

LE Magazine April 2006

On The COVER

A Natural Approach to Menopause

By Dale Kiefer



For the last few decades, doctors have had a simple solution for menopause: writing prescriptions for estrogen drugs. With millions of women taking estrogen, all seemed to be going well, until data revealed that estrogen drug use resulted in significant increases in lethal diseases ranging from breast cancer to stroke.¹ This development left both the medical profession and menopausal women paralyzed, with no direction and no answers as to how best to relieve the debilitating symptoms of menopause.

Clearly overlooked is the fact that menopause is a complex, multifactorial health condition. Addressing menopause requires a diverse approach that

both restores normal hormone balance and protects against the multitude of diseases that can arise during this period in a woman's life. The onset of menopause triggers profound changes in cardiac health, mental states, bone strength, and cell proliferation, all of which combine to greatly elevate a woman's risk for contracting heart disease, osteoporosis, and certain cancers.

These health issues are not easy to correct, especially when they occur simultaneously. The ideal approach to addressing menopause would be comprehensive and holistic, providing fast-acting, short-term symptomatic relief as well as longer-term benefits that support women's health as their body chemistry changes. While declining levels of estrogen are what gives rise to the difficulties of menopause, both nutritional and hormonal support are required to address and ameliorate the physiological symptoms and other changes that accompany menopause.

Fortunately, researchers have identified natural approaches that may safely relieve hot flashes, breast pain, insomnia, irritability, and other menopausal symptoms. Unlike estrogen-progestin drugs, the use of these natural agents is correlated with reduced risks of certain cancers, along with improved bone and cardiovascular health.

Scientists have known for years that women who consume certain plant-based nutrients are less likely to develop hot flashes, heart disease, osteoporosis, and breast cancer.²⁻⁵ In response to the health debacle arising from the use of estrogen drugs, researchers have begun digging deeper into the botanical medicine chest, critically evaluating the efficacy of various traditional herbal products that safely stimulate estrogen receptors and create estrogen-like responses.

Mounting scientific evidence indicates that menopausal women may safely benefit from inexpensive, readily available botanical extracts that do not require a prescription.⁶⁻¹⁸ This article reviews the latest research findings concerning menopause-related health conditions—ranging from depression and hot flashes to osteoporosis and heart disease—and how women may benefit from highly researched botanicals. Taken together, these findings suggest a new approach to safely and effectively managing menopause.

WHY LIGNANS ARE SO IMPORTANT

For women approaching menopause, plant lignans offer important protection against cancer, cognitive decline, and hypertension. These fibrous compounds are present in large quantities in foods such as flaxseed, whole grains, and vegetables. In the digestive tract, they are converted to beneficial estrogenic compounds by resident bacteria. Two of these metabolic byproducts, enterolactone and enterodiols, are believed to play an important role in cancer prevention in mammals.¹⁹⁻²²

A recent study published in the *Journal of Hypertension* concluded that dietary lignans, even in small amounts, are likely to normalize blood pressure and reduce hypertension, thereby lowering the risk of cardiovascular disease.²³



Research from Korea indicates that high enterolactone levels also are associated with greater bone mineral density in postmenopausal women. Furthermore, scientists have found that women with low levels of enterolactone are more likely to suffer from osteoporosis.⁵ Scientists in the Netherlands recently reported that “higher dietary intake of lignans is associated with better cognitive function in postmenopausal women.”²⁴

Surprisingly, the evergreen tree is an excellent source of potent lignans. Scandinavian researchers recently discovered that the knotwood of these majestic trees contains highly concentrated amounts of a lignan known as hydroxymatairesinol, or HMR. Numerous studies have shown that HMR is a potent antioxidant that may promote health and help protect against diseases such as cancer. In laboratory models of uterine, breast, colon, and other carcinomas, HMR lignan has demonstrated efficacy in reducing the volume and growth of existing tumors and preventing the formation of new tumors.^{22,25-29}

Bioavailability—that is, the ease with which HMR lignan is converted directly to enterolactone and absorbed into the bloodstream—is what sets HMR apart from other plant lignans. Its unique chemical composition allows natural gut bacteria to convert HMR directly to the beneficial enterolactone and enterodiol lignans. This contrasts with other plant lignans, which must undergo further metabolism.²⁹ Although flaxseed has long been recognized as one of the most concentrated sources of plant lignans, it takes far more flaxseed than HMR lignan to deliver an equivalent amount of beneficial enterolactone into the bloodstream. While one would have to eat about four tablespoons (20-30 grams) of unrefined flaxseed to get a beneficial dose of lignans, just 10-30 milligrams of HMR lignan (about 1,000 times less) provide an equivalent amount of enterolactone in the body.²⁸

PROTECTIVE EFFECTS OF POMEGRANATE

One of the more devastating long-term effects of menopause is an increase in both cancer and heart disease risk. Doctors initially thought that estrogen drugs would reduce cardiovascular risk, but these drugs instead dramatically increased a woman’s risk of contracting these lethal diseases. Fortunately, scientists are now discovering that natural agents can help protect aging women from these diseases.

Long venerated for its health-promoting properties, the fruit of the pomegranate tree is drawing new attention as a source of beneficial compounds that provide powerful protection against heart disease and cancer. Among these compounds are unique antioxidants that may dramatically improve cardiovascular health. A recent study conducted in Israel, for example, examined the effects of consuming pomegranate juice on the cardiovascular status of patients with atherosclerosis. Although some patients were followed for three years, dramatic differences were noted after just one year. Patients receiving the juice experienced a 30% improvement in atherosclerosis as measured by blood flow capacity through the carotid artery. In control patients who did not receive the juice, the same parameter of cardiovascular health actually worsened by 9%. Systolic blood pressure was reduced by 21% and total serum antioxidant status increased by 130% in the pomegranate-supplemented patients.³⁰



These dramatic improvements were achieved within one year of treatment. Subsequent years yielded no further improvements, except in low-density lipoprotein (LDL) oxidation, which continued to decrease with continued consumption of pomegranate juice.³⁰ More recent research confirms that pomegranate juice fights cardiovascular disease by preventing LDL peroxidation and by significantly suppressing the synthesis of new cholesterol by macrophages.³¹ In fact, punicalagin, the major antioxidant polyphenol ingredient in pomegranate juice, is found nowhere else in nature. But pomegranate also contains ellagic acid, the compound that makes berries the health-promoting powerhouses of the produce aisle. A recent analysis of the abilities of various components of pomegranate juice to fight cancer and quench free radicals found that pomegranate’s many compounds work synergistically and in a variety of ways to stop cancer.⁸

New research indicates that pomegranate may be particularly indicated in the prevention of breast cancer, one of the most common cancers threatening women after menopause. The most powerful estrogen in the body, 17-beta-estradiol, plays an important role in the genesis and development of breast cancers, most of which are hormone dependent in their early stages.³² Pomegranate-derived polyphenol compounds inhibit 17-beta-hydroxysteroid dehydrogenase type I, the enzyme that converts the weak estrogen estrone into its most potent metabolite, 17-beta-estradiol.³³ High expression of 17-beta-hydroxysteroid dehydrogenase type I can be an indicator of adverse prognosis in women with estrogen-receptor-positive breast tumors.³² Based on these findings, scientists hope to conduct clinical trials assessing the preventive and therapeutic applications of pomegranate in human breast cancer.

