WHAT ARE HORMONES AND WHY DO THEY EXIST?

The human body is a community of individual cells, each of which has become specialized to support the function of the community. Each of these cells needs to act in synchrony with every other cell, and all need to know something about what is going on outside of the community of the body so that they can perform the duties needed for the safety and survival of the community.

Hormones are signaling molecules that allow each cell in the body to know what is going on in the outside world and to communicate with each other to coordinate a unified response. The hypothalamus, part of the “reptilian brain,” is the part of the brain that receives and interprets information from the outside world. The organs of sense all terminate or immediately pass through this part of the brain. Interestingly, there are gender differences in sensory ability,1,2 which appear to be adaptive for procreation. The separation of the sexes for reproduction is a gamble on the part of evolution that both male and female will survive. On the other hand, it allows for increased adaptability of the group by specialization of skills. The hypothalamus is also the site of translation of that information for the pituitary (the so-called master gland) and an important area for receiving feedback information from the end organ glands, thus completing the loop of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-ovarian (HPO) axes.

Closely intertwined with the hormones of reproduction are the hormones that allow us to adapt to the food supply. For example, cortisol raises blood sugar, insulin decreases it, and both interact with estrogen, progesterone, and testosterone.3 Food is not only a main source of information about the environment; for the majority of human existence, lack of food has been a major source of stress.4,5 Likewise, gonadal hormones and the ability to reproduce are interconnected to the availability of food. Therefore, stress and nutrition are tightly bound hormonally, and food availability and the ability to reproduce are also tightly bound through the mechanisms of genetic imprinting and prenatal programming.6 These mechanisms in mammals for turning genes on and off in the embryo and placenta not only program fetal and litter size, but also prepare the fetus for the environment into which it will be born.7,8

MENOPAUSE—IS IT A DEFICIENCY STATE?

In a woman’s body, biology makes some important trade-offs to support reproduction. A reproductive-age woman’s body is replete with the trophic (growth-inducing) hormone estrogen. The female metabolism is geared toward the consumption of (women’s sense of taste discriminates and prefers sweets more than the male), storage of (estrogen increases the conversion of carbohydrate to triglycerides), and conservation of calories (estrogen increases insulin sensitivity) so that it can support a pregnancy even in times of relative famine.9,10

The human female body prepares for pregnancy each month, rather than having an infrequent estrus like other mammals. This evolutionary step increased the opportunities to procreate and virtually ensured the survival of the species. A woman’s breasts prepare to feed her growing fetus. The hormones that support the pregnancy and lactation also prepare the skeleton to support the extra weight of pregnancy and the cardiovascular system to withstand the tremendous physiologic and metabolic burdens of pregnancy and childbirth. Some would say these hormones also enable a woman to tolerate labor despite her increased sensitivity to pain11 and to put aside linear thinking for the more intuitive or whole-brain thinking needed for new motherhood. These trophic hormones come at a price, however. The stimulation of endometrium and breast, left unchecked, can lead to hyperplasia and cancer.12,13 To prevent this, women are evolutionarily adapted to go through menopause once the supply of ova is exhausted (or perhaps once the ova can no longer maintain their genetic integrity) and ovulation ceases.

During reproduction, estrogen is balanced with progesterone. Progesterone down-regulates estrogen receptors, making tissue less susceptible to the trophic effects of estrogen. Progesterone induces apoptosis if no pregnancy occurs, essentially pushing the reset button. And progesterone induces differentiation, making the cells less susceptible to the mitogenic effects of estrogen. When reproduction has ceased due to depletion of ova, these trophic hormones fall off precipitously, and the stimulation of the most estrogen-sensitive organs slowly decreases.

SOLVING THE PUZZLE OF HORMONE REPLACEMENT

Bethany Hays, MD, FACOG
es. A 1996 study clearly demonstrated the decreased rate of cancer incidence after menopause.14

T. S. Wiley’s Philosophy Versus Bethany Hays’ Philosophy

There are many ways to look at menopause philosophically. One can see menopause as the end of a woman’s fertility, or one can see it as the time in a woman’s life at which she is freed from childbirth and the responsibility of raising small children to explore her own interests and pursuits. One can see the change in levels of hormones as a deficit or as a return to less stressful levels after the high levels needed for fertility are no longer necessary. One can see menopause as a barren wasteland or as a time of power. A recent book in the popular press, Ageless (Crown Publishing Group, NY, 2006) has brought to the public’s attention the philosophy of T. S. Wiley, an “anthropologist focusing on evolutionary biology and environmental endocrinology in molecular medicine and genetics.”15 (It should be noted that Wiley does not have a graduate degree.) According to the author of this book, Ms Wiley believes that women are only “good for” reproduction, and once they can no longer reproduce, their brains “program” them for old age and death to make room for younger women who can reproduce. She believes the only way a woman can live a long healthy life is to “trick” her brain into believing it can still reproduce using high levels of administered hormone replacement given in such a way as to mimic reproductive levels.

