April 2001 Issue | Bethany Hays, MD

http://jeffreybland.com/knowledgebase/april-2001-issue-bethany-hays-md-2/

DOWNLOAD AUDIO |

Welcome to *Functional Medicine Update* for April 2001. For the past several months we have been talking about the newly emerging medical paradigm. You may remember the Price Waterhouse Coopers Healthcast 2010 report, which described three forces of change that will affect the healthcare system in the first decade of the 21st century. Those forces of change include consumer activism, e-health commerce information on the web, and genomics and the personalized medicine arising from it. Those forces will change the way we study various medical issues from a clinical and research perspective, as well as the "proof" of efficacy and safety for new therapies.

Recent dialogue and debate about clinical studies reflects this theme. Is the double-blind, placebo-controlled trial the gold standard for all questions we want to ask and have answered in the area of intervention, patient outcome, and potential new modalities for therapy? That question is now receiving attention at national governmental levels, looking at the Helsinki's new clinical rules that would be ethically and morally correct for evaluating studies with human subjects.

Evaluating the Double-Blind, Placebo-Controlled Trial

The double-blind, placebo-controlled trial assumes that one group may not do as well as another. It also raises ethical considerations. If you give one group a substance that proves to be less efficacious than that which the other group receives, how long do you have to wait before you discontinue the clinical trial and take the at-risk group out of the risk category? Statistical analysis often requires studies to be carried on longer than what might be considered ethically justifiable for the risk to the individuals participating in that study. This discussion has been taking place in regard to the way we should view studies in the future.

A recent issue of *Science* magazine contained an article titled "Helsinki's New Clinical Rules: Fewer Placebos, More Disclosure." That article indicates the possibility of vast changes in the way we prove the efficacy and safety of new substances. The risks, benefits, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods, according to the new declaration of Helsinki, approved in October of 2000. We should be less involved with placebos against something that may put patients at risk.

Functional Medicine and the Placebo-Controlled Trial

That is an interesting philosophical change. Nutritional or functional medicine interventions, with their many variables, are often criticized because they have not been subjected to randomized, placebo-

controlled, clinical, double-blind trials. Now these types of trials may be under scrutiny across the board. The widely held opinion is that the benefit/risk analysis, burdens, and effectiveness of new methods should be tested against the best available approaches, which means comparison studies. This could pave the way for limited clinical trials, case-control studies, and other methods including pattern recognition, complex data set analysis, and cluster analysis, giving rise to new ways of describing proof of efficacy.

Across the board we are seeing interesting changes in the way we address hypotheses in medicine. We have new opportunities to look at function rather than just at pathology. Function and clues to its improvement may be locked in the weblike interactions of complex variables and data sets that require more than a single agent/single outcome approach and are more amenable to comparison studies and cluster analysis types of multi-variant analysis

In addition to changing our genes and the way we look at medicine, we are also changing our memes, which includes the memory power, the transferred memory aspects of a culture that are contained in its rich written and oral history. With his book, *The Selfish Gene*, a number of years ago, Dawkins caused us to think of the gene as a selfish replicator. It cares only about replicating itself, and the organism that carries the gene is just the receptacle in which the gene is able to do its work of replicating itself. It sounded as if we humans are just being carried along by these selfish genes. In the last chapter, however, Dawkins opened up what may be the book's most enduring part. He asked if genes are only part of the story.

In fact, genes change very slowly over millennia of evolution. The memory-transferred learned behaviors, which Dawkins called "memes," may be more important in transferring survivability of the culture to its future. Through behaviors and ideas that are copied from person to person by imitation, these so-called memes have forced the human genes to make us what we are today.

Memes and Cultural Approaches to Problem Solving

This is a powerful concept. According to the author of an article in *Scientific American,* memes may be the single most powerful driving forces in creating new cultural approaches to problem solving.
In *Functional Medicine Update* we are trying to establish new memes, new perspectives, new approaches, new views, and new ways of looking at problems. We want to find ways to solve problems so those solutions can be culturally transmitted to the next generation without our having to go through the long, arduous process of natural selection that occurs through genetic modification. Memes can change quickly; genes change slowly.

Memes can have an obvious competitive advantage in allowing a culture to survive, particularly in a rapidly changing environment. Certainly, if there is anything we can say about 21st century living, it is that we are in a rapidly changing environment. I am not speaking strictly about the medical environment, the Health Cast 2010 report. I am talking about the overall cultural environment in which we live, in which its memes may determine its longevity and effects on posterity.

One of the major memes that is changing is functional genomics. A recent editorial in the *Journal of the American Medical Association* is titled "Genomic Medicine and the Individual Patient—Byte to Bedside." According to the authors, we are beginning to witness the change in the way doctors will talk to their patients related to specific signs, symptoms, and health problems of the moment, and their longer-term

health management programs.