HORMONAL EFFECTS OF SOY



Phytoestrogens are plant-derived compounds that closely mimic the natural estrogens women produce in abundance before menopause. In the body, phytoestrogens have been shown to modulate the effects that estrogen exerts on cells in a way that could reduce the risk of contracting various diseases. It was long ago established that natural estrogens play a role in the healthy function of bones, heart muscle, and blood vessel linings. Estrogens also contribute to learning and memory.³⁴

Aging women need to counter the depletion of beneficial natural hormones that occurs upon menopause. Soy contains genistein and daidzein, which are among the most extensively studied phytoestrogens. Epidemiological evidence shows that cancer and heart disease are less prevalent in populations that consume large amounts of soy.³⁵ Moreover, scientists have demonstrated in laboratory studies that genistein inhibits the proliferation of breast cancer cells.³⁶⁻³⁹

Rates of cardiovascular disease and hormone-dependent cancers are lower among Asian women who consume soy.⁴ Epidemiological evidence shows that North American women who consume the greatest amounts of phytoestrogens enjoy significantly better cardiovascular risk profiles than women who consume the least phytoestrogens.⁴⁰ Such epidemiological evidence suggests that dietary rather than genetic differences account for Asians' better health.

Numerous studies have shown that increased consumption of phytoestrogens, including genistein and daidzein, is associated with a reduced risk of breast and other hormone-dependent cancers, such as endometrial cancer.^{19,41-44} Scientists have also determined that phyto-estrogens confer protection against lung cancer.⁴⁵ Recent studies have documented significant improvements in long- and short-term memory, mental flexibility, and attention with increased phytoestrogen consumption.⁴⁶⁻⁴⁹

Phytoestrogens from soy have also been shown to reduce the loss of bone density in postmenopausal women.⁵⁰ The findings from a recent prospective study suggested that postmenopausal women who consume more soy products experience a decreased risk of bone fracture compared to those who consume little soy. This association was most pronounced in the years immediately following menopause.⁵¹

Asian women experience hot flashes less frequently than do Western women. Less than one fifth of menopausal Chinese women, for example, complained of hot flashes in one such study.³ By contrast, more than three fourths of menopausal North American and European women suffer from hot flashes. Numerous studies have demonstrated that isoflavone-rich soy extracts decrease both the frequency and severity of hot flashes in postmenopausal women.⁵² In one study, 80% of women using a soy extract experienced a significant decrease, averaging 48%, in the number of daily hot flashes. These women also reported statistically significant improvements in other menopausal symptoms, including sleep disorder, anxiety, depression, vaginal dryness, loss of libido, and bone pain.⁵³

In response to these findings, scientists conducted clinical trials using soy extracts in an attempt to relieve menopausal miseries. Because these studies produced inconclusive results, many mainstream medical doctors lost confidence in soy's ability to relieve menopausal symptoms. This is regrettable considering the many diseases associated with normal aging and menopause that soy-derived phytoestrogens have been shown to prevent. While soy phyto-estrogens by themselves may not be equal to potent estrogen drugs in alleviating menopausal symptoms, their estrogen-modulating effects merit including soy in a comprehensive approach to both reducing disease risk and relieving the symptoms of menopause.

A Natural Approach to Menopause

By Dale Kiefer



Black Cohosh (*Cimicifuga racemosa*)

BENEFITS OF BLACK COHOSH

Black cohosh (*Cimicifuga racemosa*) is a North American perennial herb that has been used to treat gynecological complaints for centuries. Native American healers and American physicians alike have prescribed black cohosh for relief from hot flashes and other menopausal symptoms.⁵⁴ Listed as an official drug in the U.S. Pharmacopoeia from 1820 to 1926, black cohosh has been rediscovered by research scientists and menopausal women.^{18,55} Several recent clinical trials of exacting randomized, double-blind, placebo-controlled design have shown that black cohosh is indeed effective in reducing the severity, duration, and incidence of hot flashes and night sweats.^{6,16,17,56}

A recent study at the Mayo Clinic in Scottsdale, AZ, examined the safety and effectiveness of black cohosh in reducing hot flashes. Weekly hot flash scores were reduced by 56% among women receiving black cohosh. Researchers noted that previous studies reported relatively high placebo effects in tests of treatments for hot flashes, but in this trial, placebo effects ranged from only 20% to 30%. "The efficacy found in this trial seems to be more than would be expected by a placebo effect," according to the researchers. Women taking black cohosh in this study also reported less trouble sleeping, less fatigue, and less sweating.⁵⁷

Another recently published study compared the efficacy and safety of black cohosh extract to a standard hormone replacement regimen (low-dose estradiol administered by skin patch). The researchers concluded that the two treatments were equally effective in reducing hot flashes. Both treatments significantly lowered LDL, but only black cohosh raised beneficial HDL. In addition, both patient groups experienced significant improvements in menopause-associated symptoms of anxiety and depression. Effects were noted within the first month of treatment and continued unabated for the three-month duration of the study. Neither treatment affected liver function or altered levels of follicle stimulating hormone, luteinizing hormone, or cortisol. The estradiol treatment, but not black cohosh, slightly increased levels of the hormone prolactin.⁵⁸

Because of the potential estrogenic activity of black cohosh, scientists have carefully evaluated whether it is capable of influencing the growth of hormone-dependent cancers. Researchers at Northwestern Medical School who performed a series of sophisticated laboratory analyses of the extract concluded, "Black cohosh extracts did not demonstrate estrogenic activity in any of these assay systems."⁵⁹ However, German researchers found that black cohosh appears to exert estrogenic effects elsewhere in the body. They concluded that the botanical product demonstrated "no action in the uterus, but beneficial effects in . . . bone."⁶⁰

In practical terms, this means that black cohosh, like estradiol, prevented bone loss in laboratory animals after their ovaries had been removed. Unlike estradiol, black cohosh did not appear to exert any influence on the uterus, which may account for its superior safety profile compared to hormone replacement therapy. Thus, black cohosh not only reduces hot flashes, anxiety, and depression in menopausal women, but also appears to prevent some of the bone loss associated with the natural decline in estrogens, without the risk of stimulating uterine or breast cancer.⁶⁰

