

Chapter 42

The New Science of Anti-Aging Hormone Replacement Therapy: A Multidimensional Approach

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ABSTRACT

Since ancient times, humans have been concerned with developing and preserving youthful vigor, stopping the running age clock, and extending lifespan. Today there is a great progress in understanding the aging process in attempt to delay it. This presentation considers the main popular and easily obtainable hormones: estradiol, testosterone, DHEA, thyroid hormone, melatonin, growth hormone, and progesterone. Many of the benefits of using these hormones are equivocal thus far, but we are seeing an increasing number of studies which, at least, recommend these hormones as viable therapies to slow down the aging process, to stop the development age-related diseases, and to stay vital and fit in the second half of life.

Keywords: Estradiol; Testosterone; DHEA; Thyroid hormone; Melatonin; Progesterone

INTRODUCTION

At present, it appears that the only way of significantly extending human lifespan is with caloric restriction. However, there are a number of factors, which seemingly can improve lifespan.

In his presentation on behalf of The Endocrine Society and The Hormone Foundation, Dr Robert B Jaffe, the Fred Gellert Professor of Reproductive Medicine and Biology at the University of California, San Francisco, discussed the impact that recently released hormonal treatment studies, such as the Women's Health Initiative (WHI), have had on patients who take or are considering taking combined estrogen and progestin treatment.

"The new research that has come out over the past few months has caused distress and confusion for millions of women, and it has changed the way that doctors practice medicine when it comes to menopause," said Dr. Jaffe. "I believe that it is essential for the medical community to translate these new data so that patients can understand how this information will impact their healthcare and doctors will understand the best ways to treat postmenopausal patients in the future."

Jaffe also discussed the need to examine lifestyle issues, such as good nutrition, weight loss when appropriate, adequate exercise, no smoking and drinking in moderation as important for optimizing postmenopausal health, saying: "As we further examine lifestyle and postmenopausal health, I think that we will find that a healthy lifestyle may be as important as pharmaceuticals."

Following the results of the WHI and Heart and Estrogen/Progestin Replacement (HERS) Studies, both The Endocrine Society and The Hormone Foundation worked to communicate the findings to doctors and patients.

This article presents a new approach to an endocrinological treatment strategy, which should encompass the following key features:

- Individual
- Custom-attracted
- Secure and multidimensional

There has been a lot of progress since Charles Edouard Brown-Sequard transplanted young guinea pigs testes into old dogs and injected himself a mixture of crushed dog and pig testicles. The great advances in medicine in the last years can realize this idea for the near future. Women and men are increasingly interested in initiating a custom-attracted and individualized HRT. We can observe a change of paradigm in nearly all medical subject areas. The standard of an individualized therapy for our patients requires more and more comprehensive epidemiological investigations, meta analyses, and genetic analysis, which has been supported by the detection of the human genome.

HORMONE REPLACEMENT THERAPY

Sexual hormones are of essential importance for reproduction, and later in life for metabolism, the cardiovascular system, and the general well being of the women (see Table 1).. Menopause, which is characterized by a dramatic decrease in estrogen secretion, and is accompanied by diminishing progesterone and androgen levels, triggers a multiple loss of functions. Especially in regions of the brain (central vegetative neuronal system, psyche, libido, cognition, memory), the bone, the skin, connective tissue, peripheral vessels, and cardiovascular system. Ultimately, this causes alterations in those systems; these alterations can lead to an increase in oxidation and a weakened lipid metabolism, resulting in high cholesterol levels and an increased risk of Alzheimer's disease, myocardial infarction, and apoplexy. From this point of view, it seems sensible to consider a long-term HRT with progestins and estrogens.

