February 2004 Issue | Allan B. Warshowsky, MD, FACOG, DABHM

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Welcome to *Functional Medicine Update* for February 2004. In this issue, we will focus on a topic that will be covered at our upcoming 11th International Symposium on Functional Medicine in May—"The Coming Storm: Reversing the Rising Pandemic of Diabetes & Metabolic Syndrome ." We will extend the discussion beyond diabetes to insulin resistance and hyperinsulinemia. This month we will discuss estrogen hormones, natural management of estrogen imbalances, and interrelationships with the insulin signaling pathway, the peroxisome-proliferated activated receptors (PPARs), and some of their effects on the metabolism of progesterone, estrogen, and testosterone.

Pharmacogenomic Uniqueness

A recent paper illustrates the controversy brewing in the world regarding the best way to intervene with patients with complex, chronic age-related diseases. This article describes a presentation made by a senior researcher, a vice president at GlaxoSmithKline (GSK), who talks about the efficacy of pharmaceutical drugs for the management of chronic health conditions.[1] I believe everyone at the conference was surprised to hear this speaker state that most prescription medications do not work on most people who take them. Dr. Allen Roses, worldwide vice president of genetics at GSK, said, "Fewer than half of the patients prescribed some of the most expensive drugs actually derived any benefit from them."

This is the first time that a mechanism has actually been ascribed to explain why this is the case, and it ties back to the area of pharmacogenomics—the unique differences from person to person and how they respond and metabolize specific substances. Dr. Roses was an academic geneticist at Duke University Medical School for many years before he joined GSK as a vice president. He further stated:

"Drugs for Alzheimer's disease work in fewer than one in three patients, whereas those for cancer are only effective in a quarter of patients. Drugs for migraines, for osteoporosis, and arthritis work in about half the patients. Most drugs work in fewer than one in two patients, mainly because the recipients carry genes that interfere in some way with the medicine. The vast majority of drugs—more than 90 percent—only work in 30 or 50 percent of the people. I wouldn't say that most drugs don't work. I would say that most drugs work in 30 to 50 percent of people. Drugs out there on the market work, but they don't work in everybody."

Doctors often think when a drug is approved that it will influence all their patients in similar ways.

Mass Marketing of Drugs

But, as pointed out in the article, "This goes against a marketing culture within the industry that has relied on selling as many drugs as possible to the widest number of patients." This type of drug marketing led to

a culture that sold one drug to lots of people, assuming that anyone with a particular diagnosis would get a specific kind of response. Now, with pharmacogenomics, we realize the response may vary greatly from one individual to another based on genetic uniqueness.

This discussion is also related to this month's theme—the modification of hormonal balance in women as part of the endocrine web, the symphonic orchestration of the messenger molecules that control cellular/tissue/organ function. Recently, the American Association of Clinical Endocrinologists developed some medical guidelines for the clinical use of dietary supplements and nutraceuticals in the modulation of these endocrine complexities.[2]

Published in *Endocrine Practice*, this paper is more than 50 pages long and contains 550 references. In this review of nutraceuticals in endocrine practice, the authors discuss alternative medicine and the definition of alternative care. They state that the problem with alternative medicine is often that the therapies are offered without explanation of mechanism.

The Functional Medicine Approach

The functional medicine approach to endocrine and metabolic disorders is discussed in Point 5 of the document:

"Physicians should remain abreast of not only advances in traditional medicine but also evolving alternative medical practices. Sorting through the seemingly endless lexicon that is articulated by alternative care practitioners is particularly challenging&ldots;. Nonetheless, analysis of alternative options may yield advantages. First, such studies can be informative and lead to 'lateral thinking' in innovative applications of proven therapies. Second, they can stimulate new ideas for the design of scientific medical research. Third, they can assist discussions with patients contemplating such therapies&ldots; One alternative practice that is gaining popularity is 'functional medicine.' This term is used by some healthcare practitioners to describe a clinical approach emphasizing (1) the physiologic and biochemical uniqueness of each patient; (2) the ability of laboratory tests to detect such uniqueness; and (3) the importance of minor symptoms to guide prevention of and therapy for suboptimal health, degenerative disease, and chronic illness. The over-arching teleologic principle is that individualized nutrition, based on a person's unique genotype and phenotype, can produce a state of optimal health. 'Functional foods' are defined as foods that contain, in adequate concentrations, one or more substances that have a positive effect upon physiologic function. In functional medicine, complex theories involving the psychoimmune-neuroendocrine axis are blueprints for natural interventions. Data from scientific studies and non-scientific studies are applied to buttress an argument against polypharmacy with traditional medicines and to favor lifestyle changes and the use of a wide variety of dietary supplements/nutraceuticals. 'Nutrigenomic' and 'nutriproteomic' therapies are nutritional interventions directed at genomic and cellular mechanisms of disease. An example would be the genomic screening of children early in life, (perhaps *in utero*) for methylenetetrahydrofolate reductase polymorphisms. A potential treatment would be to increase the dietary intake of folate or the neutraceutical 5-methyltetrahydrofolate. This approach would theoretically then help prevent pediatric leukemia, which has been linked to altered folate metabolism."

Functional Status

It is exciting to see that the functional medicine model is at least on the radar screen and described in clinical guidelines that appear in various forms, especially medicine. This month, we will discuss the specialty medicines of endocrinology and obstetrics/gynecology, and the role lifestyle, diet, and

environment can play in those disciplines.

We are really measuring functional status. Many disorders, including fibrocystic disease of the breast, cervical dysplasia, uterine fibroids, preclinical polycystic ovary syndrome, perimenopause, and premenstrual syndrome (PMS), would not be considered diseases as such, but rather conditions. We might call them functional physiological disturbances or endocrine imbalances. Our Clinician of the Month, Dr. Allan Warshowsky, will discuss a functional medicine model approach he has been using for the management of complex endocrine symptom clusters.We are really talking about how to measure functional status. A recent issue of *Arthritis & Rheumatism*, the journal of the American College of Rheumatology, contained a series of papers discussing measures of general adult functional status.[3] [4] It was interesting to see how many different ways there are to assess function, including psychological function, somatic function, physical function, cognitive and mental function, and physiologic function.

