Health Condition: Women's Health & Hormone Balance

"The standard of care would be to go to your gynecologist, your family physician, or your internist once a year for your pap smear. If you are having some hot flashes and your periods are changing you get a prescription for something and then you would hear, 'Have a nice year. I'll see you next year for your next pap smear.' For women we are seeing now (the baby boomers who are aging and coming into this whole mid-life and beyond timeframe), that is really not an acceptable option. You don't just give someone a prescription and say have a nice time. They want a conversation. They want to know what this medicine does. What are the risks and benefits? What are the other options that aren't this? We kept talking to patients, and friends, and colleagues about their frustration with health care."

—Jane Murray, MD
November 2008

Women's Health in the 21st Century

"Although women's health has been under-attended for most of the 20th century, it has gained international attention in recent decades. Medical and social research on heart disease, lung cancer, HIV/AIDS, and trachoma indicate that bio-socio variables affect women's health differently from men's."

Wolfson et al., Int J Obstet Gynecol. Volume 104, Supplement, Pages S2-S3 (March 2009)

There is no doubt about it – women are different from men physiologically – perhaps that is stating the obvious; however, that blaring fact has not always been taken under consideration by science as evidenced by the number of studies investigating chronic conditions predominantly in men.

In the 21st century, this trend is changing.

The National Institutes of Health has encouraged researchers to study women's physiology specifically, as there are several indications that they may respond differently to the effects of chronic disease. For example, women with metabolic syndrome and cardiovascular disease have lowered rates of survivability relative to men. One in three women has autoimmune disease, with higher rates of autoimmune disease in women over men. Also, women manifest symptoms differently in their bodies compared with men.

Thus, in the next decades, we hope to learn much more about the physiology of women.

Hormone Balance in Women: The Endocrine Web

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. Behind the scenes of operation is the neuroendocrine system, a system of glands that secretes different types of hormones directly into the bloodstream. These essential hormones, or cellular messengers, regulate various human functions, including metabolism, growth and development, tissue function, and mood.

In fact, you might consider the endocrine system as a web, as it interconnects the hypothalamus, pituitary gland, parathyroid and thyroid glands, adrenal glands, and ovaries (female)/testes (male) with

a series of signals that create specificity of outcome as function in cells and tissues. The concept of balance and optimal function 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.

There is still a lot of confusion.

We still haven't nailed all this down, but what has emerged is that we need to look at the individual woman. We shouldn't be using a general "rules of the road" or "one-size-fits-all" mentality. We have to really look at how each woman responds. What are her unique genetic characteristics, and how do those, then, influence her outcome?

Where does one start? They key is to start with the whole person, not the individual piece parts, because in a web, pulling just one thread can have an effect on the entire structure.

In February 2004, Dr. Jeffrey Bland interviewed Allan Warshowsky, MD, a board-certified OB-GYN practicing in New York who is also the author of a book titled *Healing Fibroids: A Doctor's Guide to a Natural Cure*. Although conventionally trained, Dr. Warshowsky has transformed his practice to combine the best of conventional medicine with integrative and holistic practices. Dr. Warshowsky described his experience with patients this way:

"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.

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.

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.

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."

In our society today, a woman may live nearly half her life in the absence of having her menstrual period. The questions we want to ask a modern woman about her health are very different than if the mean average life expectancy of women was 55 years.

What we are really asking is how do we sustain good health for a century or more in a woman?

That's a different question that requires different answers than maybe we would have used some 50 years ago…

Premenstrual Syndrome (PMS), Polycystic Ovary Syndrome (PCOS), and Fibroids

"The scientific study of menstruation has been hampered by the overpowering influence of traditions and social beliefs. We have all, men and women, been conditioned to view menstruation in a negative way. Perhaps, it is time to look at menstruation from another point of view. How many fine novels have been finished in a burst of creativity in the premenstrual period? How many great ideas have been born premenstrually?"

Speroff L. et al. Clinical Gynecologic Endocrinology and Infertility, 1999

Most women experience some degree of Premenstrual Syndrome (PMS) with approximately 85% of menstruating women experience one or more symptoms of PMS. About 5% to 10% of women have symptoms severe enough to be debilitating. Interestingly, unlike perimenopause, PMS affects women of all cultures and socioeconomic levels and more than 200 symptoms spanning physical discomforts, negative affect, and impaired cognitive function or performance (Table 1). have been associated with PMS.

The etiology of PMS remains unknown, but may be complex and multifactorial. What makes the condition even more difficult to diagnose and treat is that no laboratory tests exist to confirm diagnosis and some health conditions have symptoms similar to PMS, such as premature menopause/peri-menopause, endometriosis, IBS, chronic fatigue syndrome, hypothyroidism, and major depression. There may be underlying serotonin deficiency or fluctuations present, although not all patients respond to treatment with SSRIs. Other causes may be due to deficiencies in prostaglandins or imbalances in prostaglandin precursors, along with genetic factors.