Philosophically, it doesn’t make sense that Mother Nature—or evolution, if you prefer—would make such a big mistake at the midpoint of a woman’s potential lifespan (and yes, there have always been humans who lived very long lives, even when the average lifespan was drastically shorter than it is today). It appears that the human organism is set up with a major investment of energy (mitochondria) in 3 main organ systems: the brain, muscles, and gonads. If we were to assume that the energy is invested in evolution,16 we would have to ask, evolution of what? Or toward what? Looking at where the energy is invested, one might conclude that it is invested in the evolution of consciousness.17 The muscles allow us to roam to find food and a mate from a different genetic pool so that the species has the best chance of survival. The gonads allow us to evolve beyond one lifetime, and the brain allows us to think, learn, and evolve consciousness and pass these “memes,” these “infectious” ideas on to the next generation (regardless of whether it is genetically our own).18,20 This would suggest that a long life, at least for some men and women, is important because it allows them time to become wise and to pass their wisdom on to the younger generation.

There is no more “evidence” for this philosophy than for Ms Wiley’s, but it seems to fit the available information better, unless you assume evolution makes some pretty big mistakes.

DOES EVERYONE—OR DOES NO ONE—NEED HORMONE REPLACEMENT THERAPY?

The current debate about whether women should receive hormone replacement therapy (HRT) seems to be stated only in black or white. Depending on whom you ask, either all women should be on HRT, or no women should be on HRT. Robert Wilson proposed in his 1968 book Feminine Forever (Pocket Books, NY) that estrogen is a fountain of youth and will keep women looking and feeling younger.21 By 2001, it was the standard of care to offer hormone replacement to all women. Others have taken the stance since the publication of the Women’s Health Initiative (WHI) in 2002 that HRT is dangerous and causes breast cancer, blood clotting, and heart disease and should rarely, if ever, be used.22 This type of black-or-white thinking fails to acknowledge the physiology underlying a woman’s hormonal environment after menopause. In fact, women do need estrogens throughout their lives. Some of the earliest studies of heart disease in women were done in women who had had their ovaries removed, and they were shown to have higher levels of heart disease.23 But the needed hormones ideally should come from the woman’s own ovaries, both before and after menopause.

We began giving hormones to all women in the second half of the 20th century, in part because so many women had hysterectomies with oophorectomy, iatrogenically creating a shockingly large number of women who did need HRT. In 1977, annual hysterectomy rates peaked at 442,000 per year, with more than one third having bilateral oophorectomy at an average age of 35-40.24 The pharmaceutical industry was more than willing to take the data on hormone replacement for these women and apply them to all women, as the prevailing thought was that menopause was a deficiency state. And naturally and surgically menopausal women were not studied separately because sales of HRT to as many women as possible greatly benefited the pharmaceutical industry’s bottom line. Indeed, at one point, Premarin was the best-selling drug in America.25,26 One of the unique things about the WHI estrogen-only arm was that it did separate out women who had undergone hysterectomy. Interestingly, these women showed remarkably different patterns of risk than those who participated in the WHI estrogen/progestin arm.27

In reality, there are more reasons for abnormally low levels of ovarian hormones after menopause than simply oophorectomy. A number of women may be suffering from autoimmune dysfunction of the ovaries, which is difficult to diagnose, both before and after menopause.28 Many of these women undergo premature menopause, further increasing the time of hormone deficiency.29,30 Women also can have suppression of ovarian function with the elevation of other hormones, such as adrenaline (catecholamines), and in association with dysfunction of other hypothalamic-pituitary-end organ imbalances.31

HOW HORMONES INTERACT: THE IMPORTANCE OF THE ADRENALS IN TREATING WOMEN IN MENOPAUSE

The female hormones and those coming from the adrenal cortex are both similar in structure and interlinked in function. This is not surprising, as they arise from the same embryonic crest of tissue. In fact, each hormone in the human body is linked with every other hormone through a complex, interacting, evolv-
The adrenal cortex and medulla are also linked. When adrenaline is released from the medulla, cortisol automatically follows. When estrogen decreases at menopause, catecholamines rise, initiating some of the most troublesome symptoms of perimenopause—hot flashes and anxiety. When a woman is stressed, progesterone is used as a precursor for cortisol, and progesterone levels may decrease, or at least, the balance of estrogen and progesterone is disrupted, producing some of the menstrual abnormalities seen in perimenopause.