We are aware of the Short-Form Medical Outcome Survey questionnaire (SF-36). This questionnaire evaluates quality-of-life issues and various disabilities from a functional level and can be helpful in mapping back against psychological and physical dysfunctions that may be present prior to the onset of a cleanly defined disease that fits an ICD9 code. Well before that, there can be functional decrements.

Measuring Functional Capability and Performance
The first article in *Arthritis & Rheumatism* discusses measures of adult general functional status, using the Barthel Index, the Katz Index of Activities of Daily Living, Health Assessment Questionnaire (HAQ), MACTAR Patient Preference Disability Questionnaire, and the Modified Health Assessment Questionnaire (MHAQ). All of these questionnaires measure aspects of functional capability in the absence of a clean diagnosis.

The second review paper discusses adult general performance tests. This is a way of getting physical measurements in the office for evaluating functional status. These include the Berg Balance Scale for measuring equilibrium; the Dynamic Gait Index (DGI), Gait Velocity, Physical Performance Test (PPT), Timed Chair Stand Test, Timed Up and Go, and the Tinetti Performance-Oriented Mobility Assessment (POMA). These are ways to evaluate, at a gross level, certain aspects of peripheral and central nervous system activity, the immune system, structural balance, and how those assays track against physiological and physical functioning.

Early-Warning Measurements
These are tools for evaluating early-warning signs in patients who present with symptoms of differing severity, intensity, and duration that may be indicators of later-stage, more serious problems. For instance, patients who begin to lose smell and taste acuity are often at higher risk for Alzheimer’s disease. This may be an early warning functional assessment test to measure loss of taste and smell. When we begin to examine these markers, we are led to a different set of questions beyond just diagnosis. It relates to physical, physiologic, cognitive, and mental functioning.

Hormonal imbalances track early on in terms of changed symptoms in the absence of diagnosis. In perimenopause there is a significant change in hormone levels from period to period. Women do not simply suffer from low estrogen that results in flushing, night sweats, cognitive and sleep disturbances,

depression, and dysphoria. Estrogen levels change rapidly in perimenopause, from very high to very low, and the metabolism of the intermediaries may trigger many of the symptoms associated with menopause. There can be an imbalance of one form of an androgen/estrogen to another form, and a progesterone insufficiency relative to estrogen excess in the moment.

These are the kinds of things that create the whipsaw effect on physiology seen as functional changes in outcome that questionnaires like those I just described can pick up, well before there is a clean diagnosis. In fact, we should not view menopause as a disease. It is a condition, a normal transition that most women go through in their fifth decade of life. It is the severity of the experience that is the real concern, the symptoms and signs that result as a consequence of altering hormone values and how they influence physiological, cognitive, mental, and physical functioning.An article in *Nutrition Today* is titled "Managing Menopause Naturally?"
[5] The answer to that question is yes; it has been done throughout much of human history. When exogenous hormone replacement was not available, women had to manage menopause naturally. The real question is whether we can improve the transition with supplements like black cohosh, soy isoflavones, cruciferous vegetable glucosinolate concentrates, or various other types of adrenal adaptogenic substances like licorice. Do these substances influence the transition into menopause? Can they affect the symptoms that women experience, such as night sweats and flushing?

Alternative Medicine Review contained a paper titled "Hot Flashes—A Review of the Literature on Alternative and Complementary Treatment Approaches."
[6] The author discusses various medications that have traditionally been used in attempting to modify hot flushes and night sweats and compares them to natural interventions. Some natural interventions use selective estrogen response modulators in the form of isoflavones or lignans. Others may remove gut dysbiosis and improve digestive function.

You might consider that the human body operates like a machine. The "operator" uses feet on two pedals simultaneously—the accelerator and the brake—to balance out cellular function. The balance metabolism of estradiol through the 2-hydroxy pathway becomes an important part of modulating function.

Cruciferous Vegetables
The cruciferous vegetables, rich in glucosinolates, help increase 2-hydroxylation. The catecholmethyltransferase enzyme transfers a methyl group from S-adenosylmethionine (SAM) to the 2-hydroxyestradiol to produce 2-methoxyestradiol and 2-methoxyestrone. These estrogen-braking substances, which are anti-mitotic—anti-cellular proliferative—tend to calm down the estrogen message of estradiol which is cellular proliferative and increases mitotic activity. We see the relationship of diet to function playing out in terms of signs and symptoms that the patient experiences.

Women do not all respond identically to these interventions. In the same way that they respond differently to medications, people respond differently to diet and lifestyle interventions. We are biochemically unique. There are 2 to 3 million different single nucleotide polymorphisms (SNPs) in our genome of 30,000 to 35,000 genes, and they code for many different variations on a theme. Estrogen can modulate xanthine oxidase activity, but it does so by an estrogen-receptor-independent mechanism. You might have relationships between estrogen and estrogen metabolism on vastly different physiological functions unique to the individual, such as in purine metabolism, xanthine oxidase, or oxidative stress.

When the enzyme xanthine oxidase is upregulated, it produces superoxide. Superoxide in the presence of nitric oxide (NO) can react very rapidly chemically to produce peroxynitrite in the body. Peroxynitrite is a powerful irritating, nitrosylating reagent that injures proteins, resulting in altered protein function.

Oxidative Injury

An immune-upregulated proinflammatory state, coupled with altered estrogen metabolism, can produce an outcome of oxidative injury. These are weblike effects; they do not work in isolation. A symptom is not the result of one factor alone; it results from the weaving together of a variety of factors.

Xanthine oxidase activity and its interrelationship with postmenopausal inflammation are discussed in the journal *Antioxidants & Redox Signaling*.
[7] The authors explain that when estrogen declines, the conversion of xanthine dehydrogenase/xanthine oxidase activity increases, and xanthine oxidase produces more superoxide. This may be another component of postmenopausal lowering of estrogen, increasing the incidence of inflammatory conditions and oxidative stress in women. It might also tie together with a variety of oxidative-related and inflammatory-related disorders such as arthritis or heart disease in postmenopausal women.

These relationships are individualized to a woman's own genetic uniqueness. Her response to drugs is modified by her genetic uniqueness; so is her response to her environment, lifestyle, and diet. This topic is discussed in a paper in the *Journal of the American Medical Association*, titled "Association between Estrogen Receptorα Gene Variation and Cardiovascular Disease."[8] In this article, the authors explain that certain types of polymorphisms of the estrogen receptor have a much higher statistical correlation with cardiovascular disease, and that estrogen receptor variation has the potential to explain recent conflicting data regarding the effects of hormone therapy on cardiovascular disease susceptibility in women.