Table 1. Symptoms of PMS

Physical Discomforts	Negative Affect	Impaired Cognitive Function or Performance
Fluid retention	Tension or anxiety	Difficulty concentrating
Weight gain	Increased appetite or food cravings	Distractibility
Breast tenderness (mastalgia)	Irritability	Forgetfulness
Headache	Depression or sadness	Confusion
Fatigue	Feelings of hopelessness	Mood swings
Nausea	Restlessness	Temper outbursts
Insomnia or excessive sleep	Tearfulness	Accident prone
Abdominal cramps	Anger	Poor motor coordination
Muscle, joint, or back pain	Feeling overwhelmed	Impulsivity

Source: Dickerson LM et al. Am Fam Physician 2003; 67(8):1743-52. Singh BB et al. Altern Ther Health Med 1998; 4(3): 75-79. Tempel R. AAOHN J 2001; 49(2): 72-78.

Fibrocystic disease of the breast, cervical dysplasia, uterine fibroids, preclinical polycystic ovary syndrome (PCOS), perimenopause, and premenstrual syndrome (PMS) would not be considered diseases, but rather conditions. We might call them functional physiological disturbances or endocrine imbalances.

PCOS is a disorder characterized by chronic estrogenized anovulation, androgenism, and abnormal gonadotrophin secretions. Women with this syndrome are shifted toward a predominance of testosterone/androgen, away from normal estrogen levels, ultimately resulting in an imbalance in their androgen/estrogen concentrations. This disorder, common among premenopausal women, affects 5 to 10 percent of the population. Despite uncertainty about its primary cause, this syndrome appears to be related to hyperinsulinemia. Insulin is not just a glucoregulatory hormone. It is a cell-signaling hormone that also has an adverse effect on the expression of an enzyme in the theca cell of the ovary, called 17,20-lyase, which converts pregnenolone to dehydroepiandrosterone (DHEA) and ultimately on to estrogen. Investigators have been looking into the relationship between insulin and estrogen for many years, including John Nestler, MD, from the Department of Medicine of the Medical College of Virginia.[1]

PCOS is the late-stage diagnosis from an earlier stage increasing severity of insulin resistance that interferes with menstrual cycling and ovulation. That topic was the subject of a paper in the *Journal of the American Medical Association* in 2001 in which investigators found long or highly irregular menstrual cycles were a marker for risk of type 2 diabetes. This risk resulted as a consequence of increasing severity of insulin resistance, hyperandrogenicity, altered hormonal balance between estrogen and androgens, and the resulting reproductive and menstrual irregularities in these young women. Although screening bias in this study (i.e., greater sensitivity of screening for diabetes in women with irregular cycles) might contribute to observed results, these authors consider it an unlikely explanation for the fact that women with the menstrual irregularities (altered cycles, menorrhagia) later are much more likely to develop diabetes.[2]

Fibroids (also called uterine leiomyoma) are muscular tumors that grow in the wall of the uterus and are almost always benign (non-cancerous). Dr. Allan Warshowsky, who specializes in the treatment of fibroids, said this in 2004:

"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…

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."

Although Dr. Warshowsky described his anecdotal experiences when interviewed, the question of a relationship between fibroids and inflammation is being examined by researchers.[3] He cites the work of Elizabeth Stewart, MD, who is with the Mayo Clinic, as being an exceptional resource for information on fibroid research.[4,5]

Perimenopause, Menopause, & Hormone Replacement Therapy

"Like an electrical charge, menstruation and the ebb and flow of energy is an "alternating current". During menopause, the flow of energy becomes intensified and steady, like a "direct current". We are charged with energy to the degree we have opened ourselves to the wisdom of the Crone."

- Farida Shaw

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.

Bethany Hays, MD, a board-certified OB-GYN practicing at True North Health Center in Falmouth, Maine, was interviewed by Dr. Jeffrey Bland in 2001 and 2007. Based on her many years of clinical experience, she had this to say about the period of time called perimenopause:

"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.[6] 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.

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."

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. In perimenopause, progesterone production decreases. The balance of hormones is critical to the function of the brain. When hormones are out of balance, the resulting symptoms can lead women to seek treatment, and this is where a "one-size-fits-all" approach can go astray. Dr. Hays emphasizes the need for testing rather than prescribing treatment based on symptomatology:

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

The question of pharmacogenetics and metabolism of these hormones is an important point to emphasize. What is being discovered is that there is a lot more variability among women as to how they process these hormones through their bodies. The construct that a single dose of a therapeutic agent on body surface area will be tolerated in the same way by all women is a specious argument and underlies the need for a personalized approach.

