the nature-identical progesterone. All of these factors are further complicated by the delivery systems: transcutaneous versus vaginal versus oral (these play very different roles), or time release versus immediate release. You have many, many moving parts, many variables. The woman, herself, is the key to this puzzle. She is the person for whom these treatments are designed, and amelioration of symptoms is not enough to really understand how she is responding. We need to take a snapshot of a woman's response that is much more unique to her individual genetics and biochemistry.

Diet is an Important Environmental Modifier

This discussion leads to the question of whether we can modify or modulate the way a woman responds to her native and/or exogenous hormones based upon the environment in which she finds herself. One of the most important environmental modifiers that has appeared in a lot of the discussion we've had in *Functional Medicine Update* over the years is diet. Are there specific dietary principles that would have salutary effects on modulating hormones, and receptors, and the information (the signals) that are transduced from those hormones in the perimenopause or the menopausal period that would both help to improve symptoms in menopause while also regulating health outcomes in the woman? In our society today, a woman may live nearly half her life in the absence of having her menstrual period. The questions we want to ask a modern woman about her health, postmenopausally, are very different than if the mean average life expectancy of women was 55. What we are really asking is how do we sustain good health for a century or more in a woman? That's a different question that requires different answers than maybe we would have used some 50 years ago.

How does diet play a role in modulating these effects and maintenance of proper cardiovascular, neurological, musculoskeletal health in the case of a postmenopausal situation? I would like to address that question in a slightly more non-traditional way than perhaps you have heard before. We could jump to an answer that involves looking at specific diets that have been associated with long life and good health in women (transnational studies and things like the Japanese Women's Study, which used food anthropological records, and examined what happened when Japanese women moved from their traditional diet to a Westernized diet). What happens to the disease patterns in these women? Those are important bits of information, but I want to move down a level in our discussion here. I want to use the same type of logic that women use about hormone replacement therapy to talk about constituents of the diet, meaning in hormone replacement therapy we are talking about specific small molecules interacting with specific receptor sites to induce, in that woman, specific signals in a tissue-specific way to then promote things like what we call (generally), health (brain health, or heart health, or skeletal health).

How does that actually occur? Are there small molecules found within foods in a complex array of minimally processed things that were close to the earth, in which they were grown and harvested, that would have similar types of signaling principles to that which we talk about with hormones, and can

either affect in a positive or a negative way, the way that hormones are used by the body? I hope I'm contextualizing this for you, as a listener, in a way that you understand. Rather than looking at it as a gross effect of diet on women's health, what I want to look at is the same thing that we would with hormones: the interaction of small molecules (that in this case are found in diet versus, in the alternative case, found as small molecules in the hormonal system), and what influence they have on this crosstalk-this orchestration-of outcome of function in women from menopause right on through the end of their lives.

When I raise that question, it sounds a lot like this principle that you have been hearing me develop in *Functional Medicine Update*: hormesis. What small molecules are present in foods that have a hormetic effect, meaning small amounts of things having an unexpected large effect on outcome? This is a "small builds large," "small is beautiful" kind of conceptual framework.

Beneficial Roles of Hormetic Phytochemicals
There is compelling evidence from epidemiological studies that indicate beneficial roles of various hormetic-type phytochemicals that are found within a complex food-supply system that help to protect against virtually all the chronic diseases (cancer, heart disease, inflammatory disorders, and so forth). Emerging findings suggest that several of these dietary phytochemicals also benefit the nervous system, and when consumed regularly, may also reduce the risk of what we consider age-related neurological disorders such as Alzheimer's and Parkinson's diseases. We are starting to ask more detailed questions about the principal characteristics-the signatures of a diet that a woman might consume postmenopausally--that will have the beneficial effects on regulating her function, even with the declining level of estrogens or progestins due to ovarian... what's called ovarian failure (I don't really think it's failure... )... ovarian alteration of function with age, and still results in maintenance of health. In other words, compressing disease and rectangularizing the health span, so to speak.

The evidence supporting the health benefits of vegetables and fruits, which we have been talking about for years in *Functional Medicine Update*, provides a strong rationale for the identification of what these specific phytochemicals are that are responsible for modulating a variety of different functions. We now have the assay procedures that are starting to develop to do screening, and we have the animal models, and we ultimately even have the human clinical trials that would allow us to examine what type of diets are augmented and what kinds of phytochemicals would induce or promote proper function in the postmenopausal woman, just as we would set up clinical trials for looking at the difference between a nature identical (or bioidentical) estrogen to that of the mixed conjugated equine estrogens, which contain the B-ring unsaturated estrogens that are not natural to a woman's body and are found only in pregnant mare's urine. We could do a similar type of study with the molecular signatures of these phytochemicals to that which we might consider doing in a pharmacology experiment with the hormones. The difference, however, in this model, is that the hormetic effects of these phytochemicals are often seen to be more powerful (or I would call it synergistic), when they are combined together. We are hitting multiple things a little at a time to create an orchestral change of outcome, versus hitting one thing very hard, which is the general tendency towards drugs or pharmacology, where we come in with a single molecule like a jackhammer and we hit a specific functional status of metabolism or cellular biology.

Are there studies that are now being done to look at the effects of sub-toxic doses of these phytochemicals that are derived from specific plant foods that modulate the principles that are associated with health of women as they go through the period of menopause? The answer is an absolute "yes" to that. I think it is a

fascinating chapter that we are opening up that allows us to ask these questions at a slightly higher level of scrutiny and have the methodologies to actually provide answers as to how things work and what levels are beneficial, and even what genotypes might be most valuable or most sensitive to these particular alterations as it relates to their functional changes.

Articles in Support of Phytochemicals

I'm now actually indirectly quoting from a very nice new article that was authored by Mark Mattson and his colleagues that appeared in *Neuromolecular Medicine* in 2008.[2] In this particular article, the authors are talking about how to lower the risk to brain-related dysfunctions in age through regulation of various neurological states of function with phytochemicals, but we can identify the same thing as it is being published in the area of cardiovascular disease and also with bone health. In fact, there is a wonderful paper authored by RM Ortega in *Public Health Nutrition*.[3] This article is about components of the Mediterranean diet and how these phytochemicals have direct impact upon the health of individuals who are suffering from things like dysinsulinism, or indications of osteoporosis (or at least osteopenia), and how specific functional characteristics of the Mediterranean diet can play a role in modulation of these functional outcomes.