Some women may carry SNPs of the estrogen receptorα sensitivity. On hormone replacement therapy, these women may have a lowered risk to cardiovascular disease, whereas other women may have an elevated risk, depending on how that polymorphism receptor responds to the environment, i.e., the hormone.

Again, individualization, customization, and personalization indicate where we are going. In fact, that was the subject of an editorial that appeared in the *New England Journal of Medicine.* That article on hormone therapy discussed customized approaches to women, individualized therapy, not just one-size-fits-all; consider what the body mass of the person is, give a dose responsive to that body mass, and look at individual needs.[9]

The effect of many nutritional agents is to modify estrogen metabolism as agonists/antagonists. It is an adaptogenic effect: the highs go down and lows come up. An agonist effect is when low goes to high; an antagonist effect is when high goes to low. It tends to normalize around a setpoint. This is what has traditionally been called an adaptogen. Soy isoflavones have this effect, serving as agonists/antagonists of estrogen metabolism, or adaptogens of estrogen response.

The author of a recent paper in *Medical Hypotheses* points out that estrogen agonists and antagonists like soy isoflavones may downregulate growth hormone signaling and therefore have an influence on a variety of effects, including insulin sensitivity through IGF-1 and IGF-1 binding protein, and they may impact

lipoprotein(a), which may explain how estrogen can modulate cardiovascular risk and insulin sensitivity.[10]

It is a web. The endocrine system contains an interconnected series of signals that create specificity of outcome as function in cells and tissue. This concept of functionality is more than idle banter. It contributes to our understanding of how to manage patients with complex, chronic health problems related to the imbalance of these chemical messengers or signaling substances, such as the sex steroid hormones.

What relation does this discussion have to breast cancer and hormone replacement therapy (HRT)? We recently discussed the results of the Million Women Study. This is the largest study ever done looking at the effect of HRT on breast cancer incidence. It indicated there was a statistically significant and meaningful increase in breast cancer risk and incidence regardless of the type of estrogen used, whether it was estradiol or mixed equine conjugated estrogens.

All forms of estrogen, if unbalanced in delivery and metabolism, may pose a risk when administered exogenously. Even endogenous estrogen, if it is not properly metabolized and excreted, may pose a risk. That is why two years ago, the Institute of Medicine suggested that estrogen is a carcinogen.

Estrogen and Cancer Risk

It is unusual to think that a natural substance in the body could be a carcinogen, but estrogen or its metabolites, if they are out of balance, inappropriately metabolized, or elevated could, in fact, pose a carcinogenic risk. The Million Women Study appeared to indicate that.[11]

It is also important to remember that estrogen can be manufactured in tissues outside the ovaries. Breast and adipocyte cells, for example, particularly visceral adipose tissue, will manufacture estrogen. This estrogen can be converted into estrogen metabolites like the 4-hydroxyestrogens, which are the catecholestrogens that Dr. Rogan and others have discussed with us; they can be very caustic and cause injury in DNA adducts that pose carcinogenic risk.

The breast itself can generate estrogen. There is the isoform of cytochrome P450 (CYP) in the breast that can convert estrogen directly into the 4-hydroxyestrogens—CYP 1B1. Recent papers on polymorphisms of CYP 1B1 and their relationship to postmenopausal breast cancer risk have indicated a strong correlation between CYP 1B1 gene polymorphisms and estrogen metabolism. There is no strong influence of risk to breast cancer, however, because other modifying factors may affect the way that plays out in the phenotype.
[12] In other words, you may have a CYP 1B1 polymorphism, but secondary factors of how those catecholestrogens are metabolized by methoxylation or by glutathione conjugation may render these potential 3,4-quinone estrogens detoxified before they have an injurious effect on DNA.

It is not just a single point gene mutation or a single SNP that creates an outcome in a phenotype called breast cancer. It is a pattern of genetic uniqueness coupled with environmental exposures and dietary selections that ultimately gives rise to the outcome.

The Functional Medicine Approach

When we talk about a functional medicine approach to endocrinological outcome, we take into account

this web of interacting variables and look at the way hormones influence insulin, IGF-1, IGFBP-1, and lipoprotein synthesis such as apolipoprotein A1 or B1. All of these are part of the web of understanding how the individual woman responds to her environment.

The conversion of the hydroxylated estrogens such as 4-hydroxyestradiol into the nontoxic byproducts involves methylation. Methylation is performed by catechol-O-methyltransferase. It requires the presence of a methyl donor called S-adenosylmethionine or SAM. SAM comes from proper activity of the folate cycle. Polymorphisms in the folate cycle may impair the ability of the body to produce proper levels of SAM at the necessary site. These are polymorphisms like the MTHFR 677C→ T polymorphism, which we discussed in earlier issues of FMU.

A relationship between a polymorphism of the methylenetetrahydrofolate reductase gene and folate and riboflavin status as it tracks into homocysteine can affect the methylation of homocysteine ultimately through that cycle to produce SAM. A paper published in the *Journal of Nutrition* discussed that combined marginal folate and riboflavin (vitamin B2) status affects homocysteine methylation in people who have the homozygous MTHFR 677C→ T mutation.[13]

Having that polymorphism means being unable to handle lower levels of riboflavin and folate as well as a person who does not have that SNP. Therefore, methylation is impaired, increasing homocysteine and decreasing methyl hormone levels, and that can have a different dynamic on the web related to risk.

In a study by Dr. Lynn Bailey, titled “Folate, Methyl-Related Nutrients, Alcohol, and the MTHFR 677C→ T Polymorphism Affect Cancer Risk: Intake Recommendations,” the author explains that alcohol causes increased turnover and loss of the B vitamins, including riboflavin, pyridoxine, and folate.[14] A MTHFR 677C→ T polymorphism makes one more folate-dependent. Increased alcohol consumption lowers folate status and sufficiency of the folate cycle. It lowers SAM levels and influences relative cancer risk when an individual is exposed to the same level of carcinogens that would not pose a risk for someone who has proper folate chemistry.