We are into a very dynamic period of reevaluation of what is safe and effective as it pertains to hormone replacement therapy in the perimenopausal or postmenopausal woman. Not every woman absolutely requires hormone replacement therapy to lead a healthy life. For those women who do get hormone replacement therapy, tailoring it to their own specific needs is critically important. It is not just administration of the hormone substances in and of themselves that is important, it is also how those substances interact with receptors and how these receptors then signal cellular activity. Many estrogen-related receptors are now being seen as targets in cancer and other metabolic disorders, so estrogen

has a crosstalk with many other cellular functions, including inflammatory functions, insulin signaling functions, and relationships to detoxification. Many cellular functions have (in the web of interaction) a relationship to estrogen and its reactivity.

With regard to hormone replacement therapy and managing women as they go through perimenopause, and into menopausal and post-menopausal years, we now recognize that women respond very differently based on the principles of epigenomics and genomics. A lot of this has to do with single nucleotide polymorphisms (SNPs) that modulate the way various compounds travel through the body and are biotransformed and excreted, and also how they interact with receptor sites and are engaged in intercellular signal transduction. Some of the most critical SNPs that relate to women's health are now starting to be identified. This finding is giving birth to a whole new field of molecular genetics as applied to the female reproductive system, particularly coming out of the area of breast cancer in which certain SNPs are being identified to have higher associations with breast cancer risk and responsiveness to certain chemotherapeutic drugs.

Hormone replacement therapy (HRT) has been shown to improve the quality of life for some women who have hypoestrogenic symptoms (vaginal dryness, night sweats, even some of cognition and depression dysphoria symptoms), but then we juxtapose that benefit against the data that has come out of the Women's Health Initiative looking at mixed conjugated equine estrogen and progestins and their risk to cardiovascular outcome. The National Institutes of Health (NIH) established the Women's Health Initiative (WHI) in 1991 to address the most common causes of death, disability and impaired quality of life in postmenopausal women: cardiovascular disease, cancer, and osteoporosis. The WHI was a 15 year multi-million dollar endeavor, and one of the largest U.S. prevention studies of its kind. The three major components of the WHI were:

- A randomized controlled clinical trial of promising but unproven approaches to prevention;
- An observational study to identify predictors of disease;
- A study of community approaches to developing healthful behaviors.

The WHI trial of daily combined therapy with estrogen and progestin was terminated early, in May of 2002. In an article published in 2003 in the *New England Journal of Medicine* titled “Rethinking Postmenopausal Hormone Therapy,” the reasoning behind the early end to the trial was described this way:

> "The reason for stopping was an increased risk of breast cancer (and evidence of greater overall risk than benefit) in the hormone-therapy group. Far more surprising, however, was the associated increase in the risk of myocardial infarction.”

The WHI findings were unexpected. They caused considerable consternation and a reevaluation of our presumption about the benefits of HRT. The hormone formulations in the WHI were 0.625 mg of conjugated equine estrogen and 2.5 mg of medroxyprogesterone.

In addition to the WHI data, numerous studies have been published about the risk of venous thromboembolism with regard to hormone replacement therapy. A systematic review and meta-analysis of a variety of published studies with the title "Hormone Replacement Therapy and Risk of Venous Thromboembolism in Postmenopausal Women" appeared in the *British Medical Journal* in

2008.[7]The authors of this article started to look at the meta-analysis and the randomized trials from a larger kind of study perspective. What they concluded was that estrogen replacement does increase the risk of venous thromboembolism when given as oral mixed conjugated equine estrogens, especially during the first year of treatment when averaged across all individuals. The women most highly at risk may be those who carry the Leiden Factor V polymorphism.

When we start examining the relative risk/benefit, certainly things like route of administration, dose, and formulation need to be considered. For safe and effective use, evidence seems to indicate that bioidentical hormones are preferred over synthetic hormones, especially if an individual will use replacement for many years, as is often the case-going through perimenopause into menopause. When we talk about bioidentical hormones, we are talking about 17-beta estradiol, estrone, estriol. We are talking about progesterone as contrasted with progestins. And we are talking about testosterone. These would be considered your bioidentical hormone replacement substances.

In terms of administration, there is some interesting research in the scientific literature. In 2005, a paper was published in the journal *Maturitis* in which the authors looked at hormone replacement therapy (estrogen and progesterone), contrasting transdermal versus oral hormone therapy.[8] In this particular study, the findings were that transdermal (or even the intravaginal administration) had a more beneficial effect than the oral administration route. This finding also seems to be the case in a paper that appeared in *Arteriosclerosis, Thrombosis, and Vascular Biology* in 2004 that contrasted the effect of oral versus transdermal estrogen on serum amyloid A and high density lipoprotein serum amyloid A in postmenopausal women.[9] These are proteins (SAA) that are associated with inflammation and also with cognitive dysfunctional neuroinflammation. So the question is, is there any difference between the route of administration of estrogens and the effect they have on serum amyloid A protein? Oral estrogen was found to increase serum amyloid A and alter HDL composition to contain a higher level of SAA protein, whereas the transdermal administration did not have this same effect. These findings appear to argue for the use of a transdermal estrogen that would avoid first-pass conversion in the liver and would have a more favorable effect on cardiovascular outcomes.