This moves us away from diagnostic testing, looking for pathology, to prognostic medical thinking. It is a different meme, which considers that the future might be part of the patient's overall program. Where is the patient going? What is the trajectory of the way his or her genes are being expressed to give rise to either function or dysfunction?

Dr. Peter Kohler, from the Oregon Health Sciences University, recently wrote an article titled "From Theory to Practice in the Genomics Era," which appeared in the *Physician's Practice Digest.* According to Dr. Kohler, 25 years ago few medical practitioners imagined owning a computer that they would carry in their briefcase. Now, as a consequence of the rapid rise of information technology, we have access to the world's data bank in real time, and the Human Genome Project simultaneously is opening up the discovery of the book of life, the 23 chapters that make up our genetic heritage. We are learning not just how we will die—that event is not rigidly determined— but rather how we will live. We are learning about the various permutations and combinations of our genes that weave together to give rise to the interaction with our environment that may create the opportunity for a long, healthy life of 9, 10, or more decades.

That is a profoundly different model of medicine from that of the past. The earlier deterministic model locked the sperm with the egg to give rise to a set of characteristics called our genome, over which we had no control. Now we know that the expression of our genes determines our health from midlife on, and we can modify the expression of our genes through our environment. That is Dr. Kohler's message. Thus doctors will be counseling their patients about functional genomics.

The Future of Functional Genomics

In moving forward the field of functional genomics, reports indicate Motorola is developing a home diagnostic test, using a hand-held device, for DNA evaluation, DNA genomics. Where is this world going? Where will we be in the year 2020 with regard to the accessibility of our own unique genetic information and how it is modified by our own environment?

There is no more interesting area right now in application of this concept than hormone balance, particular the neuroendocrine balance in women, which is the focus of this month's *FMU*. Our Clinician of the Month is an expert in guiding us through the web of interacting variables encoded in our genes, whose expression is modified by our environment, nutrition, lifestyle, stress, and toxins. The expression of those variables can result in what we might call a healthy, low-morbidity aging process, or one with higher morbidity. With that theme in mind, we introduce our Clinician of the Month, Dr. Bethany Montgomery Hays

INTERVIEW TRANSCRIPT

CLINICIAN OF THE MONTH:

Bethany Hays, MD

JB: We are pleased, just a month before our Eighth International Symposium on Functional Medicine, to have as our Clinician of the Month, a doctor who will speak to us on a topic related to the focus of our symposium, functional endocrinology. By the way, for those of you who might have waited until the last minute to register for the symposium, it will take place May 22-26 at the Westin Bayshore Resort in Vancouver, British Columbia. If you haven't received the program, please call us at 800-228-0622. We will send you any information you need. One of the Symposium's keynote presenters is Dr. Bethany Montgomery Hays, our COM this month.

Bethany Hays was educated at Wellesley College and Baylor College of Medicine, and is board certified in obstetrics and gynecology. She was an assistant professor of OB/GYN at Baylor for a number of years and has been in private practice in various clinical settings. She continues as a clinical associate professor of medicine at the University of Vermont and is a faculty member in the Institute for Functional Medicine program. She works extensively with the American Holistic Medical Association. She has a wide clinical outreach, working in the Women-to-Women Clinic in Yarmouth, Maine, along with Dr. Christiane Northrup, a previous FMU COM. In our Applied Functional Medicine in Clinical Practice training program, Dr. Hays has taken on the responsibility for discussions of the female endocrine system. Bethany is highly acclaimed in our AFMCP program. It is with great pleasure, Dr. Hays, that I welcome you to FMU.

BH: Thank you, Jeff. I'm honored to be asked to do this for you.

Hormone Imbalances in Perimenopause

JB: I thought we might start with perimenopause and move into a discussion of menopause and how you have used some of the things in the medical news right now in relation to modulating hormone imbalances that occur throughout perimenopause and menopause. Just last weekend, I was visiting with doctors in Boston, Chicago, and Seattle. A number of compounding pharmacists came up to me to discuss various hormonal mixtures they are putting together to ameliorate the symptoms of menopause and perimenopause. Clearly, this is a big area of medical interest to consumers and practitioners alike.

Let's start with perimenopause. It seems almost to be a fundamental paradigm in endocrinology that when a woman in her perimenopausal period begins to show symptoms of flushing and vasomotor-related dysfunctions that seem to precede the onset of menopause, she is suffering from estrogen deficiency. When estrogen is administered to that woman, her symptoms go away, so we have jumped to the conclusion that it must be estrogen deficiency. I recall, when you talked to us at our AFMCP training program, that the story is a bit more complex. The estrogen connection to vasomotor symptoms and the interrelationship with proper management in light of new information is worthy of scrutiny. Perhaps you would describe that emerging story.