We cannot say that a single exposure to a carcinogen is the risk. Nor can we say that consumption of a single drink of alcohol is a risk. We cannot say a single dietary insufficiency of B6, B12, folate, and B2 is a risk. Nor can we say that, in isolation, a MTHFR polymorphism is a risk. But when all of these occur together—frequent consumption of alcohol, poor diet, high stress, a MTHFR polymorphism, exposure to environmental xenoestrogens that increase hydroxylation to the 4 family, or perhaps taking mixed conjugated equine estrogens—they may paint a picture of higher risk.

Individuals respond differently to dietary isoflavones based on their individual metabolism. These would be things like the soy isoflavones daidzein and genistein. When a person responds to these isoflavones, the response has principally been found through estrogen receptor β rather than estrogen receptor α . This is interesting because estrogen receptor β is present in higher amounts in osteoclastic and osteoblastic cells in bone, as contrasted to estrogen receptor α , which is very high, for instance, in the ovary and the breast.

If you preferentially activate or modulate response of estrogen receptor β, it is reasonable that the result would be a significant effect on bone dynamics. This would be like the SERM raloxifene, to use an analogy from the pharmaceutical industry, in which a substance is working more in bone than in breast.

Dietary Isoflavones and Bone

A review paper in the *American Journal of Clinical Nutrition* looked at dietary phytoestrogens and their effects on bone.[16] The authors did a meta-analysis of 24 different studies—17 *in vitro* studies of cultured bone cells, 24 *in vivo* studies of animal models for postmenopausal osteoporosis, 15 human observational/epidemiologic studies, and 17 dietary intervention studies. They looked at the role of isoflavones on bone dynamics, bone cell physiology, or on bone loss in women.

Their collective data suggest that diets rich in soy isoflavones have bone-sparing effects in the long term. Current evidence suggests that, when coupled with weight-bearing exercise as simple as a regular walking program, isoflavones may have beneficial effects on retention of bone and prevention of fracture risk similar to those of the SERMs, possibly without some of the risks of adverse side effects from the synthetic molecules.

Is HRT Necessary?

Some people believe HRT of some type is necessary because one cannot get all the benefits from a natural approach that can be derived from artificial hormone replacement. The evolving story appears to contradict that belief for most women. If a woman exercises, has lower stress, eats a high-quality diet, makes sure she's getting adequate levels of calcium, magnesium, vitamin D, and vitamin K, and adequate levels of the isoflavones that modulate estrogen receptivity, activity, and metabolism, the outcome can be positive.

Vitamin K, vitamin D, methylation, calcium, and soy isoflavones all frame a pattern of intervention. It is not a single agent, but a complex intervention using diet and lifestyle that is consistent with what women traditionally did in cultures that did not have access to these pharmaceuticals. Once they got through the age of infectious diseases and childbearing, their transition to menopause in older age was quite good.

A series of effects can occur as a consequence of hormone imbalances. One of those conditions is fibromyalgia. Fibromyalgia might be seen as a complex condition that results from an imbalance in the neuro/endocrine/immune system. A recent article in the journal *Arthritis & Rheumatism* discussed the Fibromyalgia Impact Questionnaire (FIQ).[17] If one looks at the questionnaire used to evaluate fibromyalgia, with trigger points, tender points, and certain disabilities, one can see they tie back to what appear to be immunological and neuroendocrine imbalances.

Fibromyalgia may be a heterogeneous disorder, not a single disease, with different variegated forms that lead to myalgic pain, fatigue, sleep disturbances, cognitive dysfunction, and immunological suppression.[18] We should probably concern ourselves with individualized therapy for fibromyalgia patients, rather than assume one size fits all.

Dietary Modification in Fibromyalgia

Dietary modification plays a role in modulating the signs and symptoms of fibromyalgia. A paper in *Complementary Health Practice Review* discusses dietary modification of fibromyalgia.[19] This dietary modification consists of getting rid of dietary excitotoxins such as monosodium glutamate, lowering inflammatory potential and improving redox potential by lowering oxidative stress, improving bowel flora, and lowering some of the central nervous system immunological activation through the microglia.

What Dr. Alan Logan recommends for dietary modification of fibromyalgia is the exact approach we

have been discussing from our research over the last ten plus years. Dr. Scott Rigden has achieved remarkable results in chronic fatigue syndrome (CFS) and fibromyalgia patients with a hepatic resuscitation program to improve GI and hepatic detoxification. He normalizes oxidative stress by using balanced levels of redox-active substances such as lipoic acid, coenzyme Q10, vitamin E, and N-acetylcarnitine, and rebuilds membranes using essential fatty acids of the omega 3 family.

Lipid Replacement as an Adjunct to Therapy for Chronic Fatigue, Anti-Aging and Restoration of Mitochondrial Function

Some work has recently been done on the use of omega 3 fatty acids as an adjunct to therapy for both CFS and fibromyalgia. A paper appeared in the *Journal of the American Nutraceutical Association*, written by Dr. Garth Nicolson of the Singer/Nicholson team who developed the fluid mosaic model of the lipid bilayer of membranes.[20] This model is now viewed around the world as the "plum pudding model" of cellular membranes, in which the proteins embedded in the lipid bilayer transport substances across the membranes selectively.

Dr. Nicolson talks about lipid replacement using omega 3 fatty acids as an adjunct to therapy in CFS and fibromyalgia to help build back mitochondrial cellular and cytoplasmic membranes. That would generally be done after reducing oxidative stress. Intervention would begin with a detoxification program, go on to antioxidant therapies or redox mitochondrial resuscitation programs and last, rebuild membranes with essential fatty acid supplementation.

High levels of omega 3 fatty acids should not be given to people who are in extraordinary oxidative stress because they can be peroxidized and undergo "biological rancidity." That stage of the therapy would begin after minimizing the oxidative stress.

A Metabolic Basis for Fibromyalgia and Related Disorders

A review paper in *Medical Hypothesis* discusses management of fibromyalgia and CFS. It examines the metabolic basis for fibromyalgia based upon the model of neuroendocrineimmune balance.[21]

That will take us into our discussion with our Clinician of the Month. We will look at women with endocrine disturbances and obstetrical/ gynecological problems from a holistic functional medicine perspective.