Compounding the right formulation of bioidentical hormones is a place where the practitioner can work very closely with the compounding pharmacist to produce a specific formulation that would personalize the bioidentical hormone replacement therapy for each woman. Personalization—finding the right balance—is critically important in this field.

Hormones and Breast Cancer Risk

Does estrogen produced by women naturally (and all the other hormones that come with it) have anything to do with relative risk to breast cancer? A paper appeared in the *Journal of the National Cancer Institute* in 2006 titled, "Endogenous Steroid Hormone Concentrations and the Risk of Breast Cancer Among Premenopausal Women" that asked this very question.[10] The conclusions of this study are quite clear. The levels of circulating estrogens and androgens found in women may be important in the etiology of premenopausal breast cancer.

From this same study, higher levels of total and free testosterone and androstenedione (these are the androgens in the menstrual cycle) were associated with modest, non-statistically significant increases in overall risk to breast cancer, whereas the increases in estrone/estrone sulfate were not seen to increase

risk. But if we look at estradiol, there was a much higher risk to breast cancer. So estrogen as estradiol is mitogenic (it is a substance that causes cellular proliferation) and does associate itself (as an endogenous hormone) with increasing relative risk.

The Million Women Study is the largest study ever undertaken to look at the effect of HRT on breast cancer incidence. Findings indicated there was a statistically significant and meaningful increase in breast cancer risk and incidence with use of HRT 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. In 2002, the National Institute of Environmental Health Sciences suggested that estrogen is a carcinogen. 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.

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; they can be very caustic and cause injury in DNA adducts that pose carcinogenic risk.

In April 2002—the same year estrogen was called a carcinogen—Dr. Jeffrey Bland had an opportunity to interview an expert in this field, Fritz Parl, MD, PhD, a Professor of Pathology at Vanderbilt University School of Medicine and author of the text, *Estrogens, Estrogen Receptor and Breast Cancer*. In their discussion, Dr. Parl gave a summation of the science surrounding hormones and breast cancer, which is complicated but very important:

"The early studies go back to the 1960s and 1970s. Let's talk about two sisters, one who had surgically induced menopause by removal of the ovaries at age 45, and the other who experienced natural menopause at age 55, so there is a 10-year difference of estrogen exposure. It turns out that the natural-menopause sister has about a twofold higher risk than her sibling. If the interval is even greater than 10 years, like 20 years, then the risk goes up threefold. In addition, in recent years, several prospective studies have shown that in postmenopausal women, the circulating estrogen level is significantly higher, by about 10 to 15 percent, and in those women who do develop breast cancer, so these are prospective studies.

As far as exogenous risk factors, of course there are the meta-analyses by the Collaborative Group on Hormonal Factors and Breast Cancer, which have shown that both oral contraceptives and hormone replacement therapy (HRT) are associated with increased breast cancer.[11] These studies encompass more than 50 international studies involving more than 50,000 women and 100,000 controls.

Taking all this together, one is left with the evidence that estrogens do somehow cause breast cancer. The two main questions are, first, how do estrogens cause breast cancer, and second, since all women are exposed to estrogens, why do some women get breast cancer and others do not? That's the main starting point.

If one looks at what estrogens do, what proteins they interact with, of course, there's the estrogen receptor. Having worked in the field for 15 years or so, however, I have found no real evidence that the estrogen receptor is causally involved (and I emphasize causally) in the development of breast cancer.The only thing I think is important is that it is involved by binding the estrogen and driving the cell cycle, inducing cyclin D1 production, and in the G-1 phase, driving the cell cycle, so it leads to proliferation.

But if one looks at other proteins involved, a number of them have really only come into the limelight in recent years. These are primarily enzymes that metabolize estrogens. As it turns out, it is not the estrogens such as 17-b-estradiol and estrone that may be the culprits, but rather their metabolic products. These, in particular, are the catechol estrogens.[12] The catechol estrogens are further metabolized to estrogen quinones, and these estrogen quinones are very labile, aggressive compounds that attack anything in sight, including DNA. This leads to DNA adduct formation, setting up mutations, and thereby establishing a link, at least experimentally, at this point, to cancer development.

So, how is estrogen metabolized? The key enzyme expressed in breast tissue is an enzyme called cytochrome P4501b1.[13] The body has many cytochromes. This one, in particular, is expressed in breast tissue. It metabolizes estrone by oxidizing it, leading from estradiol to the catechol estrogens.

Catecholestrogens are compounds; that's how they got their name. They have two OH hydroxyl groups next to each other, just like the catecholamines, so they are similar chemically. Of course, they have the steroid ring as part of the molecule.

These enzymes have polymorphisms, and to come back to your original question, we would have a mechanism whereby estrogens can cause cancer and some women have polymorphisms. Others have wild-type enzymes, and a difference would thereby arise over time, mainly to different catechol estrogen levels in the breast, and thereby set up a different milieu for mutations."