You'll notice that this is a different way of framing the diet-health connection. I really like a paper that appeared recently titled "Local Food and Cardioprotection: The Role of Phytochemicals."[4] This article looked at how specific families of plant-derived materials that are in our diets for millennia (so-called proven safe by food consumption), have a dramatic effect on all of the principles that we associate with the aging cardiovascular system, meaning they help to retard the dysfunction of the cardiovascular system with time-things like components of extra virgin olive oil, lycopene in tomatoes, and certain spices that we'll talk about-all of which play very important roles in modulating cellular physiology. Before we leap to the construct that we need to have a hormone that has been replaced by either synthetic or natural methods-before we jump to that--maybe we ought to be looking at how the personalities of specific plant-derived and animal-derived nutrients can influence these functions in such a way as to limit or lower the need for hormone replacement.

Let me discuss a classic example; it is one that is emerging that I think is quite fascinating. If we look historically at the French paradox, and we contrast that to northern latitude countries that didn't have available grapes and therefore they didn't have wine, their alternative, as you probably know, was beer. There are cultures that, historically, have consumed beer as a replacement for wine because wine wasn't available. What you find when you look at the actual epidemiological outcome of these populations that were consuming high hop-derived related beer is that health benefits had some very significant similarities to that of individuals who consumed wine and red grapes. People started actually looking into this question of beer and health, just like wine and health, as part of the French paradox, and they found that there were a series of compounds within the hopping of beer that could have effect on the female reproductive system.

Rather than being the agents that were commonly called the bittering agents of beer, which have names like the alpha and beta acids, these compounds that were manufactured biosynthetically by the hops plants are called the chalcones, or the 8-prenylated chalcones. These particular families of compounds, which are found in hoppy beers have an "estrogenic-like" effect. In fact, there is evidence to indicate that one of these compounds called 8-prenylnaringenin, which is a prenylated chalcone from hops, has an

estrogenicity that, in female animal studies, is just about one order of magnitude lower than 17-beta estradiol. However, it has other signaling properties that 17-beta estradiol does not have that may be beneficial in modulating things like nuclear regulatory factor 2 and how that influences the expression of genes associated with detoxification. It has multiple personality types, so to speak. It is not only an estrogenic molecule, but it also influences other aspects of the cellular function, including detoxification.

If we look at things like genistein, which as you know is a soy isoflavone that has estrogenic properties, or resveratrol (our red wine compound that has estrogenic properties), or 8-prenylnaringenin (the 8-prenylated chalcone found in hops in beer), these have all been found, recently, to be agents for not only cardioprotection, but protection against osteopenia and osteoporosis. When I say this, you'll notice I'm talking about women's health after menopause, like it was an estrogen and having multiple effects. The difference, however, is that these particular compounds derive from soy (as for genistein), or reseveratrol (from red grapes and peanut skins), or 8-prenylnaringenins (from hops), do not have the same mitotic stimulatory index as does 17-beta estradiol, and certainly have a vastly different effect on the production of the 8-hydroxy estrogens as does the family of equine estrogens, the B-ring unsaturated estrogens, found in mixed conjugated equine estrogens.

What I am saying is that they have the potential to be safer with modulating effects that may be synergistic. If we talk about what a Mediterranean diet looks like, it might have soy protein containing genistein. It might have red grapes and red wine containing resveratrol. And it might have some beer-derived components like the hop-derived 8-prenylated chalcones. It obviously has fibers. It has a whole array of other phytochemicals that also participate as antioxidants and regulators of cellular function, so we are starting to get a multiple-voiced, orchestrated approach towards modulating those things that are associated with the menopause.

It is interesting to note that when Dr. Deanna Minich and I authored the recent paper that appeared in *Nutrition Reviews* (this was the August 2008 issue-an article that was on nutrients modulating metabolic syndrome beyond macronutrients), we talked about phytochemicals, these same phytochemicals that I have just described (genistein, resveratrol, and hops-derived materials) also replicated to improve insulin signaling and to regulate inflammation.[5] We are cutting across multiple functions. These phytochemicals have voices, so to speak, that when worked together, help to regulate function in a positive way.

The question we come to, again, is: have any studies been done to look, head on head, in intervention trials, at a diet that is constructed to have the right kinds of molecules in it to send the right signals to induce appropriate regulation of bone physiology, cardiovascular physiology, neurological physiology, immunological physiology, in a natural source complete diet versus that of using hormone replacement therapy? The answer to that is "no." No such study has yet been done or published that I have seen. There have been some gross nutritional intervention trials that have been done, but not optimizing the signaling of some of these phytochemicals that play this role. By the way, for those of you who are interested, this comparison of the phytohormones genistein, resveratrol, and 8-prenylnaringenin as agents for preventing osteoporosis appeared recently in the journal *Planta Medica* in July 2008.[6] It is a very nice review paper looking at the studies being done on bone density using animals (these are female animals) in which they were supplemented with either 17-beta estradiol 3 benzoate as an active control, or genistein, or resveratrol, or 8-prenylnaringenin, or a combination of the three (genistein, resveratrol, 8-prenylnaringenin), and then looking at bone density in these animals after intervention. The results

showed very significant improvement in bone integrity, or bone density, and skeletal strength, which was actually measured in these animals because the animals were sacrificed and they looked at their skeletal bone strength. They found that these have a very positive role in helping to prevent the deterioration of bone integrity and, simultaneously, also have a positive and salutary effect on things like serum lipids, cardiovascular health, and neurological health.

I think what we are seeing is a new emerging view. Maybe we shouldn't rush too quickly to jump on the bandwagon of hormone replacement therapy until we've had the opportunity to walk through how to optimize dietary intervention for each woman, knowing that when we get into hormone therapy there may be certain genotypes, like Leiden Factor V polymorphism individuals, who have very high risk to estrogen if supplemented because of thromboembolic disorders.

You'll notice that I mentioned soy. Soy is a big controversy, isn't it? To say the least, it has been on the big board (the marquee) for discussion. We have heard recently that soy, because of its estrogenic characteristics, may encourage issues related to breast cancer in women or prostate cancer in men. It may be related to digestive disorders. It may be a highly allergic food and induce, then, immunological dysfunctions. It seems like everyday there is some voice out there finding a new way to criticize the incorporation of soy-based foods within the diet. I think we need to put this in some context because for every voice there is another voice that is a counter voice.

