February 2007 Issue | Bethany Hays, MD, FACOG True North Health Center

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Welcome to *Functional Medicine Update* for February 2007. We have changed our format for 2007. The first section you will hear is Hot Breaking News, then we'll move into our main topic. In this issue, we will be focusing on bioidentical hormone replacement therapy. We are very fortunate to have an expert in this area as our Clinician of the Month: Dr. Bethany Hays. Dr. Hays will be sharing her thoughts with us, based on her 30 years of experience in the field of obstetrics and gynecology. The last section of the issue will feature questions and answers that come from subscribers like you. Let's start right in to Hot Breaking News.

There are two topics that I think have some interest right now that I would like to talk about; the first is related to calcium and prostate cancer. A number of papers have been published recently on this subject, in which an inverse relationship between the two (increasing calcium, decreasing prostate cancer incidence) is discussed.

Calcium Intake and Prostate Cancer

One such paper is a prospective study of calcium intake and the incidence in fatal prostate cancer that appeared in *Cancer Epidemiology, Biomarkers and Prevention.* [1] In this study, the authors found that calcium intake exceeding 1500 milligrams a day in men was associated with higher risk of advanced and fatal prostate cancer. I think this is very interesting. In the past, we have said that higher calcium was associated with a lowered incidence of prostate cancer. The results of this study showed that men with the highest intake of dairy products and calcium were more likely to develop prostate cancer than men with the lowest intake, although the relative risk appeared to be fairly small (the difference in relative risk).

Why is this? I think that the mechanism that is emerging is that when you get very high calcium, you start depressing the production of parathyroid hormone. When you alter the calcium phosphate ratios in tissues, you get an altered effect on vitamin D metabolism. What happens is you start lowering the amount of vitamin D converted to 25-hydroxy and then ultimately 1,25 dihydroxycholecalciferol.

There is a need to better understand the inverse relationship between vitamin D and prostate cancer that has emerged over the last couple of years. Men who have low levels of serum 25-hydroxyvitamin D3-when I say low levels, I mean below 50 nanomols per liter (nM/L)-are men who have increasing relative risk (apparently) to prostate cancer. You can drive down the conversion of cholecalciferol vitamin D into the hormonal form through the intake of very high levels of calcium. There is most likely a zone of effective calcium intake that is probably somewhere between 800 and 1200 milligrams a day in males.

When you get above 1500 milligrams, it appears (at least from an epidemiological perspective) as if you are on the downside of a bell-shaped curve.

In order to fully answer this question, we'd like to see data related to increased calcium intake or different incremental calcium intake in males and the level of 25-hydroxy and 1,25 dihydroxy D3. That information would better allow us to make this association at a mechanistic level. From the present state of our associative knowledge through epidemiological evaluation, it appears that a high level of calcium intake in males is associated with potentially lowered active hormonal form of vitamins D and has a higher tracking with regard to prostate cancer incidence.

I think we need to keep our eyes on this because we know there is a very important correlation between vitamin D conversion to its 1,25-dihydroxycholecalciferol form and lowered incidence of prostate cancer. For clinicians, I think we want to emphasize the importance of doing serum analysis of 25-hydroxyvitamin D3. The data suggests that we would like this level to be in the range of about 80 nanomols per liter; anything below 50 we would consider to be in the suspect area (even though the normal laboratory range often goes to 20 or below, which most of us-in terms of functional vitamin D physiology-would consider too low to promote proper function).

Lactoferrin and Gastrointestinal Physiological Function

Let's move to another interesting Hot Breaking News item: an example of an orally consumed bioactive that influences gastrointestinal physiological function. I think we are learning more and more about certain agents that can be administered orally that have functional properties in the GI tract to help normalize gastrointestinal immunological or mucosal function. The specific agent I am referring to here is derived from milk (particularly bovine milk) and is found at high levels in colostrum: Lactoferrin.

You may be familiar with lactoferrin as an iron-containing protein that is found in small levels in the immune fraction of milk. It is a very important agent in milk for inducing proper immune defense in offspring, and it also has an extraordinary ability to help stabilize immunological function in older-age animals, including humans. Recently, a study was published looking at *Helicobacter pylori* eradication.[2] This study was an open, randomized, multi-center trial using bovine-derived lactoferrin administered to humans. This was lactoferrin taken with triple therapy.

I think this is an interesting example of augmentive medicine, or functional medicine. Lactoferrin was once thought to mainly act as a transport of iron to the blood, but now we recognize that it really has a very powerful effect on immunological function of the gastrointestinal tract and interacts with the MALT (the mucosal-associated lymphoid tissue). As such, in the upper GI, it helps to reduce the potential of opportunistic infection with helicobacter pylori, which of course is a very important agent in the etiology of gastritis, gastroduodenal ulcer, and gastric cancer.

I think this is a specific example of a more general theme, and that theme is that there are bioactive agents in various foods that have immunological reactivity within the gastrointestinal immune system. This is part of the list of potential therapeutic agents we have available in administration of the 4R Program (the gastrointestinal restoration program). The first "R" is Remove-removing allergens and toxic agents. The subsequent three "R's" are Replace (that would be stomach acid and pancreatic enzymes, where necessary), Reinoculate (the use of probiotics and prebiotics), and Repair. We might consider lactoferrin to be part of the Repair category because this involves using nutrients such as arginine, L-glutamine,

pantothenic acid, vitamin E, and zinc to help repair gastrointestinal immune integrity. That's the Hot Breaking News for this month, so let's move into the discussion of focus for this issue, which is bioidentical hormones, or functional endocrinology.

I was very taken by a book that won the *New York Times* Science Book of the Year Award two years ago titled, *Merchants of Immortality*, authored by Steven S. Hall. [3] This is a very well-researched book. It speaks to the development of our understanding of cell aging and how it has been appropriated into the biotech community, specifically in the areas of investment and technology. It may be that this topic has been misappropriated (or prematurely appropriated) into the general sales of overexaggerated (probably) longevity or anti-aging. This book was a 2003 book published by Houghton Mifflin.

On the subject of human life extension, there are real and exciting things happening at the molecular biology level, the cell biology level, and even at the animal biology level. We'll talk more about those things throughout the course of 2007. There is also, however, the opportunity for exploitation and exaggeration. People sometimes pay money for things that really don't deliver or may even lead to adverse outcomes. That takes us to another popular book-a 2006 publication titled *Ageless: The Naked Truth about Bioidentical Hormones.*[4]

A Recent Controversy over Bioidentical Hormones

A science-based book like *Merchants of Immortality* is highly documented from first-tier publications. A book like *Ageless* is based on anecdotal testimony and personal experience, and somehow what may be an N of one can get extrapolated to the population at large. I think we need to be somewhat concerned about this *Ageless* concept, which basically promotes the idea that we can administer hormones in a very safe fashion as long as they are bioidentical to those naturally produced by the body; that only synthetic hormones produce adverse side effects or outcomes. I think this idea could lead people down problematic roads and I want to discuss that.