Dr. Parl went on to explain the role of the BRCA1 and BRCA2 genes this way:

"In the overall picture, breast cancers can be divided into so-called sporadic breast cancer and familial or inherited forms. The latter represent around 5 percent of all breast cancers, and BRCA1, 2, and possibly 3 account for a portion of those familial forms. So we are dealing with individual proteins, and they are mutated. Because of what in genetic terms are called penetrants in genetic terms, they lead over time to breast cancer.

In the case of the more common sporadic cancers, no single gene has been identified. So the genes and the protein products, the enzymes I mentioned, act together, namely the cytochrome P450, and there are a set of associated genes called COMT which stands for catechol-O-methyltransferase and GST, glutathione-S-transferase. They act together in this catechol estrogen pathway. No one of these genes by itself does the damage alone. If that were the case, then it would appear clinically as a familial breast cancer."

When it comes to this very complicated subject of hormone balance, the watchword for the new medicine is personalization.

Some words of wisdom from Dr. Bethany Hays:

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

I have no problem with changing the levels of hormones in order to get a woman sleeping, for instance, or so you can get her adrenals calmed down, or in order to deal with issues that are related to her thyroid until you get the toxins out of her environment. I don't have a problem with that as long as you are simultaneously working on the whole picture (in the background) to get her healthier. Otherwise, I think you may be kidding yourself that you're increasing her longevity by adding some of these hormones in, as we found out with the Women's Health Initiative.

Personalized Approaches to Women’s Health & Hormone Balance

The adrenals glands are kind of a master stress thermostat that can influence the function of other parts of the body. From a mechanistic perspective, a depletion effect on the adrenals (caused by stress and other factors) can affect the sex steroid hormones—estrogen, progesterone, and testosterone. An elevated cortisol-to-DHEA ratio can be considered an age-related risk factor that is signaled from endocrine shifting. Individuals in whom this phenomenon occurs, if they are women, often are shifted toward androgen versus estrogen balance.

In September 2001, Dr. Jeffrey Bland interviewed Jesse Hanley, MD, a family practitioner who had authored a book titled Tired of Being Tired. Dr. Hanley had this to say about stress and affect if can have on the body’s balance:

“The path to adrenal burnout has five stages: driven, dragging, losing it, hitting the wall, and the most dangerous stage, burned out. In the first four stages, the demand on the adrenals causes them usually to hypertrophy. Since cortisol, cortisone, and adrenaline are such survival hormones, the body preferentially increases the function of the layers of adrenals that produce cortisone at the cost to DHEA and the sex steroid hormones. So we see a decline in them.

I began to wonder if it actually may not be natural for DHEA to decline with age. It may be that stress and the demands on our adrenals in our culture have caused that. We see vibrant people in their later years who still have good levels of DHEA without supplementing. A lot of the illnesses we see in this country have to do with excess cortisol in the first four stages, which causes immunosuppression and increases the risk for diabetes and insulin dysregulation, depression, and binge eating. It’s very much like when people take prednisone. The effects are the chronic elevation of cortisol and cortisone. By bringing that back into balance, doing the simple things we’ve all learned about, adrenals begin to repair. Human bodies are amazing in their ability to repair and recharge if we give them the chance.”

When approaching endocrine balance from a functional perspective, diet and lifestyle may be more important as primary therapies than early intervention with medications. As stress level can be tied to hormones, so too can diet. A complex diet that contains a rich array of phytochemicals may be one of the best tools (clinically) for managing estrogen-related dysfunctions or hormone-related dysfunctions in perimenopausal and menopausal women. Particular types of relative risk may be modulated or modified by dietary intervention, for example, by going more to a vegan diet with a higher density of phytochemical-rich foods-whole grains, fruits, and vegetables. Many studies have been published on this subject, with some suggesting that vegetarian women have faster turnover of hormones, lower estrogen levels, and lowered incidence of hormone-related cancers. It may actually be a much safer approach or at least a first-step before introducing hormone therapy because of the complications in trying to measure hormones and stabilize activities when they are given exogenously. By modulating the diet, we may induce proper cell signaling and allow the woman's natural estrogen, progesterone, or androgens to be properly regulated through hormone binding globulin, through cell receptive mechanisms, and ultimately through cell signaling.

Are there studies that are now being done to look at the effects of sub-toxic doses of these phytochemicals that are derived from specific plant foods that modulate the principles that are associated with health of women as they go through the period of menopause? The answer is an absolute "yes" to that. This is a fascinating chapter opening up that allows us to ask questions at a higher level of scrutiny and have the methodologies to actually provide answers as to how things work and what levels are beneficial, and even what genotypes might be most valuable or most sensitive to these particular alterations as it relates to functional changes.

Abstracts of Interest

Free Radic Biol Med. 2008 Jul 15;45(2):136-45. Epub 2008 Apr 8.

