

LE Magazine April 2005

REPORT

Jonathan Wright, MD

Pioneer of Natural Female Hormone Replacement

By Dave Tuttle

A physician who pioneered the use of natural female hormone replacement therapy more than two decades ago, Jonathan V. Wright, MD, has obtained remarkable results for his patients while avoiding the dangerous prescription drugs that are so heavily promoted by pharmaceutical companies.

In this article, *Life Extension* examines Dr. Wright's program to help aging women restore their youthful hormone balance safely without resorting to side effect-prone prescription drugs.

The mainstream news media seems to have a knack for skimming the surface of scientific studies and drawing erroneous conclusions.

One recent example involves negative reports about estrogen-progestin female hormone replacement therapy. Studies involving women who took chemically modified prescription hormones for extended periods showed that they had an increased incidence of breast cancer,¹ along with a higher risk of heart attack, stroke, and pulmonary embolism.² In reaction to these studies, the mainstream media generated headline news containing dire warnings that hormone therapy is dangerous.

The media ignored the fact that these results occurred in women taking synthetic hormones, which are patented chemical alterations of the body's natural messengers. Television, radio, and newspaper reports made blanket assertions that the risks of hormone replacement therapy exceed the benefits. The result is that millions of women are now going "cold turkey" trying to cope with age-diminished hormone levels.



ACHIEVING NATURAL HORMONE BALANCE

According to Dr. Wright, the allegedly inevitable negative outcomes of hormone supplementation are avoidable. By using natural hormones and following a program of regular blood testing, women can develop an individualized hormone replacement regimen that is safe and effective.

"You need to use natural means to restore the body's hormone balance," says Dr. Wright, a member of the Life Extension Foundation's Medical Advisory Board. "Bioidentical hormones are superior to patentable drugs because they are exact copies of what the body produces. They work better than the deformed, inexact copies that are required to get a patent."

Dr. Wright pioneered the use of bioidentical estrogens and DHEA in the 1980s, and he has more clinical experience in hormone replacement therapy than any other practitioner. He and Ed Thorpe, an innovative compounding pharmacist, were the first to offer women an alternative to conventional synthetic drugs.



"By replacing the hormones that decline as time goes by, you can sustain your health and promote longevity," explains Dr. Wright. "It's never too late, either. I have had patients in their eighties who saw their health improve. For example, in cell cultures, gender-specific bioidentical estrogen or testosterone supplementation slows the accumulation of tau protein, neurofibrillary tangle, and amyloid in human neurons, reducing the potential for Alzheimer's disease. The bioidentical versions of these two hormones reduce the risks of cardiovascular disease and osteoporosis as well. By returning to the physiological hormone levels you had earlier in your life, you can slow down the aging process and maximize your quality of life."

PROGESTERONE: FIRST HORMONE TO DECLINE



While traditional medicine focuses on diminished estrogen levels, progesterone is the first hormone that declines during the aging process. Some women in their late twenties have progesterone deficiencies, while other women in their late forties and even early fifties are still producing youthful levels of progesterone. This is why hormone testing and individually designed treatments are so essential.

Progesterone is primarily manufactured in the adrenal glands and ovaries, though some is produced in the brain. This hormone is necessary for gestation to occur, and miscarriages are common when progesterone is deficient. Symptoms of a deficiency include premenstrual discomfort, night sweats, hot flashes, and a loss of well being, often including depression. Supplementation with natural progesterone reduces the prevalence of these negative events.

John Lee, MD, originated the clinical use of bioidentical progesterone. Reports by Dr. Lee and others have suggested that natural progesterone stimulates new bone formation by increasing osteoblast activity, which helps to prevent osteoporosis.³ While vitamin and mineral deficiencies, poor eating habits, and lack of exercise also contribute to osteoporosis, hormone imbalances—especially estrogen and progesterone deficiencies—play a significant role in the progression of osteoporosis in women.

Several studies have found that topical progesterone creams effectively combat aspects of the aging process. A one-year trial in postmenopausal women saw a significant reduction in vasomotor symptoms such as hot flashes in a group using a bioidentical transdermal progesterone cream.⁴ Researchers also noted reduced thickening of the uterine lining produced by an estrogen drug when postmenopausal women used a transdermal or vaginal progesterone cream for four weeks.⁵ This antiproliferative effect is one of the main reasons that traditional doctors prescribe medroxyprogesterone, a progestin (progesterone-like drug) known as Provera® that has numerous side effects. Synthetic progestin drugs do not function the same way as natural progesterone. Moreover, because progesterone enhances the sensitivity of estrogen receptors in cell membranes, the use of a natural progesterone cream may permit a reduction in estrogen supplementation.