There are safe and effective ways for utilizing hormone replacement therapy. But to assume that these substances that have very high activities at very low doses (on cellular proliferation, cellular turnover, and gene expression) can be used with no worry about overdose is truly an exaggeration of fact. The ideas promoted in this book have led to a backlash. A number of press releases and media services have covered the controversy over bioidenticals, and almost all the periodicals have advocated for intervention by the Food and Drug Administration (FDA). The College of Obstetrics and Gynecology has become so alarmed that they have now mounted publicity campaigns to warn patients about the risk of excessive hormone exposure.

We are into a very dynamic period of reevaluation of what is safe and effective as it pertains to hormone replacement therapy in the perimenopausal or postmenopausal woman, or in the climacteric male. I'm not speaking to situations where there is growth hormone deficiency in children, or there is a very significant hormone deficiency in adults (which can lead to a number of endocrinopathies). I am speaking now to the natural transition in hormones that occurs as a consequence of "normal" aging, what level of replacement would be required (if any), and if needed, what would be used? This is the topic that we are going to be discussing in this issue of *Functional Medicine Update*.

To put this into context (as it relates to the risk/benefit/safety profile), I want to cite a recent paper that appeared in the *Journal of the National Cancer Institute* in 2006 titled, "Endogenous Steroid Hormone

Concentrations and the Risk of Breast Cancer Among Premenopausal Women." [5] The question the authors are asking is, does estrogen produced by women naturally (and all the other hormones that come with it) have anything to do with relative risk to breast cancer? We're not talking about exogenously administered hormones; we are talking about endogenous hormones-I want to emphasize that. If a bioidentical estrogen was completely safe, would we say it didn't matter whether a woman had high estrogens or low estrogens-that, in fact, she would be at the same low risk if it is bioidentical?

I think most of you know the conclusions of this study are quite clear. The levels of circulating estrogens and androgens found in women may be important in the etiology of premenopausal breast cancer. Those women who had the higher levels of estrogens are the women who had a relative risk that was about two-fold higher than those women who had the more normal levels of estrogen (again, these are endogenous estrogens).

Higher levels of total and free testosterone and androstenedione (these are the androgens in the menstrual cycle) were associated with modest, non-statistically significant increases in overall risk to breast cancer, whereas the increases in estrone/estrone sulfate were not seen to increase risk. But if we look at estradiol, we had a much higher risk to breast cancer. So estrogen as estradiol, which is very mitogenic (it is a substance that causes cellular proliferation), does associate itself (as an endogenous hormone) with increasing relative risk. I don't think we can say this about hormones at large, but when we start looking at individual contributors such as estradiol, we certainly see that high levels are associated with increased risk. I think the concept that bioidentical hormones are safe and synthetic hormones are dangerous is specious and not correct. It's about balance. It's about metabolism. And it's about cellular activity. These are the things that really relate to the question of safety versus risk.

If we look at ovarian cancer risk (this is the recent association of a diet and its relationship to hormone metabolism and cancer risk), I think it is a very interesting evolving story. It seems that one of the major determinants for how hormones interact with the body and ultimately mitigate relative risk is through diet and lifestyle. Although we can't directly control our hormones as they get secreted from glands, we can control the fate of those hormones as it relates to their metabolism, their excretion, their cellular effects, and their transport through dietary and lifestyle variables. This information is taken from an article in the *Journal of the National Cancer Institute*, which talks about the fact that long durations of unopposed estrogens (and of estrogen plus progestin) are associated with increased ovarian cancer risk. [6] However, these particular types of relative risk may be modulated or modified by dietary intervention, for example, by going more to a vegan diet with a higher density of phytochemical-rich foods-whole grains, fruits, and vegetables.

Many studies have been published on this subject, with some suggesting that vegetarian women have faster turnover of hormones, lower estrogen levels, and lowered incidence of hormone-related cancers. I think we need to put the diet component in perspective as a very important variable. We also need to look at not only at estrogen, but also the balance with androgens and progesterone. There are progesterone receptor sites on virtually every tissue, and certainly on breast cells. Progesterone can be proliferative, even in the bioidentical form. There is an interesting recent paper that just appeared on a cancer link of genes regulating estrogen effect on breast cells, showing an inter-relationship. [7] I think we need to be cautious about the use of progesterone (which is often used to balance estrogen) because excessive progesterone signaling can also induce cell proliferation. I'm talking about bioidentical progesterone,

here, not progestins (the synthetic variants thereof).

What roles do various nutrients found in the diet play in either reducing the relative risk to hormone-related cancers or to increasing the risk? An interesting paradoxical observation has been made recently that has to do with folic acid. We know that folic acid, vitamin B12, vitamin B6, and betaine are all very important for support of the folate cycle. The folate cycle is the cycle that generates active methyl groups through S-adenosylmethionine. S-adenosylmethionine then serves as the donor of methyl transfer reactions that are useful through the enzyme catechol-O-methyltransferase (or COMT) to partially metabolize estrogens to form the methoxylated estrogens. This would be like the conversion of 2-hydroxyestrone or 2-hydroxyestradiol into 2-methoxy compounds. These methoxylated estrogens are antiproliferative and they may be seen as (kind of) estrogen's break.

Think of estradiol as a cellular accelerator (meaning it increases the turnover of cells, the replication of cells, and their division). In physiology, for every accelerator you always have a repressor or a break (that's the yin and yang upon which physiology is built). One of the breaks of estrogen's induction of cellular replication is the methoxylated estrogen, 2-methoxyestradiol. So the balance between estradiol and 2-methoxyestradiol is very important in regulating aspects of cellular turnover and cell cycling. First is the hydroxylation of estrogen to form the 2-hydroxy compound by cytochrome P450 1A2, then the hydroxyestrogen gets methylated by S-adenosylmethionine. You would assume, then, that it is desirable for a woman to have proper folate, B12, B6, and betaine nutritional support for proper methylation of her estrogens, and that has been proven correct in a number of studies. But the question is what happens if you give very high levels of folate? Does that have any effect that is continuously beneficial, or is there a bell-shaped curve? This is where the controversy starts to exist.

Data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

I'm now quoting from a review article that appeared in *NutritionReviews* in 2006. The title of this article is, "Does a High Folate Intake Increase the Risk of Breast Cancer?" [8] Although not uniformly consistent, there is an epidemiological series of studies that generally suggests an inverse association between dietary intake and blood measurements of folate and breast cancer risk. However, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial has recently reported for the first time a potential harmful effect of too high a folate intake on breast cancer risk. We've generally said that the higher the folate, the lower the incidence of colorectal, ovarian, prostate, and lung cancer. But now this new study says that with too high a level there was a statistical association with an increased risk.