Specific Risks - Specific Benefits	Overall Risks - Overall Benefits
↑ 29% cardiovascular diseases (MI) ↓ 37% colon cancer	↑ 22% total CVD events ↓ 24% total rate fractures
↑ 26% breast cancer ↓ 17% endometrial cancer	↑ 3% total cancer rate ↓ 2% total mortality
↑ 41% apoplexies ↓ 34% hip fractures (osteoporosis)	↑ 15% "Global Index"
↑ 113% embolic diseases (lung) ↓ 8% mortality (other reasons)	
↑ denotes Increased risk; ↓ denotes Decreased risk	

In the last few years we have been bombarded by a lot of data from studies (e.g. WHI, HERS), which concluded that the risks associated with HRT composed with progestins far outweigh any benefits (see figure). This was in contrast to the findings of other studies, which praised the benefits of HRT.

It seems to be that the results of WHI and HERS showed the typical problems of a non-individual, custom-tailored HRT, that leads to problems in a definite percentage of the female population. Many of whom have genetic or lifestyle dependent alterations in their steroid-hormone metabolism, which increases their risk of CVD and cancer, especially of the breast and endometrial mucous membranes

This presentation displays the new approach to an endocrinological treatment strategy, which as we said before, should be individual, custom attracted, and secure. The great advances in medicine in the last few years will make this new type of HRT a reality in the near future.

This is the hypothesis:

- The individual reaction to HRT is caused by the genetic conditions.
- Long time HRT is correlated with higher risk of breast cancer and CV.
- Breakdown mechanism and productive mechanism of steroidogenesis are correlated with higher tissue levels of estrogens.

Today we are able to answer three main questions:

1. Cardiovascular disease: Who will benefit the most from hormone replacement therapy?
2. Thrombosis: Which patients have a high risk of clotting and cardiovascular complications?
3. High plasma levels of estradiol, DHEA, and testosterone: How can we avoid suprphysiological hormone plasma levels, which have been recognized as a high risk for breast cancer, thrombosis, and eventually CVD? In men: how can we have impact on the risk of prostate cancer in testosterone therapy?

The very interesting overview by Clemons and Goss and their presented studies substantiates the assumption that the continued increased burdening of the organism by suprphysiological doses of 17- β -estradiol increases the proliferation pressure of the mammary glands, increases the radiological density of the mammogram, and increases the lifetime risk of breast cancer. Furthermore, it appears that the risk of breast cancer is dependent upon the cumulative risk of lifetime estrogen exposure.

Therefore, it seems necessary to maintain low estrogen levels. The effort to maintain estrogen concentrations in the sex-steroid dependent tissues at as low as level as is possible is a demand on the evidence based medicine. However, the demand for estrogen replacement is based upon the experience that estrogens have a positive influence on many age-related health problems, especially on the support of bone metabolism, and the improvement of the lipid profile, which can affect the risk of cardiovascular disease.

17- β estradiol acts directly on the genome, and is bound by the estrogen receptor complex. Suprphysiological increased estradiol levels has an impact on cell metabolism, cell division, and transcription of DNA. Therefore, should the HRT practice of administering female sex steroids without knowledge of the production and breakdown of estrogens and other sex steroids hormones, especially the genetically dependent influence of the steroid metabolism, belong to the past?

Since we know that the difference between individuals is based upon genetic mutations and polymorphisms, the HRT managing physician should utilize the following when assessing a patient for HRT in order to obtain an overview of their estrogen history and ascertain their individual risk if prescribed HRT:

1. Personal history (of particular importance is weight gain in pregnancy, endometriosis, breast cysts, and ovarian cysts).
2. Clinical profile, for example hormone plasma tests (be on the look out for high estrone and/or high estradiol levels).
3. Image producing diagnostics; such as a bone density scan mammogram and ultrasound. (High bone density, high tissue density, cysts, and a high endometrium are all suggestive of increased breast cancer risk.)
4. Polymorphism diagnostics.

POLYMORPHISMS

The possibilities of the new molecular genetic diagnostics, especially the gene chip techniques allow us to weigh up the risk of HRT. These technologies mean that we can estimate the benefits of HRT for women in terms of cardiovascular disease risk reduction. As we know, weight reduction, exercise, and smoking cessation lower our cardiovascular disease risk. We also know that the possibility of cardiovascular disease increases dramatically after the menopause, with 10 years latency compared with men.