INTERVIEW TRANSCRIPT

Clinician of the Month
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JB: It's time for our Clinician of the Month. For the past several months we have been following the theme of hormone metabolism and balance, with particular emphasis on estrogen, progesterone, and androgens. Today we follow up on those research discussions with some "news to use" from an obstetrician/gynecologist who is at the forefront of this field, dealing with these problems in his patients on a daily basis—Dr. Allan Warshowsky.

Dr. Warshowsky is a graduate of Downstate Medical Center at the State University of New York and has worked extensively in obstetrics and gynecology for more than 30 years. For the past decade, he has focused on integrative medicine, managing complex patient problems in the area of women's health. There is no more interesting time to collaborate and work in this area. The Women's Health Initiative Study and new data have changed the thinking on the issue of hormone replacement therapy.

Dr. Warshowsky's Background in Women's Health Issues

With great enthusiasm I welcome Dr. Warshowsky to Functional Medicine Update. He plays a role in managing women's health issues both in his private practice and as Director of the Women's Program at Beth Israel's Continuum Center in New York City. Welcome to FMU, Dr. Warshowsky.

AW: Thanks very much, Jeff. It's a pleasure to be on FMU and to have an opportunity to talk about some of the things I've been doing over the last 10 years. It's been an interesting decade in terms of women's health from the perspective of hormone replacement, hormone balance, and a lot of new information on the catecholestrogens. Listening to FMU for the past several years, we have heard about a lot of new information, a lot of controversy, and a lot of new questions on these issues. It seems that every time we learn something, it opens up an entirely new avenue of exploration.

I've been working with a holistic or integrative approach to women's health for 15 to 20 years, perhaps even longer. When I started in medicine, I was dealing with issues of premenstrual syndrome (PMS), which wasn't regarded as a true clinical entity, but I found that women were really suffering. Back in the mid 1970s, I found that when I supplemented these women with a few vitamins, worked with them to clean up their diet, and actually listened to them (giving a mind/body therapeutic effect), they started to improve.

The Need for Individualized Therapy

Soon after that, I found that women were not dealing well with the "one size fits all" therapy of menopause, using Provera and Premarin. There were many negative side effects related to Premarin, and I found that by using bioidentical hormones, those identical to what the human ovary was producing, and individualizing care, I got better results, fewer negative effects, and better therapeutic effects on alleviation of symptoms.

In continuing to develop and evaluate my own therapeutic programs, I started dealing with issues of hormone imbalance in the reproductive years. Fibroid tumors of the uterus were a major issue. I was concerned about unnecessary hysterectomies and other unnecessary surgeries. Doing a lot of surgery myself at that time, I noticed that normal-size uteruses were being removed for conditions such as bleeding. I knew at that time that if I was doing a more integrative or functional approach, I could alleviate those symptoms and the need for surgery was certainly diminished.

Developing an Integrative Approach

I put together programs from an integrative or functional approach that would alleviate a lot of the symptoms. I found I could no longer just deal with a uterus or an ovary in terms of helping to alleviate some of the common symptoms and conditions associated with fibroids, PMS, or polycystic ovaries. I started looking at some of the other issues, such as gastrointestinal (GI) problems like detoxification, inflammation, and sugar dysregulation. Certainly, the hormonal imbalances involved more than estrogen and progesterone. They also involved adrenal and thyroid hormones and the hypothalamus-pituitary axis

(HPA).

Issues such as emotional states were also important, because they seemed to affect hormone imbalance and, in looking at the limbic system, which affects the HPA, we can see an emotional component that would affect hormonal balance. Instead of simply looking at estrogens or progesterone, and conditions associated with the uterus and ovaries, my focus became one involving the total body, looking at GI dysbiosis states or permeability problems, yeast and bacterial overgrowth and parasites.

Whole-Body Effects on Balance of Hormones

All of these seemed to be affecting how hormones were balanced or imbalanced. Liver detoxification and other detoxification systems in the body also came into play. If the GI tract was not functioning adequately, the body's detoxification capabilities carried an additional burden, and that led to an imbalance of hormones. It wasn't just giving hormones, or working with hormones in a replacement sense; it was working with detoxification and GI issues before we could affect a hormone imbalance.

Then we started looking at sugar dysregulation and insulin levels. We found, certainly in the case of polycystic ovary conditions, a major piece is related to sugar dysregulation and insulin resistance. (I'm now finding this in other conditions of hormone imbalance as well, such as fibroid tumors or functional ovarian cysts.) In turn, that will affect estrogen/progesterone balance and, more importantly, inflammation in the body.

The Inflammation Connection

From this viewpoint, I moved on to look at inflammatory states, because we know that increased insulin levels, sugar dysregulation, and deposition of adipose tissue in the body are going to increase inflammatory messenger molecules that will also have a major impact on hormone balance.

From an initial approach of just looking at what's going on in the pelvis, as a traditional obstetrician/gynecologist is trained, my approach now encompasses the entire body. That includes the emotional state of the patient, and trying to put the whole body back into balance rather than just trying to work on a small piece of it, without acknowledging all the other issues that come into play.

Developing a Practice Based on Communication

JB: That is a very impressive program. Obviously, it deals with the patient as a unique individual, rather than hammering her into some diagnostic criterion and then treating her as if she were a diagnosis. I imagine that also increases the complexity of your life, both from a professional perspective and in the way you integrate these things, including the business perspective.

It takes time to ask the right questions and engage in proper communication. How have you gone from that highly mechanized setting of the traditional approach built on efficiency, to this model built around relationships and understanding?

AW: I'm glad you asked that question. I decided about four years ago that I was going to stop doing obstetrics because I couldn't devote the amount of time necessary for a good obstetrical practice in addition to doing this kind of integrative or holistic approach to health care.

Before that, I had been doing both. I had been setting aside a couple of days a week just to see integrative

medicine patients, and to devote the amount of time necessary. A new patient would require an hour to an hour and a half. Revisits would be 30 to 45 minutes, so I would devote two days a week just for these kinds of patients, but I found that with my obstetrical practice, I'd be canceling my hours frequently because I'd be up all night.

Fee-for-Service Practice

Four years ago, I stopped doing obstetrics and devoted myself to this kind of approach to health care. At the same time, I also stopped taking all managed care. I took myself out of that loop completely, where I was dependent on reimbursements through insurance companies, and I became a fee-for-service practitioner. I found it made no difference for the patients who needed this kind of approach. They had already been to half a dozen or more physicians with their chronic complaints. There is no good ICD9 code for these chronic conditions, and there really aren't good treatments for them. Medical treatments just deal with symptoms, and surgical treatments simply remove the tip of the iceberg, the piece of the problem that we can see.