When we look at the weight of the evidence of one voice versus the other in this area of soy, what do we see? There is a very nice review that appeared in *Atherosclerosis* in August 2008 titled "Nutritional and Nutraceutical Approaches to Dyslipidemia and Atherosclerosis Prevention."[7] The authors of this paper focus on dietary proteins and they look at different protein sources, like whey-based proteins, or wheat-based proteins, or soy-based proteins, or milk-derived proteins like casein. They ask questions as to the differences in influence that these particular proteins have on functional health over time.

The authors of this paper are quite well-known collaborators in this whole area, including James Anderson from the University of Kentucky, who has been very well-published over the years in terms of nutritional endocrinology, and Cesare Sirtori, who is also very well known and a nutritional pharmacologist at the University of Milano. In this particular paper, these colleagues review what is really happening and what has been published in the literature. When they look at soy proteins and the risk/benefit of soy protein inclusion in the diet, it is quite, I think, a very realistic perspective for us to take away. What they point out is that soy proteins are unique in their composition as contrasted to animal proteins because of their high arginine content relative to their lysine content. As contrasted to animal proteins that are generally higher in lysine and lower in arginine and higher in sulfur amino acids, the soy proteins are uniquely different in their composition, having higher arginine and lower lysine. This arginine composition seems to be one of the contributors to the effect that soy protein has on regulating things like endothelial nitric oxide synthase activity and influencing in a positive way vascular compliance, lowering blood pressure, and improving endothelial function within the vasculature.

But beyond the individual amino acids-and here's where the story gets very, very interesting and I hope I can say this so that it is cogent and understandable-the proteins that are within soy, when partially hydrolyzed by the gut digestive process, liberate little oligopeptides that now have been identified to have influence, on their own, as information molecules that are differing than the breakdown products of other food proteins. They set up cellular signals across the GI signaling process to induce things systemically

that have salutary effects on inflammation, cholesterol levels, lipid biosynthesis, and metabolism.

Research on the Absorption of Intact Proteins

We have now kind of moved into a new era of looking not only at the intact proteins and their amino acid composition (which has been a historical way we have looked at dietary protein physiology), to now looking at the information content within dietary proteins as a consequence of their partial digestion and the potential adherence or binding of those proteomic molecules or smaller polypeptides with receptors that trigger new signals that have new structure-function relationships. I know what I just said is pretty dramatic because most of us learned that dietary protein nutriture was based principally on the digestion of protein down to its requisite amino acids, and then the absorption of those amino acids into the plasma, and those would then be resynthesized on the other side of the gut wall to produce the body's native proteins. It was told to us that there was no absorption of intact protein from our food. What is now being seen, however, is that small fragments of the intact protein can be absorbed to the extent that they can have impact upon cellular signaling across the gut mucosal wall and, as such, across the lumen they can then influence, systemically, through action at a distance, these signaling processes. This is a revolutionary change in thinking in both nutrition and physiology. Once we start accepting there may be dietary proteins that have differing signaling properties beyond that of the amino acids from which they are made that then influence systemic function, we now have a whole new ballpark opening up and a new ball game relative to how you utilize specific dietary proteins to modulate function.

That seems to be what is occurring in the relative understanding of how soy protein differs from that of animal protein because you can take the exact composition of amino acids found in soy protein and administer those to animals in the same amount that you had given the native protein, and you will get different physiological outcomes in terms of lowering serum lipids, lowering inflammation, and modifying vascular endothelial function. It is more than just the amino acids, themselves. It is also the composition of the amino acids as they are found along the chain that when delivered in smaller fragments have differing effects on function.

I think that that is a pretty powerful concept. When we talk about protein, it's a family of all sorts of different molecules, just like when we talk about gluten. Gluten is a generic term for a class of molecules which run similar in electrophoresis, but underneath that peak-that electrophoretic peak-reside many, many different molecules that all make up the family that we call gluten. Some of those molecules may have different effects on the immune system than others, so we generalize it to say gluten, but it may be that you can have gluten in your diet that was free of one those protein fractions and it would not produce a gluten response, whereas there may be one or a smaller factor of offending gluten molecules within that family that trigger, then, specific immunologic effects by receptor-binding.

I'm trying to get you to sense that we are seeing shifting sand right now, shifting understanding. With regard to soy protein, we know there are specific fractions that have the most health beneficial effects, and that these, then, lower LDL in animals, they lower total cholesterol, they increase HDL slightly, and they lower CRP (C-reactive protein). We can say these are positive benefits that are accrued to soy protein as a protein, itself. I'm not even talking about the other phytochemicals, like the beta-sitosterol or stigmasterol (the neutral plant sterols). I'm not talking about isoflavones, like genistein or daidzein. I'm not talking about lignans that have additional effects like those that are metabolized to equol. I'm just talking about the protein, in and of itself.

When people say now that soy protein is dangerous, or bad, or has adverse health effects, I just don't think it stacks up at all against the weight of evidence in the literature that is now getting much more precise as to how these particular characteristics in soy protein, in a full complement of materials, influences physiological function. It may have hypotensive effects and cause the vasculature to relax by increasing endothelial nitric oxide synthase activity. It has ACE-inhibition effects by modulating angiotensin-converting enzyme activity to help regulate blood pressure.

Recent Papers on Soy Protein Intervention

As always, I want to emphasize everything in moderation, but I think this backlash against soy is a very ill-founded approach. It may prevent many women from consuming soy in their diet, and as such have a detrimental effect or a lower-than-desirable effect on how diet will influence their function (cardiovascular, neurologic, and skeletal function) post-menopausally. There is a very nice meta-analysis on the effects of soy protein containing isoflavones and lipid profiles that was published in the *American Journal of Clinical Nutrition* in 2005.[8] The authors of this article looked at 23 randomized controlled trials published from 1995 to 2002 on soy protein intervention in humans (these are all human trials) to examine the effect on cholesterol (LDL cholesterol), triglycerides, HDL, and oxidative stress factors. What they found was that soy protein in its intact form, containing isoflavones, significantly reduced total serum cholesterol, LDL cholesterol and triglycerides, and increased HDL. The changes were related to the level (about 25 grams a day), the duration of intake, the sex (females having a positive impact), and the initial lipid levels. Those who had the highest lipid levels had the most positive effects.