Prevention of estrogen-DNA adduct formation in MCF-10F cells by resveratrol.

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Abstract

Resveratrol (Resv), a natural occurring phytolexin present in grapes and other foods, possesses chemopreventive effects revealed by its striking modulation of diverse cellular events associated with tumor initiation, promotion, and progression. Catechol estrogens generated in the metabolism of estrogens are oxidized to catechol quinones that react with DNA to form predominantly depurinating estrogen-DNA adducts. This event can generate the mutations responsible for cancer initiation. In this regard, Resv acts as both an antioxidant and an inducer of the phase II enzyme NAD(P)H:quinone oxidoreductase 1 (NQO1). In this report, we present the effects of Resv on the metabolism of estrogens in normal breast epithelial cells (MCF-10F) treated with 4-hydroxyestradiol (4-OHE(2)) or estradiol-3,4-

quinone (E(2)-3,4-Q). Resv induced NQO1 in a dose- and time-dependent manner, but did not affect the expression of catechol-O-methyltransferase. Ultraperformance liquid chromatography/tandem mass spectrometry was used to determine the effects of Resv on estrogen metabolism. Preincubation of the cells with Resv for 48 h decreased the formation of depurinating estrogen-DNA adducts from 4-OHE(2) or E(2)-3,4-Q and increased formation of methoxycatechol estrogens. When Resv was also present with the 4-OHE(2) or E(2)-3,4-Q, even greater increases in methoxycatechol estrogens were observed, and the DNA adducts were undetectable. We conclude that Resv can protect breast cells from carcinogenic estrogen metabolites, suggesting that it could be used in breast cancer prevention.

J Steroid Biochem Mol Biol. 2007 Oct;107(1-2):127-9. Epub 2007 Jun 6.

Aromatase inhibition by bioavailable methylated flavones.

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Abstract

Previous studies have shown chrysin, 7-hydroxyflavone and 7,4'-dihydroxyflavone to be the most potent flavonoid inhibitors of aromatase. However, very poor oral bioavailability is a major limitation for the successful use of dietary flavonoids as chemopreventive agents. We have recently shown that methylated flavones, including 5,7-dimethoxyflavone, 7-methoxyflavone and 7,4'-dimethoxyflavone, are much more resistant to metabolism than their unmethylated analogs and have much higher intestinal absorption. In this study, we examined these fully methylated flavones as potential aromatase inhibitors for the prevention and/or treatment of hormone-dependent cancers. Whereas 5,7-dimethoxyflavone had poor effect compared to its unmethylated analog chrysin, 7-methoxyflavone and 7,4'-dimethoxyflavone were almost equipotent to their unmethylated analogs with IC(50) values of 2-9 microM. Thus, some fully methylated flavones appear to have great potential as cancer chemopreventive/chemotherapeutic agents.

Int J Cancer. 2009 Jul 1;125(1):181-8.

Greater vegetable and fruit intake is associated with a lower risk of breast cancer among Chinese women.

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Abstract

The effect of vegetable and fruit consumption on breast cancer risk is controversial. We examined the association between vegetable and fruit intake and breast cancer risk in a hospital-based case-control study conducted in Guangdong, China. Four hundred and thirty-eight cases were frequency matched to 438 controls by age (5-year interval) and residence (rural/urban). Dietary intake was assessed by face-to-face interviews using a validated food frequency questionnaire. Multivariate logistic regression was used to estimate the odds ratios (ORs) and 95% confidence interval (CI) after adjusting for various potential confounders. Total vegetable and fruit intake was found to be inversely associated with breast cancer risk. The ORs of the highest quartile relative to the lowest quartile of total vegetable and fruit intake were 0.28 (95% CI 0.18-0.43) and 0.53 (95% CI 0.34-0.82), respectively. Consumption of individual vegetable and fruit groups such as dark green leafy vegetables, cruciferous vegetables, carrots and tomatoes, banana, watermelon/papaya/cantaloupe were all inversely and significantly related with breast cancer risk. An inverse association was also observed for vitamin A, carotene, vitamin C, vitamin E, and fiber intake. These data indicate that greater intake of vegetables and fruits is associated with a decreased risk of breast cancer among Chinese women residing in Guangdong.

Reprod Domest Anim. 2002 Apr;37(2):96-9.

Vitamin A and beta-carotene levels in plasma, corpus luteum and follicular fluid of cyclic and pregnant cattle.

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The highest beta-carotene levels in the plasma, CL and FF were found during pregnancy when there is maximal luteal function, and the beta-carotene level of the CL was significantly correlated with the weight and diameter of CL. Furthermore, the intrafollicular beta-carotene level was negatively correlated with the follicle diameter. There was a positive correlation between plasma progesterone level and the weight and diameter of the CL, but a negative correlation between plasma progesterone level and follicle diameter. Moreover, plasma, FF and CL beta-carotene levels were positively correlated with plasma progesterone levels.