When assessing a patient for HRT is it important to be aware of several very important polymorphisms. These include:

- **17-Beta Hydroxysteroid Dehydrogenase Type 1 (17 β -HSD1):** This is a key enzyme in the production of estradiol. 17- β HSD1 works by converting the less active estrone into 17- β estradiol. A mutation in the promotor region of HSD1 (-27A \rightarrow C) leads to 45% decrease of enzymatic activity, which therefore affects estradiol levels.
The change of T by C in the Promotor area of the CYP17 gene in position 34 produces a new "SP1-type (CCACC box) promotor site." Women, who carry cytosine in this position (A2/A2), have significantly higher estradiol, estron, progesterone, and DHEA plasma levels. Feigelson et al showed that A2/A2-women are half as likely as A1/A1 women to be HRT users (odds ratio = 0.52) because of side-effects such as breast tenderness and weight gain.
- **Cytochrome P450, 19 Gene, CYP19, Aromatase:** Knowledge of the activity of aromatase, which is coded by the CYP19 gene, is very important. High activity of this enzyme leads to a faster conversion rate from testosterone to estradiol and from androstenedione to estrone, which increases tissue and plasma estrogen levels. We are aware of several polymorphisms of this gene, which are all of great practical importance. The C1558 T Mutation doubles the risk of breast cancer, while another CYP19 mutation significantly decreases the risk of developing breast cancer over lifetime.

GOOD NEWS: CARDIOVASCULAR RISK

Diabetic women who use hormone replacement therapy (HRT) are more likely to have their blood glucose under control, and have lower cholesterol levels than women who never used hormone therapy, a study by University at Buffalo, the State University of New York, epidemiologists has found. Furthermore, the study results also showed that non-diabetic women who were using HRT had lower total cholesterol levels, as well as higher levels of beneficial cholesterol.

A new study, published in the current issue of Diabetes Care, adds yet another twist to the murky risks-benefits scenario surrounding HRT. The federal government suspended a nationwide clinical trial of HRT in July, citing, among other concerns, that the combination of estrogen and progesterone used in the trial did not protect against cardiovascular disease as expected. Yet, the University at Buffalo researchers found that HRT had a positive effect on two important risk factors for heart disease – blood levels of fats and glucose – in a population-based study of 2,786 diabetic and non-diabetic postmenopausal women between the ages of 40 and 74. Carlos Crespo, associate professor of social and preventive medicine at University at Buffalo School of Medicine and Biomedical Sciences, noted that the national HRT clinical trial did not include women with diabetes, and that scientists haven't researched the benefits or risks of hormone replacement in this group.

"Although there may be some risk in using certain types of HRT among certain women, there might be a segment of women who would be better off using HRT," Crespo said. "These findings indicate that diabetic women may be one such segment."

The study, based on data from the Third National Health and Nutrition Examination Survey (NHANES III), compared lipid profiles, glucose and insulin levels, and concentrations of selected blood components known to increase or decrease the risk of heart disease in diabetic and non-diabetic women. Participants were grouped into one of three HRT-use categories: current, previous, or never.

Results showed that diabetic women on HRT had significantly lower fasting levels of total cholesterol compared to diabetic women who were previous or never users: 225 mg/dl, 247 mg/dl, and 241 mg/dl, respectively. The difference in fasting glucose levels among diabetic women according to HRT status were equally significant: 112 mg/dl for current users, compared to 151 mg/dl and 154 mg/dl for previous and never users.

Among non-diabetic women, current HRT users had significantly higher levels of beneficial high-density lipoprotein (HDL) than previous or never users -- 64 mg/dl, 57 mg/dl, and 55 mg/dl, respectively.

HRT also appeared to have a beneficial effect on several additional markers of heart health and glycemic control in both diabetic and non-diabetic women:

- **Fibrinogen** – a protein associated with increased risk of coronary heart disease, stroke, and peripheral artery disease through its role in blood clotting and platelet aggregation was lower among HRT users in both groups of women compared to never users.
- **ApoA** – a protein component of HDL that allows it to remove excess cholesterol from the bloodstream, was higher among HRT users in both groups of women, compared to never users.
- **ApoB** – associated with vessel blockage, was lower among HRT users in both groups of women, compared to never users.
- **HbA1c (GHb), or glycosylated hemoglobin** – an indicator of poor glycemic control, was lower among diabetic women using HRT, compared to previous and never users.