BH: We should begin by defining perimenopause, because a lot of definitions are floating around out there. The World Health Organization defines perimenopause as the period from the time abnormalities associated with hormone changes begin to occur to one year after the last menstrual period. That's an interesting definition. I believe that the heart of the issue for women's hormones at midlife centers around the fluctuating levels of hormones that usually begin in a woman's 40s, if you use 52 as the peak time for menopause to occur, and probably go on for several years after menopause.

It's these fluctuating levels, where the levels of hormones are sometimes high and sometimes low, that produce a lot of the problems. In a review article, Jerilynn Prior went back and looked, basically, at all of the studies where they had measured hormone levels in the perimenopause. I think it's an exquisite article. She discovered that long ago, before the idea that hot flashes mean low estrogen came about, they actually measured hormone levels in the perimenopause and found that the estrogen levels were elevated. Jerilynn went back and reviewed the raw data. She found that in fact, in the perimenopause, until very soon before the last period, and even for a while afterwards, there are fluctuations above the normal level of estrogen, that estrogen levels overall, the area under the curve, are elevated and not depressed.

Estrogen Elevations in Perimenopause

That makes perfect sense when you're a clinician looking at the women coming in to your office, because what are they complaining about? They're complaining about heavy periods, fibroid growths, endometriosis, and breast tenderness. Those are all symptoms of high estrogen, not low estrogen. Then they tell you about their hot flashes. You become confused, because everybody says hot flashes are from low estrogen and certainly we treat hot flashes with estrogen, so what's going on?

In this article Jerilynn points out that hot flashes are probably related to changes in estrogen levels. I think the hot flash issue has led clinicians astray for quite awhile. The real importance of perimenopause is elevated estrogen, because it produces the symptoms that lead women to situations like hysterectomy, and perhaps breast cancer and endometrial cancer, and that's where the real heart of the matter is in the menopausal transition. By the time you get through this fluctuating hormone level, a lot of the problems have straightened out.

Clinical Management of Perimenopause Symptoms

JB: That is fascinating. Typically in Western medicine we are taught that good medicine requires doing something. There is a demand to intervene and give the patient something. Here we have a symptom—vasomotor reactivity. It's producing an adverse response, and quality of life is diminished, so we need to jump in and rescue by giving hormones. I think the assumption was that we were treating the estrogen deficiency, so treatment was related to the cause. But now you are telling us, based on Jerilynn Prior's work, that is not true. In the late 1980s, I recall reading about estrogen supraphysiological levels associated with perimenopause. How does that lead the clinician into managing? Do you just do watchful waiting?

BH: No. I think it leads you to two possibilities. The second part of perimenopause that we haven't really discussed is that the balancing hormone for estrogen in women is progesterone. We know that, because progesterone downregulates estrogen receptors and has a number of other activities that modulate estrogen function and make it safe to have all of this growth-producing hormone around. In perimenopause, and every fertility specialist in the world knows this because they always put their 40-year-olds and older women on progesterone, progesterone production decreases.

What you really have in perimenopause is an increase in estrogen, but a decrease in progesterone. That leads you to a couple of things. First is the idea that a woman has hot flashes so we should give her estrogen. I can't tell you how many women I've seen who are estrogen-toxic because they were treating their symptoms with more and more estrogen. In fact, what you want to do is modulate the swings in

estrogen. You want to try to lower the peaks and raise the troughs so that the swing is not so fast and furious and doesn't produce the symptoms.

Modulating the Swings

These are serious symptoms. The symptom of hot flashes leads to sleep disturbance. That leads to irritability and depression, which lead women to come in to your office and tell you they are falling apart. They can't do their jobs, can't take care of their families. They're a mess, and they want you to please do something. These are important symptoms that we need to address and not just ignore. My approach is to address the modulation by using the things we know that affect estrogen metabolism in terms of downregulating the overall estrogen effect at the cellular level. Then we substitute phytoestrogens, for instance, for the troughs, the low parts of the estrogen swings, and add progesterone in to balance the amount of estrogen with a progestagen that keeps the overgrowth situations from occurring.

Assessing Hormone Levels

JB: A number of questions arise to follow up from that kind of design. Before we discuss the therapeutic aspect, we first need to ask questions related to assessment. A lot of clinicians will say that if they're going to offer that kind of assistance in helping a woman find this rhythmic dance of hormones during this perimenopausal period, what tests do they need to conduct? Do I need plasma measurements? Do I need to measure urinary metabolites? Do I need to measure salivary levels? What is your thought about the evaluation of hormones? Is it more clinically focused, or is it a combination of lab plus clinical to make these assessments?