In 2004, the North American Menopause Society added its stamp of approval to the use of black cohosh. In fact, it recommended black cohosh as a first-line approach. Its position statement reads, in part: "In women who need relief for mild [hot flashes and night sweats], NAMS recommends first considering lifestyle changes, either alone or combined with a nonprescription remedy, such as dietary isoflavones, black cohosh, or vitamin E."^{61,62}

SOOTHING PROPERTIES OF CHASTEBERRY

Chasteberry (*Vitex agnus castus*), also known as monk's pepper, has served humankind for thousands of years. To be more precise, the berries of this deciduous shrub have benefited womankind for many years. In the ancient world, chasteberry was used to treat various gynecological complaints. For the past half century, chasteberry has been used to treat premenstrual syndrome (PMS), breast tenderness, and other gynecological conditions. In Europe, it is approved for the treatment of menstrual cycle irregularities, PMS, and breast discomfort by the German Commission E, which serves as a governmental regulatory agency for herbal medicines.^{15,63}

Studies have shown that chasteberry acts in the brain to affect the neurotransmitter dopamine, which in turn indirectly affects the

release of prolactin. Oscillating prolactin levels are thought to contribute to the breast tenderness and discomfort associated with PMS. Chasteberry has been shown to beneficially regulate several hormones including progesterone.¹⁵

Clinical trials of chasteberry for the treatment of PMS have demonstrated that it reduces a number of symptoms, especially breast pain or tenderness, headache, water retention, constipation, irritability, depressed mood, and even anger.^{13,15,64-70} Many small limited studies have confirmed these effects.¹⁵ Recently, a more rigorously designed study added further credence to these findings. This randomized, double-blind, placebo-controlled study of 170 women with PMS found significant improvement in self- and physician-assessed symptoms of irritability, mood change, anger, headache, breast fullness, and bloating. Symptoms decreased by 50% or more for more than half of the women taking chasteberry compared to placebo. Side effects were few and mild.¹³ Another double-blind, placebo-controlled trial examined chasteberry's effects on at least three menstrual cycles in 104 women. Women in the treatment group showed significant improvement in cyclical breast discomfort.⁷¹

An intriguing study conducted in 2003 found that chasteberry was at least as effective as the popular antidepressant fluoxetine (Prozac®) in relieving premenstrual dysphoric disorder, a severe form of PMS characterized by extreme emotional and physical distress. Fluoxetine was somewhat better at improving psychological symptoms, but chasteberry did a better job of diminishing physical complaints.⁷² Last year, Italian researchers published a comprehensive review of all the relevant clinical data and concluded, "the data available seem to indicate that [chasteberry] is a safe herbal medicine."⁶³ Although no drug interactions have been reported, chasteberry might interfere with dopaminergic antagonist drugs. It should also be avoided during pregnancy or lactation, according to the Italian researchers.

PROTECTIVE ACTION OF LICORICE ROOT

Licorice (*Glycyrrhiza glabra*) is native to the Mediterranean, where it has been used medicinally for thousands of years. Today, women may benefit from this sweet and fragrant root in a number of ways. Recent data indicate, for instance, that extracts of a *Glycyrrhiza* species exhibit estrogenic activity and put the brakes on breast cancer cells in the laboratory.⁷³ Specifically, the licorice extract induced apoptosis, or programmed suicide, in a line of human breast cancer cells.

Remarkably, this flavorful herb also exhibits activities that may ameliorate other common menopausal maladies, including depression, osteoporosis, and cardiovascular disease. In 2003, Israeli scientists reported that certain flavonoids extracted from licorice root inhibit the re-uptake of serotonin, much as estradiol does. Serotonin is a neurotransmitter that is thought to play an important role in regulating mood. Modern antidepressant drugs such as sertraline (Zoloft®) and fluoxetine (Prozac®) act in precisely this manner to alleviate depression. "This study showed that several isoflavans are unique phytoestrogens," wrote the researchers, "and, thus, potentially may be beneficial for mild to moderate depression in pre- and post-menopausal women."⁷⁴



Licorice (*Glycyrrhiza glabra*)

Noting that postmenopausal women are at greater risk of cardiovascular disease, possibly due to declining estrogen levels, another team of Israeli researchers investigated licorice root's effects on blood vessels. Because it has estrogen-like properties, licorice extract stimulated DNA synthesis in human endothelial cells and affected the production of human vascular smooth muscle cells. "We suggest the use of glabrene [extracted from licorice root] with or without estradiol as a new agent for modulation of vascular injury and atherogenesis for the prevention of cardiovascular disease in postmenopausal women," the scientists concluded.⁷⁵

Finally, Korean researchers recently determined that glabridin, a biochemical extracted from licorice root, exerted powerful influences on bone precursor cells known as osteoblasts in the laboratory. The extract acted in several ways to promote the growth and health of these crucial bone cells. According to the researchers, "Our data indicate that the enhancement of osteoblast function by glabridin may result in the prevention of osteoporosis and inflammatory bone disease."⁷⁶ Scientists at Israel's Tel-Aviv University have also demonstrated an osteoporosis-fighting effect of licorice components.⁷⁷

A CHINESE REMEDY FOR MENOPAUSE

Dong quai (*Angelica sinensis*) is a traditional Chinese medicinal herb that has long been used to manage gynecological conditions. Few clinical trials of sufficient size and rigor have been conducted, so Western scientists tend toward skepticism regarding the use of this time-honored botanical for the relief of menopause symptoms. However, tantalizing research indicates that dong quai root contains a number of bioactive compounds that may help reduce menopause-related hot flashes, prevent cancer, boost immune function, and improve bone health.⁷⁸⁻⁸²

Not surprisingly, Chinese re-searchers have taken it upon themselves to validate claims for dong quai's potential healing properties. Although one randomized, controlled clinical trial failed to find a significant difference between dong quai and placebo in relieving hot flashes,⁸³ it should be noted that Chinese healers never prescribe dong quai alone. It is always administered in combination with one or more other herbs. In fact, a Chinese study of one such traditional herbal combination that included dong

quai, among other botanicals, concluded that hot flashes and other menopausal complaints were reduced by 70%.^{80,84}

Another recent study examined the effects of a combination of dong quai and chamomile in treating menopausal symptoms. This randomized, placebo-controlled study of 55 women found a significant difference in relief of hot flashes, insomnia, and fatigue between the treatment and placebo groups. Effects materialized in the treatment group within the first month of taking the herbs. "Treatment . . . seems to be effective for menopausal symptoms without apparent major adverse effects," according to the researchers.⁸⁵

A recent study of dong quai's purported anxiety-relieving effects found that the essential oil of this Asian herb was about as effective as the prescription anti-anxiety drug diazepam (Valium®) in stress tests performed on laboratory mice.⁸⁶ Another recent experiment showed that dong quai extract significantly halted replication of cancer cells in the laboratory, and induced apoptosis (programmed suicide) in the cells.⁸¹

In Chinese medicine, dong quai is often used in combination with other herbs to treat bone injuries. Seeking to understand how it affects bone health, scientists in Pennsylvania cultured human bone precursor cells with varying amounts of dong quai extract. They found that the extract stimulated proliferation of bone cells, while enhancing protein, collagen synthesis, and the activity of an enzyme associated with bone building.⁸²

COMPREHENSIVE HORMONE MODULATION

While plant-derived compounds such as phytoestrogens and lignans successfully counter menopausal symptoms in many women, others may need additional therapeutics to achieve optimal relief.