Bioidentical progesterone has also been shown to reduce the incidence of breast cancer. Researchers at National Taiwan University Hospital found that progesterone reduces the proliferation rate of breast epithelial cells.⁶ Another study examined cancer incidence in women with progesterone deficiencies.⁷ The scientists discovered that hormone-deficient women were 5.4 times more likely to have premenopausal breast cancer and 10 times more likely to die from all malignant neoplasms than were women without a progesterone deficiency.

An even more intriguing study revealed that survival rates for breast cancer surgery are strongly correlated with the patient's progesterone level on the day of surgery. Because it is involved in the menstrual cycle, progesterone concentrations vary dramatically at different times of the month. This study noted that 65% of women with a progesterone level of 4 nanograms (ng) per ml or more on the day of their surgery were alive 18 years later, while only 35% of women with low progesterone levels on that day were still living after 18 years. The researchers noted that progesterone lowers the expression of vascular endothelial growth factor, which promotes the increase in new blood vessels (angiogenesis) that is essential for tumor growth. This strongly suggests that women should time their surgery to match their monthly peak in progesterone.⁸



“The best results from progesterone supplementation are obtained when the natural monthly fluctuation in this hormone is followed as closely as possible,” notes Dr. Wright. “There should be a monthly pause in progesterone supplementation, because that’s what our bodies naturally do. Progesterone and estrogen are produced and received by their hormone receptors in cyclic fashion, with a brief lull every month. This ‘down time’ probably helps prevent long-term receptor down-regulation.

“As a general rule, I recommend using a progesterone cream from day 12 of the cycle until three to five days before the start of the next cycle. However, women with a family history of osteoporosis may need more days of progesterone exposure because this hormone positively influences bone formation.”

THE SAFEST ESTROGEN: ESTRIOL

Traditional medical doctors usually prescribe estrogen as the primary hormone for women going through menopause. In fact, unless a woman has had her ovaries removed, most physicians will prescribe only estrogen, and often the more toxic estrone and estradiol forms of the hormone at that. This is mainly the result of decades of drug company propaganda that has established the more harmful synthetic drugs made from these forms—such as Premarin®, Estrace®, and Estraderm®—as the standard of care for postmenopausal women.

Of course, recent disclosures about the dangers of these drugs, including the much-publicized halt to the Women's Health Initiative study in 2002, have made clear that estrogen replacement therapy can have its risks.² The unfortunate result of the media's superficial reporting on this topic, however, is that millions of women have given up on estrogen therapy altogether, when the utilization of the more benign estriol, in conjunction with balanced levels of other hormones, can produce significant relief from menopausal symptoms without the dangers inherent in traditional "solutions" to the problem.



Estriol is used extensively in Europe by peri- and postmenopausal women for estrogen replacement therapy. Available in the US from a compounding pharmacy with a doctor's prescription, it has been shown to provide many of the benefits of the traditional approaches without the harsh side effects of the trademarked synthetic drugs.⁹ Estriol is a weak estrogen, so higher doses are necessary for symptom relief. Nevertheless, this hormone provides a protective effect in the body. During pregnancy, estriol levels rise 1,000-fold, which guards against maternal breast cancer by antagonizing the effects of estradiol.

"Estriol is a fully detoxified estrogen," explains Dr. Wright. "This was demonstrated in an unpublished 35- to 40-year prospective case-cohort study funded by the Department of Defense.¹⁰ This analysis compared 15,000 women who had pregnancies between 1959 and 1967. The women, who all belonged to the same health plan in California, had samples of their serum frozen for 30 years or more. In 1997, the researchers thawed the serum and analyzed steroid hormone levels in the women's blood during their pregnancies. They then compared the results to the California Cancer Registry to determine the relationship between estriol levels during pregnancy and

subsequent prevalence of cancer. The researchers found that breast cancer risk was reduced by 58% among women in the highest quartile of estriol production compared to those in the lowest quartile. The scientists also discovered that estriol levels were higher in Asian and Hispanic women, who are known to have a reduced risk of breast cancer. As a result, not only did estriol not increase the risk of this cancer—as estradiol and estrone do—but it actually reduced the risk."