There is even a more recent paper that I think you'll find interesting, again talking about post-menopausal women and the effect of soy protein on modulating their function. This is a systematic review looking at randomized control trials in humans and the association between the intake of 25 grams of soy protein a day and the effect on blood cholesterol and appeared in the *Atherosclerosis* in 2008.[9] After looking at an extensive amount of literature, these authors report that the inclusion of modest amounts of soy protein (at least 25 grams a day) into the diets of adults with mild hypercholesterolemia, (which is often seen in the post-menopausal woman), resulted in reductions in LDL.

I just don't buy this model that has been talked about with phytochemically-enhanced diets-that Mediterranean diets and soy protein-containing programs are somehow not desirable for women as they move from perimenopause into menopause. If we were to optimize dietary variables and introduce women to these diet and lifestyle programs with exercise and stress management, the discussion about bioidentical hormone replacement would be a lot less important because many of these women who have need can modulate or modify it just by lifestyle and diet intervention alone. If there was still need to modify symptoms such as vaginal dryness, or night sweats, or dysphoria, you could use an appropriate amount of a bioidentical hormone. I think that's the approach we are moving toward..

Research on Red Rice Yeast

Let's look at traditional Chinese medicine. There is a condiment that has been used in Chinese cooking for years that modulates cardiovascular health, and we call it red rice yeast. Red rice yeast is a condiment in the traditional Chinese sense. The fungus grows on rice and produces not only the red color, but it also produces a class of compounds called monacolins, one of which is related to lovastatin, or the cholesterol-lowering agent that acts via its effect on HMG-CoA reductase. Many studies have been published on the effects that red rice yeast has on coronary events in the Chinese population. A secondary prevention trial was just published in the *American Journal of Cardiology* looking at the effect of red rice yeast on

Chinese men and women who had previously had a heart attack, and compared the secondary heart attack incidence in 5000 patients versus those who would have been on traditional pharmacological statin therapy.[10] They found that the individuals on a daily intake of red rice yeast actually had a lowered level of secondary heart attacks.

I think there is so much yet to be learned about how these molecules in nature modulate function at the cellular level and go through similar mechanisms of actions. The difference is they don't work as a sledgehammer; they work by modulating, or tickling, metabolism to produce altered function. With that in mind, let's go to our extraordinary clinician of the month to take this to the next level of discussion about bioavailable hormones.

## INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
Jane Murray, MD
Women in Balance
PO Box 12004
Overland Park, KS 66282
www.womeninbalance.org

Here we are back at that section of Functional Medicine Update that we look forward to every month and that is our clinician or researcher of the month component. We are privileged this month to have a leader in a field that is at the forefront of our discussions about the transitions that occur as a person ages into middle-age and beyond. One of these issues, of course, has to do with the transition into menopause for women and the transition into climacteric for men. What are the various things we can do to assist that transition to be as healthy as possible and to compress morbidity and increase life expectancy? We are very privileged to have Dr. Jane Murray, who will be sharing with us some work that she has been doing with Women in Balance on the state of the science of bioidentical hormones for mid-life women, which I think, for all of us, is a very important ongoing discussion. We have had a number of discussions about this in Functional Medicine Update over the last few years, but I think you are going to find this interview takes it to the next level of discussion.

Let me give you a quick introduction of Dr. Murray. She is at the Sastun Center for Integrative Health Care in Overland Park, Kansas. I first had the privilege of meeting her through the Institute for Functional Medicine, when she was the Chair of the Department of Family Medicine at the University of Kansas Medical Center. Dr. Murray is obviously one of those people we hold at high esteem as a functional medicine expert. She has also worked with the American Academy of Family Practice; she and Dr. David Jones actually gave a course at one of their recent meetings on functional medicine in the family practice environment. She was the Chair of the AAFP course in Complementary and Alternative Practices in 1999 and core faculty in the AAFP Fundamentals of Management. Dr. Murray comes with a very broad and deep understanding of the issues surrounding family practice and also how that interfaces with healthcare issues throughout the lifecycle. Today we are particularly going to focus on this issue of mid-life women. With that as a brief introduction, Dr. Murray, I would like to introduce you once again to Functional Medicine Update, and thanks so much, Jane, for being with us.

JM: Well, Jeff, it's a true honor to be able to have a conversation with you, someone who has been such a

leader and that we all learn so much from. Thank you for inviting me.

A New Publication on Bioidentical Hormones

JB: This review paper that you and your colleagues have been working on, which, as I mentioned briefly, is the state of the science of bioidentical hormones for mid-life women…really below what's written is a tremendous amount of experience that you and your colleagues have clinically, as well as a very deep amount of information from both clinical and basic research science. I think before we jump right in to that review, maybe you can just give us some introduction to your historical experience with hormonal issues and women going through the menopause.

Women in Balance: A National, Nonprofit Organization

JM: Okay. I think all of us, as clinicians, really think of ourselves as students, and many times patients are our best teachers. About 15 years ago, when I was not, myself, quite in the mid-life transition yet, I had a series of mid-life women who really were very interested in having as much information as possible about their transition and were doing some things that I had not been exposed to with their hormone therapy. Specifically, they were using some bioidentical and compounded hormones.

I got curious and started to look into this whole new field of individualizing medicines for patients and became very fascinated. I had not learned about compounded medications. I was not very familiar, at that time, with bioidentical hormones and what they were. So, again, as often happens, my patients really spurred me to learn more. And the more I learned, the more fascinated I became.

In the late 90s I started reading things-articles, research papers-about progesterone, in particular, and how it was very different from synthetic progestins such as medroxyprogestone acetate that was being used commonly in hormone therapy for women. And I was sort of shocked that this wasn't more widely known, this very clear, cogent research data about the differentiation between these two forms and some of the actual improvement in benefits for patients in using the real (in this case, progesterone) hormones. I actually kind of got so interested I wrote a little paper that was published in a primary care journal about progesterone and its benefits, and that kind of took its own legs and got me introduced to some other people who were very interested in the field and we started meeting and talking and decided that really women needed more information, and clinicians needed more good, unbiased, clear information about the various hormone options women might have and why some might actually be physiologically superior to others. After a lot of conversations and meetings and discussion, we decided to start a national nonprofit organization called Women in Balance, which I can talk more about if you are interested.