In this study, the risk of developing breast cancer was significantly increased by 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} in women who reported supplemental folic acid intake compared with those that reported just normal dietary intake of folate. Although food folate intake was not significantly related to breast cancer, total folate intake (mainly from folic acid supplements) significantly was associated with increased breast cancer incidence by 32{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}. So then the question is, why? Is there any reasonable rationalization for this? There is no real compelling supportive evidence at this point as to how (mechanistically) these associations tie together; however, we have to take this with some degree of sobriety because the data was published and was of concern.

Folate Appears to Possess Dual Modulatory Effects on Carcinogenesis

I think this story of folate, methylation, the pleotrophic effects of folate, whether there is a difference

between folic acid from a supplement versus food folates (polyglutamyl folates), and whether 5-methyltetrahydrafolic acid has a different effect than folic acid are all questions that remain to be better understood. Certainly I think we recognize that folate appears to possess dual modulatory effects on carcinogenesis. We know that folate deficiency has an inhibitory effect on carcinogenesis, whereas high folate has a promoting effect on the progression of established neoplasms. Folate deficiency in certain normal tissues appears to predispose them to neoplastic transformation and modest supplemental levels suppress, whereas supraphysiological doses of supplementation may enhance the development of tumors.

As an essential cofactor for the de novo biosynthesis of purines and thymidylate, folate plays an important role in DNA synthesis. Folate may also modulate DNA methylation, which is an important epigenetic determinant in gene expression, in the maintenance of DNA integrity, in chromosomal modifications related to gene expression, and also in protection against mutational injury. So proper folate intake is very important for supporting proper methylation and these epigenetic effects that folate has, as well as its effects on DNA repair mechanisms.

What happens when you give supraphysiological doses of folate? How does it promote rapidly replicating preneoplastic cells to increase their cellular turnover and cell cycling? The mechanism that is emerging-it's still in the early stages-is that associated tumor promoting effect may be due to the enhanced de novo methylation of CpG islands of the tumor suppressor genes with consequent gene inactivation, which could result, then, in tumor progression. I want to, again, put this in the context that this is early stage news, but I think it is well worth looking at because we know most every substance has a dose-response, parabolic-type of curve. Too low a level is not good, too high a level is not good, and somewhere in the middle is where we should be and that's certainly true for all nutrients.

As we look at this folate connection, it may not be that if a little is good then a whole lot more is better; it may be finding the right folate level to support proper methylation of hormones and proper conversion of homocysteine to S-adenosylhomocysteine and then ultimately onto SAM (S-adenosylmethionine and the methylated derivatives). How do you clinically evaluate this? One method that is used as a surrogate marker is homocysteine. If you have a patient with elevated homocysteine (I believe that is above, say, 8 or 9 micromol/L), that may be a patient who is then going to benefit from folate B6, B12, and betaine supplementation. You want that homocysteine to be in the range of 4 to 7, or 4 to 8, and you can use that as a surrogate marker for folate B12, B6, and betaine.

Let's move from this discussion over to looking at a review of the safety and efficacy of bioidentical hormones for the management of menopause and related health risk. There is a review that was published in *Alternative Medicine Reviews* in 2006 authored by Deborah Moskowitz on this topic. [9] When we talk about bioidentical hormones, we are talking about 17-beta estradiol, estrone, estriol. We are talking about progesterone as contrasted with progestins. And we are talking about testosterone. These would be considered your bioidentical hormone replacement substances.

Bioidentical versus Synthetic Hormones

When we start examining the relative risk/benefit, certainly I think we have to look at things like route of administration, dose, and formulation. I believe the overwhelming evidence is that for safe and effective use, bioidentical hormones are preferred over synthetic hormones, especially if an individual will use replacement for many years, as is often the case-going through perimenopause into menopause. This does not necessarily connote that all women have to be on hormone replacement therapy, but we are talking

about the relative risk/benefit based on literature. It appears we have much better evidence that bioidentical hormones, in the right range of concentration and administered correctly, have a higher safety profile.

Transdermal versus Oral Hormone Administration

In terms of administration, there is some interesting new information. I'm now quoting from a recent paper in the journal *Maturitis* in which the authors looked at hormone replacement therapy (estrogen and progesterone), contrasting transdermal versus oral hormone therapy. [10] In this particular study, the findings were that transdermal (or even the intravaginal administration) had a much more beneficial effect-a safer effect-than the oral administration route.

This also seems to be the case in a recent paper that appeared in *Arteriosclerosis, Thrombosis, and Vascular Biology* that contrasted the effect of oral versus transdermal estrogen on serum amyloid A and high density lipoprotein serum amyloid A in postmenopausal women. [11] These are proteins (SAA) that are associated with inflammation and also with cognitive dysfunctional neuroinflammation. So the question is, is there any difference between the route of administration of estrogens and the effect they have on SAA (serum amyloid A protein)? Oral estrogen was found to increase serum amyloid A and alter HDL composition to contain a higher level of SAA protein, whereas the transdermal administration did not have this same effect. These findings appear to argue for the use of a transdermal estrogen that would avoid first-pass conversion in the liver and would have a more favorable effect on cardiovascular outcomes.

There is a wide body of literature on the benefit of transdermal over oral administration. I don't think I need to take you through all of the data, but certainly we see-as it relates to metabolism-the more favorable effect on inflammation. You see a lot of studies showing elevated CRPs after oral administration and you don't see that with transdermal administration. We see changes in fibrinolytic activity with oral that we don't see with transdermal. We see changes in lipoproteins (adverse changes in lipoproteins) with oral that we don't see with transdermal. So it seems to really argue fairly strongly for the transdermal route of administration. Assuming that a woman can absorb transdermally, there are different vehicles to help transport. There is also intervaginal transmucosal transport, and Dr. Hays will talk a little bit about that in this particular issue.

Personalized Hormone Replacement Formulations

Now we'll talk about formulations, and of course that gets into compounding pharmacies and compounding the right formulation of bioidentical hormones. There is some discussion of this in the journal *Integrative Medicine* in 2006. [12] This is a place where the practitioner can work very closely with the compounding pharmacist to produce a specific formulation that would personalize the bioidentical hormone replacement therapy for each woman. I think it is important to recognize that personalization is probably what should be done and not every woman absolutely requires hormone replacement therapy to lead a healthy life. For those women who do get hormone replacement therapy, tailoring it to their own specific needs is critically important. Dr. Hays will talk about this in greater detail as part of our clinician of the month discussion. In fact, she has authored an interesting paper that gives an overview to this whole field titled, "Giving Menopause It's Proper Place." [13] This was published in *Integrative Medicine* in 2006. Her article goes through the whole concept of menopause, knowing about estrogen and where it is going and how it reacts with a woman's body, and then finding the right balance. She will speak to this in

greater detail in our interview with her.

