"Drug think" is responsible for much of the current confusion about hormone supplementation. The public and physicians think about pharmacology rather than physiology. From a physiology textbook one would never get the impression that hormones are anything other than chemical messengers necessary for health. Without hormones, we cannot live. Why then do we speak as though hormones are dangerous substances? And why do we assume that the harmful effects of non-hormones will be like those of our endogenous hormones?

The answer is suggested by the fact that medical students and doctors in training have minimal exposure to physiology and massive exposure to pharmacology. Exogenous chemicals, different from the actual hormone they are meant to replace, are used interchangeably in clinical practice, the popular press, and in prestigious medical journals, producing much of the controversy that surrounds hormone replacement.

Conflicts of Interest

A few billion dollars can purchase a lot of advertising to sway the public, hire hundreds of lobbyists, and buy influence with the FDA. According to Public Citizen's Congress Watch: 'The drug industry spent $262 million on political influence in the 1999-2000 election cycle: $177 million on lobbying, $65 million on issue ads, and $20 million on campaign contributions. This was more than any other industry spent over the same period for political persuasion."

Additionally, a lot of money is spent to manipulate physicians—through sponsoring speakers, organizing symposia, and even conducting studies published as scholarly articles in prestigious journals. All these efforts are designed to give the impression that "evidence-based medicine" means the use of patented exogenous compounds. Physicians are dazzled with innumerable studies asking which is better—drug A or drug B? We seem to forget that sponsored studies have been shown to be biased, and we fall into the trap of assuming the answer must involve using patentable exogenous chemicals.

In this discussion we are choosing neither drug A or B. We suggest the best solution is to work with the body and restore normal physiology—without introducing foreign compounds to the body's delicate web of interactions.

What Is a Biodentical Hormone?

Supplementation with a compound of the exact molecular structure as a hormone produced by the body is often termed "biodentical hormone therapy." The term does not indicate the source of the hormone, but rather refers to the chemical structure. Synonyms include biologically identical, bidentical, or human hormones. For the sake of brevity, we will focus primarily on three commonly used hormones: progesterone, estradiol, and estradiol.

Physicians who prescribe these hormones typically emphasize the importance of hormones for health, the significance of using compounds identical to the normal ones, the need for progesterone, the essential balance between progesterone and estrogen, the use of compounding pharmacies, and the importance of avoiding exogenous chemicals in chronic conditions.

Hormones Are Critical for Health

With the increase in life expectancy we enjoy in the 21st century, we can expect to live a substantial part of our lives in a state of hormonal deficiency. The age-related decline in hormones produces many of the diseases associated with midlife. We have several options: 1) do nothing and experience the adverse effects of hormonal deficiency; 2) take exogenous chemicals (drugs) to ameliorate the effects resulting from this decline; or 3) treat the root causes of disease by replacing exactly what is missing. Hormonal decline is associated with a loss of function as well as an increase in diseases such as heart disease. Effects include bone loss, cognitive decline, loss of muscle mass, and thinning of skin.

There are many specific benefits of hormonal supplementation. Testosterone reduces neuronal secretion of Alzheimer's β-amyloid peptides and improves cognitive function. Progesterone increases bone mass. Mood is improved with testosterone and progesterone. Hormones also improve sleep; decrease inflammation; ameliorate chronic fatigue; improve sexual function, mood, muscle strength, and body composition; normalize blood clotting; improve spatial recognition; and induce apoptosis of breast cancer cells.

The Importance of the Identical Structure

Molecular structure determines activity. The smallest of changes can completely change the physiologic effect. Consider testosterone and estrone, whose structures are shown side by side in Figure 1.

The mere existence of an effect similar to that produced by a hormone does not make a compound a hormone. If it did, plastic would be a hormone. For example, bisphenol A (BPA) is an

![Figure 1 Structures of Testosterone and Estrone](image)
estrogen receptor agonist. When BPA binds with the estrogen receptor, the complex so formed interacts with DNA and can lower sperm counts and increase the risk of developmental problems, cancer, schizophrenia, neurologic disorders, and weight gain. The interaction with the hormone receptor does not make BPA a hormone—but rather the hormone mimics interfere with normal physiologic processes, causing a wide variety of adverse effects.31-34