REPORT

Jonathan Wright, MD

Pioneer of Natural Female Hormone Replacement

By Dave Tuttle

Estriol is also effective in relieving menopausal symptoms. A six-month study of 52 women with severe symptomatology found that supplementation with 2-8 mg of estriol succinate produced significant improvements within one month, which continued throughout the therapy.¹¹ Estriol also reversed vaginal atrophy and improved the quality of cervical mucus. No breakthrough bleeding occurred in subjects, and biopsies of the inner uterine mucous membrane showed no endometrial hyperplasia (excessive proliferation of the uterine lining cells), a condition that can precede uterine cancer. The reduction in menopausal symptoms occurred without any reported side effects. As expected, symptom improvement was related to the dose.

A longer-term study of estriol therapy revealed that this treatment was successful in 92% of the cases.¹² In 71% of the subjects, hot flashes and sweating were eliminated completely, while in 21% they were weaker and occurred less frequently. Depressive moods were abolished in 24% of the cases and were reduced in severity in another 33%. Reductions in forgetfulness, loss of concentration, irritability, and heart palpitations also were recorded. The number of patients who experienced migraine headaches dropped by two thirds. Even subjective improvements in the quality of the subjects' skin, as noted by both the patients and physicians, were reported. All of this occurred without notable side effects.



While many women will get complete relief with estriol supplementation, some will need to add small amounts of the more potent estrogens. Two of the most popular prescription estrogen formulas are Bi-Est and Tri-Est. Bi-Est consists of bioidentical estriol and estradiol. The most common version of this formula is 80% estriol and 20% estradiol, though the amount of each hormone can be titrated at a compounding pharmacy to provide maximal symptom relief. Tri-Est consists of 80% estriol, 10% estradiol, and 10% estrone. These creams are usually applied on the inner thigh or inner upper arm, though they are sometimes inserted vaginally. The site of application should be changed on a daily basis to maximize absorption.

"These bioidentical hormones are much better than those that are isolated from the urine of pregnant mares or synthesized so they can be patented," Dr. Wright notes. "However, even with bioidentical molecules, you will get into problems if you take too much. If you are utilizing triple estrogen therapy, you should take no more than 2 mg of estriol, 0.25 mg of estradiol, and 0.25 mg of estrone per day. If you are using bi-estrogen, it's still advisable to limit your amount of estradiol to 0.25 mg daily unless a follow-up test shows you definitely need more. These moderate doses will allow you to get the benefits of estrogen replacement without the risks inherent in prescription drugs. As with progesterone, there should be a lull every month to match the body's natural cycle and to prevent long-term receptor down-regulation."

DHEA: ADDITIONAL ANTI-AGING BENEFITS

Dehydroepiandrosterone, or DHEA, is another hormone that declines during the aging process. It is produced in women in the adrenal gland and brain. Youthful levels begin to drop around the age of 30, and most women have a deficiency of this vital hormone by the age of 40. The rate of decline varies for each person, so blood testing is essential to determine the appropriate supplementation dosage. Deficiencies of DHEA have been correlated with numerous age-related conditions, including chronic inflammation, immune dysfunction, depression, rheumatoid arthritis, increased risk for certain cancers, excess body fat, cognitive decline, osteoporosis, and some complications of type II diabetes.¹³

Despite the findings of hundreds of peer-reviewed studies, the benefits of DHEA replacement therapy are still not recognized by mainstream medicine, which prefers to steer women to estrogen-related prescription drugs. Nevertheless, given that youthful levels of DHEA can decline as much as 95% by age 85, the case for bioidentical hormone supplementation is clear.



Advancing age results in an increase in inflammatory cytokines, which are destructive cell-signaling chemicals that contribute to many degenerative diseases. Rheumatoid arthritis, a disease that overwhelmingly strikes women, is a classic autoimmune disorder in which excess levels of cytokines play a significant role in inflammation. Studies have shown that DHEA is an important component in the treatment of rheumatoid arthritis because of its ability to lower levels of the pro-inflammatory cytokines interleukin-6 and tumor necrosis factor-alpha, and to protect against their toxic effects.^{14,15} Interleukin-6 also plays a role in promoting bone loss and joint deterioration, and aberrantly high levels of this cytokine are associated with atherosclerosis, Alzheimer's disease, and some cancers.¹⁶ DHEA's ability to reduce inflammation makes it safer and more effective in the long run than the corticosteroids usually prescribed by mainstream physicians.