BH: Because the levels of hormones are fluctuating so dramatically during this period, any single level of either salivary or serum hormones can be anywhere. It can be all over the map. You can get high, normal, or low. I know a lot of people believe in doing salivary hormone levels as a way of looking at where you are in the picture, and what to do therapeutically, but I've found them to be uniquely unhelpful. I use salivary hormone levels more to determine what effect I've had with my therapeutics than I do to determine where in the situation the woman is and how to start a therapeutic regimen.

I tend to use clinical signs to tell me whether the dominant situation is high or low estrogen. The clinical situation that correlates with high estrogen, or the most finely tuned piece, is breast tenderness. The symptoms of low estrogen—probably the only short-term clinical symptoms—are hot flashes. Hot flashes don't necessarily mean you have low estrogens; they mean you have falling estrogens. If I have women with breast tenderness, I assume their overall estrogen situation is high. If I have women having increasing numbers of hot flashes, then I may look at how many times out of the month they're in a low estrogen environment. Long-term, you can look at things like vaginal epithelium, skin and hair changes, cardiovascular disease, and effect on lipid levels—things like that. I basically go with the clinical information before I investigate the laboratory data.

Cultural Differences in Reports of Menopausal Symptoms

JB: In Jerilynn Prior’s excellent review article in Endocrine Reviews in 1998, to which you referred, she states that different cultures report very different prevalence of these vasomotor symptomatologies at perimenopause/menopause. It raises the question of whether women in different cultures are simply stoic

about it, or whether there's really a difference in the frequency based upon their gene/environment interaction. Do you have any thoughts about the prevalence of that condition in the United States versus other countries? Is it just the way women approach these things, or is there a difference based on lifestyle in the appearance of these flushing syndromes?

BH: The functional medicine answer to that question is that it's more complex. Certainly, dietary issues come into play. If you have a diet rich in B vitamins and soy products, you're going to metabolize estrogens differently. Another issue that may come into play is the effect of the adrenal stress profile on those changes and how estrogens interact with that profile. In countries in which there has been an overuse of antibiotics and there is a lot of overgrowth of yeast in the GI tract, you will have higher levels of estrogen related to microestrogens from yeast in the gut. It's simplistic to think that women in other cultures are more stoic. They may actually have less swinging around of their hormone levels than women in this culture do.

Managing Symptoms of Menopause: B Vitamin Status

JB: In referring to B vitamin status, you are moving from assessment and understanding to management. I saw a paper a number of years ago that was referenced by Carlton Fredericks in his 1977 book, Winning the Fight Against Breast Cancer: the Nutritional Approach. He talked about Morton Biskind and his work as an endocrinologist at Beth Israel Hospital in New York in the 1930s.

I found a paper published in 1938 on his studies in female animals, discussing the role of B vitamins and the passage of estrogen through the liver. The detoxification mechanisms for estrogen were not discovered until after 1971, so this was long before we really knew how things were detoxified, although we knew the liver played a role in removing or modifying estrogen passage. Would you give us your view of the B vitamin family in estrogen modulation, knowing that many women are probably subclinically deficient or insufficient with regard to B vitamins?

BH: This is an interesting area partly because, as you say, there was some really good information back before the 1970s and then it just got left behind. I don't even know why. It may have to do with the prejudice against anything nutritional on our medical radar screen. It just fell off the radar screen, but I think it's really important. There's some pretty reasonable evidence that B vitamins are involved in liver metabolism of estrogen, so that's one of the areas I look at to try to modulate estrogen levels.

There's some pretty good data about B vitamins and premenstrual syndrome, which is also sometimes a situation of elevated estrogen and depressed progesterone. I think there is enough information in the literature, and when you add that to the information from, say, the Nurses' Health Study that says you take a multi-vitamin and you decrease your risk of cardiovascular disease by a quarter of the total risk. You can hardly avoid recommending a good multi-vitamin with a B complex.

B Vitamins and Hormone Detoxification

JB: You shared a paper by Biskind with me on a collaborative study on the nutritional insufficiency in the etiology of metrorrhagia, cystic mastitis, and premenstrual tension. The authors cited some interesting work that I was unaware of until I reviewed my biochemistry, regarding the fact that B vitamin insufficiency in female animals reduces the ability for estrogen to be detoxified, but it does not have an

effect on the detoxification of androgens. You get this interesting differential effect. I think I have a biochemical explanation for that effect, which relates to flavin adenine nucleotides (FAD), which are very important in the detoxification of estrogen.