POLYMORPHISMS THAT AID CARDIOVASCULAR RISK ASSESSMENT

Despite this good news, we should consider the possible polymorphisms of women, who use HRT, before starting with this therapy, because by doing so we can estimate the risk of possible CV events in our patients, and thus avoid the danger.

- **Plasminogen Activator Inhibitor Type 1 (PAI-1):** Mutation of the promoter region of the PAI-1 gene (del/ins 4G/5G) leads to increased PAI-1 plasma levels. Increased activity of PAI-1 leads to reduced fibrinolysis, which in turn increases the risk of blood clotting.
- **Angiotensinogen (AGT):** AGT and its products AT I, II, III, IV play a very important part in the regulation of sodium homeostasis and fluid retention and excretion. Polymorphism of the AGT gene (M 235T) is related to hypertension.
- **Endothelial Nitric Oxide Synthetase (NOS3):** NOS3 encourages vasorelaxation. A mutation of the promoter region of the NOS3 gene reduces nitric oxide levels and is related to coronary spasms and hypertension.

We can further estimate the risk of thrombosis in candidates for HRT by considering Prothrombin Factor II (F2) and Factor V Leiden (F5).

- **Prothrombin Factor II (F2):** Prothrombin factor II is a vitamin K-dependent blood clotting factor. Increased expression of F2 by mutation of the F2 gene (G20210) causes an increased risk of blood clotting. (Psaty et al. JAMA 2001;285:906-913)
- **Factor V Leiden (F5):** The G1691A mutation of the F5 gene is known to cause activated protein C resistance (APC resistance). Carriers of this mutation are at high risk of thrombosis.

BREAST CANCER

Polymorphisms that Aid Breast Cancer Risk Assessment

Being aware of the polymorphisms of the genes of steroid metabolizing enzymes gives us the possibility to estimate the risk of non-familial dependent breast cancer. Personal history, mammogram (high density), ultrasound (ovarian cysts, high build up endometrium), and bone density (increased bone density leads to the suspicion of elevated lifelong estradiol levels) are all helpful in determining breast cancer risk. The following polymorphisms may also help to clarify a woman's risk:

- **CYP 1A1 and 1B1 Gene Polymorphism:** These genes code for the two major enzymes controlling the break down of estrogens and xenobiotics from toxic environment. Mutations in those genes lead to higher levels of estradiol, and increased pressure on the proliferation of female hormone dependent tissues. Furthermore, it cuts the estrogens to form 2 OH-estrogens and 16 OH-estrogens
- **CYP 1A1: Hydroxylation to 2-OHE (2 Polymorphisms: T3801C and A2455G):** CYP 1A1 has anti-carcinogenic effects against the estrogen agonist 16 alpha OHE1, however smokers have a higher risk for breast cancer if they display the A2455G Polymorphism. CYP 1A1 is inducible by dietary modification and supplementation with active components of cruciferous vegetables, such as indole-3-carbinol (I3Carbinol), or diindolmethane (DIM).
- **4-OH Estradiol:** Displays over-expression in breast cancer cells. Murray et al found that P450 CYP1B1 is a tumor-specific antigen. According to Liehr et al, 4-Hydroxylation of estrogens can be used as a marker of human mammary tumors.

