


## MEETING BRIEF

# Fountain of Youth? Hormonal and Molecular Interventions in Aging

by Randolph Fillmore

(Posted May 29, 1998  Issue 31)



### **Abstract**

*At the International Symposium and Forum on Endocrine and Molecular Interventions in Aging, participants discussed therapeutic applications of DHEA, testosterone, and estrogen, and looked at responses to IGF-1, melatonin, and antioxidants.*

The International Symposium and Forum on Endocrine and Molecular Interventions in Aging was held March 7-11, 1998 in Tampa, Florida. Participants, emphasizing their role in preventing or modifying the effects of age, discussed potential benefits in therapeutic applications of dehydroepiandrosterone (DHEA), the positive and negative effects of testosterone and estrogen replacement therapies, and looked at responses to insulin-like growth factor 1 (IGF-1), melatonin, and antioxidants.

### **Testosterone Replacement Therapy: Pros and Cons**

Will androgen replacement therapy reverse some of the changes associated with aging? asked William Bremner of the Department of Veterans Affairs Health System and professor of medicine at the [University of Washington School of Medicine](#) in Seattle. Can it be as beneficial as estrogen replacement for post-menopausal women? The answer is both yes and no.

Bremner outlined what we know about testosterone's roles. It preserves bone mineral content and reduces fat while promoting lean body mass - two pluses that could lead to fewer fractures in elderly men and could prevent cardiovascular diseases and diabetes. When Bremner put two groups of men whose average age was 67 on alternating testosterone treatments, he found that injected testosterone increased their libido and overall health. "They knew which arm of the study they were on based on how they felt," Bremner said.

Monique Cherrier (Puget Sound Veterans Administration, Washington), a research associate of Bremner's, recently found that testosterone replacement had a beneficial effect on spatial and verbal memory in elderly men. Her work may have application in treating Alzheimer's disease. "Testosterone's effects are presumably mediated through the androgen receptor, which is widely but selectively distributed throughout the brain," Cherrier said. "The hippocampus and medial temporal regions, which underlie certain spatial abilities, are a particular target for gonadal hormones and demonstrate neural growth in response to androgen release. These same brain regions are affected by Alzheimer's disease."

Increasing evidence that testosterone replacement therapy can have many of the same benefits as estrogen replacement therapy for women continues to fill the professional and lay literature. Bremner pointed to a study, discussed in the January 16, 1998 issue of [Science](#), that looked at weight gain and diminished testosterone.

"A well-controlled, pilot clinical trial of testosterone replacement in elderly men has reported encouraging

results," Bremner said. "This study reported improvements in muscle mass, bone, sexual function, and LDL levels. The two areas of greatest concern in considering the role of testosterone replacement in the elderly are effects on the prostate and cardiovascular disease."

Peter Snyder ([University of Pennsylvania Health System](#)) elaborated on the risks associated with what may at first look like a fountain of youth for elderly men. "The risks and benefits must be weighed," Snyder said. "We have to consider the possibility that treating with testosterone could contribute to clinically significant prostate cancer."

In drawing the link between natural amounts of testosterone and prostate cancer, Snyder pointed to a study of blood samples taken in 1982 from physicians who were then between the ages of 40 and 84. When the samples were analyzed 15 years later, researchers found that higher testosterone levels in 1982 were associated with a 2.5 times greater chance of developing prostate cancer.

"Testosterone predicted prostate cancer in that study," said Snyder, who fears side effects to testosterone replacement: prostate enlargement, prostate cancer, sleep apnea, increased hypercoagulability, and an unidentified effect on lipids.

Snyder discussed the paradox presented by an apparent relationship between testosterone and prostate cancer in elderly men. Why, he asked, when testosterone is reaching its lowest level, after age 60, does it appear to cause prostate cancer? "I can't explain it," he said. "But my guess is that there is still sufficient testosterone to play a role in the development of prostate cancer."

### ***Estrogen Replacement Therapy: Benefits and Risks***

While cardiovascular protection and increased bone density have become clear benefits of postmenopausal estrogen replacement therapy, and its potential for lowering the risk of Alzheimer's disease is being explored, cloudy still is the relationship between long-term estrogen replacement therapy - more than three years - and the development of breast cancer. Risk begins to appear at five years.

"Short-term hormone replacement therapy in postmenopausal women is effective for the treatment of estrogen-deficient symptoms of vasomotor flushes and vaginal dryness," said Kathryn Martin ([Harvard Medical School](#)). "No study has demonstrated an increased risk of breast cancer with short-term use. Therefore many, if not most women, except those with a history of breast cancer, are candidates for short-term treatment for symptomatic relief."

Martin added that while there are concerns about adding progestins to estrogen replacement therapy - necessary to prevent endometrial complications in women with a uterus - progestin does not appear to reduce estrogen's beneficial affects on the heart.

Graham A. Colditz ([Harvard School of Public Health](#)) said that non-cancer-causing strategies for the relief of menopausal symptoms and long-term prevention of osteoporosis and heart disease are "urgently needed." "The magnitude of the increase in risk of breast cancer per year of use of hormones is comparable to that of delaying menopause," he said. He concluded by saying, "The decision to use estrogen replacement therapy must be an individualized one. It should be based on each woman's medical history and personal choice."

### ***Can DHEA Replacement Keep Us Young?***

Plasma concentrations of dehydroepiandrosterone (DHEA), a natural hormone, decrease over time in both men and women, said Etienne-Emile Baulieu ([INSERM](#), France). While DHEA has become a popular over-the-counter item and its pros and cons are discussed in the mass media, Baulieu said that its affect on the prostate and its relationship to other hormones, such as testosterone, are unclear.