Bioidentical hormone replacement is an option for managing the uncomfortable effects of menopause. This method involves first assessing hormone levels with blood testing and then correcting deficiencies using hormones that are identical to those found naturally in the body. By restoring estrogens (using only natural forms), progesterone, DHEA, pregnenolone, and testosterone to the levels found in healthy women in their twenties, bioidentical hormone replacement therapy helps to relieve menopausal symptoms and enhance well-being. Supplementation with phytoestrogens, lignans, and cruciferous vegetable extracts may help protect against the increased cancer risk that even some natural estrogen drugs may induce.

A Natural Approach to Menopause

By Dale Kiefer

CANCER-PREVENTIVE CRUCIFEROUS VEGETABLES

Epidemiological evidence strongly suggests that abundant consumption of cruciferous vegetables such as broccoli, from the Brassica genus, correlates with lower breast cancer incidence. A recent study in China concluded: **“Greater Brassica vegetable consumption . . . was associated with significantly reduced breast cancer risk among Chinese women.”**⁸⁷

The bioactive chemicals in cruciferous vegetables that are responsible for cancer protection derive from a family of chemicals called gluco-sinolates. When consumed, gluco-sinolates are converted to highly beneficial compounds, including sulforaphane and indole-3-carbinol (I3C). These compounds are believed to inhibit numerous types of cancers, including breast and cervical cancers, by a variety of mechanisms.^{88,89} In a recent article published in the Journal of Nutritional Biochemistry, scientists noted: **“Mounting preclinical and clinical evidence indicates that indole-3-carbinol (I3C), a key bioactive food component in cruciferous vegetables, has multiple anticarcinogenic and anti-tumorigenic properties.”**⁹⁰

I3C appears especially effective in protecting against hormone-dependent cancers such as breast, cervical, and prostate cancers, due to its favorable influence on the body’s balance of estrogens.⁹¹⁻⁹⁵ I3C further affects health by undergoing a natural conversion in the body to yet another potent anti-cancer compound, diindolylmethane (DIM). In addition to stopping hormone-dependent cancer cells in their tracks, DIM inhibits breast cancer cells that are not hormone dependent, through a number of mechanisms.



For example, scientists at the University of California, Berkeley, recently discovered that DIM causes breast cancer cells to boost production of interferon gamma, an immune system component that plays an important role in preventing the development of primary and transplanted tumors.⁹⁶ This finding is only the latest in a long line of discoveries regarding the healing properties of cruciferous vegetables. It is likely that researchers will continue to unravel the many ways in which cruciferous vegetable compounds work to prevent and destroy different types of cancer.

HORMONES USED IN MENOPAUSE MANAGEMENT

Estrogens. Estriol is the main component of bioidentical estrogen replacement therapy, often used with smaller proportions of estradiol and estrone. Estriol offers many of the benefits of more conventional estrogen-replacement therapies, without the harsh side effects or long-term dangers associated with conventional hormone replacement therapy.⁹⁷

Some popular prescription estrogen formulas are BiEst and TriEst. BiEst consists of estradiol and estriol, while TriEst contains all three estrogens.⁹⁸

Progesterone is important to hormone replacement, serving as a counterpoint to estrogen. One of progesterone’s most valuable benefits may be its ability to fight cancer. Studies have shown that progesterone has anti-proliferative effects on at least two different types of breast cancer cells.⁹⁹ Natural progesterone has also demonstrated neuroprotective properties.¹⁰⁰ Progesterone deficiency has been linked to migraine.¹⁰¹

Most natural progesterone products are derived from soybeans and yams, and can be purchased over the counter. A common form of natural progesterone is dispensed in a cream that is applied topically to the skin.^{102,103} Many physicians recommend using progesterone therapy only during the last half of the month to simulate a young, healthy progesterone cycle.

DHEA is a hormone secreted by the adrenal gland, the gonads, and the brain.¹⁰⁴ Although women usually have less DHEA than men, both sexes lose DHEA at about the same rate, suggesting that its decline is related to aging.^{105,106} Decreased levels of DHEA are associated with cancer, diabetes, lupus, and psychiatric illness.^{107,108}

DHEA has been shown to improve mood, neurological functions, immune function, energy, and feelings of well-being, and to maintain muscle and bone mass.¹⁰⁹⁻¹¹¹ One study demonstrated DHEA and pregnenolone help enhance memory.¹¹² DHEA

may also improve insulin sensitivity and lower triglyceride levels.¹¹³

Testosterone levels gradually decrease with age.¹¹⁴ Loss of testosterone adversely affects libido, bone and muscle mass, vasomotor symptoms, cardiovascular health, mood, and well-being.^{115,116} Testosterone therapy, combined with estrogen therapy, has been shown to improve quality of life, vigor, mood, ability to concentrate, bone mineralization, libido, and sexual satisfaction.¹¹⁷⁻¹²⁰ This combination therapy also produces improvements in hot flashes, sleep disturbances, night sweats, and vaginal dryness. In women, DHEA often converts to testosterone, thereby making it possible to raise testosterone levels using DHEA supplements.^{114,119}

Pregnenolone levels likewise decline with age, decreasing significantly in women after the age of 30.¹²¹ Reduced pregnenolone levels result in decreased amounts of all other hormones, and pregnenolone deficiencies have been associated with diminished brain function and dementia.^{122,123}

CONCLUSION

Menopause marks an important life transition for women, one potentially fraught with challenges to health and quality of life.

While many women wish to avoid the risks associated with estrogen drugs, they are keenly interested in finding relief from hot flashes, depression, irritability, insomnia, breast pain, and possible declines in cognition and bone and cardiovascular health.

Fortunately, the wisdom of ancient folk medicine combined with the objective application of modern science may now help women obtain effective, reliable relief from these menopausal conditions, without significant side effects.

HORMONE REPLACEMENT THERAPY, THEN AND NOW

For decades, hormone replacement therapy was essentially the standard treatment for menopausal complaints. This changed abruptly in 2002, when the National Institutes of Health announced that it had halted a comprehensive study of the effects of hormone replacement therapy on various aspects of women's long-term health.