When you oxidize an estrogen to its metabolite, you have to have something to which to transfer the electrons, which turns out to be FAD. So if you're riboflavin-insufficient, you don't have the appropriate electron receptor, so you can't do an oxidation without doing a reduction, where that doesn't pertain to the effects found with conversion of the androgens to estrogen. You can end up getting into a hyperandrogenic state by B vitamin insufficiency.

BH: I think that's perfectly logical. The secondary effect of that is that elevated androgens depress sex hormone-binding globulin, and then the amount of free estrogen goes even higher. You really have a snowball effect.

Hypoandrogenic/hyperestrogenic Situation

JB: You said it correctly. I said it incorrectly. I meant a hypoandrogenic/hyperestrogenic situation. You have an underconversion of estrogen and you continue to have the normal conversion of androgens. Differential effects by B vitamin insufficiency are that the person looks as though she has too much estrogen because she can't process it correctly to the oxidized derivatives.

BH: Right. But since most of the serum assays for estrogen are bound and unbound, you wouldn't pick up the added effect of the elevated androgens.

Available versus Unavailable Forms of Estrogens and Androgens

JB: That leads me to the next area of this very complicated discussion. I think a lot of clinicians forget about the role of sex hormone-binding globulin and the fact that it is also modifiable by stress, diet, and lifestyle. Would you tell us about the issue of the available versus the unavailable forms of estrogens and androgens?

BH: Sex hormone-binding globulin is affected by a number of steroid hormones, as well as by insulin. This brings in another of the web factors, glycemic control and the folks who are insulin-resistant. Sex hormone-binding globulin is just 1 of 24 things I have on my list that affect estrogen at the cellular level.

I want to emphasize that the amount of estrogen in the system doesn't tell you about the estrogen effect in the cell. What's causing the problems for women is the estrogen effect in the cell. You can get an estrogen effect in the cell, or you can get a mitogenic effect in the cell, for instance, with elevated insulin levels. There is more than one pathway in which that happens. It's really complex. I had no idea when I started studying this how complex it was going to end up being.

Tissue versus Plasma Hormone Levels

JB: What you are saying is extraordinarily important for the clinician. I recall a paper in which analysis of breast tissue in women with breast cancer revealed E2 levels, estradiol levels, which were 10 to 50 times higher than in the plasma. Of course, it's the drive that occurs within tissues that's the most important, as

you point out, not how much is floating around in the extracellular space. This article pointed out that due to localized production—which could be through aromatase in adipose tissue in the breast—there could be a much higher production, not only of estradiol, but the metabolites like the 2- 4- and 16-hydroxylated compounds. These compounds, at least in the case of the 4 and 16, may be more genotoxic than estradiol itself. I think you are helping clinicians to understand that they shouldn't jump to simple conclusions based on what is floating around in the plasma.

BH: I think that's correct. I've been reading recently about progesterone's effect on breast tissue. It turns out progesterone primes breast tissue cells for cross-talk with paracrine factors. For instance, progesterone increases the number of insulin receptors in breast tissue. I think that might have a critical implication when you're giving progesterone, for instance, even natural progesterone, which doesn't seem to have nearly as strong an effect as the artificial progestins, but still has this effect.

When you give natural progesterones to someone with insulin resistance and high levels of insulin, you may be putting her at risk instead of decreasing her risk related to the effects of progesterone on apoptosis and estrogen receptors. We are still lacking a lot of information. I find it a little scary that there has been this 50-year uncontrolled experiment on women's bodies of giving them hormone replacement therapy.

Evaluating Insulin Sensitivity

JB: You just said something I want to make sure everyone caught, because it's a very powerful potential clinical insight. According to Reaven, 20 percent of the non-diabetic population suffers from some form of insulin resistance/hyperinsulinemia, and more than 50 percent of those people are women. In that case, if you administer androgenic-like hormones, including DHEA, testosterone, and/or progesterone, those androgenic substances may produce a negative rather than a favorable effect. I think that's a very important clinical insight. The watchword is to look at where the patient is on insulin sensitivity before you start administering androgenic substances.

BH: I think that's an important reason why the information about hormone replacement therapy, meaning estrogen and progestins, as compared to estrogen alone, may actually be more dangerous for breast tissue. It explains some of the confusion that we see about why progesterone, which downregulates estrogen receptors and creates apoptosis, may have a different effect, but the different effect occurs only in some women. I remember a slide I showed at the AFMCP in which we looked at luteal phase levels, and there were groups of women who did the opposite from the majority. When we say that progesterone downregulates and produces a certain effect, there was a group of women who went in the other direction. Those may have been women with elevated insulin levels.