While DHEA supplementation remains controversial, William Regelson ([Medical College of Virginia](#)) said that DHEA demonstrates antitumoral activity, can be used to treat lupus, and has appeared in "clinical anecdotal reports" as being of value in treating myeloma, lymphoma, and pancreatic and renal cancer.

"Adequate clinical studies are needed - alone and in conjunction with chemotherapy," said Regelson, who has been taking DHEA for twelve years and is unhappy that because DHEA is a naturally occurring hormone, it will not be approved by the FDA in the near future. "Its clinical safety has been established, as it has been available as Prasterone in Europe for menopausal treatment for some twenty years," he said. He added that DHEA enhances viral and bacterial infection resistance, is an effective antidepressant, and can reverse chronic fatigue.

"Instead of being intimidated by the over-the-counter availability of DHEA, we physicians should insist that our patients join with us in establishing baseline values governing hormone replacement and therapeutic application," Regelson concluded.

### ***Melatonin and Aging***

"The effects of melatonin on cellular physiology may be related to aging in a number of ways," said Russel J. Reiter ([University of Texas](#)). "Melatonin has been shown to be an effective scavenger of the highly toxic hydroxyl radical as well as detoxifying singlet oxygen, the peroxy radical, the superoxide anion radical, and the peroxynitrite anion. Additionally, melatonin stimulates antioxidative enzymes. Since free radicals are believed to play a prominent role in both aging and a variety of age-related diseases, melatonin's potential effects in delaying these processes is apparent." Reiter added that there is no "definitive proof" that melatonin has a function in determining the rate of aging or the longevity of organisms, and that tests of melatonin supplements have not been "uniformly successful."

Walter Pierpaoli (INTERBION Foundation for Basic Biomedical Research, Bellinzona, Switzerland) discussed his studies of night administration of melatonin to mice in which the animal models "postponed" their aging, delayed the onset of autoimmune disease, and increased resistance. His success with animal models lead him to speculate on the age-preventing properties in melatonin.

"We have conducted extensive investigations aimed at possibly understanding the mechanism by which melatonin can correct practically all age-related derangement measured, including immunity, mineral levels, lymphocytes, testosterone, corticosterone, cholesterol and others," Pierpaoli said. "We are confident that our models *in vivo* will allow us to progressively elaborate the methods and to identify vehicles that allow for maintaining perfectly synchronized neuroendocrine and immune functions, and to prevent aging-related diseases such as cardiovascular, autoimmune diseases, and cancer."

Reiter cautioned against overoptimism. "The role of melatonin, if any, in the process of aging and the development of age-associated disease, must await further experimentation," he said.

### ***Antioxidants and Reducing Oxidative Stress***

"The free radical theory of aging," said Jeffrey Blumberg ([Tufts](#)), "hypothesizes that the degenerative changes associated with aging might be produced by the accumulation of deleterious side reactions of free radicals produced during cellular metabolism and generated *in vivo* by environmental exposure to pro-oxidant radicals." At the cellular level, oxidation of amino acids can cause cell damage, and at the DNA level, oxyradical-induced DNA cross links could lead to somatic mutations and loss of essential enzyme expression, he added. Daily oxidative hits are generally repaired quickly, but small numbers of unrepaired lesions caused by inadequate antioxidant defenses could cause permanent DNA changes.

Blumberg concluded that understanding how antioxidants reduce oxidative stress offers opportunities for

health promotion - via diets rich in antioxidants - and the treatment of chronic disease. According to Blumberg, recent studies have shown that high antioxidant intake may reduce risks for age-related conditions and diseases such as atherosclerosis, cancer, Parkinson's disease, and Alzheimer's disease.

### ***Growth Hormones and Aging***

A research team from the Research Center for Endocrinology and Metabolism, [Sahlgrenska University Hospital](#), Goteborg, Sweden, suggested that there are "striking similarities" [in obesity and insulin resistance] between the "metabolic syndrome" (syndrome X) and untreated growth hormone (GH) deficiency in adults. Their nine-month trial of GH treatment reduced total body fat, improved insulin sensitivity, improved diastolic blood pressure, and suggested a potential role for GH in treating cardiac irregularities.

"In GH deficient adults who receive GH substitution therapy, an improvement in systolic function and normalization of left ventricle mass has been found," said team member Bengt-Ake Bengtsson. The group also found that after six months of GH therapy, elderly patients on dialysis improved their lean body mass, muscle strength, and walking capacity.

*[Randolph Fillmore](#) is a freelance medical technical writer and science journalist who has written for Faulkner and Gray, Prudential Health Care, Stars and Stripes, and The Baltimore Sun.*

*The illustration is a detail from Thomas Moran, Ponce de Leon in Florida, 1878, evoking the explorer's legendary search for the Fountain of Youth.*

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### ***Endlinks***

[Journal of Anti-Aging Medicine](#) - premiered at the symposium. The new journal will reportedly "provide a common meeting ground, a venue, and perhaps a sense of community . . . for dreamers, skeptics, pragmatists, all sharing a common suspicion that we can understand aging . . . a common intent that we can alter it, and a common hope that it will benefit us all."

[Endocrine Society](#) - meets June 24-27, 1998, in New Orleans.


[Society for Endocrinology Electronic Journals](#) - publishes the [Journal of Endocrinology](#), the [Journal of Molecular Endocrinology](#), and [Endocrine-Related Cancer](#). The full text of the last journal is freely available online, and abstracts of the combined journals may be searched.

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