DHEA supplementation has other advantages for older women. A six-month trial at the University of California at San Diego found that 50 mg of DHEA daily increased physical and psychological well-being in women by 84%.¹⁷ Another study found that DHEA supplementation produced significant elevations in insulin-like growth factor.¹⁸ Deficiencies of this factor contribute to a loss of lean body mass, excess fat accumulation, neurological impairment, and age-related immune dysfunction. Additional benefits of DHEA include inhibition of abnormal blood platelet accumulation,¹⁹ improved mood and libido,²⁰ and increased skin protection against environmental contaminants.²¹

"Unlike progesterone and estrogen, DHEA production does not follow the menstrual cycle, so there is no need to cycle your daily dosage," says Wright. "DHEA has many benefits for life extension, so if a woman hasn't started supplementing by then, she will need to start at menopause. The average dose I recommend for women is 10-15 mg of oral or transmucosal DHEA daily. I have found that this is sufficient to provide the immune-boosting and cancer-preventive effects of this multifaceted natural hormone."

The Life Extension Foundation recommends regular blood testing of DHEA-sulfate levels to ensure that women remain within the optimal range of 350-430 mcg per dL. However, because DHEA can convert to estrogen, supplementation is contraindicated for women with hormone-receptive breast cancer.

THE IMPORTANCE OF TESTOSTERONE

While often considered a man's hormone, testosterone is essential to women as well. This hormone is produced in women's ovaries and adrenal glands at about one tenth the level as in men. Testosterone is important for maintaining sexual interest and function, and provides many other health-enhancing benefits. As with men, testosterone concentrations in women begin to decline around the age of 30. By the time they reach menopause, some women have very low levels of testosterone. These deficiencies are a key predictive factor for heart disease in women who have had hysterectomies.²² A lack of this hormone can also promote breast cancer. A study in 2003 found that testosterone inhibits breast cell growth, much like progesterone's protective effect on the uterus.²³

"Testosterone is an important part of a hormone replacement program for women," Dr. Wright explains. "It promotes bone development and muscular strength while improving the libido and fighting cancer. Women with congestive heart failure have also found that this hormone increases cardiac strength."

Several studies have shown benefits from testosterone supplementation in women. A study published in the *New England Journal of Medicine* found that a transdermal testosterone patch containing only 300 mcg provided significant improvement in sexual function, mood, and general well-being in women who had had their ovaries removed.²⁴ Additional research by Dr. Susan Davis at the Jean Hailes Foundation in Australia has shown that testosterone supplementation improves sex drive, arousal, and frequency of sexual fantasies in pre- and postmenopausal women.²⁵ Her investigations also show that testosterone is important in maintaining a woman's energy level and sense of well-being regardless of age.²⁶



"Natural testosterone levels peak at ovulation and reach a nadir during menstruation, so I test at different times to see how much of a cycle there is," adds Dr. Wright. "Also, because of possible testosterone dominance [a period in some older women when progesterone and estrogen levels are low and testosterone is still relatively high], replacement dosages vary considerably among individual women. Supplementation should follow the same monthly cycle as estrogen. I recommend the transmucosal route of administration for all hormones."

CONCLUSION



The aging process is hard enough for women without their also having to cope with preventable declines in hormone levels. Once women realize the differences between bioidentical hormones and the now-disgraced synthetic drugs, the choice should become clear. Women can prolong the quality of their lives by replacing the natural hormones that their youthful bodies produced in abundance. When accompanied by a sound supplement regimen and a sensible diet and lifestyle, hormone replacement allows women to maximize their longevity and be healthy enough to enjoy it as well.

Editor's note: Women with estrogen receptor-positive breast cancer should not use any form of estrogen. Some doctors are still concerned that even natural bioidentical estrogen and testosterone could induce breast and other cancers by stimulating excess cellular proliferation.