- **4-Hydroxylation of Estradiol – Estrogen Metabolism and the Risk of Breast Cancer:** To learn more about this I recommend reading the following articles: Muti et al (*Epidemiology*. 2000;11:635-640), and Liehr et al (*Proc Natl Acad Sci U S A*. 1995;92:9220-9224.)
- **CYP 1B1:** Metabolizes polyaromatic hydrocarbons, aromates, and different xenobiotics from a toxic environment, however it also produces the carcinogen 16 - alpha OH-estrone. We have a very easy Elisa test from morning urine to measure the content of 2-OHE2 and OHE1 ratio to 16-alpha OHE1, which seems to be a model for the risk of breast cancer and other epithelial cancers. Women with breast or endometrial cancer have increased estrogen-16-alpha hydroxylase activity. 16-OHE1 has the unique capacity to bind covalently and irreversibly with the endoplasmic reticulum. Agents that increase 2-OHE1 inhibit carcinogenesis. Exposure of mammary epithelial cells to 16-alpha OHE1 results in genotoxic DNA damage and increased cell proliferation, similar to that induced by the carcinogen DMBA (7,12,-dimethylbenzanthracene.) Data from women with breast cancer and age-matched controls shows a strong inverse association of the 2/16alpha ratio with cancer. Cancer Gene Activation by CYP 1B1:
 - Dibenzopyrene: Pottenger et al (*Arch Biochem Biophys*. 1991;286:488-497.)
 - Aflatoxin B1: Crespi et al (*Mutagenesis*. 1997;12:83-89.)
 - Dietary Heterocycloamines
 - Hydroxylation of Testosterone
- **Catechol-Ortho-Methyl-Transferase (COMT) and CYP 1A1, CYP 1B1:** COMT is responsible for the breakdown of catechol-estrogens by hydroxylation. These are converted from estradiol by P450 oxidases (Cytochrome P450 1A1 (CYP 1A1) and (P450 CYP 1B1). The intermediary produced catechol-estrogens are highly carcinogenic.

Polymorphisms of the CYP 1A1 gene leads to increased levels of estrogens and catechol-estrogens, which are themselves a risk factor for the development of breast cancer. Mutation of the COMT gene leads to a slower breakdown rate of catechol-estrogen, thus a greater amount of cancer stimulating intermediary estrogen products is present in the breast cells.
- **Steroid-5 alpha Reductase Type II (SRD 5A2):** This is responsible for the breakdown of testosterone. A mutation of this gene (89val→leu) is known, which reduces the enzymatic activity of SRD 5A2, thus people carrying this mutation have increased levels of testosterone. Women who carry this mutation can develop androgen side effects, while men are at higher risk of prostate cancer.

Alternative Therapies and Prevention of High Estradiol Levels and Breast Cancer

1. Progesterone (sulphatase inhibitor), because estradiol is sulphated in breast tissue.
2. Livial (Tibolone), is a synthetic steroid, which is fully absorbed after intake and is metabolized to the metabolites: delta 4-isomer, 3-alpha hydroxy-tibolone, and 3-beta hydroxy-tibolone. Tibolone activates estradiol in the brain, vagina, and bone. However, it inhibits estradiol in breast tissue (like progesterone). In a DMBA mouse model, Tibolone had a tamoxifen-like effect on tumor growth.

Breast Cancer and Smoking

Palmer et al's (Am J Epidemiol. 1991;134:1-13.) review of two case-controlled studies of women with breast cancer, revealed that women who had never smoked had a relative breast cancer risk of 1.0. Whereas, the odds ratio for women who smoked 25 or more cigarettes per day as compared

with never smokers was 1.2. In both studies, breast cancer risk was more strongly related to smoking at a young age. Among women who started smoking aged 16 and under the relative risk of breast cancer was 1.7 in the Canadian study, and 1.8 in the US study.

The Diet Connection

Important – No Alcohol: (Rosner and Colditz, J Natl Cancer Inst 1996;88:359-364.):

- directly toxic effects, weakened detoxification of xenobiotics, which take the same breakdown pathway as estrogens.
- Activated carcinogens by alcohol->acetaldehyde by stimulating CYP P450 enzymes.
- Increased oxidation.
- Inhibited DNA repair.
- Loss of B-vitamins, vitamin A and retinoids (anti-cancer vitamins).
- Energy→increased fat mass.
- Destroying immune system.
- Increased toxicity of tobacco.
- Increased estrogens.
- Stimulation of sulphatase.

An anti-cancer diet should be rich in fiber, cruciferous vegetables (indole-3-carbinol), and isoflavones (lentils, soy, red clover).