JB: Yes, I would, but before we get to that, I always find it fascinating that people who rise to be the leaders in a discipline (and you certainly fulfill that definition) have very nonlinear paths to how they got to a certain point in their life that we all respect as their leadership position. I find it interesting that you started off at UCLA, and you went up through what obviously is the "southern California" experience, with family practice residency at the Santa Monica Hospital Medical Center. Then you became the Director of the Division of Education for AAFP (so you become kind of institutional medicine as well as your clinical medicine), and you move on from there to Kansas, which might not be seen (for most people) as the kind of commonplace transition. You end up in this family practice residency chair position at the department of family medicine, University of Kansas Medical Center, and then later into private practice, and now in your center. How did you get guided through these experiences? It is very interesting because it doesn't seem like a linear path.

JM: No. Well, you know, I think in primary care and family medicine, you have to be sort of interested in the broad picture, and I always was. Going through medical school, I liked every rotation, and what I liked was the people and the patients and trying to see if I could put things together for them from different fields and different specialties. For myself, I always felt that trying to do a narrow specialty would be way too constricting and not as beneficial as if I could maybe pluck information and experience from a variety of areas.

What has resonated so much with me over the last, maybe, eight years since I've been exposed to functional medicine and your fine work is that there are just exceptional mind-expanding opportunities to see how we can take the individual patient and look at them in the bigger, broader perspective and not worry about labels, but worry about what is happening with them and what they need. I think what I found, through my whole experience in all of these different venues, was people being very unique and situations being very unique and needing to pull experience and knowledge from a variety of areas, whether it was running a meeting in the family medicine department or meeting with the other chairs or putting together educational programs for the Academy of Family Physicians. It helped to have a breadth of experience to be able to be effective in those areas.

You know, you keep referring to me as an expert…I just feel like I'm a lifelong student and I'm always trying to learn and pick up new information and be more well-rounded and be able to do a better job with patients. I would say that that has been what has driven me. As a young resident, I would listen to patients tell me that their back pain was better with their chiropractor, which, you know, back in the 80s was not something that doctors really recommended a great deal-"Go see your chiropractor." I was always a little bit of a rebel. I got into a little bit of trouble for not using enough drugs in my residency and maybe not a high enough dose-"Oh my goodness, you're telling a patient it is alright to go to a chiropractor?" My response would be, "Well, you know what? It's helping them, and it's helping them in a different way and a better way than anything I have been able to do." So I think that's what we want: helping people. That's really been my trajectory: to take the best of whatever we can find and see if we can help someone.

JB: That then helps us to understand, obviously, the segue to the next point, which is probably why you and your colleagues decided to spend the time and energy to form Women in Balance. It just seems like an extension-the interface and links. Tell us a little bit about that.

JM: We all felt that women were getting information primarily from healthcare providers about their options for mid-life transitions. At this moment, we are talking about hormones, but there is certainly a broader palette of options than hormones. The standard of care would be to go to your gynecologist, your family physician, or your internist once a year for your pap smear. If you are having some hot flashes and your periods are changing you get a prescription for something-say Prempro-and, you know, then you would hear "Have a nice year. I'll see you next year for your next pap smear." For women we are seeing now (as you mentioned, the baby boomers who are aging and coming into this whole mid-life and beyond timeframe), that is really not an acceptable option. You don't just give someone a prescription and say have a nice time. They want a conversation. They want to know what this medicine does. What are the risks and benefits? What are the other options that aren't this? We kept talking to patients, and friends, and colleagues about their frustration with health care. They don't want to just take horse urine. They want to know what else might be available.

We really felt that in a way there was kind of an injustice for women that they were not having access to the full range of information and therapies, largely because the information that doctors receive about healthcare options comes from continuing education programs and other opportunities that are highly pharmaceutical-company driven. The things that pharmaceutical companies don't know about or don't sell are not as often (or have not, maybe, until more recently) been what doctors learn about. We felt there needed to be some kind of an opportunity, and we basically created a website that has tools, information, resources, primarily for women, but also for healthcare providers interested in caring for women, to really put forth what some of the options might be.

One of the big interests that we have had and that stemmed from that paper that I wrote a long time ago about is the differences between progesterone and synthetic progestins; we need to know more about this. When patients would say, "Well, my doctor says there is no research about these bioidentical hormones," we felt that that was a significant inaccuracy. One of the first things we put on our website was the research that has been done (the papers that have been published) about bioidentical progesterone and bioidentical estrogen, and what we do know so that there at least is some data to support that there isn't zero science in this field. Now we are moving forward and developing tools for women to use when conversing with their clinicians about hormone options, and very soon (hopefully by the end of the year 2008), we will have a practitioner locator for women who want to have a physician/clinician who is somewhat knowledgeable in this area and at least willing to have a conversation with them.

JB: So obviously you need to tell us the URL for this website...

JM: Yes! It is www.womeninbalance.org.

JB: Great. And it is all run together?

JM: All run together: www.womeninbalance.org.

Polarized Views of Hormone Replacement Therapy

JB: You hear this interesting discussion that is going on right now. I have heard it back and forth among clinicians as I travel around the country. Some people say, "You know, going through the menopause is a natural process of transition that has been going on--it is the circadian rhythms of life--in women since time in memoriam. We didn't have access to all of these hormone replacement things before and women did just fine, so why do even need to consider this? It's a natural process." And then on the other side (I'm giving the two polar extremes here just to make a point), people are saying, "You know, women need to be supported with every possible thing we can think of so that their physiology will look like that of a 30-year old or a 25-year old. If you expect them to live healthily out to 100 years, then you've got to use the whole pharmacopeia." Could you kind of characterize where Women in Balance is in that continuum?

JM: Yes, and I think that's a good polarization, as you have said. Certainly there are women who live a very healthy lifestyle. They have always taken good care of themselves. They are balanced in mind, body, and spirit, and many times they don't experience a great deal of difficulty (disruption of their life, their sleep, their mood). They are able to transition what can be a bumpy path for some very gracefully and very easily and they don't need to do anything pharmacologic at all. That would certainly be, I think, our ideal situation.

Then there are women who are very disabled by hot flashes and night sweats and their sleep is terribly interrupted and so then the next day they are fatigued and they don't focus well. They can't do their jobs. They can't care for their families. And so there is a wide spectrum here and I think it comes back to we need to practice individualized medicine and take a person where they are at and help them find their way (it's their own way) through this trajectory, but we have some tools and some experiences that might be helpful to them.

