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EVENTS

DHEA

Comes To The Mainstream

DHEA AND AGING

Exclusive Meeting Report, Part 1

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A major meeting entitled **DHEA AND AGING** was held at the Washington Vista Hotel in Washington, DC on June 18-19, 1995. Originally instigated by the National Institute on Aging, the meeting was held under the auspices of the **New York Academy of Sciences (NYAS)** through **John E. Nestler** (Medical College of Virginia, Richmond) as the liaison and was funded by NIH, The Glenn Foundation, the Henry and Lucy Moses Fund, Merck, Pfizer, Wyeth-Ayerst, and a company called Paradigm Biosciences.



This meeting continues a recent John E. Nestler tradition of the NYAS to focus on interventive gerontology in a big way, but the publicity was anything but traditional. A total of about 150 people gathered from all over the world for this meeting, and I detected an uncommon level of excitement among the attendees.

Background: Why DHEA? (see Anti-Aging News 1: 33-36, 1981), **DHEA** is a natural hormone made primarily by the adrenal glands that peaks around the age of 25-30 and then drops by 85-90% by the age of 70. DHEA has been associated with the ability to stay thin, to make muscle, to avoid death from breast cancer (for women), death from cardiovascular disease (for men), and death "from all causes" and appears to help improve memory, stress resistance, and one's sense of "well-being".



Scandalously, controlled clinical trials of DHEA replacement therapy to prevent the age-related decline in circulating DHEA seem not to have been tried in humans until 1990, according to a press release by Dr. Samuel S.C. Yen (W.R. Persons Professor of Reproductive Medicine, University of California at San Diego School of Medicine, La Jolla, California), who did that first trial. The meeting was organized in part to promote the results of Yen's DHEA replacement trials.

DHEA comes in two forms - DHEA and DHEA-sulfate (DHEA-S), the latter being a storage form of DHEA. The ratio of DHEA to DHEA-S is constant over the lifespan.

Most mammals, other than primates, don't make significant amounts of DHEA due to the presence of an enzyme (3-beta-hydroxysteroid dehydrogenase type 5 [3HSD]) that breaks down DHEA in non-primates (F. Labrie, MRC Group in Molecular Endocrinology, CHUL Research Center & Laval University, Quebec, Canada, and Peter Hornsby, Huffington Center on Aging, Baylor College of Medicine, Houston, Texas). Therefore, any effect of DHEA reported in non-primates is truly a pharmacological effect and might not reflect what happens in humans.

Intriguingly, Hornsby was able to make cow adrenal glands, which normally do not make significant amounts of DHEA, produce DHEA by using a drug known as trilostane that inhibits 3HSD, the DHEA destroying enzyme. I phoned Hornsby after the meeting and asked him if this drug could be used to boost DHEA in older men and women. The answer was no, because the drug is not selective for inhibition of DHEA breakdown and therefore has too many side effects (including inhibition of progesterone synthesis), but that the principle is sound, and if one could develop a selective drug, it might work. Such a selective drug currently does not exist.

Why Do We Lose DHEA with Age? in the *Journal of Clinical Endocrinology and Metabolism* (JCEM) that we lose DHEA with age because "an enzyme (17,20 desmolase) [17,20 lyase] essential for synthesis of DHEA is functionally reduced with aging" (JCEM 71:900-906, 1990) and stated that it is "not possible to activate or replace the enzyme"

Peter Hornsby has noted that the zona reticularis of the adrenal gland, where DHEA is made, atrophies with age, as can be seen easily using a light microscope. He presented evidence that this could be due to the reticularis cells reaching their Hayflick limit (reticularis cells become unable to divide as the zona reticularis shrinks), a problem that could require Geron's telomerase technology to correct.

The surprising good news is that, whatever the cause of the DHEA loss may be, it is at least partially reversible in humans, according to J.E. Nestler's results.