Estrogen Metabolism and the Diet-Cancer Connection Lord et al (*Altern Med Rev.* 2002;7:112-129; Lu et al (*Cancer Res.* 2000;60:1299-1305.)

- Indole-3-carbinol (I3C) reduces the frequency of carcinogen-induced mammary tumors in rats by 75%.
- Dietary indoles inhibit aromatic hydrocarbon-induced neoplasia in mice stomach.
- I3C strongly influences estradiol metabolism in humans by increasing 2-Hydroxylation.
- I3C has specific anti-growth effects on human breast cells but little effect on cells not responsive to estrogen.
- Dietary indoles and isothiocyanates generated from cruciferous vegetables can both stimulate apoptosis and confer protection against DNA damage in human colon cell lines.
- I3C increases 2-hydroxylation in human cancer cell cultures.
- Human subjects taking I3C at 400 mg/d for 3 months show sustained elevation of 2-OH/16OH1-alpha ratio with no detectable side effects.
- Using the 2OHE/16alpha OHE1 ratio Elisa assay as the surrogate endpoint biomarker, an I3C minimum effective dose schedule of 300mg/d is proposed for long-term breast cancer chemoprevention.
- Metabolism of cigarette smoke carcinogen is increased by dietary supplementation with I3C in mice.

Omega-3 Fatty Acids

The Omega-3 class of polyunsaturated fats has emerged as a promising therapy for adjunctive cancer prevention. Possible mechanism:

- Favoring series 3- eicosanoid synthesis.
- Modulation of estrogen metabolism and estrogen receptor binding.

- Increased 2-hydroxylation of estradiol.
- DHA (Docosahexaenoic acid) causes decreased binding to estradiol.

A high intake of Omega-6 and arachidonic acid inhibits the CYP 1A1 detoxification of estrogens by 2-hydroxylation, and increases 16 α OHE1. Omega-3 fatty acids suppress the growth of estrogen sensitive tumors. DHA specifically inhibits the growth of HPV-induced cervical cell growth.

Flaxseed Cancer Prevention

The lignans and phytoestrogens present in flaxseed are metabolized in the intestine by bacteria into enterolactone and enterodiol, which have a structure similar to estradiol. Thus, flaxseed may:

- Inhibit breast cancer and colon cancer growth.
- Stimulate sex hormone-binding globulin (SHBG).
- Inhibit aromatase activity.
- Have direct chemo-protective effects, by helping remove endogenous estrogens via increased retention within the gut for elimination in the feces (entero-hepatic circulation decreased).

Flaxseed induces 2-hydroxylation of estrone. Dietary intake of 10 grams of ground flaxseed per day for seven weeks produced the most dramatic effects in estrogen metabolism. No change in 16 α OHE1 was observed.

Soy and Isoflavones Anti-Cancer Effects

Soy and isoflavones have been linked to breast cancer risk in epidemiological studies. Isoflavones are found in: beans, legumes, lentils, red clover, and soy. Soy isoflavones are referred to as natural selective estrogen receptor modulators (SERMs), molecules that interact with estrogen receptors, inhibit steroidogenic enzymes, and interfere with binding to SHBG.

Soy isoflavones reduce circulating levels of 17- β estradiol in women, and activate both 2-hydroxylation and 16- α hydroxylation, but have a stronger effect upon 2-hydroxylation. These effects have not been evidenced in postmenopausal women.

A definitive statement, that soy reduces cancer risk in women cannot be made at this time, but there is considerable evidence of protective effects on estrogen metabolism.

Beer (Milligan et al *J Clin Endocrinol Metab.* 2000;85:4912-4915; Rong et al (*Eur J Cell Biol.* 2001;80:580-585.)