Typically, hormones initiate a cellular response by combining with either specific intracellular or cell membrane receptor proteins. The interaction of hormone and receptor will frequently produce both cytoplasmic and nuclear effects. The former include protein phosphorylation, increasing the concentration of intracellular secondary messengers (i.e., cyclic AMP), or changing ion channel permeability. In the nucleus, the hormone-receptor complex bound to DNA stimulates or represses the expression of certain genes, thereby affecting protein synthesis.35,36

Since the hormone and hormone receptor complex often work together to mediate the hormonal activity, a complex made up of a receptor and a foreign compound is likely to result in an abnormal physiologic response.37,38 Much of the confusion about bioidentical hormone replacement flows from the failure to distinguish hormones from non-hormones. Obtaining FDA approval for a hormone-mimicking compound, such as medroxyprogesterone (Provera) or conjugated equine estrogens (Premarin), does not turn it into a hormone. Unfortunately, many scholarly articles have even referred to Provera as "progesterone," and to conjugated equine estrogens as "estrogen."39,40

Before the release of the results of the Women's Health Initiative (WHI), the medical community expected PremPro to help mitigate the postmenopausal increase in cardiovascular disease. While the extract of pregnant mares urine known as Premarin does contain one human estrogen, estrone, it also contains numerous equine estrogens foreign to human physiology. The WHI study demonstrated that the combination of Premarin with Provera produces the following adverse effects: a 26% increase in risk of invasive breast cancer; a 29% increase in risk of myocardial infarction or death from CHD; a 41% increase in risk of stroke; and a 200% increase in risk of thromboembolism.

The Importance and Safety of Progesterone Supplementation

Many of the adverse effects in the WHI apparently result from the failure to use the human hormone progesterone. We should not expect the exogenous chemical medroxyprogesterone to necessarily have the same physiologic effect. Physicians who prescribe bioidentical hormones emphasize the importance of balancing estrogens with progesterone, rather than progestins. There are critically important differences between the two.

Progesterone is a pregnancy class B drug. It is used in assisted reproductive technology as Crinone38 and may be useful for preterm labor.39-43 Medroxyprogesterone is a pregnancy class X drug—a compound known to cause birth defects, and never to be used in pregnancy. Progesterone and physiologic levels of estrogens downregulate inflammation. Medroxyprogesterone prevents the cardioprotective and anti-inflammatory effects of estradiol.44

In contrast to medroxyprogesterone, several lines of evidence suggest that progesterone reduces breast cancer risk. It is known to have an anti-proliferative effect.45 A low endogenous progesterone level has been correlated with a five-fold increase in premenopausal breast cancer risk in women experiencing infertility when compared with women with normal hormone levels.46 Contrariwise, a higher progesterone level in premenopausal women correlates with lower risk of breast cancer. Comparing the highest with the lowest tertile for progesterone in women with regular menses, the adjusted RR for breast cancer was 0.12 (95% CI, 0.03-0.52, P for trend = .005).47

A potential mechanism for the protective effect is suggested by an in vitro study that evaluated the effect of progesterone on the growth of T47-D breast cancer cells. It demonstrated increased apoptosis as mediated by regulation of the controlling genes.48

A cohort study involving 1,150 French women who received topical progesterone cream for mastalgia due to benign breast disease showed no increase in cancer (RR=0.8). Moreover, researchers noted a decrease in breast cancer risk among women using progesterone cream plus an oral progestogen (RR=0.5), compared with women using oral progestogens alone.49

Two recent studies point to a difference in breast cancer risk when comparing synthetic progestins to bioidentical progesterone for hormone replacement therapy (HRT). A French cohort study involving 3,175 postmenopausal women predominantly using natural HRT (83% using transdermal estradiol and progesterone and non-medroxyprogesterone progestins) found no increased risk.50 The French E3N-EPIC cohort study assessed the risk of breast cancer associated with HRT use in 54,548 postmenopausal women and found the risk was significantly greater (P<0.001) with HRT-containing synthetic progestins (RR=1.4) than with HRT containing micronized progesterone, which actually reduced the risk (RR=0.9).51

While we await prospective trials to evaluate the safety of bioidentical progesterone with respect to the breast, these large cohort studies, along with the effects of progesterone on normal and cancerous breast cells, provide a large body of evidence supporting the safety of bioidentical progesterone. We know from prospective studies such as the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial that progesterone is safer than medroxyprogesterone, yet many physicians continue to use the latter.52

The Essential Balance Between Progesterone and Estrogen

Physiologically, progesterone levels fall faster than estrogens; therefore, progesterone supplementation is typically needed years before estrogen declines. The physiologic role of progesterone goes far beyond the need to prevent unopposed estrogen stimulation of the endometrium. The E3N-EPIC cohort study showed that estrogen alone slightly increased the risk of breast cancer (RR=1.1), but the risk was actually reduced when estrogen was combined with progesterone (RR=0.9). Independent of the presence or absence of the uterus, progesterone (not progestins) should always be used to balance estrogen.53

Why Estriol?