**WHAT YOU NEED TO KNOW ABOUT ESTROGEN, PROGESTERONE, AND TESTOSTERONE**

**Estrogen**

Estrogen is produced in the ovarian theca cell during the reproductive period of life by aromatase (a CYP450 enzyme) from precursors, primarily androstenediol and testosterone from the granulosa cell. After menopause, the bulk of estrogen is formed in fat cells from aromatization of androgens from the adrenals, but aromatase can be found in many other cells, such as the synovial cells of the joints, and in the brain.

Estrogen is found in minute amounts (picograms) in the circulation compared to progesterone (nanograms), testosterone (nanograms), dehydroepiandrosterone (DHEA; micrograms) and other steroid hormones, suggesting that it is a powerful and potentially dangerous chemical. Estrogen is metabolized down 3 major pathways by the same CYP450 detoxification enzymes that are used to get rid of many toxins, drugs, and foreign substances in the body. Each step in detoxification—phase 1, oxidation; phase 2, conjugation; binding to sex hormone-binding globulin (SHBG); and excretion in the bile or urine—is designed to decrease the effect of estrogen or to render it non-toxic but at the same time allow for the possibility of reuse when needed. For this reason, the use of estrogen replacement should be undertaken with caution, and the type, dose, and route of administration should be aimed at minimizing the number of molecules that need to be detoxified.

When estrogen is metabolized down the 16-hydroxylation pathway, the result is a stronger estrogen metabolite than when it is metabolized down the 2-hydroxylation pathway. When estrogen is metabolized down the 4-hydroxylation pathway, it can rapidly degrade into a DNA-damaging quinone. When genetic polymorphisms (such as the one coding for the common, up-regulated version of CYP 1B1) increase the production of 4-hydroxy compounds, DNA damage in organs with local production of these molecules can cause highly reactive estrogen intermediates to accumulate, which also may be damaging to DNA or increase estrogen's effect on cell turnover. Finally, detoxified estrogens are excreted via the bile into the gut, where bacterial flora can perform enzymatic reversal of the detoxification, making the molecules available for re-absorption and reuse.

**Progesterone**

Progesterone, like DHEA and pregnenolone, is an “upstream molecule.” In other words, it sits upstream biochemically in the steroid pathway from many of the molecules of sex and adrenal function. These “upstream molecules,” when administered exogenously, may rapidly go “downstream” to end products such as cortisol, estrogen, or testosterone that the unwary clinician did not intend to increase and should therefore be used with caution or only when downstream molecules (such as estrogen, testosterone, and cortisol) are measured.

Progesterone is an estrogen-balancing hormone. It down-regulates the estrogen receptor and inhibits estrogen transcription action at the DNA. Although originally thought of as a uterine-calming agent during pregnancy (a use which is enjoying a resurgence), progesterone has many other effects. Every cell in the brain with estrogen receptors also has progesterone receptors. Therefore, when estrogen is increased, care must be taken to ensure that the right balance of progesterone exists; otherwise, symptoms of irritability or anxiety may influence compliance with therapy. Bone cells have both estrogen and progesterone receptors as well, and better bone metabolism may accompany combined therapy. Progesterone also has an effect of inducing cross-talk between the estrogen receptor and peptide growth factors, an important potential mechanism for inducing breast cancer in diabetics or those with elevated insulin, IFG-1, or other peptide growth factors.

Although some feel that progesterone is safer (or completely safe) with regard to its effect on the breast than progestins such as medroxyprogesterone acetate (the progestin used in the WHI), Mueck and Seeger have demonstrated that although progesterone and several other progestins had no effect on the growth/apoptosis ratio in normal cells in vitro, progesterone had a slightly worse profile than medroxyprogesterone acetate (MPA) in cancer cells. Although this information may not translate to the in vivo situation, it demonstrates that the effect of HRT, especially progestogens, may not be the same on normal vs cancerous cells. It also
suggestions that natural progesterone may be better in some situations (pre-cancerous cells) and worse in others (cancerous cells).