Alarmed by emerging findings, researchers cancelled the massive trial, known as the Women's Health Initiative, before it was completed. Although the combination of estrogen and progestin improved healthy menopausal women's bone health compared to placebo, it was also clearly associated with significant increases in heart disease, stroke, blood clots, and breast cancer. Hormone replacement therapy increased the incidence of breast cancer alone by as much as 26%, while increasing heart attack incidence by nearly 30%.¹

Accordingly, menopausal women were encouraged to discontinue hormone replacement therapy, and millions of women complied.¹²⁴ Although hormone replacement therapy offers slight improvements in osteoporosis risk and incidence of colon cancer, NIH officials noted, "The balance of harm versus benefit does not justify any woman beginning or continuing to take estrogen plus progestin." While the use of hormone replacement therapy has dropped precipitously, the health problems associated with menopause remain. What to do about the erosion of quality of life, sleeplessness, irritability, hot flashes, and brittle bones that accompany menopause? Data indicate that women have been reluctant to turn to traditional herbal remedies such as black cohosh and soy.¹²⁴

However, mounting evidence suggests that women should embrace these time-honored remedies, as science makes progress in proving what traditional healers have long known: botanicals work. Indeed, nature seems to know best, offering all the benefits of hormone replacement therapy with few, if any, of the side effects. Herbal remedies in use for centuries are gradually regaining acceptance in the wake of hormone replacement therapy's fall from grace.

References

1. Available at: www.nhlbi.nih.gov/new/press/02-07-09.html. Accessed February 2, 2006.
2. Wietrzyk J, Gryniewicz G, Opolski A. Phytoestrogens in cancer prevention and therapy—mechanisms of their biological activity. *Anticancer Res.* 2005 May;25(3c):2357-66.
3. Tang GW. The climacteric of Chinese factory workers. *Maturitas.* 1994 Oct;19(3):177-82.
4. Lissin LW, Cooke JP. Phytoestrogens and cardiovascular health. *J Am Coll Cardiol.* 2000 May;35(6):1403-10.

5. Kim MK, Chung BC, Yu VY, et al. Relationships of urinary phyto-oestrogen excretion to BMD in postmenopausal women. *Clin Endocrinol (Oxf)*. 2002 Mar;56(3):321-8.
6. Fugate SE, Church CO. Nonestrogen treatment modalities for vasomotor symptoms associated with menopause. *Ann Pharmacother*. 2004 Sep;38(9):1482-99.
7. Geller SE, Studee L. Botanical and dietary supplements for menopausal symptoms: what works, what does not. *J Womens Health (Larchmt)*. 2005 Sep;14(7):634-49.
8. Seeram NP, Adams LS, Henning SM, et al. In vitro antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. *J Nutr Biochem*. 2005 Jun;16(6):360-7.
9. Kim ND, Mehta R, Yu W, et al. Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer. *Breast Cancer Res Treat*. 2002 Feb;71(3):203-17.
10. Mehta R, Lansky EP. Breast cancer chemopreventive properties of pomegranate (*Punica granatum*) fruit extracts in a mouse mammary organ culture. *Eur J Cancer Prev*. 2004 Aug;13(4):345-8.
11. Chidambara Murthy KN, Jayaprakasha GK, Singh RP. Studies on antioxidant activity of pomegranate (*Punica granatum*) peel extract using in vivo models. *J Agric Food Chem*. 2002 Aug 14;50(17):4791-5.
12. Sudheesh S, Vijayalakshmi NR. Flavonoids from *Punica granatum*—potential antiperoxidative agents. *Fitoterapia*. 2005 Mar;76(2):181-6.
13. Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ*. 2001 Jan 20;322(7279):134-7.
14. Wuttke W, Jarry H, Christoffel V, Spengler B, Seidlova-Wuttke D. Chaste tree (*Vitex agnus-castus*)—pharmacology and clinical indications. *Phytomedicine*. 2003 May;10(4):348-57.
15. Roemheld-Hamm B. Chasteberry. *Am Fam Physician*. 2005 Sep 1;72(5):821-4.
16. Frei-Kleiner S, Schaffner W, Rahlfs VW, Bodmer C, Birkhauser M. *Cimicifuga racemosa* dried ethanolic extract in menopausal disorders: a double-blind placebo-controlled clinical trial. *Maturitas*. 2005 Aug 16;51(4):397-404.
17. Osmers R, Friede M, Liske E, et al. Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms. *Obstet Gynecol*. 2005 May;105(5 Pt 1):1074-83.
18. Branca F, Lorenzetti S. Health effects of phytoestrogens. *Forum Nutr*. 2005;(57):100-11.
19. Linseisen J, Piller R, Hermann S, Chang-Claude J. Dietary phytoestrogen intake and premenopausal breast cancer risk in a German case-control study. *Int J Cancer*. 2004 Jun 10;110(2):284-90.
20. McCann SE, Muti P, Vito D, et al. Dietary lignan intakes and risk of pre- and postmenopausal breast cancer. *Int J Cancer*. 2004 Sep 1;111(3):440-3.
21. Saleem M, Kim HJ, Ali MS, Lee YS. An update on bioactive plant lignans. *Nat Prod Rep*. 2005 Dec;22(6):696-716.
22. Wang LQ. Mammalian phytoestrogens: enterodiol and enterolactone. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2002 Sep 25;777(1-2):289-309.
23. Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, van der Schouw YT. Dietary phytoestrogens and vascular function in postmenopausal women: a cross-sectional study. *J Hypertens*. 2004 Jul;22(7):1381-8.
24. Franco OH, Burger H, Lebrun CE, et al. Higher dietary intake of lignans is associated with better cognitive performance in postmenopausal women. *J Nutr*. 2005 May;135(5):1190-5.
25. Saarinen NM, Huovinen R, Warri A, et al. Uptake and metabolism of hydroxymatairesinol in relation to its anticarcinogenicity in DMBA-induced rat mammary carcinoma model. *Nutr Cancer*. 2001;41(1-2):82-90.