Some of the most important results of the meeting were presented or referred to by John Nestler in his talk. Nestler hypothesized that the age-related drop in DHEA and DHEA-S may be due in part to the normal age-related rise in circulating insulin levels. This rise in insulin levels with age is of great significance in its own right, quite apart from its possible relevance to depressing DHEA/DHEA-S levels: elevated insulin levels are correlated with obesity, hypertension, and type II diabetes. The breakthrough reported by Nestler consists of the observation that certain drugs can reverse this pernicious aging trend and, in so doing, restore DHEA levels in old men to what they were in middle age or youth!

The Connection Between Insulin and DHEA Nestler showed in several different ways that increased levels of insulin drive DHEA levels down. Nestler also cited evidence obtained in his laboratory that insulin inhibits the adrenal 17,20-lyase activity in man that is needed for DHEA synthesis (JCEM 74: 362-7, 1992) In addition, according to Peter Hornsby's talk, insulin increases the activity of the 3HSD enzyme that destroys DHEA. Thus, insulin both inhibits the synthesis of DHEA and accelerates the breakdown of DHEA. However, DHEA has no effect on insulin levels, and has no effect on insulin sensitivity (type II diabetes) in humans.

DHEA as an Inhibitor of Brain Aging Majewska referred to the GABA theory of aging (described in *Neurobiology of Aging* 15: 69, 1994). The brain enzyme that makes GABA (CAD) rises with age and may stimulate GABAergic effects that slow down the brain and promote neurodegeneration. Flumazenil, an antagonist of GABA function, improves memory and extends life in rats (see above ref.). DHEA-S would be expected to have similar effects. DHEA-S in the cerebrospinal fluid of men falls with age (*J. Neural. Sci.* 120:87, 1993).

Furthermore, excessive GABA lowers nerve growth factor in the brain, and lowered NGF has been linked to Alzheimer's disease. By blocking this effect, DHEA would promote neuronal survival in the aging brain and might help to stave off Alzheimer's disease. Interestingly, DHEA-S tends to be low in Alzheimer's and other dementia patients. In response to a question, Majewska suggested that DHEA-S might be better to use than established anti-GABA drugs by virtue of having fewer side effects.

Contraceptives may Boost DHEA Requirements According to a delegate from Australia who made a comment from the audience, oral contraceptives lower DHEA, although not DHEA-S. This suggests that women taking contraceptives should also take DHEA to counteract this DHEA-depleting effect.

Does Caffeine Raise DHEA? (Univ. of Texas Southwestern Medical Center, Dallas, TX) showed that a human adrenal tumor cell line chums out DHEA in response to agents that increase intracellular cyclic AMP concentrations. Caffeine is well-known for boosting cell cyclic AMP.



DHEA REPLACEMENT THERAPY

The front page of most major newspapers carried an article on the newly discovered anti-aging benefits of DHEA on January 12, 1995. These articles were based on a paper published in the respected *Journal of Clinical Endocrinology and Metabolism*.

The conclusions of the study were:

"DHEA will improve the quality of life over a longer period and will postpone some of the unpleasant effects of aging, such as fatigue and muscle weakness."

The report also stated that those patients receiving DHEA supplements slept better, had more energy, and

were better equipped to handle stress compared to the placebo group not receiving the DHEA.

DHEA's OTHER BENEFITS: DHEA is produced by the adrenal glands. At the age of 21, we produce abundant levels of DHEA. By the time we reach age 40, our DHEA production is about half of what it was when we were 21. Elderly people sometimes have virtually no DHEA production. The result of Chronic DHEA deficiency are the multitude of diseases we become vulnerable to the older we get.

Here are some of the potential benefits of **DHEA Replacement Therapy:**

- Immune Enhancement (via several known mechanisms)
- Anti-diabetic Actions (via several known mechanisms)
- Anti-cancer Effects (against some cancers)
- Anti-atherosclerotic Effects (via several known mechanisms)
- Anti-depression (unipolar depression)
- Life Extension (animals live longer on supplemental DHEA)
- Cognitive Enhancement (including potential therapy for Alzheimer's and Parkinson's disease)

Men with prostate cancer and women with reproductive cancers should avoid DHEA.

DHEA in the Spotlight part 2

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