Determining Therapy

JB: That has really come through to me very strongly, thanks to the education you provided. It was as if a very strong light went on. You shared an article in Molecular Endocrinology by Lange, Richer, and Horwitz, which is a powerful discussion about progesterone priming breast cancer cells for cross-talk and the concept that progestins may in fact decrease expression of the p53 tumor suppressor gene, when given at high dose, single pulse. Then we get into the question of what dose, what type, and what length of therapy. It appears as if there's a real difference between single-dose, high-potency and maybe progestagins versus progesterone and how that may then be translated into a physiological message in the

woman.

BH: I think that's true. I'm beginning to think about the factors that are important in terms of determining the clinical approach to hormone replacement therapy. I guess I would say you're not replacing hormones if you're giving Premarin and Provera; you're substituting hormones. I am actually referring to replacement of estradiol and natural progesterone. You need to consider that the effect of continuous progesterone is different from the effect of intermittent progesterone, so progesterone two weeks out of the month. I think the amount of estrogen you're dealing with is going to have a significant effect on whether you should cycle or give progesterone continuously.

The third piece that's going to be really important is this priming for cross-talk with insulin and insulin-like growth factor, so I think glycemic control and looking at glucose metabolism is going to be really important.

Guy Abraham and the Importance of Magnesium

JB: Guy Abraham published some landmark studies, at least preliminary studies, over a number of years. I know you're familiar with his work and probably know him personally. He talked about the important role of magnesium, along with calcium, in postmenopausal women for the maintenance of bone integrity. Magnesium, he felt, is an under-appreciated nutrient that also has effects on hormone balance and that in conjunction with vitamin B6 and the other B vitamins, it may be very important in promoting salutary effects on menopause. What are your thoughts regarding Dr. Abraham's concepts?

BH: I think he's got a lot of the pieces nailed down absolutely correctly. I do worry, as do I think a number of the people who considered this issue when the recommendations came out to put women on high doses of calcium. I do worry about people not having enough magnesium. It's one of the superstar supplements, the ones you can pretty much guarantee you can give to anybody and they're going get a positive effect, because so many people are deficient. Magnesium is important for bone metabolism. I think anybody who prescribes calcium without also prescribing magnesium may be doing harm instead of good.

Normalizing Effects of Magnesium

JB: In one of Dr. Abraham's studies back in the 1980s, he showed that increased magnesium intake was associated with decreasing estradiol and increasing progesterone levels in patients with estrogen/progesterone imbalances, indicating that it had a kind of normalizing effect in the metabolism of those hormones.

BH: I think that's really fascinating, too. I don't know the biochemistry. Do you?

DHEA Supplementation Considerations

JB: He made some speculation in his papers as to how he thought it affected various aspects of Krebs cycle functioning and cell signaling. I think perhaps in light of the year 2001, some of those concepts may need to be reevaluated, but certainly the clinical evidence seems pretty strong.

Let me go to another area that a lot of people are asking about and that is when, if ever, given these imbalances that might appear throughout the menopausal transition, would a woman be considered for DHEA supplementation? Over the last few years a number of at least preliminary clinical trials have been published on DHEA in relation to conditions including depressive disorders, insulin resistance/hyperinsulinemia, obesity, and areas related to hormone imbalances, particularly androgen decreases, with low sense of well being and an altered libido. What's your feeling about DHEA and where it might be employed?

BH: I think falling levels of DHEA may be highly important in terms of perimenopausal bone loss. I'm looking at DHEA as a key to getting bone-building activity going, as opposed to stopping bone resorption. I think that's an interesting area to look at. This is actually a place where I would use salivary hormone levels to assess what I'm doing and whether I'm doing what I think I am. The situation in which I usually use DHEA is for a person with fatigue who has an adrenal stress index that shows low DHEA levels and possibly low cortisol levels, as well. I will check salivary estrogen/progesterone/testosterone and then start the DHEA.

After they've been on the DHEA for a while, I'll reassess the estrogens, progestins, and testosterone to see where that DHEA is going. We tend to think of it in a linear fashion. We always draw the graphs on the board about how cholesterol goes to this, goes to progesterone, goes to estrogen. In fact, they all exist together in a soup. The question is, when you throw in extra amounts of one chemical, how do you change the soup? If you repeat your salivary hormone levels and find out that your DHEA is all being poured down into estrogen, you better be careful about that. If it's going to cortisol, you may be getting the effect you're looking for.

Menopause as Disease

JB: Let me close with a question that may be on the minds of many listeners. The suggestion is made that this period from perimenopause into menopause is associated with increasing risk to breast cancer and cell cycling events in which cells have more mitogenic drive and begin to become atypical. Certain genes are up- or downregulated during that period. Therefore, there is this concept that perhaps menopause is an unhealthy event, that it is dangerous and something we need to fight against, and that it's not associated with good health. Reports in the literature, however, indicate that menopause is just a natural rhythm of life that can be gone through without compromise of health. According to these reports, what happens with unnatural menopause is that one gets into imbalances associated with unhealth, and perhaps we forced the equation in our Western world over into the unhealthy part rather than the natural, healthy menopause. Could you comment on whether menopause is a disease and we should treat it that way?