None of this gets to the "why" of the problem. I see several conditions that stand out as the "why" of the problem—inflammatory imbalances, what we call the Th1/Th2 imbalances; immunological issues; hormone imbalance; GI detoxification issues; and certainly, sugar dysregulation issues. The conventional approach wasn't looking at any of the "whys." To look at the "whys," you need the time; especially in Manhattan, you need to be able to pay your bills and monthly overhead charges.

Getting Out of Managed Care

Getting out of managed care was very helpful. I have found over the last few years that I don't need to do surgery any longer. Most of the surgical procedures I was doing are no longer necessary because of this particular approach. For the cases that do need surgery, there's always somebody around that would be happy to do it. The patients then come back to see me because they still want this kind of care for their chronic issues.

That was the direction I decided to take, and I've been very happy with it. I've changed my identity. At this stage in my life (I've been in practice over 25 years), I never thought I would move completely to another field of medicine. It has been very fruitful and satisfying, however, because patients with these chronic conditions, for whom there is no good conventional therapy, are getting better. When I ask myself, what have I done? I've given up my identity. I loved doing obstetrics; I delivered three of my five children. I enjoyed doing surgery. What have I done?

Then a woman will come in and thank me because after having gone to half a dozen doctors over the last half dozen years with no improvement, and after being on my program for three months, her menstruation has been normalized. Her energy level is better; her mood is better, and her husband wants to thank me. These kinds of comments, which I get on a regular basis, keep me going and show me not only the efficacy but also the utility of this kind of approach. It seems phenomenal to me; it amazes me all the time.

Dr. Warshowsky's Reputation

JB: In my very busy travel schedule, I frequently get to the New York City area. I can testify as to how many people have been your patients. Through interesting and sometimes second-level connections, your name comes up in conversation and I'll hear that "Dr. Warshowsky is a savior," that they've never been

treated as they are in your program. They say, “It’s an amazing form of medicine,” and “Every doctor should be like that.” Obviously, your reputation precedes you. You are making a big difference.

AW: Thanks, Jeff; I appreciate that. When I hear things like that, especially from patients, it keeps me going. I know I’m on the right track. When I see a patient who has really severe fibroids, for example (I can think of two or three patients who have actually come in from the hospital after having blood transfusions for their fibroids), I put them on a program which certainly includes evaluation of the GI tract.

I find that more than 90 percent of the time, the GI tract is full of bacterial imbalance, yeast overgrowth, and very often parasites that haven’t been picked up. Doing a gut restoration program and supporting liver detoxification, dealing with sugar dysregulation issues and the inflammatory states, and putting them on a simple program to begin dealing with stress reduction and a nutritionally-rich program, within three weeks, most of these people start to feel better.

Bleeding Issues

When I deal with bleeding issues, I do a lot of herbal therapies and other antiinflammatory therapies. I would say that within three to four weeks, 80 to 90 percent of these people are incredibly improved in terms of their energy, their state of well being, resolution of their sleep issues, and clearing up of their skin problems.

They are extremely thankful. If I follow them over a couple of months, their menses lighten up and the pressure and pain symptoms all seem to subside. For the first time in years, they feel they can get out of their houses during their menstrual periods. They don’t have to be confined to the bathroom because they’re hemorrhaging so badly. These are real issues.

Avoiding Surgery for Fibroids

A majority of women who come to me with fibroids are already scheduled for surgery. They come to me for a third opinion. Two or three gynecologists may have already recommended total hysterectomies or other invasive surgical procedures as the only way to deal with their issues.

I would say that 80 percent or more of them never have surgery. Their conditions and symptoms seem to clear up to the point where they don’t need surgery; they’re extremely happy; they’re functioning in society again; they’re able to do their work. It’s extremely gratifying. It takes time, but the results are well worthwhile.

Dr. Warshowsky’s Book

JB: Your book, Healing Fibroids: A Doctor’s Guide to A Natural Cure, a Simon & Schuster publication, is an excellent overview. In the book, you describe what you do and why you do it in a way that’s very understandable.

AW: I wanted to get it out to the public. As you probably know, almost 300,000 hysterectomies are done every year in this country for fibroids. I would say the vast majority of them are unnecessary. We could deal with the issue of fibroids from a functional approach. Even the American College of Obstetrics and Gynecology, in its recent Practice Management Bulletin, has said that fibroids as benign tumors do not need to be removed surgically unless symptoms necessitate it.

If we could deal with symptoms, it leaves a lot of time to work with the issues that are causing the fibroids to grow. Elizabeth Stewart at Brigham and Women's Hospital in Boston has been doing a lot of work on growth factors found in fibroid tumors and how they are influenced by inflammatory states.

Fibroids and Inflammation

I have found that more than 90 percent of women with fibroids have some kind of intestinal inflammation issues. Consider that the intestines are lying on the fibroids right in the pelvic area where estrogens are being produced. (Estrogen is a growth hormone.) There are inflammatory messenger molecules stimulating cellular change within the myometrium of the uterus and the estrogens are causing the fibroids to grow, so inflammatory issues in the gut need to be cleared up.

It's almost a no-brainer to me. These are the issues that need to be cleared up. I use the 4R Program, and thank you so much for it. Patients are thrilled with it. For the first time in years, they don't have bloating and other digestive problems associated with their irritable bowel syndrome or inflammatory bowel disease. Clearing up these things and then working on the symptoms of the fibroids themselves are extremely beneficial. Fibroids stop growing and start shrinking.

Polycystic Ovary Conditions and Insulin Balance

Similarly, other conditions of hormone imbalance improve. Polycystic ovary conditions seem to be in the medical news more and more recently because of the connection with insulin. If you can use PPAR agonists and PPAR modulators and diminish insulin resistance, reduce insulin levels, and increase sugar utilization, a lot of these inflammatory issues also seem to clear up. You can clear up polycystic ovary conditions and all the problems associated with it, whether it's cardiovascular disease, type 2 diabetes, or other chronic conditions of aging that now seem to be associated with inflammatory states. If you can clear up sugar dysregulation issues, you can reduce the incidence of many of the diseases of aging. It's not just gynecological issues; it's not just reducing surgical procedures in terms of fibroids.