Testosterone

Testosterone is a woman’s hormone. After menopause, it is produced about equally by the adrenals and the ovary. When the ovary is removed, testosterone levels fall below the ideal physiologic level and may need to be replaced. Testosterone has a relatively narrow normal range in women, and it does not change dramatically at menopause. The testosterone:estrogen ratio may have more to do with libido than the absolute level. Women have increased libido (defined as a desire to initiate sex) at ovulation, when there is a spike of both estrogen and testosterone. There may be a second surge of testosterone just before the menstrual cycle, as many women describe increased libido at this time as well, or this may be due to alterations in the estrogen:testosterone ratio. After menopause, a woman with normal hormone levels has a ratio that favors increased interest in sex. Women’s desire for sex, however, is greatly influenced by their desire for relationship and their imagination. Therefore, a complex set of variables—not just testosterone—influences the libido.

Testosterone lowers SHBG, freeing estrogen molecules. Therefore, testosterone should be given with caution in women for whom increased free estrogens would not be desirable. On the other hand, when vaginal atrophy is a primary complaint, freeing estrogen by giving testosterone is a very successful strategy. (It should be noted that the effect is mediated by the liver’s production of SHBG; therefore, local administration of testosterone to the vulva or vagina will be successful only in so far as testosterone is absorbed into the circulation.)

Bioidentical Hormones Versus Synthetic and Equine Hormones, and Formulating Pharmacies Versus Big Pharma

There is a great deal of difficulty interpreting the growing body of literature about what hormones to use and why, in part because of the biases of the authors and because of the influence of the pharmaceutical industry on both the funding and publication of the research. Bioidentical hormones are laboratory-fabricated hormones that are identical to the ones made by a woman’s body. They, like the synthetic hormones sold by pharmaceutical companies and often touted as “natural” or “plant-based,” are fabricated from plant molecules (genistein and diosgenin) from yam and soy plants, but it is a mistake to think that a plant-based pharmaceutical is bioidentical or that taking the precursor molecules will provide the bioidentical hormones. Both are common areas of confusion for patients. The human body does not have the enzymes to make the conversion, and although some of these plant substances may affect hormone levels by inducing the CYP enzymes (isoflavones), they are not hormonally active in their native form. If the molecule is bioidentical, it should be handled in the same way as hormones that are produced by the body, using the same pathways of metabolism and the same conversions to other hormones. If the molecule is converted to a synthetic chemical by the pharmaceutical industry, a pharmaceutical company can patent it and make more money selling it, but it may have different mechanisms of action in different cells (as do selective estrogen receptor modulators, or SERMs) and it may be metabolized by different enzymes. Sometimes these differences are unimportant; other times they are critically important.

For instance, progesterone is metabolized into the brain-active, Gamma-aminobutyric acid (GABA) receptor agonist allopregnanolone. This has a brain-calming effect, which for some women balances the brain-activating effects of estrogen (or other brain-activating neuropeptides, such as catecholamines). If a woman who needs this brain-calming effect is given synthetic progestins, which are not metabolized into allopregnanolone, she may become anxious or irritable. If she doesn’t need this balancing because of her unique brain chemistry, synthetic progestins, such as in oral contraceptives, may have no negative brain effect (particularly once estrogen levels are suppressed by the pill and don’t need as much balancing effect from progesterone).

On the other side of the argument, there is no evidence that estradiol as opposed to synthetic or equine estrogens does not also put a woman at risk for cancer of the breast and uterus. In fact, the evidence is very clear that endogenous estrogen does increase the risk of breast cancer. What may turn out to be important is the way in which different estrogens are metabolized. Equine estrogens, estrone and estradiol are all metabolized to 4OH quinones, which damage DNA. The difference is the number of molecules of equine estrogen needed to get an appropriate effect. Given that the primary human estrogen in conjugated equine estrogens is estrone (a much weaker estrogen that may work only when it is converted to estradiol), which must be given in higher doses to get the same effect, giving conjugated estrogens by mouth increases the numbers of molecules of both estrone and equine estrogens that must be metabolized, potentially creating more of the DNA-damaging quinones. Ethinyl estradiol, on the other hand, because of the addition of the ethinyl group, stays in the body longer, and much smaller (oral) doses are required to obtain the same estrogen effect. In addition, it is not metabolized by CYP enzymes into the DNA damaging quinones—the only estrogen that does not use this pathway, according to Dr Eleanor Rogan (oral communication, April 2006)—and therefore might be an ideal hormone replacement after menopause. Obviously, until there is research to support this idea, it is not clinically applicable, but it underscores the need to avoid attachment to the idea that bioidentical hormones are always better.