26. Saarinen NM, Penttinen PE, Smeds AI, Hurmerinta TT, Makela SI. Structural determinants of plant lignans for growth of mammary tumors and hormonal responses in vivo. *J Steroid Biochem Mol Biol.* 2005 Feb;93(2-5):209-19.
27. Katsuda S, Yoshida M, Saarinen N, et al. Chemopreventive effects of hydroxymatairesinol on uterine carcinogenesis in Donryu rats. *Exp Biol Med (Maywood).* 2004 May;229(5):417-24.
28. Kangas L, Saarinen N, Mutanen M, et al. Antioxidant and antitumor effects of hydroxymatairesinol (HM-3000, HMR), a lignan isolated from the knots of spruce. *Eur J Cancer Prev.* 2002 Aug;11 Suppl 2S48-S57.
29. Saarinen NM, Warri A, Makela SI, et al. Hydroxymatairesinol, a novel enterolactone precursor with antitumor properties from coniferous tree (*Picea abies*). *Nutr Cancer.* 2000;36(2):207-16.
30. Aviram M, Rosenblat M, Gaitini D, et al. Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. *Clin Nutr.* 2004 Jun;23(3):423-33.
31. Fuhrman B, Volkova N, Aviram M. Pomegranate juice inhibits oxidized LDL uptake and cholesterol biosynthesis in macrophages. *J Nutr Biochem.* 2005 Sep;16(9):570-6.
32. Pasqualini JR, Chetrite GS. Recent insight on the control of enzymes involved in estrogen formation and transformation in human breast cancer. *J Steroid Biochem Mol Biol.* 2005 Feb;93(2-5):221-36.
33. Kim ND, Mehta R, Yu W, et al. Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer. *Breast Cancer Res Treat.* 2002 Feb;71(3):203-17.
34. Cornwell T, Cohick W, Raskin I. Dietary phytoestrogens and health. *Phytochemistry.* 2004 Apr;65(8):995-1016.
35. Holzbeierlein JM, McIntosh J, Thrasher JB. The role of soy phytoestrogens in prostate cancer. *Curr Opin Urol.* 2005 Jan;15(1):17-22.
36. Singeltary KW, Frey RS, Li JY. Differential effects of genistein cell proliferation, cyclin B1, and p34cdc2 in transformed and nontransformed human breast cells. *Pharm Biol.* 2002;40:35-42.
37. Jeune MA, Kumi-Diaka J, Brown J. Anticancer activities of pomegranate extracts and genistein in human breast cancer cells. *J Med Food.* 2005;8(4):469-75.
38. Frey RS, Li J, Singeltary KW. Effects of genistein on cell proliferation and cell cycle arrest in nonneoplastic human mammary epithelial cells: involvement of Cdc2, p21(waf/cip1), p27(kip1), and Cdc25C expression. *Biochem Pharmacol.* 2001 Apr 15;61(8):979-89.
39. Rowell C, Carpenter DM, Lamartiniere CA. Chemoprevention of breast cancer, proteomic discovery of genistein action in the rat mammary gland. *J Nutr.* 2005 Dec;135(12 Suppl):2953S-9S.
40. de Kleijn MJ, van der Schouw YT, Wilson PW, Grobbee DE, Jacques PF. Dietary intake of phytoestrogens is associated with a favorable metabolic cardiovascular risk profile in postmenopausal US women: the Framingham study. *J Nutr.* 2002 Feb;132(2):276-82.
41. Hedelin M, Klint A, Chang ET, et al. Dietary phytoestrogen, serum enterolactone and risk of prostate cancer: the cancer prostate sweden study (sweden). *Cancer Causes Control.* 2006 Mar;17(2):169-80.
42. Xu WH, Zheng W, Xiang YB, et al. Soya food intake and risk of endometrial cancer among Chinese women in Shanghai: population based case-control study. *BMJ.* 2004 May 29;328(7451):1285.
43. Sarkar FH, Li Y. Cell signaling pathways altered by natural chemopreventive agents. *Mutat Res.* 2004 Nov 2;555(1-2):53-64.
44. Sarkar FH, Li Y. The role of isoflavones in cancer chemoprevention. *Front Biosci.* 2004 Sep 1;9:2714-24.
45. Schabath MB, Hernandez LM, Wu X, Pillow PC, Spitz MR. Dietary phytoestrogens and lung cancer risk. *JAMA.* 2005 Sep 28;294(12):1493-504.

46. Hogervorst E, Williams J, Budge M, Riedel W, Jolles J. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. *Neuroscience*. 2000;101(3):485-512.
47. File SE, Jarrett N, Fluck E, et al. Eating soya improves human memory. *Psychopharmacology (Berl)*. 2001 Oct;157(4):430-6.
48. Duffy R, Wiseman H, File SE. Improved cognitive function in postmenopausal women after 12 weeks of consumption of a soya extract containing isoflavones. *Pharmacol Biochem Behav*. 2003 Jun;75(3):721-9.
49. Lee YB, Lee HJ, Sohn HS. Soy isoflavones and cognitive function. *J Nutr Biochem*. 2005 Nov;16(11):641-9.
50. Lydeking-Olsen E, Beck-Jensen JE, Setchell KD, Holm-Jensen T. Soymilk or progesterone for prevention of bone loss—a 2 year randomized, placebo-controlled trial. *Eur J Nutr*. 2004 Aug;43(4):246-57.
51. Zhang X, Shu XO, Li H, et al. Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. *Arch Intern Med*. 2005 Sep 12;165(16):1890-5.
52. Upmalis DH, Lobo R, Bradley L, Warren M, Cone FL, Lamia CA. Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter, double-blind, randomized, placebo-controlled study. *Menopause*. 2000 Jul-Aug;7(4):236-42.
53. Albert A, Altabre C, Baro F, et al. Efficacy and safety of a phytoestrogen preparation derived from *Glycine max* (L.) Merr in climacteric symptomatology: a multicentric, open, prospective and non-randomized trial. *Phytomedicine*. 2002 Mar;9(2):85-92.
54. Mahady GB, Fabricant D, Chadwick LR, Dietz B. Black cohosh: an alternative therapy for menopause? *Nutr Clin Care*. 2002 Nov;5(6):283-9.
55. Anon. *Cimicifuga racemosa*. Monograph. *Altern Med Rev*. 2003 May;8(2):186-9.
56. Mahady GB. Black cohosh (*Actaea/Cimicifuga racemosa*): review of the clinical data for safety and efficacy in menopausal symptoms. *Treat Endocrinol*. 2005;4(3):177-84.
57. Pockaj BA, Loprinzi CL, Sloan JA, et al. Pilot evaluation of black cohosh for the treatment of hot flashes in women. *Cancer Invest*. 2004;22(4):515-21.
58. Nappi RE, Malavasi B, Brundu B, Facchinetti F. Efficacy of *Cimicifuga racemosa* on climacteric complaints: a randomized study versus low-dose transdermal estradiol. *Gynecol Endocrinol*. 2005 Jan;20(1):30-5.
59. Lupu R, Mehmi I, Atlas E, et al. Black cohosh, a menopausal remedy, does not have estrogenic activity and does not promote breast cancer cell growth. *Int J Oncol*. 2003 Nov;23(5):1407-12.
60. Seidlova-Wuttke D, Hesse O, Jarry H, et al. Evidence for selective estrogen receptor modulator activity in a black cohosh (*Cimicifuga racemosa*) extract: comparison with estradiol-17beta. *Eur J Endocrinol*. 2003 Oct;149(4):351-62.
61. Neff MJ. NAMS releases position statement on the treatment of vasomotor symptoms associated with menopause. *Am Fam Physician*. 2004 Jul 15;70(2):393-4, 396, 399.
62. Anon. Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. *Menopause*. 2004 Jan;11(1):11-33.
63. Daniele C, Thompson CJ, Pittler MH, Ernst E. *Vitex agnus castus*: a systematic review of adverse events. *Drug Saf*. 2005;28(4):319-32.
64. Blumenthal M. German Federal Institute for Drugs and Medical Devices. Commission E. Herbal Medicine: expanded Commission E monographs. 1st ed. Newton, MA: Integrative Medicine Communications; 2000.
65. Gorkow C, Wuttke W, Marz RW. Effectiveness of *Vitex agnus-castus* preparations. *Wien Med Wochenschr*. 2002;152(15-16):364-72.
66. Lauritzen C, Reuter HD, Repges R, Bohnert KJ, Schmidt U. Treatment of premenstrual tension syndrome with *Vitex agnus castus*. Controlled, double-blind study versus pyridoxine. *Phytomedicine*. 1997;4:183-9.