Hormone "Therapy" Rather Than "Replacement"
What I find in my practice (and I think the view of our organization, Women in Balance, is) is that balance is everything, and to find your own balance is a very individual path and it might involve changing your diet, changing your lifestyle, getting more exercise, seeing a therapist if you are having stress-related emotional issues, doing some mind-body practices with calming yourself and balancing and being sure you do some good self-care. And then sometimes we need to help some of the symptoms that people are having with some kind of hormone supplementation. We're not really calling it "replacement" any more; we are calling it hormone therapy now. It's the broad array of the hormones that women might have deficiencies in or symptoms related to their being out of balance. We take that individual person and help them find what they might need for a period of time (months to years).

And then, of course, there is a whole other arena of women's health research: finding some actual (perhaps) benefits from replacing or supplementing hormones relative to density for years, which we have known about for years, and now we are getting into some other areas, such as preventing cardiovascular disease, if we start some of these hormones early in the transition, and maybe even some brain protection. So there is beginning to be scientific and clinical arguments being made that, "Gee, you're right. We could keep people healthier and happier through their next 40 years if we could balance their hormones better." I don't know that anybody knows what the right answer is. My approach with patients is to say, "Well, if it looks like you are a candidate and that hormones might be helpful to you and we can talk about, perhaps, what we think the safest ways to use them are, then we'll have this conversation at least every year, because the state of the science will change, the state of you will change, and we'll see if we want to continue, or change your regimen, or add something new, take something away, see how things are going." This is a very big moving target. We are getting new and more exciting research all the time about the risks and benefits and the options about hormone therapy, and we need to have a lot more information than we have to make the best choices. But, you know, we are kind stuck in the here and now and we have to practice medicine with the information we have and try to use it in the best way.

JB: I think you have said so many fantastic things in that very, very condensed and dense bit of information you shared with us. Let me go back and pick up a few things. First of all, I think what you said (matter of factly) is probably, for the average listener, a pretty big deal because I think it implies something quite different. You said that we've changed our terminology from hormone replacement to hormone therapy. That, to me, connotes (and raises the question), what does therapy mean? And you went on to say, then, that has to do with personalization and the fact that we have changes that are going on through time. There is not just a formula or a recipe. It is not just a woman of a certain age with a certain dose-response. You basically are looking at a much more complex array. You are basically treating the web of that individual.

JM: Exactly.

JB: These are very big conceptual changes, aren't they, than the way that most practitioners were trained in school around differential diagnosis and seeing menopause maybe as a disease that you treat?

Mid-Life Brings Development Issues

JM: A disease with, "Here's our three tools that we have to treat it." Absolutely. It is so much a web, and this is one of the reasons I love this field and I am kind of passionate about working with women in this transition time because it is exactly the web. There is so much going on with a woman and a man, even (and we don't have time to talk about men's hormones), with the aging process, with the changes in hormones, with the changes in life responsibilities. For many of my patients, their teenagers are going off to college and their parents are going into nursing homes all at the same time. They are having more stresses with their own work environment. They are being subjected, possibly, to ageism in their corporate structures. They are possibly reevaluating the whole purpose of their life. In fact, mid-life has developmental issues just like every stage of development from birth through death. One of the developmental issues at mid-life is, "What's my purpose?" And very often people find, you know, "this work I'm doing isn't what I wanted to be doing. This isn't what I want my legacy to be." And so they are having a lot of emotional angst and self-exploration and there is a tremendous amount of anxiety, and depression, and worry, and doubt along with all of these hormonal changes and family situations. It is the perfect, ripe opportunity for working with the web and thinking about how one aspect of this person's life experience is affecting something else.

JB: With that as a context, let's now go down a level into the reality of what this might mean. You talked about what I call the three "big Bs:" bone, brain, and breast. And we could tie that also to cardiovascular, so we maybe have the "big four." Do you need to assess using diagnostic profiling or some kind of clinical/biochemical testing before you get involved with this, or can you use symptoms as your guide?

The Complexity of Hormone Testing

JM: I would say it depends. I think certainly the whole issue of hormone testing we could spend hours discussing. Women who are over about 45, I honestly don't think we need to even bother checking something like progesterone because it is going to be very low and we might as well not waste their money because you just don't ovulate, you don't make progesterone, and there is no point in checking for that.

Checking various estrogen levels might be something useful to do, but honestly I think a woman is her own best bioassay, probably, for estrogen levels. Is there vaginal dryness? Are there vasomotor symptoms? Those are the biggies that tell us that there is estrogen deficiency. It doesn't really matter if her estrogen level is "x" in her blood, or saliva, or urine. If she's got these symptoms, we are probably going to do some things to help improve her estrogenation. Now some of that can be done with diet and with exercise and so forth, but perhaps a little local vaginal estrogen, if that's the biggest problem. If libido is an issue, I will probably, personally, never give anybody testosterone without knowing that their level is deficient, because that has a lot more intricacies in treatment than some of the other hormones do.

I think what you might test is worth thinking about, and, you know, not just looking at hormones, but also cholesterol and blood sugar. Does she have metabolic syndrome? What's your thyroid doing? How's her adrenal gland? All of these things are very important in terms of finding balance, and it isn't all just about estrogen and progesterone. I think, again, you sort of take it individually. What is the scope of symptoms here? Can we maybe even try some things empirically? A little bit of bioidentical estrogen, a little bit of bioidentical progesterone…get the sleep better, get the vasomotor symptoms better, then sort of see

where we are. Now, is she ready to work on some of her emotional issues? Now is she ready to exercise more? She's sleeping better, she's got more energy, can she think about changing some of her eating patterns? Again, you really have to take it from an individual perspective.