It is not just administration of the hormone substances in and of themselves that is important, it is also how those substances interact with receptors and how these receptors then signal cellular activity. Many estrogen-related receptors are now being seen as targets in cancer and other metabolic disorders, so estrogen has a crosstalk with many other cellular functions, including (as I already mentioned) inflammatory functions, insulin signaling functions, and relationships to detoxification. Many cellular functions have (in the web of interaction) a relationship to estrogen and its reactivity.

There is a review paper about estrogen-related receptors and their relationship to cellular function that appeared in *Current Topics in MedicinalChemistry* in 2006. [14] I think the very important takeaway is that estrogen-receptor-targeted therapeutics are now showing success in not only the treatment of breast cancer, but orphaned estrogen related receptors have also become novel targets for future development because these are receptors that are different than the traditional estrogen receptor alpha and estrogen receptor beta.

ERα is the receptor that is traditionally activated be 17β-estradiol. It is involved with cellular cycling and cellular proliferation. It is the receptor that is most often upregulated in oncogenesis. The estrogen receptor β is more associated with bone metabolism and this appears to be the differentiation of the SERMs, tamoxifen and raloxifen, and estrogens. The SERMs apparently have more effects on ERβ, although these effects are mixed slightly as it relates to modulatory effect (their selective estrogen response modulators).

We now recognize that there are effects that compounds have beyond that of just the traditional estrogen receptor alpha and beta, which are called the estrogen-related receptors, or ERRs. This is a very interesting family of receptors whose agonist or antagonist can crosstalk with the estrogen receptors, and so you might have amelioration of estrogen-related symptoms without ever directly affecting the estrogen receptor with that ligand. We now know this crosstalk takes place across such processes as cellular detoxification, and that ties together the estrogen activity with things like nuclear regulatory factor 2, or NRF2, which is a ligand-dependant interaction with estrogen that then helps to regulate detoxification functions. This could be occurring both as a consequence of stimulation of estrogen receptors directly and of nuclear receptors that influence then the gene expression of the detoxifying enzymes.

What I am really trying to say is that if we look at how to modulate estrogen's effects on the body, part of it is modulating the actual level of estrogen in the body as measured by serology or a urine 24 analysis, and part of it is really regulating the responsiveness of estrogen by how it affects receptors and how it is metabolized and excreted. This takes us to the concept of how diet may influence estrogen, not just directly through modulation of estrogen receptor α and β, but also through these ERR pathways (through the estrogen-related receptor pathways).

There is an interesting paper published in the *Journal ofEndocrinology* in the latter part of 2006 titled "Selective Activation of Estrogen Receptor β Transcriptional Pathways by Herbal Extract." [15] In this paper, the authors show that some of the bioactive phytoestrogens in various plant foods don't work strictly through ERα or β, but work through these ERR pathways (the Estrogen-Related Receptors) that then modulate things like flushing and night sweats without having a direct cell proliferative effect.

Study on Use of a Phytoestrogenic Substance to Alleviate Menopausal Symptoms
Recently, a prospective randomized double-blind, placebo-controlled use of a standardized extract to alleviate menopausal discomfort was reported. This was using a substance derived from *Humulus lupulus* (hops). A fraction from the hops plant, the so-called hydrophilic fraction (the water-soluble fraction) from spent hops, was shown, when concentrated, to have a very interesting menopause symptom reducing outcome, without apparently having a direct serious effect on activation of the estrogen ERα mechanism. This study was published in *Maturitas* in 2006. [16] It is a very interesting report of this highly "phytoestrogenic" substance from hops. It is about 100 times more phytoestrogenic than that of genistein (about ten-fold less estrogenic than 17-β-estradiol), but it doesn't appear to have the cellular proliferative effects that estradiol does, so it make work through other mechanisms (through these ERR mechanisms or other crosstalk mechanisms), or even maybe a mixed effect through alpha and beta estrogen receptor agonist activities and these other response elements.

What I'm really trying to get you to understand is that the complex diet that contains a rich array of phytochemicals may be one of the best tools (clinically) for managing estrogen-related dysfunctions or hormone-related dysfunctions in perimenopausal and menopausal women. It may actually be a much safer approach or at least a first-step before we introduce bioidentical hormone therapy because of the complications in trying to measure hormones and stabilize activities when they are given exogenously. By modulating the diet, we may then induce proper cell signaling and allow the woman's natural estrogen, progesterone, or androgens to be properly regulated through hormone binding globulin, through cell receptive mechanisms, and ultimately through cell signaling.

I think this sets a context for what we want to speak to with Dr. Hays: How do you take all of this extraordinary information that is emerging around bioidentical hormones and apply it in a crucial area (30 million women will be going through menopause over the next 10 years). These women are questioning what to do (if anything), what is safe and effective, and what will give them better long-term health outcome. Those are the questions we will be addressing when we talk with our expert, Dr. Hays.

I want to contextualize that this conceptualization that hormone therapy will alleviate symptoms is built around the principle that we understand how those hormones are signaling, what cells are being influenced, and how safe and effective outcomes are differentiated. As we really dig deep into the literature, we find that we are still at a very early stage in our understanding of the complex web of interactions. The concept of "Doing less can do more" may be a good watchword. Maybe rather than jump in and try to do watch repair with a jackhammer, we ought to be treading very carefully, using the least aggressive therapy possible to modulate symptoms that are associated with menopause.

With that, let's turn to Dr. Hays and talk about her clinical expertise in this area.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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In this issue of Functional Medicine Update, we've been focusing on what I call functional endocrinology, or the relationship-specifically, in this case-to hormone replacement therapy (the bioidentical hormone story). We are very fortunate to have as our clinician of the month this month an expert in the field, Dr. Bethany Hays. Many of you know of Dr. Hays if you are in our field of functional medicine. She is a leader in the area of women's health issues, has been a teacher at the functional medicine Symposia and Applying Functional Medicine in Clinical Practice training programs, an author, and the founder and director of the True North clinic consortium (which has a functional medicine underpinning) in Maine. I've had the privilege of visiting her facility and meeting her colleagues. It is just a remarkable way to apply functional medicine in a clinical setting-using a comprehensive, multifactorial group of practitioners to address these very complex issues from a central theme.

Dr. Hays (for those of you not familiar with her background) went to Wellesley, where she graduated with a major in philosophy, which is probably why she is such a good medical doctor, because she started off with the right underpinning-a broad base of humanities understanding. From there she went on to Baylor College of Medicine and to her OB/GYN residency at the Baylor-affiliated hospitals, and she has been in practice for more than 20 years. She is the mother of three sons (all adults now) and is involved with their complex lives. So she is one of these superwomen who has many things going on and seems to do them very adroitly; we can only envy those skills.