BH: A lot of information suggests that menopause is healthy. It's perimenopause that gets everything out of whack. For instance, with breast cancer, we know that most breast cancers are very slow growing. Breast cancer that you discover postmenopausally in your 50s or 60s may have been initiated in perimenopause. That would make perfect sense if you're looking at the increased stimulation of breast tissue by an elevated estrogen, and the failure of apoptosis created by decreased progesterone. The area I'm the most interested in looking at is the way our culture unbalances this program. I don't think normal perimenopause was supposed to be such a big deal. I think it's gotten to be a big deal primarily because of nutritional changes that are influencing estrogen metabolism, and possibly gut-associated problems related to the overuse of antibiotics. Add to that the bad food. If you get people invested in being healthy

during the perimenopause, menopause will mean just not having periods anymore.

Continuing this Discussion at Eighth International Symposium

JB: That's a wonderful finish for this discussion. The Eighth International Symposium on Functional Medicine will provide you and your colleagues with more opportunity to address these questions. The focus of the Eighth International Symposium on Functional Medicine in Vancouver is on functional medicine approaches to endocrine disturbances associated with aging. Dr. Hayes, we'll look forward to being with you in May. Thank you so much for spending time with us today. You have opened our minds and eyes to a lot of important clinical facts.

BH: Thanks, Jeff. I can't wait for the Symposium.

Bibliography

1. Enserink M. Helsinki's new clinical rules: fewer placebos, more disclosure. *Science.*2000;290:418-419.
2. Dawkins R . *The Selfish Gene.* New York, NY: Oxford University Press; 1992.
3. Blackmore S. The power of memes. *Sci Amer*. 2000;283(4):64-66.
4. DeAngelis CD, Rosenberg RN, Smith JM. Genomic medicine and the individual patient--byte to bedside. *JAMA*.. 2000;284(20):2642.
5. Kohler PO. From theory to practice in the genomics era. *Physician's Practice Digest.*Jan/Feb 2001.
6. Prior JC. Perimenopause: the complex endocrinology of the menopausal transition. *Endocrine Rev.* 1998;19(4):397-428.
7. Biskind MS, Biskind GR, Biskind LH. Nutritional deficiency in the etiology of menorrhagia, metrorrhagia, cystic mastitis, and premenstrual tension. New York Acad Med; 1943.
8. Lange CA, Richer JK, Horwitz KB. Hypothesis: progesterone primes breast cancer cells for cross-talk with proliferative or antiproliferative signals. *Mol Endocrinol.*1999;13(6):829-836.
9. Abraham GE, Grewal H. A total dietary program emphasizing magnesium instead of calcium. Effect on the mineral density of calcaneous bone in postmenopausal women on hormonal therapy. *J Reproductive Med.* 1990;35(5):503-507.
10. Abraham GE. Nutritional factors in the etiology of the premenstrual tension syndromes. *J Reproductive Med.* 1983;28(7):446-464.
11. Abraham GE, Rumley RE. Role of nutrition in managing the premenstrual tension syndromes.
12. *J Reproductive Med.* 1987;32(6):405-422.
13. Bider D, Mashiach S, Serr DM, Ben-Rafael Z. Endocrinological basis of hot flushes. *Obstetrical & Gynecological Survey.* 1989;44(7):495-499.
14. Jaiswal K, Krishna A. Effects of hormones on the number, distribution and degranulation of mast cells in the ovarian complex of mice. *Acta Physiologica Hungarica.* 1996;84(2):183-190.
15. Fekete CS, Strutton PH, Cagampang RA, et al. Estrogen receptor immunoreactivity is present in the majority of central histaminergic neurons: evidence for a new neuroendocrine pathway associated with luteinizing hormone-releasing hormone-synthesizing neurons in rats and humans. *Endocrinol.* 1999;40:4335-4341.