The Importance of Re-checking Levels

Now, having said that, I will say that one of the things that got me intrigued about looking at how I did hormone treatment differently a number of years ago was that it occurred to me that we've got people on estrogen replacement therapy, and then we never check them. We never think that it is important to know what is going on biochemically with them. We don't even give people refills of thyroid medication without checking their TSH at least every year; that's mainstream medicine. Yet we give women Premarin for years on end without ever asking, "What's their estrogen level?" So I started (again, about 15 years ago) checking people's total estrogen level on regular doses of Premarin, and for some people these levels would come back 3-,4-,5-times higher than any physiologic needed to treat symptoms. And I got to thinking that maybe it is those kinds of patients in whom we are overstimulating breast receptors, and maybe those are the patients who are likely to have problems with breast cancer, and uterine bleeding, and so forth. Even though the state of the science of testing for hormone replacement doses is still very much in its infancy, it just got me thinking that it is probably not totally responsible to give people a drug and never check to see if it's the right dose. Even though I would (maybe), personally, start somebody on something empirically, I might want to check down the road, periodically, to make sure they are still in a safe physiologic range on the replacement doses or the treatment doses.

JB: So now a number of questions derive from that that are very important. When you are testing, do you test plasma, or do you test urine, or a combination? What is the timing of your testing? When do you draw samples?

Evaluating Different Delivery Systems

JM: Exactly. I used to think I knew how to do this a number of years ago, and of course, every year it gets more and more difficult. The more you know, the less you know. It turns out that probably what kind of testing one does depends on many factors. What's the delivery system?

If a person, for example, is using a transdermal estradiol or progesterone, the way we do the serum test is to draw blood and spin off the red cells and measure it in the serum. Well, when you put, particularly, estrogen and progesterone on transdermally, the hormone is picked up by the capillaries in the subcutaneous tissues and carried around to the various receptor sites throughout the body, and the red cell membrane holds these hormones and releases them at the tissue level, so we get good tissue responses. But when we measure serum levels, we have thrown away the red cells and there's not much left in the serum. So then we think, "Oh my gosh, these levels are so miniscule. These hormones aren't doing anything." So for transdermal delivery systems, we may need to think about saliva or urine or capillary blood testing rather than serum testing.

If we are doing something that is a transmucosal delivery system like a lozenge or a sublingual drop, which some of the compounding pharmacies are very good at making, then testing saliva is kind of difficult because those hormones are now concentrated in the salivary glands, so saliva levels will be very inordinately high. Like I said, I used to think, "Oh yeah, well, we'll just check your levels, you know, halfway between doses. If you're taking a dose once a day, we'll do it at 12 hours. If you are taking a dose of something twice a day, we'll do it at 6 hours." And that stood me in very good stead until I started

realizing from the work of Frank Stanczyk, for example, at the University of Southern California, a reproductive endocrinologist. Basic science has discovered this issue with progesterone transdermally being attached to red cells and then serum levels are pretty useless.

I think this is a whole arena that just cries out for more data, more research, more study, and more standardization of the testing modalities as well because they're not as standardized as maybe a blood sugar or a potassium level might be. This isn't unique, either. In fact, I think it was a recent Functional Medicine Update that talked about how even cholesterol levels vary from lab to lab and from day to day. One cholesterol level may not tell the whole story about someone's cholesterol. So this whole idea of testing I think is very important, but it is not the be all and end all. The whole chapter has not been written on what's the right way to test, how to test, who to test, when to test. This is still very anecdotal. You talk to 10 different clinicians and you'll get 10 different models of how they are doing testing because there is really no textbook on this yet.

JB: So that leads me, then, to the question of once you have made your clinical judgment and you're going to use a bioidentical estrogen, do you use 17-beta estradiol, transdermally? Do you use a mixture of estrone and estradiol, now knowing that we've got some questions about estriol? (Probably you're not using that.) Give us some thought about where you go from there.

JM: Yes, that's a very good question. Again, the more data we get, the more complicated this seems to become. When I sit with a new patient and we talk about options, I tell her my preference would be to use a bioidentical estrogen because it sits on your receptors properly. There are three bioidentical estrogens, we know: estriol, estradiol, estrone. Estradiol is probably the most potent. It is the one that has the most studies. When you look at all the research, there is some from Europe and Japan about estriol. Estradiol has probably had more data.

It turns out that now we are finding that giving estrogen of any kind-bioidentical or otherwise-orally versus transdermally makes a big difference in vascular inflammatory markers, thrombotic tendencies, blood vessel reactivity. Probably from 5 to 8 years now of good research, it looks like transdermal delivery of estrogen is probably, in the whole, much safer, and that we get a better inflammatory and thrombosis profile when we use patches, or creams, or gels through the skin, or some non-oral estrogen preparation, so the estrogen itself doesn't go through the liver and then stimulate the liver to make all these various proteins that may not have the best outcome for us. Again, that's another whole layer. What's the right delivery system? What's the right molecule? I think the issue about estrogen is that we haven't been comparing apples to apples. We've got oral estrogens (equine estrogens). There are oral estradiols. But we only really have transdermal 17-beta estradiol. There are not too many other available (commercially or compounded) estrogens that are not at least partly estradiol. So we're not comparing transdermal conjugated equine estrogen to transdermal estradiol. That's kind of a just a scientific flaw.

However, there is a huge amount of information about the difference between progesterone and all of the synthetic progestins that just don't have the biochemical and physiologic benefits that real progesterone has, and that's whether it is given orally, transdermally, transmucosally, or any other way. Progesterone is just so far superior in everything that is in the research to the synthetic progestins that I almost don't why we even use medroxyprogesterone acetate or any of the other synthetic progestins at this point in our medical knowledge.

JB: Let me just give a parenthetical and see if this washes with you. I think we use medroxyprogesterone acetate because in the way that the bioassay was set up to evaluate progestin activity, it was set-up with a rat uterine assay that was very, very sensitive to the chemical nature of those progestins. So if you start to develop a bioassay that selects for certain activities, which may have to do with pregnancy, then it starts to make that molecule look like it is preferential to others because you forgot about all the other activities that the other molecules might have had if you ran different bioassays.

Large-Scale French Studies Yielding Important Data

JM: Exactly. And we do know that all the synthetic progestins and real progesterone do protect the uterus in a very similar way and they are all safe and effective for that in that regard. However, the synthetic progestins are not safe in pregnancy, whereas real progesterone, of course, we use it to preserve pregnancy in women who have recurrent early miscarriages. But you are right. The science is coming out now about all of the other things progesterone does in the body in terms of some very powerful data about breast cancer and looking at different hormone combinations. Even the Women's Health Initiative was halted in the arm that had conjugated equine estrogens and medroxyprogesterone acetate, but not in the arm with the estrogen alone.