MELATONIN

Melatonin is synthesized from 5-Hydroxytryptophan (5-OH-Trp), after being converted to serotonin by the support of phenylalanine. This is done mostly in the pineal gland. β -blocking agents cause a decline in melatonin secretion. At least two melatonin receptor subtypes have been recognized. Melatonin is a calcium or calmodulin antagonist, which indicates that it plays an important role in cellular homeostasis. Melatonin modulates the TRH-TSH-thyroid axis, and is one of the most potent free radical scavengers. It can accumulate in the nucleus of cells, where it can bind nuclear proteins and DNA, and can help to protect against protein over-expression or

excessive cell replication. It protects the Cytochrome I and IV complex in the mitochondria, together with Ginkgo, which effects complex III.

Melatonin supports age-related T3-decrease. Thus, there is a lot of interest in melatonin as a treatment for sub-clinical hypothyroidism. Melatonin has important effects on the menstrual cycle. We see a significant decrease of melatonin at the last step from peri to postmenopausal life phase. This correlates with FSH increase. On the other hand, melatonin normalizes the short hypergonadotropinemia in perimenopause. Women with amenorrhoea display significantly amplified nocturnal melatonin secretion. There is a negative correlation between melatonin and estradiol. Women with secondary amenorrhoea display significantly higher levels of melatonin. On the other hand, we find an increase of melatonin secretion by administering estradiol in post menopause. Estrogens amplify melatonin receptor density. Walter Pierpaoli believes that aging is undeniably initiated in the pineal gland. Exogenous melatonin has been shown to increase the lifespan of mice by 25%. Melatonin interacts with the immune system and inhibits platelet aggregation. It also decreases glucose tolerance and Insulin sensitivity. Nocturnal labile hypertension is an indication to administer melatonin. We find impaired melatonin secretion in coronary heart disease and prostate cancer. Finally, melatonin inactivates norepinephrine.

DHEA

The typical postmenopausal androgen is the adrenal DHEA, which is mostly converted to testosterone and sometimes further converted to estradiol by aromatase, especially in obese women. Peri and postmenopausal women, with the typical clinical profile of lack of sexual desire, decreased orgasm frequency, lack of well being, and blunted motivation virtually always have decreased free testosterone plasma levels. This may be caused by:

- Lack of ovarian production (LH levels increased, low T-testosterone).
- Lack of ovarian production (LH and FSH low, low T-testosterone induced by increased psychic stress).
- Normal ovarian production (increased SHBG levels, induced by oral contraceptives or oral HRT).
- Decreased DHEA production by the adrenal gland, with low ovarian testosterone production.

Study results have showed that pharmacological doses of 4x 400 mg DHEA /day in women, produce an increase in lean body mass, accompanied by a decrease in fat mass. Meanwhile, a daily oral dose of 50 mg DHEA, yielding DHEA-S levels as observed in young women, caused an increase in testosterone and androstenedione levels to high-normal range. IGF-1 levels increased and IGF-BP decreased, however BP3 remained unchanged. Most patients reported a remarkable increase in perceived physical and psychological well being. With the higher dose of 100 mg /day, DHEA-S levels increased to three to four times above the upper-normal limit.

Other research has shown that percutaneous administration of a DHEA cream to postmenopausal women for 6-months results in a significant increase in bone mineral density of the hip. This suggests that DHEA may act as a bone re-modeling agent. Some authors have found an inverse correlation between DHEA-S levels and the severity of osteoporosis.

There is an enormous increase of β -endorphin levels after the first month of DHEA -therapy. This supports the theory that it has an estrogen-like effect on the brain. Treatment with DHEA induces a restoration of β - endorphin reaction similar to that seen with clonidine and naloxone.

DHEA affects directly the CNS. DHEA and DHEA-S are considered to be neurosteroids because they are, in part, produced in the CNS. In fact, the concentration of DHEA-S in the CNS is five to ten times greater than plasma levels. Cytochrome P450, the enzyme involved in the



Anti-Aging Wisdom from the A4M

SUBJECT: Human Models Suggesting Near-Term Safe and Effective Medical Interventions to Modify Aging Metabolism