16. Labrie F, Belanger A, Luu-The V, et al. DHEA and the intracrine formation of androgens and estrogens in peripheral target tissues: its role during aging. *Steroids.*1998;63:322-328.
17. Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR. Dehydroepiandrosterone treatment of midlife dysthymia. *Biol Psychiatry.*1999;45:1533-1541.
18. Rubino S, Stomati M, Bersi, et al. Neuroendocrine effect of a short-term treatment with DHEA in postmenopausal women. *Maturitas.* 1998;28:251-257.
19. Stomati M, Rubino S, Spinetti A, et al. Endocrine, neuroendocrine and behavioral effects of oral dehydroepiandrosterone sulfate supplementation in postmenopausal women. G*ynecol Endocrinol.* 1999;13:15-25.
20. Casson PR, Lindsay MS, Pisarska MD, Carson SA, Buster JE. Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: a case series. *Human Reproduction.* 2000;15(10):2129-2132.
21. Ceresini G, Morganti S, Rebecchi I, et al. Evaluation of the circadian profiles of serum dehydroepiandrosterone (DHEA), cortisol, and cortisol/DHEA molar ratio after a single oral administration of DHEA in elderly subjects. *Metabolism.* 2000;49(4):548-551.
22. Gordon CM, Grace E, Emans SJ, Goodman E, Crawford MH, Leboff MS. Changes in bone turnover markers and menstrual function after short-term oral DHEA in young women with anorexia nervosa.
23. *J Bone Miner Res.* 1999;14(1):136-145.
24. Toth MJ, Sites CK, Eltabbakh GH, Poehlman ET. Effect of menopausal status on insulin-stimulated glucose disposal. *Diabetes Care.* 2000;23:801-806.
25. Andersson B, Mattsson LA. The effect of transdermal estrogen replacement therapy on hyperandrogenicity and glucose homeostasis in postmenopausal women with NIDDM. *Acta Obstet Gynecol Scand.* 1999;78:260-261.
26. Cucinelli F, Paparella P, Soranna L, et al. Differential effect of transdermal estrogen plus progestagen replacement therapy on insulin metabolism in postmenopausal women: relation to their insulinemic secretion. *Eur J Endocrinol.* 1999;140:215-223.
27. Jansson G. Oestrogen-induced enhancement of myeloperoxidase activity in human polymorphonuclear leukocytes--a possible cause of oxidative stress in inflammatory cells. *Free Rad Res Comms.* 1991;14(3):195-208.
28. Sattar N, Perera M, Small M, Lumsden MA. Hormone replacement therapy and sensitive C-reactive protein concentrations in women with type-2 diabetes. *Lancet.*1999;354:487-488.
29. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA.*283(4):485-491.
30. Rundle A, Tang D, Hibshoosh H, et al. The relationship between genetic damage from polycyclic aromatic hydrocarbons in breast tissue and breast cancer. *Carcinogenesis.*2000;21(7):1281-1289.
31. Shibutani S, Ravindernath A, Suzuki N, et al. Identification of tamoxifen-DNA adducts in the endometrium of women treated with tamoxifen. *Carcinogenesis.*2000;21(8):1461-1467.
32. Neven P. Local levonorgestrel to prevent tamoxifen-related endometrial lesions. *Lancet.* 2000;356:1698-1699.
33. Lee JR. Osteoporosis reversal with transdermal progesterone. *Lancet.* 1990;336:1327.
34. Lee JR. Use of Pro-Gest cream in postmenopausal women. *Lancet.* 1998;352(9131):905.
35. Lee JR. Is natural progesterone the missing link in osteoporosis prevention and treatment? *Med Hypotheses.* 1991;35:316-318.
36. Stevenson JC, Purdie DW. Use of Pro-Gest cream in postmenopausal women. *Lancet.* 1998;352:905-906.

37. MacFarland SA. Use of Pro-Gest cream in postmenopausal women. *Lancet.*1998;352:905.
38. Cooper A, Spencer C, Whitehead MI, Ross D, Barnard GJ, Collins WP. Systemic absorption of progesterone from Progest cream in postmenopausal women. *Lancet.*1998;351:1255-1256.
39. Burry KA, Patton PE, Hermsmeyer K. Percutaneous absorption of progesterone in postmenopausal women treated with transdermal estrogen. *Am J Obstetrics Gynecol.*1999;180(6 Pt1):1504-1511.
40. Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstetrics Gynecol.* 1999;94(2):225-228.
41. *Harvard Women's Healthwatch*. October 1999;7(2).
42. Carey BJ, Carey AH, Patel S, Carter G, Studd JW. A study to evaluate serum and urinary hormone levels following short and long term administration of two regimens of progesterone cream in postmenopausal women *Br J Obstetrics Gynaecol.*2000;107:722-726.
43. Mercuro G, Pitzalis L, Podda A, et al. Effects of acute administration of natural progesterone on peripheral vascular responsiveness in healthy postmenopausal women. *Am J Cardiol.* 1999;84(2):214-218.
44. Bell MC, Crowley-Nowick P, Bradlow HL, et al. Placebo-controlled trial of indole-3-carbinol in the treatment of CIN. *Gynecol Oncol.* 2000;78(2):123-129.

p>