There was a very large study out of France in 2005 (Fournier's group) that looked at over 90,000 women on a variety of estrogen and progestin/progesterone combinations and the relative risk of breast cancer after five years.11 In the women on any estrogen plus a synthetic progestin, there was about 1.4 relative risk to women on nothing. The relative risk for women on any estrogen preparation and actual progesterone was 0.9. So they did not conclude that there was a protective benefit for progesterone in breast cancer, but it certainly did not increase the risk. That, to me, is a piece of information that I think is incredibly powerful and that was an incredibly huge study; I don't think anyone can argue with the power of it.

Other things are coming out that are so fascinating about progesterone regarding the nervous system. It turns out glial cells in the brain make progesterone, and that progesterone is a pro-myelinating hormone that is necessary for the nervous system to function well. Again, this is information out of France. There was a huge paper from 2007 from a group at the University of Paris looking at all of the neuroendocrine effects of progesterone and why it probably is a preferential part of hormone therapy in lieu of synthetic progestins in terms of helping keep GABA receptors healthy and prevent brain degenerative diseases related to aging and so forth.12 Again, this information is in its infancy, but it is just fascinating. I think you are right that when you look at that one uterine animal model assay, yes, the synthetic progestins are great. But when you look at all these other effects-and we haven't even talked about cardiovascular yet-progesterone is just head and shoulders above anything synthetic that we know of yet.

JB: Yes, and I think you hit on something (again, there's just so many topics that you have hit on that could be deep drilled for hours): this whole neuroactive sterol area which seems to be emerging and then how that relates to statins and whether there is some (in certain sensitive individuals) adverse effect of statins on reducing the precursors to these neuroactive sterols and what effect that could have on affect in mood, brain, and so forth…

JM: Absolutely, yes, and memory.

JB: You are hitting on such fascinating areas. You know, when we go back to Robert Wood Wilson and Feminine Forever and read that book today (which is disgusting, I might add, but if we can force

ourselves through it…), what we recognize is so much of what seemed to be (in the way it was presented) factual information was really spun so seriously, and it affected generations, really almost three decades of thinking about this whole topic.

JM: Yes.

JB: Let me, if I can, talk about one other ADR (adverse drug reaction), which I know has come up because you alluded to it: thrombotic risks pertaining to hormone therapy. It seems like one of the ways that the Women's Health Initiative has now been stratified and analyzed is to look at women who have certain single nucleotide polymorphisms that make them more susceptible to the coagulation problems associated with hormones. Can you tell us a little bit about how your thoughts relate to those women who may be unique in their SNPs pertaining to these coagulation parameters?

Contraindications for Estrogen
JM: Yes, absolutely. Certainly, whenever we would contemplate using an intervention with anybody, including bioidentical hormones, we have to think about contraindications. So with a person who has a history of antiphospholipid antibodies, antithrombin III, or Factor V Leiden genetic predispositions, we know that adding estrogen of any kind to that mix could precipitate problems with thrombosis. Those are the kinds of patients we'd want to be particularly careful with whether we even went down that road of hormones with them or not. So you are right, and I think this whole idea of pharmacogenomics and finding out an individual person's risk for developing a problem with a drug is going to help us a great deal in knowing what is safe and what might not be safe for a person.

As kind of a little aside, there is a great deal of information coming out, and even stratifying, as you said, the Women's Health Initiative, about the age at which hormones are started probably making a big difference in cardiovascular risk. This doesn't relate to the women with higher thrombotic genetic risks, but the blood vessels actually change as we age. In the Women's Health Initiative, where we all know the average age was 62, these women had a little bit more risk of thrombolic stroke and cardiovascular events. But the younger women, when those early 50-year-old women in the Women's Health Initiative were pulled out, did not have this increased risk. It looks as if early intervention, if we are going to do it for cardiovascular protection, is quite important. I think the results of the ELITE trial coming out of USC that is in process now looking at early versus late administration of estrogen and the KEEP Study (estrogen and progesterone intervention trial) that is being looked at in a multicenter trial, when those come out in a 2010, I think we'll have some very good information about this whole timing issue of when to start hormones if we are going to do it.

JB: Obviously we could carry this conversation on for hours…

JM: Days!

JB: You have all of that information just sitting in reserve-you could do that-but unfortunately we are going to have to draw this to a close. Maybe you could just give us your thoughts as you look forward to the future as to where you see the future of managing postmenopausal health may take us.

JM: I'm hoping more and more clinicians will be willing to have a longer conversation with patients because that is what women want. They want to know: what are their options, what are their choices,

what can they be doing? I'm hoping the future of menopause health management will really include a lot of self-care that women are doing themselves (lifestyle, in particular). I would hope that we would continue to have good, high-quality research with all of the questions that are still left very much unanswered after the Women's Health Initiative. That was not the definitive women's health hormone study by any means, and just in our conversation today we have brought up dozens of questions we still have that we need answers for. I also think we haven't looked enough at the role of the adrenal and thyroid parts of the endocrine system and how they affect a woman's experience of this mid-life transition, and that I hope we can flesh out and develop much more clearly. And then I sort of briefly mentioned the whole life cycle and developmental issues that happen at this stage. We don't have a lot of information and ways to really help women through all of this. I hope that the mind-body aspects that are so critical at this time can also become a really standard part of our armamentarium with women in mid-life and beyond.

JM: Dr. Murray, I can't tell you how much we appreciate this. If this is not titillating everybody's neurons then we've got a little problem with neuronal deficiency because this was really a tremendously interesting and evocative presentation. I want to again recommend that people check into the website, www.womeninbalance.org. I think it is a tremendous resource. And this new state of the art science review paper that you are going to be publishing I think will put another step in the road forward. Thank you for all of your hard work and being the clinician you are and being willing to share with us.

JM: Jeff, it's my honor. Thank you so much.

In the course of this issue of Functional Medicine Update, I hope your takeaway might be that there are things we can tell women responsibly now as they go through their menopausal period about the risk/benefit trade-offs of various kinds of intervention trials, but that starting with lifestyle and diet intervention, and getting them on a therapeutic lifestyle change program, is-without question-the first and most important way of starting down this road before we start adding exogenous things in. Then, on top of that, let's know something about that individual woman. Let's make sure we are just not treating her as the average; treat her as the i

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ndividual. Look at her metabolism. Look at her genetics. Look at her history. And make prudent choices based upon the information that you have heard beautifully shared with you today

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