Cancer Res. 2006 Jun 1;66(11):5960-7.

Grape seed extract is an aromatase inhibitor and a suppressor of aromatase expression.

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Abstract

Aromatase is the enzyme that converts androgen to estrogen. It is expressed at higher levels in breast cancer tissues than normal breast tissues. Grape seed extract (GSE) contains high levels of procyanidin dimers that have been shown in our laboratory to be potent inhibitors of aromatase. In this study, GSE was found to inhibit aromatase activity in a dose-dependent manner and reduce androgen-dependent

tumor growth in an aromatase-transfected MCF-7 (MCF-7aro) breast cancer xenograft model, agreeing with our previous findings. We have also examined the effect of GSE on aromatase expression. Reverse transcription-PCR experiments showed that treatment with 60 mug/mL of GSE suppressed the levels of exon I.3-, exon PII-, and exon I.6-containing aromatase mRNAs in MCF-7 and SK-BR-3 cells. The levels of exon I.1-containing mRNA, however, did not change with GSE treatment. Transient transfection experiments with luciferase-aromatase promoter I.3/II or I.4 reporter vectors showed the suppression of the promoter activity in a dose-dependent manner. The GSE treatment also led to the down-regulation of two transcription factors, cyclic AMP-responsive element binding protein-1 (CREB-1) and glucocorticoid receptor (GR). CREB-1 and GR are known to up-regulate aromatase gene expression through promoters I.3/II and I.4, respectively. We believe that these results are exciting in that they show GSE to be potentially useful in the prevention/treatment of hormone-dependent breast cancer through the inhibition of aromatase activity as well as its expression.

Br J Nutr. 2006 May;95(5):989-95.

High tea consumption diminishes salivary 17beta-estradiol concentration in Polish women.

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Abstract

We hypothesized that among reproductive-age women consuming large quantities of tea, the production of estradiol would be suppressed. It has been shown that catechins and theaflavines, the major constituents of tea, inhibit aromatase, an enzyme which catalyses the conversion of androgens to oestrogens. Our study included Polish women living in urban (n 61) and rural (n 48) areas. Women collected daily saliva samples for one complete menstrual cycle and filled out dietary questionnaires. Saliva samples were analysed by RIA for concentration of 17beta-estradiol (E2). Women with high (above the median) average daily consumption of black tea had reduced levels of salivary E2 in comparison with women who drank less black tea (below the median). This effect was observed within the whole study group, as well as separately within urban (P=0.0006) and rural (P=0.013) groups. High intake of the sum of subclasses of tea catechins and epigallocatechin gallate, assessed using the United States Department of Agriculture database (http://www.nal.usda.gov), was also associated with lower concentrations of E2 within all women (P=0.01 and P=0.0001, respectively) and within the urban group (P=0.0001 and P=0.004, respectively). Similar relationships were observed between the sum of subclasses of theaflavines and thearubigines and E2 levels for the whole group (P=0.002) and for urban women (P=0.02). Women with high consumption of tea had lower levels of E2 concentration throughout the entire menstrual cycle. These results may have implications for reducing hormone-related cancer risk by a relatively easy dietary intervention.

Cancer Res. 2000 Mar 1;60(5):1299-305.

Increased urinary excretion of 2-hydroxyestrone but not 16alpha-hydroxyestrone in premenopausal women during a soya diet containing isoflavones.

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Abstract

Asian diets high in soy are associated with lower risk for breast cancer compared with Western diets. Moreover, higher levels of two putative carcinogenic metabolites of 17beta-estradiol, 4- and 16alpha-hydroxyestrogen, and lower amounts of anticarcinogenic metabolites, 2-hydroxyestrogens, have been associated with greater breast cancer risk. In this study, we tested the hypothesis that consumption of a soya diet containing the weakly estrogenic isoflavones genistein and daidzein may alter the metabolism of 17beta-estradiol to 2- and 16alpha-hydroxylated products. Eight pre-menopausal women were placed on a soya-containing, constant diet in a metabolic unit. The diet provided 400 kilocalories from soymilk and 113-202 mg/day (158 +/- 26 mg/day, mean +/- SD) isoflavones daily for a complete menstrual cycle. After a washout period of 4 months, the subjects consumed the same diet, but with soymilk that contained <4.5 mg/day isoflavones ("isoflavone-free"). Urine samples were collected for 24 h daily for the entire cycle during each soya diet period for the analysis of daidzein, genistein, and 2- and 16alpha-hydroxyestrone. Subjects excreted measurable amounts of daidzein (11.6-39.2 mg/day) and genistein (2.9-18.2 mg/day) during the isoflavone-rich soya diet but not during the isoflavone-free soya diet. The diet rich in isoflavones increased the cycle mean daily urinary excretion of 2-hydroxyestrone (averaged over the entire cycle) from 11.6 +/- 2.06 to 17.0 +/- 2.96 nmol/12-h (P = 0.03), a 47% increase. However, the mean daily excretion of 16alpha-hydroxyestrone did not change (7.0 +/- 1.14 nmol/12-h during the isoflavone-free and 7.7 +/- 1.25 nmol/12-h during the isoflavone-rich diet; P = 0.36). The ratio of 2-hydroxyestrone to 16alpha-hydroxyestrone was higher during the isoflavone-rich soya diet (2.6 +/- 0.34) than during the isoflavone-free diet (2.0 +/- 0.32; P = 0.01), a 27% increase. These results suggest that soya isoflavones increase the metabolism of endogenous estrogens to the protective 2-hydroxylated estrogens in women, and this may play an important role in lowering 17beta-estradiol levels and the long-term risk for breast cancer.