JANUARY 2002: Scientists from Johns Hopkins University report in the *Proceedings of the National Academy of Sciences* that they discovered a gene that appears to have an important role in determining a person's lifespan. The gene, which has been named Klotho after the Greek Fate who spun the thread of life, was discovered when the scientists were studying the genes of adults aged 65 and above and comparing them with those of infants. Results showed that 3% of the infants had the Klotho gene variant, compared with just 1% of those aged 65 and older. According to the researchers, these findings suggest that **infants possessing two copies of the Klotho gene variant are more than twice as likely to die before they reach 65.** [Arking DE, Krebsova A, Macek M Sr, Macek M Jr, Arking A, Mian IS, Fried L, Hamosh A, Dey S, McIntosh I, Dietz HC, "Association of human aging with a functional variant of klotho," *Proc Natl Acad Sci U S A.* 2002 Jan 22; 99(2); 856-861]

FEBRUARY 2002: Icelandic biotechnologists announce they have isolated a gene which they believe could lead to the development of drugs enabling people to live longer. Scientists at DeCode Genetics have given the gene the name of the Methuselah gene, for which they know the location and soon they predict to discover the exact DNA sequence and how it works in the body. The researchers discovered that **those who lived longer appeared to have inherited a single gene that protected them against old age**, rather than being born into families which did not inherit genes that made them vulnerable to illnesses. [Dalton A, "Scientists find key to eternal life," *The Scotsman*, Feb. 4, 2002]

OCTOBER 2002: Results of a recent study presented at the annual meeting of the American Neurological Association in New York City suggest that the food supplement **coenzyme Q10 could slow down the progression of Parkinson's disease.** Lead researcher Professor Clifford Shults of the University of California in San Diego and his colleagues enrolled 80 Parkinson's patients for the trial. All exhibited early-stage Parkinson's, and did not yet need levodopa. After 8 months of treatment with coenzyme Q10, patients who had received the highest dose of Q10 exhibited a 44% reduction in disease progression, compared with the placebo group. Even patients treated with the lowest dose the supplement were more able at carrying out simple daily activities, for example dressing and washing, and demonstrated better mental functioning and mood. The authors conclude that their findings: "are supportive of the view that mitochondrial dysfunction does play a role in the pathogenesis of sporadic Parkinson's disease." [*Archives of Neurology* 2002; 59:1541-1550.]

OCTOBER 2002: Blood pressure drugs called **ACE inhibitors**, which help diabetics to lower their risk of developing complications, have been suggested to be of value in **developing drugs that delay the effects of aging.** Part of the reason why diabetics tend to age faster than non-diabetics is that their high-blood sugar levels encourages the body to produce complex proteins called advanced glycation end products (AGEs). These proteins interfere with cell functioning, accumulate in skin making it look wrinkly, and stiffen blood vessels. Now researchers at the Baker Institute in Melbourne, Australia have found that ACE inhibitors appear to exert their anti-aging effects by preventing the build-up of AGE's. ACE inhibitors work by blocking the production of the enzyme angiotensin II, which is thought to encourage the production of cell-damaging free radicals that stimulate the production of AGE's. According to the *New Scientist*, "ACE inhibitors are unlikely to become an elixir of youth because they cause unpleasant side effects such as coughing and irregular heartbeat." However, there is hope that drugs designed to have a similar effect on AGE's without the adverse effects of current ACE inhibitors could provide us with a new class of age-delaying drugs. [reported by www.bbc.co.uk on the 2nd October 2002.]

APRIL 2003: The Progeria Research Foundation announced the discovery of the gene that causes progeria, a rare, fatal genetic condition characterized by an appearance of accelerated aging in children. Children afflicted with progeria typically die from complications of cardiovascular disease or arteriosclerosis at an average of 13. As reported in *Nature* magazine, Dr. Francis Collins, director of the National Human Genome Research Institute and senior study author, **mutations to the gene Lamin A cause progeria. Because heart disease and stroke are the first and third leading causes of death in the US, accounting for more than 40% of all mortalities, it is hoped that the PRF discoveries will shed insight into interventions for these adult diseases.** ["Identification of Gene Gives Hope to Children with Progeria, May Shed Light on Phenomenon of Aging," The Progeria Research Foundation, April 16, 2003.]