Dr. Hays, it is wonderful to have you as a clinician on Functional MedicineUpdate, and to have a chance to talk about this controversial but very important area of hormone replacement therapy.

BH: Thanks, Jeff. I'm happy to be here.

Different Theories of Why Hormones Decline

JB: I want to start, if I could, with three questions (or comments/statements) that have been made in recent literature meant for the general public, which often then brings women to doctors to ask about hormone replacement or bioidentical hormone replacement therapy. I'd like to get your opinion of these three statements because they are made as statements of fact, but I think we both (probably) would question the factual veracity. Statement #1 is: We age because our hormones decline; our hormones don't decline because we age. I think I'll take each of these three separately. What's your thought about that statement of purported fact?

BH: Well, I'd like to see some evidence of either part of that statement. The first part is, "We age because our hormones decline." I'm not sure that is a true representation of what is going on. I suspect that our hormones decline in order to allow us to age well. In other words, I think the hormones of our younger years, particularly the premenopausal hormones of women, are toxic-level hormones that allow us to reproduce. Then when we don't need to be reproducing anymore, we're allowed to have normal levels of hormones so that we can age gracefully and not end up with the toxicities that those high levels of hormones produce.

The second part is, "Our hormones don't decline because we age." I think our hormones probably decline in part by intention (as I said, in order to age gracefully), and then there's the abnormal decline in our hormones that are due to toxins in the environment, poor metabolism of hormones, and hormone attack from autoimmune disease that attacks the glands.

JB: That segues nicely into the second statement that has been made as if it were a statement of fact, and that is: Bioidentical hormone replacement is the only answer to ward off illness, weight gain, and other symptoms of hormonal decline that occur during menopause.

BH: I think that's clearly not true because we all know some 93-year-old women who are sharp as tacks-driving their own cars, running their own households, not obese, not sitting in wheelchairs somewhere without their brains intact. So, clearly, it is possible to do that without hormone replacement therapy if you have the right environment in which to bathe your genes. That environment would include a clean, balanced diet, movement (stretching your muscles and moving your muscles so that they stay oxygenated and don't tighten up and affect joints), and a positive attitude. I think people stay alive a long time for two reasons. One is because they are very connected to their physiology. And the other is because they are very connected to their future. If you have a reason to be alive a week from now, a month from now, or ten years from now, you are much more likely to be alive then than if you can't see any reason to be alive.

JB: That's a wonderful statement and I think it bears on the last statement that has been thrown out into the universe as a statement of fact, which is questionable. That is, "Without hormone replacement, we will end up as mere shells of our former selves." This sounds a little bit like post-Robert Wilson, Feminine Forever, in the '60s.

BH: It does, doesn't it? It brings to mind this advertisement for hormone replacement from 15 years ago, with a woman looking out over parched land, and the title is, "The fate of the untreated menopause." I think where we need to be headed is healthy aging. We need to be looking at what we've done to our environment. We need to be looking at what we've done to our food supply. We need to be looking at what we've done to women to make them feel worthless once they go through menopause.

JB: That's magnificent. So let's move from that discussion/platform to another. What players are we really talking about when we talk about hormone replacement therapy? Of course, there's quite a large array of hormones, but the ones that are most commonly discussed when we talk about bioidentical hormone replacement therapy are things like the estrogens-estradiol, estrone, estriol, progesterone, testosterone. We might include dehydroepiandosterone, cortisol, thyroxin and triiodothyronine (for thyroid), insulin, and maybe even human growth hormone (in some subsets). When we start going down that laundry list, from your very rich experience (and now the work that you are doing at True North), how do these different hormone substances fit into the development of a comprehensive program for a woman who is having some complicated symptoms that grow out of her menopause transition?

Why Women Seek Hormone Therapy

BH: I think, first of all, women tend to come for hormone therapy because they are having symptoms, not because they are worried about the fate of the untreated menopause. The symptoms they are having, primarily, are problems with their brains. They are having problems with hot flashes; they are having trouble with insomnia; they are having trouble with cognition, memory, and sometimes depression.

The balance of hormones is critical to the function of the brain. When you note that one-third to half of women have had hysterectomy at a average age of...it used to be 35, now it's a little bit older than that, you know that a lot of women either are missing their ovaries (about half of those women), or have had damage to their ovarian blood supply by severing the utero-ovarian ligament at the time you remove the uterus. So, a significant proportion of the population is not going through normal menopause.

I think another group that we are not yet able to clearly define is women who have autoimmune destruction of the ovary. And the reason we can't define that is because there are so many antigens involved with the ovary that the researchers can't really come up with an appropriate panel of antigens to look for antibodies for them. We have largely ignored that as a cause for abnormal menopause.

When I see a menopausal woman, the first thing I want to do is measure her hormone levels. This is an easy thing to do because these hormone levels are fluctuating, particularly at the time when women come in for hormone replacement, which is often in perimenopause, and not actually in complete menopause. So they come in and they are having problems, but what they are really having problems with is the inability of their hormones to dance with each other. They don't have enough reserve in several of their organ systems to allow an easy transition to menopause. These hormone levels go up one day, they are down the next, they're up the next day, they're down the next day...The brain doesn't have time to adjust to those changes in hormones, so they are having symptoms. Because you can get rid of those symptoms by nailing estrogen to the ceiling (by giving high doses of estrogen), we've come to believe that if women have any complaints you just give them estrogen. And, boy, have I seen some women on high doses of estrogen with complications of that.

The Importance of Measuring Hormones before Therapy
What I do is start with a measurement, so that we have some idea of what's going on. And I don't just measure estrogen. I measure estrogen, estrone, estriol. I measure testosterone, progesterone, DHEA. I measure sex hormone-binding globulin. I measure the 2-to-16 hydroxyestrogen metabolites. I'd like to be able to measure more than that, but that's what I can get, reasonably-priced, in a pretty well-accepted laboratory environment. So, I start with measuring them. Then, if they are low, the first question I ask is, "Why are they low?" Are they low because the ovary is missing? Are they low because the ovary is underproducing? Or are they low because that ovary is dancing with another hormone that is too high? In this case, the treatment would not be to raise the level of estrogen, it would be to lower the level of the hormone that is too high.

So I go at it in a systematic manner. If I decide I'm going to replace the hormone because it is low and because I think I know the reason why it is low, I get informed consent from my patient. The data in the literature is so constantly changing that what may be considered standard of care today is going to change tomorrow. You need to have documentation in your chart that you have talked about these issues with patients; that they understand the risks they are taking; and they agreed to those risks. Then, we start with low levels of the hormone regimen I prefer, and then we recheck the levels to make sure than we are in the right range. That's sort of (in a nutshell) the approach I take.