What I'm now doing is dealing with all the conditions of aging, from dementias to arthritides to cancer to cardiovascular disease to diabetes, which you've called a pandemic. They all seem to be connected with the major issues that I mentioned. When I see a patient with "hormone imbalance" represented by fibroids, functional cysts, fibrocystic breast problems, or even cervical dysplasia, that to me is just the tip of the iceberg.

Finding the "Why" of Chronic Conditions

Consider the other conditions, the "why" conditions, why is this happening? Those are the basic conditions—inflammation, immunological conditions, hormone imbalance, sugar dysregulation, GI and detox issues. They need to be cleared up first so that you can reduce the risks of the diseases of aging in later life.

That's what I've gotten out of this approach and the journey that I've been on. I have moved from the traditional gynecology medical school curriculum—basically fallopian tubes, ovaries, uterus, and vagina—to a total body approach and, ultimately, to increase the optimal health of the individual and reduce the degenerative aging process at the same time.

The 4R Program

JB: For listeners who may not be familiar with the 4R acronym, those Rs stand for Remove, Replace,

Reinoculate, and Repair. That is the gut restoration program. It involves removing allergens, toxins, parasites, and bacterial overgrowth; replacing digestive enzymes where necessary; using pre- and probiotics to reinoculate the gut with friendly bacteria; and last, repairing with nutrients like pantothenic acids, glutamine, and vitamin E to help restore gut mucosal integrity.

AW: That's something I started doing about 10 to 15 years ago, and it's been a mainstay of therapeutic treatment for these chronic conditions.

Bioidentical Progesterone

JB: As we all know, we lost a great pioneer and leader in our field with the passing of Dr. John Lee. Perhaps you could tell us a bit about your experience with bioidentical progesterone and where you think it fits into the puzzle.

AW: Progesterone gets depleted in a number of different ways in our society. Certainly, there is enough stress in our society with the concomitant elevations in cortisol and alterations in DHEA and progesterone, that I think increased progesterone deficiency states in the reproductive years are common. I suspect numerous nutritional deficiencies also play a role.

It's been estimated that more than 70 percent of the population doesn't achieve the RDA of things like magnesium and zinc, both of which are extremely important minerals for hormone balance. B vitamins also get depleted very easily in stressful situations, B6 in particular. I have found low levels in some of the testing I've done.

Progesterone as a Marker of Stress

Progesterone, is a very sensitive marker of stress. Certainly, stress also has a major impact on ovulation. We know that when women don't ovulate, they don't make any progesterone in the ovaries. My feeling is that whatever progesterone is being produced elsewhere, as in the adrenals, is going more toward production of stress hormones like cortisol. Low progesterone levels or abnormal estrogen/progesterone ratios are extremely common in many of the conditions I see.

Replacing or restoring the normal ratio between estrogen and progesterone becomes extremely important. Natural progesterone transdermal creams work very well to restore that ratio. It's not the only thing we do, but in someone who is premenstrually symptomatic of excess estrogens, natural progesterone can be extremely helpful. I also use the 3 percent progesterone cream that John Lee promoted in menopausal issues.

Hormones in Menopause

In menopause, I use bioidentical hormones or hormones that are identical to what the human ovary makes. In addition to the estrogens, I also use natural progesterone. The conventional thinking is that once a woman has a hysterectomy and has her uterus removed, she can just use estrogens and doesn't need progesterone to balance it out in the uterus because there's not going to be any uterine cancer.

I don't understand the thinking that there are estrogen and progesterone receptors in other parts of the body—in the brain, in bone, in heart, and in blood vessels. If we're giving estrogen and we're not replacing any progesterone, we're going to be stimulating more of an imbalance. In those cases, I also like to use the 3 percent progesterone creams.

Transdermal Progesterone Absorption

It's been suggested that the transdermal progesterone creams don't get into the body. My understanding is that when conventional progesterone serum levels are done, they throw away the red cells, but the red blood cells are, in effect, carrying the progesterone. They're basically throwing away evidence that progesterone is being absorbed transdermally. However, saliva testing for progesterone will show that progesterone is being absorbed transdermally.

I think the transdermal progesterones are very effective. They're certainly absorbed and can be very helpful in a complete program in restoring estrogen/progesterone balance.

Some of Dr. Lee's work on osteoporosis treatment using the 3 percent progesterone creams has not been borne out in subsequent studies. I think it's certainly helpful in a total approach, but not by itself. Other interesting work done by Helene Leonetti actually showed that using the 3 percent progesterone cream in menopausal women with a uterus would protect the uterus using a 0.625 Premarin.
[22] We know there's a lot of efficacy in using the 3 percent creams, and it can be very helpful as part of a total program.

Soy Isoflavones

JB: Another controversial area in which I know you certainly have some experience is the modulation of estrogen-related symptomatologies with soy isoflavones. There has been a recent backlash against soy in the fear that it will stimulate estrogen receptors and cause problems. What is your experience and position on this question?

AW: My experience has been that using levels of soy that approach what's been found in the Asian diet—somewhere between 30 and 100 mg per day—has a modulating effect on estrogen levels. If estradiol has a strength of 1 in terms of its estrogenic effects, soy would have a much lower estrogenic effect, maybe 1/500 to 1/1000.

Soy acts more as a tonic. If estrogen levels are very high and soy is added to the mixture, it is going to compete with the stronger estrogens for the receptor sites. That's going to bring down the total estrogen effect. If the estrogen levels are low, as they can be in menopause, adding the soy isoflavones will help fill up some of the receptor sites that would have been empty, and that would raise the estrogen effect. As with anything else, you can overdo it. You could take very large levels of isoflavones and perhaps get into trouble, perhaps with thyroid conditions, but my feeling is that using soy in moderation only acts as a modulator of estrogen in the body, or a tonic of estrogen in the body, and that it is not harmful.

Soy Studies

Dr. Messina published a reviewon the safety of soy in breast cancer survivors.
[23] After evaluating all of the studies, his take was that soy in moderation is not harmful and is probably helpful, and would not be contraindicated, even in women who are breast cancer survivors.