67. Berger D, Schaffner W, Schrader E, Meier B, Brattstrom A. Efficacy of *Vitex agnus castus* L. extract Ze 440 in patients with pre-menstrual syndrome (PMS). *Arch Gynecol Obstet*. 2000 Nov;264(3):150-3.
68. Loch EG, Selle H, Boblitz N. Treatment of premenstrual syndrome with a phytopharmaceutical formulation containing *Vitex agnus castus*. *J Womens Health Gend Based Med*. 2000 Apr;9(3):315-20.
69. Turner S, Mills S. A double-blind clinical trial on herbal remedy for premenstrual syndrome: a case study. *Complement Ther Med*. 1993;1:73-7.
70. Halaska M, Raus K, Beles P, Martan A, Paithner KG. Treatment of cyclical mastodynia using an extract of *Vitex agnus castus*: results of a double-blind comparison with a placebo. *Ceska Gynekol*. 1998 Oct;63(5):388-92.
71. Wuttke W, Splitt G, Gorkow C, et al. Treatment of cyclical mastalgia: results of a randomized, placebo-controlled, double-blind study (in Czech). *Ceska Gynekol*. 1998;63:988-92.
72. Atmaca M, Kumru S, Tezcan E. Fluoxetine versus *Vitex agnus castus* extract in the treatment of premenstrual dysphoric disorder. *Hum Psychopharmacol*. 2003 Apr; 18(3):191-5.
73. Jo EH, Kim SH, Ra JC, et al. Chemopreventive properties of the ethanol extract of chinese licorice (*Glycyrrhiza uralensis*) root: induction of apoptosis and G1 cell cycle arrest in MCF-7 human breast cancer cells. *Cancer Lett*. 2005 Dec 18;230(2):239-47.
74. Ofir R, Tamir S, Khatib S, Vaya J. Inhibition of serotonin re-uptake by licorice constituents. *J Mol Neurosci*. 2003 Apr;20(2):135-40.
75. Somjen D, Knoll E, Vaya J, Stern N, Tamir S. Estrogen-like activity of licorice root constituents: glabridin and glabrene, in vascular tissues in vitro and in vivo. *J Steroid Biochem Mol Biol*. 2004 Jul;91(3):147-55.
76. Choi EM. The licorice root derived isoflavan glabridin increases the function of osteoblastic MC3T3-E1 cells. *Biochem Pharmacol*. 2005 Aug 1;70(3):363-8.
77. Somjen D, Katzburg S, Vaya J, et al. Estrogenic activity of glabridin and glabrene from licorice roots on human osteoblasts and prepubertal rat skeletal tissues. *J Steroid Biochem Mol Biol*. 2004 Aug;91(4-5):241-6.
78. Yang T, Jia M, Mei Q. Effect of *Angelica sinensis* polysaccharide on lymphocyte proliferation and cytokine induction. *Zhong Yao Cai*. 2005 May;28(5):405-7.
79. Tsai NM, Lin SZ, Lee CC, et al. The antitumor effects of *Angelica sinensis* on malignant brain tumors in vitro and in vivo. *Clin Cancer Res*. 2005 May 1;11(9):3475-84.
80. Anon. Monograph. *Angelica sinensis*. *Altern Med Rev*. 2004 Dec;9(4):429-33.
81. Cheng YL, Chang WL, Lee SC, et al. Acetone extract of *Angelica sinensis* inhibits proliferation of human cancer cells via inducing cell cycle arrest and apoptosis. *Life Sci*. 2004 Aug 13;75(13):1579-94.
82. Yang Q, Populo SM, Zhang J, Yang G, Kodama H. Effect of *Angelica sinensis* on the proliferation of human bone cells. *Clin Chim Acta*. 2002 Oct;324(1-2):89-97.
83. Hirata JD, Swiersz LM, Zell B, Small R, Ettinger B. Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial. *Fertil Steril*. 1997 Dec;68(6):981-6.
84. Chang HM, But PP. *Pharmacology and application of chinese material medica*. World Scientific. 1987;1:489-505.
85. Kupfersztain C, Rotem C, Fagot R, Kaplan B. The immediate effect of natural plant extract, *Angelica sinensis* and *Matricaria chamomilla* (Climex) for the treatment of hot flushes during menopause. A preliminary report. *Clin Exp Obstet Gynecol*. 2003;30(4):203-6.
86. Chen SW, Min L, Li WJ, et al. The effects of angelica essential oil in three murine tests of anxiety. *Pharmacol Biochem Behav*. 2004 Oct;79(2):377-82.