JB: Good. Could I interrupt and just ask a question quickly because I know a lot of clinicians probably would like your answer to this? In measuring these, obviously you have different compartments you could measure, or different fluids you could measure. You could measure serum, you could measure urine, or you could measure saliva. Is there a preemptory biological fluid you select, or do you vary that based upon what you are trying to answer relative to each of those hormones?

BH: I do check different fluids depending on the hormone I'm checking. With regard to estrogen, I usually use blood. The reason I use blood is because of two things. One thing is that I have found more data in the literature about what normal levels look like. And the second thing is it is often covered by insurance and so patients can get their insurance to pay for it. I think you can use other fluids to measure

those hormone levels, provided you get good at knowing what the fluctuations look like in that fluid-what levels you would expect to find in different clinical settings-so that you know when you are looking at a hormone that doesn't look right. So if I measure a hormone and I'm looking at a woman whose got high estrogen symptoms, and I measure her estrogen level and it's very low, I know that I've picked a trough instead of a peak, and I need to, perhaps, repeat those hormone levels, or think through, "Why would her estrogen level be low with symptoms of elevated estrogen?"

JB: You've helped us all to really understand-those of us who have had the pleasure of attending your courses-because you've showed some very interesting data on perimenopause that shows exactly what you are saying as it pertains to estradiol levels in a perimenopausal woman who is maybe showing the symptoms of estrogen excursions. At one point of the analysis her estrogens are very low, but at another her estriol is very high. As you said, depending on where you point to freeze frame, you might get a very different sense of what the level is.

BH: That's really true. I think you have to remember that it's probably the overall area under the curve that's going to influence things like breast cancer, uterine cancer, and perhaps bone loss. When you have an area under the curve analysis of perimenopause, you see that perimenopausal women (early in the transition) actually have higher levels of estrogen than they did when they were ovulating and having regular periods. I think perimenopause is a potentially dangerous time, and it is dangerous because you have higher levels of estrogen, so if you're not metabolizing them well, you are creating chemicals that can induce breast cancers. And it is dangerous because you will (at the same time) be having symptoms of this fluctuation of estrogen that produces brain symptoms and some doctor is going to come along and say, "Oh, you are having hot flashes so you must be menopausal, so let's put you on estrogen...." And now you have added to the risk.

JB: I think you raised a very important point that we need to probably emphasize for our listeners, and that's the question of pharmacogenetics and metabolism of these hormones. What is being discovered is that there is a lot more variability among people (among women, in this case) as to how they process through their bodies these hormones. So the construct that a single dose on body surface area will be tolerated in the same way by all women is a pretty specious argument, so that argues for your personalization approach, it would seem.

The Role of Genomics in Hormone Therapy

BH: I think that's really true. Now that we have some genomics available to us in laboratories that are clinically available, you begin to see why so many people don't respond the way you expect them to with hormones. If you are not paying attention to how they metabolize hormones, these are the cytochrome enzymes that are detoxifying enzymes, which implies to me that the human body sees estrogen as a toxin. The other thing it implies is that nanogram amounts of estrogen suffice, whereas microgram amounts of progesterone and milligram amounts of DHEA are produced, but picogram amounts of estrogen are produced daily. This is a potentially dangerous and toxic chemical and the body has many layers that it puts between that active molecule and the cell systems that are being affected by it. If those layers of protection are not working properly because of your genetics, or because of your environment, or because of your food, then giving a hormone is, I think, potentially a very dangerous undertaking.

JB: So let's now talk a little bit about the delivery system because I know there is still a lot of question as to what's the best way of introducing hormones when you are doing replacement therapy. Is it oral, is it

vaginal, or is it some kind of transdermal? What is your opinion of this first-pass detoxification based on route of administration? Do you have a thought as to what is the best way of administering these hormones?

BH: Yes, I do. I think some hormones are safer to take orally, but the way glands administer hormones is directly into the circulation. Something that administers the hormone more directly into the circulation without as much metabolic transformation would be more physiologic. This is so complex because these hormones dance with each other and the levels are constantly changing. I am very humble about my ability to mimic Mother Nature, but I try. I try to do the best I can to do it the way Mother Nature does it.

So, with estrogen, I think there is good data now that says transdermal estrogens are much safer than oral estrogens, partly because you don't get a first-pass effect through the liver, and partly because you can administer one-tenth of the dose. I think progesterone (because it is rapidly metabolized both into downstream hormones and into metabolites, some of which are active, like allopregnenolone, which is a brain-active chemical that is calming)...because progesterone disappears so rapidly, it is very easy to get the impression that you can give very high doses of progesterone, and because it doesn't change the levels of progesterone, it's perfectly safe. But, in fact, you better be measuring some of those downstream hormones and making sure that you're not changing the level of estrogen or the level of testosterone when you give high doses of progesterone. So I tend to prefer the bioidentical hormones, and I prefer the transdermal route.

Then you get into the trouble of, how do you get women to absorb transdermally? Some women don't absorb very well transdermally. Then you can go to a vaginal route of administration, but the vaginal route of administration you absorb much more rapidly. In fact, I see estradiol, given transvaginally, doesn't change the estradiol level very much, but, boy, it runs up the 2 and 16-hydroxy metabolites significantly. And I think that could potentially be an issue in women with breast cancer, for instance.

The Chronobiology of Hormone Administration

JB: You raised the question of chronobiology. Hormones are secreted, as you indicated, more on a pulsatile basis, not statically throughout the day. Do you try to mimic that cycle when you have women administer bioidentical hormones, or do you do it in a static dosing regime?

BH: If you mean the day-to-day, minute-to-minute pulsations, I don't think we can mimic that because I don't think anyone has ever been able to document what those look like. I know that from day to day, estrogen levels will fluctuate dramatically, but I don't know if they are fluctuating from second to second, or from minute to minute, or from hour to hour, and I don't think there's any administration technique that mimics a fluctuation along those lines. So I admit that I am giving a hormone once (sometimes twice) a day, and getting a curve that doesn't look much like physiology. But until somebody makes the delivery system that does that, or documents for me what levels I should be getting fluctuations of, I have to go with a cruder system.

As far as the fluctuations of the hormones across the month, I think the evidence is (when you have premenopausal levels of estrogen) it is safer to give progesterone in a sequential manner, but when you have normal postmenopausal levels of estrogen (and I emphasize "normal"), the progesterone is supposed to come from the adrenals; it's already there. You probably don't have to administer progesterone at all, as long as your adrenals are healthy. But then, how many women in our culture have healthy adrenals after

menopause? I don't know, but I don't think it's a lot. So, yes, if you're not making enough progesterone from the adrenals, you'd better add that in. And then what happens to it? If you've got the enzymes upregulated to make stress hormones, you're going to put progesterone in and get cortisol out. All these things have to come into play. If you're not working on stress reduction with that woman, you're going to put a lot of progesterone in and get a lot of cortisol out.