Although estriol has been used in western Europe since the mid-1900s, most U.S. physicians are not familiar with it. In vivo, estriol is produced from estrone and directly from androstenedione.54-56 It offers most of the benefits of estradiol, such as relief of vasomotor symptoms and vaginal atrophy, but appears safer.

One argument for the safety of estriol (as well as progesterone) is that human zygotes have been demonstrated to experience healthy embryogenesis and development in a milieu of high estriol and progesterone concentrations—levels present physiologically during pregnancy. If carcinogenesis does not occur with high levels of estriol during the most fragile phase of life, why should it be expected at much lower levels in mature adults? In animal models estriol has not shown carcinogenesis unless used in high doses, and it has even been shown to protect against carcinogen-induced breast
cancer. Clinical studies have demonstrated that daily dosing results in minimal proliferation of breast and endometrial tissue.\textsuperscript{44}\textsuperscript{46}

Studies on the ability of estriol to prevent bone loss have produced inconsistent results. For this reason many physicians use Bi-Est with 20\% estradiol and 80\% estriol.\textsuperscript{41}

Currently the FDA is threatening to ban the use of estriol on the basis that it has not gone through new-drug FDA approval—even though the FDA has said that there is no safety issue with estriol and despite its inverse correlation with breast cancer (i.e. the more estriol, the lower the rate of cancer).\textsuperscript{44} Under the Food and Drug Administration Modernization Act, Congress specifically recognized and approved the use of active ingredients that have a USP monograph as appropriate for use in compounding. Estriol has a USP monograph.

Compounding Pharmacies

The key issue is the use of human hormones at the appropriate dose—not the type of pharmacy. Most physicians using bioidentical hormones have a significant percentage of prescriptions filled at compounding pharmacies rather than non-compounding retail pharmacies. This is because compounding affords advantages such as customized dosing, so that the lowest effective dose can be used, and allows the prescribing of hormones such as estriol that are not available at non-compounding retail pharmacies.

Compounding pharmacies are regulated by state governments. Usually, the board of pharmacy is the responsible agency. Compounding pharmacies follow regulations set by the U.S. Pharmacopeia. We agree that there are concerns about variable potency, impurities, and contamination. Thus, we encourage the use of pharmacies accredited by the Pharmacy Compounding Accreditation Board (PCAB). Most compounding pharmacies do not perform “sterile compounding.” State regulations require consistency in purity and dosage. U.S. Pharmacopeia potency regulations require that the active ingredient in all compounded preparations be between 90.0\% and 110.0\% of the amount stated.\textsuperscript{44}\textsuperscript{46}

Wyeth, the maker of Prempro, has been a leader in opposing the use of compounding pharmacies and has effectively petitioned the FDA to assist in eliminating competition. Could this be related to the fact that Wyeth made more than $1 billion annually from the sale of Premarin and Prempro before the WHI study? These drugs are still on the market although they are known to increase cancer risk.

Exogenous Chemicals (Patentable Drugs) and Chronic Conditions

It is stated that allopathic drugs are the fourth to sixth leading cause of death in the U.S. In hospitalized patients, fatal adverse drug reactions (excluding errors in drug administration, noncompliance, overdose, drug abuse, therapeutic failures, and possible adverse drug reactions) numbered about 106,000.\textsuperscript{46} Modern pharmacologically based medicine is dangerous. These deaths result from properly prescribed, FDA-approved drugs.\textsuperscript{46}

Conclusions

The use of exogenous chemicals as hormone substitutes has been shown to be unsafe and should be stopped. Hormone supplementation should be done with compounds identical to the natural molecules. Although more research is needed, there is already evidence of the benefits of hormone supplementation in the proper doses and in proper balance. The future of medicine is in physiology rather than pharmacology.

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