Finally, the use of bioidentical hormones has become, in many people’s minds, synonymous with the use of formulating pharmacies. There are pros and cons to this argument as well. As has been pointed out by many well-known researchers, the preparations made by formulating pharmacies are not as carefully regulated by the FDA as those made by traditional pharmacies. What is not usually pointed out is that there also have been problems with regulated drugs. Remember the flak that was raised when it was noted that Synthroid (levothyroxine;
Solving the Puzzle of Hormone Replacement

Knoll Pharmaceutical Co, Mount Olive, NJ) had never gone through a new-drug application and the product was noted to have a significant variability in hormone level from lot to lot.54 Clearly a mistake in a whole lot would affect more women than a mistake in formulating one woman’s preparation; however, the pharmaceutical industry is required to test for this problem intermittently, and the formulating pharmacies are not.

This problem can be addressed in several ways. First, patients should be made aware that when they refill a prescription of any kind, they should watch for and report any change in symptoms related to the drug. Second, hormone levels should be checked regularly (although the expense of checking all hormones may prohibit checking after each renewal of prescription). Third, the credentials of the formulating pharmacy should be checked. (See, for example, the International Academy of Compounding Pharmacists: http://www.iacprx.org/.) And finally, there are bioidentical estrogens and progesterone, in both oral and trans-dermal form, available from the pharmaceutical industry at your local drugstore, a fact that seems to escape those familiar with the pros and cons of use and the variables in collection, sensitivity, and response to hormone therapy. There are problems with each of these forms of evaluation, but no evaluation at all is also unacceptable.

Measuring Hormone Levels

Although determining what a normal hormone level is may be practically impossible, as all hormones fluctuate with the environment and in response to each other, levels can be a useful place to start and an important means of evaluating the effect of treatment and to avoid over dosing. There are 3 primary methodologies for evaluating hormone levels, and each has its advantages and drawbacks.

Saliva

Salivary hormone levels have been used in healthcare for more than 30 years.59 Salivary cortisol is both accurate and useful, as blood draws may produce stress and perturb the hormonal level.59

There has been considerable debate about the reliability of progesterone levels in saliva.52 Although the levels of endogenous hormone appear to correlate with blood, when hormone replacement is administered, the type and route of administration dramatically effect progesterone levels in saliva, and determining the correct level of replacement is therefore difficult.52,55

Salivary estriol has been used in pregnancy and appears to be accurate but has little clinical usefulness except in pregnancy. Estradiol and estrone appear reliable but have not been used in large studies until recently, and therefore, normal levels and levels after therapy have not been reported in large numbers of women. It should be noted that reference ranges for pre-menopausal hormone levels often include the broad range of fluctuations in hormone and therefore are not helpful.50 Reference ranges in menopause include women who have undergone hysterectomy or who have under-functioning ovaries and are equally unhelpful.

Serum

Levels of hormone in the blood fluctuate dramatically, especially in the perimenopause and from day to day during a woman’s menstrual cycle.” This provides considerable difficulty when relying on single samples, and multiple sampling is both difficult and expensive. Reliable values for hormone levels have broad ranges of normal but are available in the literature, provided one is careful to find studies that do not include surgically menopausal women. Protein binding must be taken into consideration, and levels must be correlated with symptoms when treating postmenopausal patients.

Urine

Urinary collections for determining hormone values appear to be reliable but have the drawback of being time-consuming and difficult to collect correctly. They have the advantage of combining a whole day’s worth of metabolic product and therefore averaging the fluctuations of hormone within a given day. Once again, day-to-day hormone levels vary, and this must be taken into account.

Whichever method is used, the practitioner must become familiar with the pros and cons of use and the variables in collection, sensitivity, and response to hormone therapy. There are problems with each of these forms of evaluation, but no evaluation at all is also unacceptable.