If we're talking about soy isoflavones as potentially dangerous, then we also have to look at some of the other foods that contain isoflavones. There are fruits, like apples and pomegranates, and several others that contain fairly high levels of isoflavones. Are we also going to restrict all those things from the diet? It doesn't make much sense to me.

Flax and Soy

I'm a proponent of using soy in beneficial amounts. As I said, that would approximate the amounts found in the Asian diet. I also use other modulators of estrogen from foods. Flaxseeds are extremely important for modulating estrogen levels. They also have their own isoflavones. Using flaxseeds and soy in combination, which I often do with soy protein powders, seems to be very helpful in reducing some of the symptoms of menopause.

Many of my patients are businesswomen in Manhattan; they don't have time for breakfast. When they run out of the house without eating, they begin the insulin resistance picture. I have them use a soy protein powder shake first thing in the morning, getting them about 20 mg of the isoflavones from the soy, and using flaxseeds along with that, and adding some extra fiber. Most of my patients love it and feel great. It gives them energy for a good part of the day and alleviates a lot of symptoms. I'm a major proponent of using soy in moderate amounts.

Cruciferous Vegetables

JB: I'd like to ask about one other nutritional modulator and that's crucifers. People have different opinions about whether the glucosinolates found in cruciferous vegetables and their secondary metabolites like indole-3-carbinol (I3C) and diindolemethane (DIM) are beneficial for modulating hormones. What's your experience?

AW: I certainly use the I3C and DIMfor women who have hormone imbalances. I measure the 2:16 (estrogen) ratio, although right now I'm not sure where we're going with that. I feel you need to have good levels of the 2-hydroxyestrones in comparison to the 16s. I also feel there is an inverse relationship between the 4-hydroxycatecholestrogens and the 2-catecholestrogens, and the 2s need to be a little bit higher, compared to the 16 catechols.

I will be happy to see the day when we can measure the 4s or we can measure the effects of the 4-catechols on DNA, but I have certainly found that in women, using I3C or DIM seems to increase the 2-hydroxyestrones. I believe that the crucifers are extremely important for liver detoxification, and I have a quick personal story to share in that regard.

Brussels Sprouts and Health: A Personal Story

When I was an intern, I came down with serum hepatitis and for some reason, I couldn't eat anything. My weight dropped from about 170 to 139; I was just getting ready to be hospitalized. For some reason, I started eating Brussels sprouts. I hadn't eaten them before, but there was a package of Brussels sprouts in the freezer. I ate those and then started eating them twice a day. Within a short period of time, my enzymes started coming down, my weight started back up, and since that time, which was almost 30 years ago, Brussels sprouts are my favorite vegetable.

As a food, Brussels sprouts have a lot of glucosinolates and affect liver detoxification. I think crucifers should be an important part of everyone's diet, and I certainly recommend one to two servings for everyone every day.

The Effects of Dietary Change

JB: I saw a paper published recently by Dr. Elizabeth Jeffery and her group at the University of Illinois on the direct influence of broccoli extract on glutathione S-transferase and the detoxifying phase 2 enzyme

systems and hepatic cells. They found broccoli extracts protect against oxidative injury and upregulate phase 2 detoxification. This article was published in the journal, Nutraceuticals and Functional Medical Foods. [24] People who increase their consumption of cruciferous vegetables can realize positive benefits. In fact, as you say, you can measure the alteration in 2- to 16-hydroxylated estrogen ratios with an increased crucifer-rich diet.

AW: If I had to pick one thing that works best or has the most impact, I would say it's dietary change. Getting the hormones out of the diet, removing the commercial sources of poultry and meats, getting the acidic foods and dairy products out of the diet, helps reduce inflammation. Gluten grains (wheat, rye, and barley) also seem to have a tremendous impact on increasing hormone imbalance, thyroid imbalance, and immunological and inflammatory imbalance.

I started doing celiac panels on anybody who comes in with a hormone problem. I have found that almost 50 percent of women have some elevation of the IgG gliadin antibody. I don't think anybody is doing that regularly, but just getting these people off the gluten grains for three to six months has a tremendous impact on their energy, their sense of well being, and all the hormonal symptoms.

Food Instead of Vitamins: Getting a Foot in the Door

You don't always have to go to a medication or an herb. You don't even always have to use supplements. There are many people who, for one reason or another, don't like taking supplements. They don't like taking vitamins, but if you can get them to change their diet and remove some of the inflammatory foods, the acidic and allergenic foods, they start feeling better.

If you can just get a foot in the door you can show them that simple lifestyle changes can help them start feeling better. Then they can start picking up on some of the other things that need to be done, whether it's gut restoration or supplements for PPAR agonists. Whatever it is, if you can get a foot in the door, and they start to feel better, they can move on and become committed to their own health.

Self-Nurturing

I think that probably the major thing that I do is to get people committed to self-nurturing. So many of my patients have been nurturers. They nurture everybody else. Whether they're businesswomen or housewives, they're nurturers, but they don't nurture themselves. A major piece of what I do is to get people to understand that they can nurture themselves; they're entitled to be nurtured. Just getting them to understand that helps them to become committed to a program where they're going to be optimally healthy.

Finding Joy in Life

JB: That's a great message that must play wonderfully with your patients. I'm sure they have not heard that as the standard line from their other physicians. It frames a different type of medicine. I guess that's why we've coined the term "functional medicine," because it sounds like it has a connection of function between the provider, the practitioner, and the patient.

AW: I always ask my patients what it is that gives them joy in life. When I get a patient who tells me that nothing gives him or her joy in life, I know that's going to be a difficult patient. Whatever the condition is, if there's nothing that gives them joy in life, that's a real challenge. They need to find something that is going to give them some joy.

Many of these patients are put on Prozac or antidepressants just so they can get out of bed and start seeing that there are roses to smell. It's not even stop and smell the roses; they don't know there are roses they can smell because they can't even get out of bed in the morning.

The Holistic Medicine Model
JB: We have all learned a tremendous amount from the wisdom you've shared with us in the last 30 minutes. It is what holistic medicine was designed to be. You look at the individual as a functioning whole organism in whom the sum of the parts is greater than the whole, and recognize that you're not treating organs; you're treating people. Thank you, Dr. Warshowsky, for sharing this with us. I hope it can be a stimulus to produce many more physicians like you across the country.

AW: Thank you very much, Jeff. I really appreciate that.

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