Free Radic Biol Med. 2010 Aug 1;49(3):392-400. Epub 2010 May 31.

N-acetylcysteine blocks formation of cancer-initiating estrogen-DNA adducts in cells.

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Abstract

Catechol estrogens, especially 4-hydroxylated metabolites of 17beta-estradiol (E(2)), are responsible for estrogen-induced carcinogenesis. 4-Hydroxyestradiol (4-OHE(2)), a major metabolite of E(2) formed preferentially by cytochrome P-450 1B1, is oxidized to E(2)-3,4-quinone, which can react with DNA to yield the depurinating adducts 4-OHE(2)-1-N3Ade and 4-OHE(2)-1-N7Gua. The apurinic sites generated by the loss of these depurinating adducts induce mutations that could lead to cancer initiation. In this study, we have evaluated the effects of N-acetylcysteine (NAcCys) on the metabolism of two cell lines, MCF-10F (a normal human breast epithelial cell line) and E6 (a normal mouse mammary epithelial cell line), treated with 4-OHE(2) or its reactive metabolite, E(2)-3,4-quinone. Extensive HPLC with electrochemical detection and UPLC-MS/MS analyses of the cell media demonstrated that the presence of NAcCys very efficiently shifted the estrogen metabolism toward protective methoxylation and conjugation pathways in multiple ways, whereas formation of depurinating DNA adducts was inhibited. Protection by NAcCys seems to be similar in both cell lines, irrespective of their origin (human or mouse) or the presence of estrogen receptor-alpha. This finding suggests that NAcCys, a common dietary supplement, could be used as a potential chemopreventive agent to block the initial step in the genotoxicity caused by catechol estrogen quinones.

Nutr Cancer. 2008;60 Suppl 1:36-42.

Prevention of oxidative DNA damage by bioactive berry components.

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Abstract

The hormone 17ss-estradiol (E(2)) causes oxidative DNA damage via redox cycling of its metabolites such as 4-hydroxy estradiol (4E(2)). In this study, ACI rats (8 wk old) were fed either AIN-93M diet or diets supplemented with 0.5% each of mixed berries (strawberry, blueberry, blackberry, and red and black raspberry), blueberry alone (BB; 2.5%), or ellagic acid (EA; 400 ppm) from 2 wk prior to and up to 12 wk of E(2) treatment. The liver DNA was analyzed for the presence of 8-oxo-7,8-dihydroguanine (8-oxodG) and other polar adducts by 32P-postlabeling. Compared to sham treatment, E(2) significantly increased the levels of both 8-oxodG and P-1 subgroup (259% and 214%, respectively; P< 0.05). EA diet significantly reduced E(2)-induced levels of 8-oxodG, P-1, P-2, and PL-1 by 79, 63, 44, and 67%, respectively (P< 0.001). BB diet also significantly reduced the levels of P-1, P-2, and PL-1 subgroups by 77, 43, and 68%, respectively (P< 0.001). Mixed berries were, however, ineffective. In addition, aqueous extracts of berries (2%) and EA (100 microM) were tested for their efficacy in diminishing oxidative DNA adducts induced by redox cycling of 4E(2) catalyzed by copper chloride in vitro. EA was the most efficacious (90%), followed by extracts of red raspberry (70%), blueberry, and strawberry (50% each; P< 0.001).

For a final word about the future of this field, let's return to Dr. Jane Murray**:**

"I'm hoping more and more clinicians will be willing to have a longer conversation with patients because that is what women want. They want to know: what are their options, what are their choices, what can they be doing? I'm hoping the future of menopause health management will really include a lot of self-care that women are doing themselves (lifestyle, in particular). I would hope that we would continue to have good, high-quality research with all of the questions that are still left very much unanswered after the Women's Health Initiative. That was not the definitive women's health hormone study by any means, and just in our conversation today we have brought up dozens of questions we still have that we need answers for… I briefly mentioned the whole life cycle and developmental issues that happen at this stage. We don't have a lot of information and ways to really help women through all of this. I hope that the mind-body aspects that are so critical at this time can also become a really standard part of our armamentarium with women in mid-life and beyond."

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