JB: So now we ask the question about form of dose. We've obviously heard a lot in this field about compounds, or formulations such as Bi-Est or Tri-Est. Do you have any kind of inclination as to what is the best formulation to be using?

Creating a Healthy Balance

BH: I think estrone and estriol are part of the normal metabolism of estradiol. So I don't think you have to put them in. I think if you put estradiol in, it is going to get converted very rapidly to estrone. If you have estrone, it is going to get sulfated to estrone sulfate. It is also going to get bound to sex-hormone-binding globulin. And then it's going to get converted to 2 and 16-hydroxyestrogen, and the 16-hydroxyestrogen is going get converted to estriol. I think a lot of people think you should administer all three of those, thinking that if you can create a healthy balance of those three chemicals, that you will decrease the risk of, say, breast cancer. But I think that healthy balance comes from the cytochrome P450 enzymes that are metabolizing estradiol, not from the level of estrone, estriol, estradiol. So what you want to do, if you want to have the correct balance of those three, is not administer some artificial balance of them, but work on the metabolism so that you're metabolizing them appropriately.

How Diet Influences Hormones

JB: Well, given that, then I think my next question follows very logically. In your experience, what role does diet have in influencing these hormones (this dance of hormones you are describing)? Things like lignans, isoflavones, omega-3 fatty acids, enteric bacterial function-is this a major player?

BH: It has everything to do with it. As you've taught me, we bathe our genes in the food we eat. If we're eating food that our genetics evolved with to create a healthy organism and create healthy aging, our genes are going to listen to that food and metabolize these hormones appropriately and we're not going to see the problems. It is only when you eat the standard American diet, which is high in carbohydrates, high in chemicals, high in empty calories, and low in vegetable proteins, lignans, isoflavones-all of the things that you just listed-that we get into these aberrant ways of metabolizing these hormones that produce problems.

JB: I was very intrigued-I'm sure you were, as well-about the paper that appeared in JAMA a couple of years ago, showing a statistically significant increase in breast cancer in women who had repetitive antibiotic exposure. 17 It certainly argues for a gut-hormone connection, I would say, through that data.

BH: Absolutely. There are a number of pathogens in the gastrointestinal tract which affect beta-glucuronidase. Glucuronidation of estrogen is one of the three main Phase II detoxification pathways, along with methylation (which we really need to be paying attention to given how many people have problems with methylation and activation of B vitamins), and sulfation, given the number of people who don't have enough sulfate groups in their diet, or can't access those sulfate groups because they have genetic abnormalities in sulfation.

JB: So that, then, leads to a clinical challenge that I know you deal with all the time in this personalization of hormone therapy in women that really need it and that's the body composition issue. We recognize that high levels of adipocyte hypertrophy can increase these adipocytokines, which, then, increase regional cortisol. They influence insulin signaling, they have effect on inflammatory mediators, and they also influence the production of the 4-hydroxy estrogens. How do you handle hormone replacement in women who have, say, elevated percent body fat?

Hormone Replacement in Women with Elevated Percentage of Body Fat

BH: The first thing is that we have a very aggressive program at True North to get those women on a diet that helps them to lose weight and create a healthier metabolism. We don't just say, "Well, you should go lose weight," and then leave them hanging out to dry. We give them programs; we give them information; we give them consultation; we do bioimpedance analysis to show them how they are doing; we have cooking classes to really show them what it looks like when you are eating good food and how fabulous the food can taste. So we have a lot of support to change that situation of obesity.

Then there's the big problem of obesity that I see in women at mid-life, which is really stress. We have a number of programs that help people to deal with stress-mindfulness-based stress reduction, yoga, meditation, HeartMath-there are a panoply of ideas out there if you can get patients to understand that their obesity is related to their stress and their stress is important to change, now, at mid-life. If you change those patterns of behavior at mid-life when you really have your body yelling at you to do that, then you're going to be able to modulate your stress according to your adrenal reserves for the rest of your life, which in my opinion is why women live a long time.

JB: You've given me a variety of very important insights, one of which has to do with breast density and lobular structure of the breast and how that might individualize relative risk in certain women. Is this an area that you also look at as a risk factor and deal with in terms of personalization of the program for a woman?

Progesterone and Breast Cancer Risk

BH: I think the differentiation of the breast, which occurs under the influence of the hormones of pregnancy and lactation, does allow a woman to go through a period of increased risk, but eventually get to a situation of decreased risk for breast cancer. If she goes through that period of increased risk and then out to decreased risk when she is young, she's much less likely to get breast cancer. If she goes through it in her late 30s or 40s, she's got more abnormal cells that she may stimulate into a cancer. However, if she gets beyond the first year or two after the pregnancy without getting a breast cancer, then she's got the same protection that a younger woman would have from having a baby. And that protection is that the terminal ducts become lobular ducts, which then are resistant to the growth stimulation that produces ductal breast cancers. It is beginning to look like the progestin issue is related to lobular cancers. Those lobules may continue to be able to be stimulated by progestins or progesterone, and that's part of what I'm beginning to be really interested in about the differences between premenopausal and postmenopausal administration of progesterone, and the difference in administration of progesterone in normal cells versus cancer cells (or precancerous cells, perhaps), and the influence of progesterone on the non-hormonal growth factors like EGF, IGF-1, and insulin, which I think is clearly a factor in the production of breast cancers in women.

JB: So with all of this in mind (which you've done a marvelous job of summarizing for us), what is a

good assessment panel that you would recommend for women? I know a lot of women think mammography (followed serially to see if there is any relative risk). Or maybe it is vaginal cytology. Or maybe it is chemistry, like a 2-16 estrogen quotient. What do you do to help women allay some of their fear or to give them kind of a longitudinal assessment profile?

High-frequency/Low-penetrance Genes Can Be Modified

BH: I do recommend mammograms, although clearly mammograms are not prevention, they are early diagnosis. And there are a lot of false positives in mammography, so it is not an ideal form of risk assessment. Family history is important, but there are two sides to that. One is the low-frequency/high-penetrance genes like the BRCA breast cancer gene, and the other is the high-frequency/low-penetrance genes like the cytochrome P450 enzymes, the glutathione transferase enzyme or methyltransferase, MTHFR. If you stack enough of them up against yourself, you're going to have as high a risk of breast cancer maybe as a woman with a BRCA gene.