87. Fowke JH, Chung FL, Jin F, et al. Urinary isothiocyanate levels, brassica, and human breast cancer. *Cancer Res.* 2003 Jul 15;63(14):3980-6.
88. Rouzaud G, Young SA, Duncan AJ. Hydrolysis of glucosinolates to isothiocyanates after ingestion of raw or microwaved cabbage by human volunteers. *Cancer Epidemiol Biomarkers Prev.* 2004 Jan;13(1):125-31.
89. Anon. Indole-3-carbinol. Monograph. *Altern Med Rev.* 2005 Dec;10(4):337-42.
90. Kim YS, Milner JA. Targets for indole-3-carbinol in cancer prevention. *J Nutr Biochem.* 2005 Feb;16(2):65-73.
91. Bradlow HL, Michnovicz JJ, Halper M, et al. Long-term responses of women to indole-3-carbinol or a high fiber diet. *Cancer Epidemiol Biomarkers Prev.* 1994 Oct;3(7):591-5.
92. Ashok BT, Chen Y, Liu X, et al. Abrogation of estrogen-mediated cellular and biochemical effects by indole-3-carbinol. *Nutr Cancer.* 2001;41(1-2):180-7.
93. Ashok BT, Chen YG, Liu X, et al. Multiple molecular targets of indole-3-carbinol, a chemopreventive anti-estrogen in breast cancer. *Eur J Cancer Prev.* 2002 Aug;11 Suppl 2S86-S93.
94. Yuan F, Chen DZ, Liu K, et al. Anti-estrogenic activities of indole-3-carbinol in cervical cells: implication for prevention of cervical cancer. *Anticancer Res.* 1999 May;19(3A):1673-80.
95. Liu H, Wormke M, Safe SH, Bjeldanes LF. Indolo[3,2-b]carbazole: a dietary-derived factor that exhibits both antiestrogenic and estrogenic activity. *J Natl Cancer Inst.* 1994 Dec 7;86(23):1758-65.
96. Riby JE, Xue L, Chatterji U, et al. Activation and Potentiation of Interferon- γ Signaling by 3,3'-Diindolylmethane in MCF-7 Breast Cancer Cells. *Mol Pharmacol.* 2006 Feb;69(2):430-9.
97. Head KA. Estriol: safety and efficacy. *Altern Med Rev.* 1998 Apr;3(2):101-13.
98. Taylor M. Unconventional estrogens: estriol, biest, and triest. *Clin Obstet Gynecol.* 2001 Dec;44(4):864-79.
99. Formby B, Wiley TS. Progesterone inhibits growth and induces apoptosis in breast cancer cells: inverse effects on Bcl-2 and p53. *Ann Clin Lab Sci.* 1998 Nov;28(6):360-9.
100. Stein DG. The case for progesterone. *Ann NY Acad Sci.* 2005 Jun;1053:152-69.
101. Colson NJ, Lea RA, Quinlan S, MacMillian J, Griffiths LR. Investigation of hormone receptor genes in migraine. *Neurogenetics.* 2005 Feb;6(1):17-23.
102. Komesaroff PA, Black CV, Cable V, Sudhir K. Effects of wild yam extract on menopausal symptoms, lipids and sex hormones in healthy menopausal women. *Climacteric.* 2001 Jun;4(2):144-50.
103. Uchibayashi M. Forgotten episodes of the birth of cortisone. *Yakushigaku Zasshi.* 2001;36(1):70-5.
104. Williams GH, Dluhy RG. Disorders of the adrenal cortex. In: *Harrison's Principles of Internal Medicine.* 15th ed. New York: McGraw-Hill; 2001.
105. Khorram O. DHEA: a hormone with multiple effects. *Curr Opin Obstet Gynecol.* 1996;8(5):351-4.
106. Wilder RL. Adrenal and gonadal steroid hormone deficiency in the pathogenesis of rheumatoid arthritis. *J Rheumatol Suppl.* 1996 Mar;44:10-2.
107. Berkman LF, Seeman TE, Albert M, et al. High, usual and impaired functioning in community-dwelling older men and women: findings from the MacArthur Foundation Research Network on Successful Aging. *J Clin Epidemiol.* 1993 Oct;46(10):1129-40.
108. Salek FS, Bigos KL, Kroboth PD. The influence of hormones and pharmaceutical agents on DHEA and DHEA-S concentrations: a review of clinical studies. *J Clin Pharmacol.* 2002 Mar;42(3):247-66.

109. Kroboth PD, Salek FS, Pittenger AL, Fabian TJ, Frye RF. DHEA and DHEA-S: a review. *J Clin Pharmacol*. 1999 Apr;39(4):327–48.
110. Proctor DN, Balagopal P, Nair KS. Age-related sarcopenia in humans is associated with reduced synthetic rates of specific muscle proteins. *J Nutr*. 1998 Feb;128(2 Suppl):351S–5S.
111. Yen SS, Morales AJ, Khorram O. Replacement of DHEA in aging men and women. Potential remedial effects. *Ann NY Acad Sci*. 1995 Dec 29;774:128–42.
112. Rupprecht R, Holsboer F. Neuropsychopharmacological properties of neuroactive steroids. *Steroids*. 1999 Jan;64(1–2):83–91.
113. Casson PR, Faquin LC, Stentz FB, et al. Replacement of dehydroepiandrosterone enhances T-lymphocyte insulin binding in postmenopausal women. *Fertil Steril*. 1995 May;63(5):1027–31.
114. Schneider HP. Androgens and antiandrogens. *Ann NY Acad Sci*. 2003 Nov; 997:292-306.
115. Burd ID, Bachmann GA. Androgen replacement in menopause. *Curr Womens Health Rep*. 2001 Dec;1(3):202-5.
116. Watt PJ, Hughes RB, Rettew LB, Adams R. A holistic programmatic approach to natural hormone replacement. *Fam Community Health*. 2003 Jan;25(1):53-63.
117. Bachmann GA. Androgen therapy in menopause: evolving benefits and challenges. *Am J Obstet Gynecol*. 1999 Mar;180(3 Pt 2):308-11.
118. Braunstein GD. Androgen insufficiency in women: summary of critical issues. *Fertil Steril*. 2002 Apr;77(Suppl 4):S94–9.
119. Cameron DR, Braunstein GD. Androgen replacement therapy in women. *Fertil Steril*. 2004 Aug;82(2):273-89.
120. Davis A, Gilbert K, Misiowiec P, Riegel B. Perceived effects of testosterone replacement therapy in perimenopausal and postmenopausal women: an internet pilot study. *Health Care Women Int*. 2003 Nov;24(9):831–48.
121. Havlikova H, Hill M, Hampl R, Starka L. Sex- and age-related changes in epitestosterone in relation to pregnenolone sulfate and testosterone in normal subjects. *J Clin Endocrinol Metab*. 2002 May;87(5):2225-31.
122. Maurice T, Phan VL, Urani A, Kamei H, Noda Y, Nabeshima T. Neuroactive neurosteroids as endogenous effectors for the sigma1 (sigma1) receptor: pharmacological evidence and therapeutic opportunities. *Jpn J Pharmacol*. 1999 Oct;81(2):125–55.
123. Yao ZX, Brown RC, Teper G, Greeson J, Papadopoulos V. 22R-Hydroxycholesterol protects neuronal cells from beta-amyloid-induced cytotoxicity by binding to beta-amyloid peptide. *J Neurochem*. 2002 Dec;83(5):1110–19.
124. Kelly JP, Kaufman DW, Rosenberg L, et al. Use of postmenopausal hormone therapy since the Women's Health Initiative findings. *Pharmacoepidemiol Drug Saf*. 2005 Dec;14(12):837-42.

All Contents Copyright © 1995-2008 Life Extension Foundation All rights reserved.

LifeExtensionSM

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.