References

1. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med.* 1995 Jun 15;332(24):1589-93.
2. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002 Jul 17;288(3):321-33.
3. Heersche JN, Bellows CG, Ishida Y. The decrease in bone mass associated with aging and menopause. *J Prosthet Dent.* 1998 Jan;79(1):14-6.
4. Leonetti HB, Longo S, Anasti JN. Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss. *Obstet Gynecol.* 1999 Aug;94(2):225-8.
5. Leonetti HB, Wilson KJ, Anasti JN. Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium. *Fertil Steril.* 2003 Jan;79(1):221-2.
6. Chang KJ, Lee TT, Linares-Cruz G, Fournier S, de Lignieres B. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. *Fertil Steril.* 1995 Apr;63(4):785-91.
7. Cowan LD, Gordis L, Tonascia JA, Jones GS. Breast cancer incidence in women with a history of progesterone deficiency. *Am J Epidemiol.* 1981 Aug;114(2):209-17.
8. Mohr PE, Wang DY, Gregory WM, Richards MA, Fentiman IS. Serum progesterone and prognosis in operable breast cancer. *Br J Cancer.* 1996 Jun;73(12):1552-5.
9. Head KA. Estriol: safety and efficacy. *Altern Med Rev.* 1998 Apr;3(2):101-13.
10. Sitieri PK, Sholtz PI, Cirillo PM, et al. Prospective study of estrogens during pregnancy and the risk of breast cancer. Unpublished study performed in at the Public Health Institute in Oakland, California, and funded by the US Army Medical Research and Material Command under DAMD 17- 99-1-9358.
11. Tzingounis VA, Aksu MF, Greenblatt RB. Estriol in the management of the menopause. *JAMA.* 1978 Apr 21;239(16):1638-41.
12. Lauritzen C. Results of a 5 years prospective study of estriol succinate treatment in patients with climacteric complaints. *Horm Metab Res.* 1987 Nov;19(11):579-84.
13. Gaby AR. Dehydroepiandrosterone: biological effects and clinical significance. *Alter Med Rev.* 1996;1(2):60-9.
14. Cutolo M. Sex hormone adjuvant therapy in rheumatoid arthritis. *Rheum Dis Clin North Am.* 2000 Nov;26(4):881-95.
15. Kipper-Galperin M, Galilly R, Danenberg HD, Brenner T. Dehydroepiandrosterone selectively inhibits production of tumor necrosis factor alpha and interleukin-6 [correction of interlukin-6] in astrocytes. *Int J Dev Neurosci.* 1999 Dec;17(8):765-75.
16. Haden ST, Glowacki J, Hurwitz S, Rosen C, LeBoff MS. Effects of age on serum dehydroepiandrosterone sulfate, IGF-I, and

IL-6 levels in women. *Calcif Tissue Int.* 2000 Jun;66(6):414-8.

17. Morales AJ, Nolan JJ, Nelson JC, Yen SS. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J Clin Endocrinol Metab.* 1994 Jun;78(6):1360-7.
18. Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. *Clin Endocrinol (Oxf).* 1998 Oct;49(4):421- 32.
19. Jesse RL, Loesser K, Eich DM, et al. Dehydroepiandrosterone inhibits human platelet aggregation in vitro and in vivo. *Ann NY Acad Sci.* 1995 Dec 29;774:281-90.
20. Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR. Dehydroepiandrosterone treatment of midlife dysthymia. *Biol Psychiatry.* 1999 Jun 15;45(12):1533-41.
21. Hastings LA, Pashko LL, Lewbart ML, Schwartz AG. Dehydroepiandrosterone and two structural analogs inhibit 12-O-tetradecanoylphorbol-13-acetate stimulation of prostaglandin E2 content in mouse skin. *Carcinogenesis.* 1988 Jun;9(6):1099-102.
22. Rako S. Testosterone deficiency: a key factor in the increased cardiovascular risk to women following hysterectomy or with natural aging? *J Womens Health.* 1998 Sep;7(7):825-9.
23. Dimitrakakis C, Zhou J, Wang J, et al. A physiologic role for testosterone in limiting estrogenic stimulation of the breast. *Menopause.* 2003 Jul;10(4):292-8.
24. Shifren JL, Braunstein GD, Simon JA, et al. Transdermal testosterone treatment in women with impaired sexual function after oophorectomy. *N Engl J Med.* 2000 Sep 7;343(10):682-8.
25. Davis SR. Androgens and female sexuality. *J Gend Specif Med.* 2000 Jan;3(1):36-40.
26. Davis SR, Tran J. Testosterone influences libido and well being in women. *Trends Endocrinol Metab.* 2001 Jan;12(1):33-7.

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension[®]

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.