The Binding Proteins

Estrogen and testosterone are primarily bound in serum to SHBG. The higher the estrogen level, the higher the SHBG; the lower the testosterone level, the higher the SHBG. Therefore, knowing the level of SHBG can be useful in determining the reason for symptoms and can also give a hormonal “intermediary of metabolism” to verify the estrogen effect. SHBG does not fluctuate as rapidly as do levels of estrogen or testosterone and can sometimes provide a clue to the true recent hormonal environment when absolute levels do not correlate with symptoms. For instance, a patient with breast tenderness (suggestive of elevated estrogen) has a low estradiol level but elevated SHBG. The first question would be what her testosterone level is. If it is normal, then SHBG should largely reflect the recent effect of estrogen in the liver and also be low, provided she does not having any other endocrinopathy. If it is high, the level of estrogen may have recently been high but might be in a downward phase of fluctuation. Decreased SHBG levels often are seen in cases of hirsutism, acne vulgaris, and polycystic ovary syndrome. SHBG levels may be modestly reduced in the presence of hyperthyroidism, acromegaly, Cushing’s disease, obesity, and hyperprolactinemia. Increased SHBG is seen in hyperthyroidism, cirrhosis of the liver, estrogen dominance or low progesterone, during pregnancy and hormone therapy, and in women carrying the Asn polymorphism for SHBG production.58

Steroid hormones also are potentially bound to the lipid membrane of red blood cells. This mechanism was proposed to

54 ALTERNATIVE THERAPIES, may/june 2007, VOL. 13, NO. 3
explain the high levels of progesterone in saliva after transdermal application. Lewis disproved this theory.39

BALANCING HORMONES: WHO NEEDS PROGESTERONE? TESTOSTERONE?

Women need hormone therapy for both short- and long-term indications. Short-term indications would be those that would be expected to improve, such as severe hot flashes related to lifestyle issues that can be changed. Sleep deprivation due to hot flashes is a common and important reason to treat someone short-term, as improving sleep can decrease stress and improve the hormonal environment causing the hot flashes.60 These women may temporarily have higher levels of hormone than would be considered ideal for menopause with the attendant increased risk of breast cancer. However, because they would not be treated for long periods of time, presumably only long enough to make diet and lifestyle changes, this risk would be considered acceptable.61,62

Long-term treatment regimens would include treatment of women who have had to undergo oophorectomy and would be presumed to need long-term replacement of estrogen, testosterone, and possibly progesterone. These women would correlate with the WHI’s estrogen-only arm and presumably would be at lower risk for breast cancer with treatment. Another group to consider would be women with increased risk for osteoporosis and minimal risk of breast cancer. (It should be noted that both are now understood to be inflammatory diseases, so some women will be at risk for both, and a safer therapy for these women may be alternatives to HRT). These women will have to be evaluated on a case-by-case basis.

In general, the lowest dose of hormone that achieves the desired result is likely to be the safest. Metabolites must be included in the evaluation, as the overall estrogen effect and the local estrogen production must be considered, not just the level in blood, urine, or saliva. This is especially important because of the need to keep the number of estrogen molecules as low as possible in order not to overwhelm the metabolic pathways.

Transdermal estradiol allows for maximum effect with the fewest administered estrogen molecules. Oral preparations must be given in much higher doses and may overwhelm liver detoxification pathways. There are some data to suggest that the primary functional estrogen is estradiol and therefore giving estrone or estriol simply adds estrogen molecules, which may have to be converted to estradiol for effectiveness. This will add greatly to the number of molecules of estrogen that have to be metabolized.

Progesterone, in postmenopausal women, comes primarily from the adrenals, but if the patient is stressed, progesterone levels may be low, as progesterone serves as a precursor for cortisol. Many organ systems require progesterone to balance estrogen other than the uterus, so hysterectomy should not be the only criterion for use or non-use of progesterone. The risk of breast cancer should also be a consideration in using or withholding progesterone. It can be given orally, vaginally, or transdermally, depending on the desired effect. Patients should be cautioned that they might experience progesterone effects (drowsiness, diuresis) or cortisol effects (irritability and fluid retention) depending on which cytochromes are up- or down-regulated in their bodies.

It is important to have a discussion with the patient about the physician’s expectation for the length of therapy. Otherwise, the patient may fail to make necessary dietary or lifestyle changes and require extended therapy, which may put her at risk for breast cancer. Conversely, the woman who has undergone oophorectomy must understand that hormone normalization should be a lifelong pursuit and that maintaining normal levels for menopause does not put her at the same risk as does hormone therapy in a woman with ovarian function.63

SAFETY AND INFORMED CONSENT

No competent physician would treat someone for hypothyroidism without measuring thyroid function in some way. The current treatments for thyroid replacement are primarily bioidentical T3 and T4. Once a treatment is initiated, a competent physician gives the patient information about symptoms to watch for and instructions about when to return to have the levels checked before continuing therapy. In addition, many physicians require that the patient have repeat levels of hormone or thyroid-stimulating hormone (TSH) each year before renewing the prescription.