What I love about that is the BRCA gene is not something you can change. You've got that gene and you're stuck with it. But the high-frequency/low-penetrance genes are amenable to change. They are amenable to modifying with diet, lifestyle, exercise, and stress reduction. So, instead of just sitting on the railroad tracks and waiting for the train to hit you, you can move off to the side and let the train go past you, and I really like that image. So I tell women that if you've noticed that the light at the end of the tunnel is a train, it's time to start getting off to the side. I will do the 2,16 hydroxy metabolites, and then I also (if I can get patients to buy into having more information about their genetics) will get a genetic profile that gives me some of these high-frequency/low-penetrance genes. And then women sort of feel like they've taken charge; they've taken control of their metabolism and their genetics and their lives and they are not just sitting on the track waiting to be hit.

JB: So, I guess my concluding question, could be (obviously) a question that would open hours of discussion. I know that you have more than enough resources to fill those hours, but I think we need to summarize. If a person is listening to this and they are saying, "I've been doing hormone replacement therapy and now you have raised a lot of questions and now I'm not as sure about what I was doing before because you've opened up all sorts of new perspectives that I wasn't considering before," what would be your recommendation? How do you get down the road to feel comfortable in the way you are managing women?

Asking the Right Questions

BH: I would say if you feel that way after hearing this, you're a very smart physician. I think this is a very complex area and we've been far too casual about it. Going through the Robert Wilson era and then the era of where we gave hormones to everyone and nobody had done the proper studies to know that we were producing problems for women, should be a lesson to us about how carefully we should tread when we are changing hormones. Because all these hormones dance with each other, if you change one then you are changing potentially all of them. So I would say that you need to have a logical reason to know why that hormone should be replaced. Has the gland been removed? Is it being destroyed by antibodies? If not, why isn't it producing the way it ought to be?

I have no problem with transiently mucking around in it-you know, changing the levels of hormones-in order to get a woman sleeping, for instance, so you can get her adrenals calmed down, or in order to deal with issues that are related to her thyroid until you get the toxins out of her environment. I don't have a

problem with that as long as you are simultaneously working on the whole picture (in the background) to get her healthier. Otherwise, I think you may be kidding yourself that you're increasing her longevity by adding some of these hormones in, as we found out with the Women's Health Initiative.

JB: I want to thank you. I'm saying what is clearly obvious: your patients are very privileged to have access to True North and your skill. I would like to think that we could form a functionally based medicine where these opportunities would be available throughout the whole of the country. We really appreciate you sharing with us what I think is a very thoughtful and rational perspective on this whole concept of bioidentical hormone replacement. We wish you the very best and look forward to visiting with you again, Bethany, real soon.

BH: Thanks, Jeff, and thanks for all the wonderful information that I have received from you and that you have put out into the world because it really has changed my life. If my patients are benefiting, it is because of what I've gotten from functional medicine.

JB:Well thank you very much. Best to you and we'll talk to you soon.

As part of our new format for 2007 for *Functional Medicine Update*, we are finishing each issue with questions from you-the listener participants. We have an interesting start to this with a question that relates to the sulfites in red wine as the cause of the "red wine headache" syndrome. This is a specific question to a more general theme that I would like to speak to.

Red Wine and Symptoms of Sulfite Sensitivity

We have often attributed these sulfite-related headaches to an allergy-like response because individuals have inabilities to properly metabolize sulfites, so that begs the question: how does sulfite get metabolized? It is done through an enzyme called sulfite oxidase. Sulfite oxidase is a molybdenum-containing enzyme, and as a consequence this is one of the few examples where molybdenum is an essential nutrient for physiological function. In the case where an individual has a sulfite oxidase slow spot, then it would indicate that he or she may need to either remove the sulfites from his or her diet or, possibly to increase the molybdenum content of his or her diet through nutritional supplement or foods. Generally around 200 to 300 micrograms of molybdenum is considered to be in the safe and effective range. We can't say that all individuals, with molybdenum supplementation alone, will get benefits; it may also be reducing the sulfite load from the food as well.

We also recognize that vitamin B6 plays a role in the sulfite oxidase pathway, as well, so sometimes the administration of B6 along with molybdenum and magnesium will help to eliminate (or at least reduce) the sulfite sensitivity. But again, in extreme cases of sensitivity, even small doses can produce very large physiologic responses, so clearly the person needs to be very conscious about sulfite exposure. Beyond sulfite, however, in red wine, there is another series of phytochemicals that often mimic what people think to be sulfite sensitivity. These are the ethylamines, like phenylethylamine which is a dopamine-like conjuger. These particular amine-like compounds-organic amines-are vasoconstrictive and can induce, then, vascular changes (including small vessel changes) and produce headaches.

One of the other things that we see in red wine, cheese, chocolate, and bananas is the phenethylamine-like compounds, which then require monoamine oxidase the detoxifying enzyme. If you look at the package insert for MAO-inhibiting drugs they say that while you are on these medications to be cautious about

consuming foods that contain these amine-like substances. The reason for this is that the vascular response could produce headaches. If you have a genetic polymorphism of monoamine oxidase that makes that a slow step in the detoxification of amine-like substances that come from food, then you are more sensitive to these foods in a normal diet, of which red wine may be another member of that family because it contains these ethylamine-like substances.

I don't believe we should jump to the conclusion that headaches only come from sulfite; they can also come from these bioactive amines, and of course they can also come from the overuse of alcohol as well (we should probably throw that in there, as it pertains to the response to any alcoholic beverage). In the case, specifically, of red wine-induced headaches, however, I think it is probably a combination of sulfite sensitivity and other factors. As you know, in asthmatics, there is an increased risk to sulfite sensitivity-this tends to be a covariable constitutional issue-and so you generally have a higher level of red wine sensitivity in asthmatics. We know that sulfite sensitivity includes symptoms of skin rash, redness, hives, itching, flushing, and tingling, but we also recognize that these can be associated with other vasoactive substances. Differentiation of red wine syndrome as a headache probably is more related to that of the phenylethylamines. Red wine syndrome as it relates flushing and to the vasomotor effects is probably more related to the sulfites. I would differentiate those two classes of responses to wine or chocolate or bananas or cheese, with the sulfites being more the skin erythemas (hive and itching), and the problems related to headaches more coming from the bioactive amines. This is clearly an indication of unique detoxification-again, through monoamine oxidase. It means that person is less able to metabolize their adrenaline as well, so they are more sensitive to states of hyperadrenaline, like stress. So all this kind of fits together in a pattern, I believe, that is related to lifestyle, diet, and specific nutrients for modulating these pathways.

I hope that's helpful in answering that question, and please do send in your questions (email them into our website) to *Functional Medicine Update*, and we'll be pleased to put the answers onto upcoming issues. This concludes the February issue of 2007. The website address, for those of you unfamiliar with it, is www.jeffreybland.com.

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