Ask yourself what would happen to a physician who based the diagnosis of hypothyroidism on symptoms alone, who did not measure hormone levels, or who gave non-physiologic substitutions for thyroid hormone. Ask yourself what the medical community would think about giving supra-physiologic levels of hormone at the patient’s request or on the basis of failure to resolve symptoms. What would the medical community think if the physician did not recheck hormone levels once the treatment was initiated to be sure the patient was not being made hyperthyroid?

Now ask how we have been prescribing HRT for women for the past 50 years. We have been treating women on the basis of a symptom (hot flashes) that is not caused by a deficiency of the hormone we replace, with a mixture of many hormones (conjugated equine estrogens), the effects of many of which we don’t know, and treating them for many years without ever evaluating the levels of hormone produced. Now ask why the standard of care for hormone therapy in women is so different from that for treatment with thyroid hormone. Wouldn’t it be prudent to treat hormone therapy for gonadal dysfunction in the same way we treat dysfunction of the thyroid or any other endocrine organ?

Because our ability to measure and respond to environmental and inter-organ fluctuations is so primitive, it is imperative to inform our patients of our relatively poor ability to find the perfect treatment without adjustments or to predict the outcome of long-term hormone therapy. Had we been doing this all along, we might not have gone through a prolonged period of over-treatment with high levels of hormones that were unnecessary for many women, a period of treatment with estrogen only, which caused increased endometrial cancer, and a period of...
treatment with oral equine estrogen/progestins that caused a significant increase in deep vein thrombosis, embolism, and blood clotting and a small but important increase in breast cancer. Any doubt about the effect of HRT on breast cancer should be laid to rest by the epidemiologic finding of the precipitous decrease in breast cancer incidence since the drop in HRT use after the WHI.44

It seems reasonable, therefore, to apply the same standards to hormonal therapy for women in menopause that are currently demanded of therapies for thyroid dysfunction. These would include the following.

1. An evaluation through blood, saliva, or urine of hormone levels of at least estradiol, progesterone, testosterone, and possibly estrone, estriol, cortisol, thyroid, DHEA, the 2-hydroxyestrone (2-OH) and 16-OH metabolites, and SHBG.

2. Other tests that might be of interest include pregneneolone, androsterone, androstenedione, and cholesterol and various gene tests for CYP enzymes, and other available genes representing the high-frequency, low-penetration genes for breast cancer, including those for methylation and glutathione transfer and sulfation.

3. Investigation of why hormones levels are low, including history of surgery, evaluation of adrenal and thyroid function, and autoantibody screening.

4. Collaborative decision making with the patient, including informed consent.

5. Decision making regarding the best hormone and route of administration to address the patient’s unique history, genetics, and symptom complex.

6. Discussion about side effects, appropriate parameters for continuation or cessation of therapy, and next contact.

7. Plan for timing of laboratory re-evaluation of hormone levels.

8. Appropriate adjustment of hormone therapy and ongoing monitoring.

SUMMARY

The current debate about HRT and bioidentical hormones seems to be largely based on emotional arguments for and against their use. A calmer evaluation that looks at the evidence for a positive outcome of normal menopause and the reasons that the current arguments for and against have evolved over time is in order. When hormone replacement is indicated by symptoms in addition to laboratory evaluation, replacement should not be withheld. However, a careful, dispassionate approach that takes into account our relatively primitive ability to measure and modulate hormones is needed. The therapies should be chosen on the basis of the patient’s individualized needs and capacity to follow a prescribed regimen. Informed consent should be included in the discussion. Bioidentical hormones allow for the possibility of following hormone levels, especially when metabolites are also evaluated. The careful practitioner will want to engage the patient’s ability to determine if the therapy is working and when symptoms suggest that a refill might contain more or less of the preparation than prescribed.

When the pharmaceutical industry, the journals publishing scientific findings, educators, practitioners, and the proponents of complementary and alternative therapies put the needs of the patient before their own, we will all have an easier time determining which therapies to use and when to use them.

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Solving the Puzzle of Hormone Replacement