

today, according to data from the United Network for Organ Sharing.

Daniel C. Brennan, M.D.

Washington University School of Medicine
St. Louis, MO 63110
dbrennan@wustl.edu

Paula Buchanan, M.P.H.

Mark A. Schnitzler, Ph.D.

Saint Louis University Center for Outcomes Research
St. Louis, MO 63104

Dr. Buchanan reports receiving a grant from the American Society of Transplantation. Dr. Schnitzler reports receiving consulting fees from Novartis Pharma, lecture fees from Genzyme, and grant support from Genzyme, Novartis Pharma, Astellas, and TransMedics.

1. Humar A, Johnson EM, Payne WD, et al. Effect of initial slow graft function on renal allograft rejection and survival. *Clin Transplant* 1997;11:623-7.

DHEA and Testosterone in the Elderly

TO THE EDITOR: In their report on the effects of dehydroepiandrosterone (DHEA) and testosterone when used as antiaging supplements, Nair et al. (Oct. 19 issue)¹ conclude that low-dose testosterone replacement in elderly men has no “physiologically relevant beneficial effects on body composition, physical performance, [or] insulin sensitivity.” However, this conclusion is premature, since the testosterone replacement administered failed to achieve physiologic testosterone levels throughout the study period (Fig. 2 of the article). Moreover, despite the marginal increase in testosterone levels achieved, improvements in fat-free mass, fasting insulin levels, and bone mineral density were observed.

Other studies of testosterone replacement, including those cited to support the authors’ conclusions,² have shown a decrease in fat mass (12.5%) and an increase in lean mass (4%) when physiologic testosterone levels are achieved in elderly men. Studies of standard doses of testosterone in the treatment of testicular failure³ have shown additional positive effects on muscle strength, physical performance,⁴ and bone mineral density.⁵ Large, long-term trials are clearly needed to assess the risks and benefits of testosterone replacement in elderly men, and caution should be exercised regarding the treatment of andropause in men. However, the serum testosterone level achieved should be within the normal range to assess the effect on outcome measures adequately.

Stephanie T. Page, M.D., Ph.D.

University of Washington
Seattle, WA 98195
page@u.washington.edu

Alvin M. Matsumoto, M.D.

Veterans Affairs Puget Sound Health Care System
Seattle, WA 98108

William J. Bremner, M.D., Ph.D.

University of Washington
Seattle, WA 98195

1. Nair KS, Rizza RA, O’Brien P, et al. DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med* 2006; 355:1647-59.
2. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84:2647-53.
3. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2006;91:1995-2010. [Erratum, *J Clin Endocrinol Metab* 2006;91:2688.]
4. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab* 2005;90:1502-10.
5. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 2004;89:503-10.

TO THE EDITOR: The findings of Nair et al. cannot be generalized, because the study included relatively healthy subjects. To investigate the benefits and risks of androgen-replacement therapy, it is essential to make judicious choices regarding the subjects to be included in the research. In this study, the average baseline scores for the quality of life (on the Health Status Questionnaire [HSQ] and the Medical Outcomes Study 36-item Short-Form General Health Survey [SF-36]) of all the subjects were above 50 for both the physical and mental components. The average score on both instruments in the general U.S. population is 50.¹ The high scores of these subjects suggest that the

study included healthier elderly persons than those who would be representative of the general elderly population.

Moreover, physical exercise is expected to improve and maintain physical functioning in older people.^{2,3} Not only androgen administration but also well-designed physical training is needed to improve the physical performance of elderly persons. The androgen level might be a mediator that could be elevated by exercise training, which would then increase physical performance. The administration of androgen in the absence of exercise may not be enough to improve physical performance among the elderly.

Mitsuko Yasuda, M.D., Ph.D.

Shigeo Horie, M.D.

Teikyo University
Tokyo 173-8605, Japan
shorie@med.teikyo-u.ac.jp

1. van Hooren SA, van Boxtel MPJ, Valentijn SAM, Bosma H, Ponds RW, Jolles J. Influence of cognitive functioning on functional status in an older population: 3- and 6-year follow-up of the Maastricht Aging Study. *Int J Geriatr Psychiatry* 2005;20:883-8.
2. Mian OS, Thom JM, Ardigo LP, et al. Effect of a 12-month physical conditioning programme on the metabolic cost of walking in healthy older adults. *Eur J Appl Physiol* (in press).
3. Tsuji I, Tamagawa A, Nagatomi R, et al. Randomized controlled trial of exercise training for older people (Sendai Silver Center Trial: SSCT): study design and primary outcome. *J Epidemiol* 2000;10:55-64.

TO THE EDITOR: DHEA was banned in 1985 by the Food and Drug Administration because clinical safety and efficacy data were lacking to support claims of cures for cardiovascular disease and aging. After the passage of the Dietary Supplement Health and Education Act in 1994, DHEA, which had not previously been labeled as a drug, again became available. It is amazing that a previously banned substance can now be sold directly to the public, and it speaks to the lack of oversight and protection afforded by the Dietary Supplement Health and Education Act.

Hormones have long been equated with youth by the public and are thus a favorite type of substance for marketing by the antiaging industry.¹ As one substance falls out of favor, another quickly replaces it: the miracle of melatonin² was replaced by the superhormone promise³ of DHEA. The heir apparent now seems to be growth hormone, which, paradoxically, is illegal to distrib-

ute for antiaging uses but constitutes a market estimated at more than \$600 million per year in the United States alone.⁴

Thomas T. Perls, M.D.

Boston University Medical Center
Boston, MA 02118
thperls@bu.edu

1. U.S. Senate Special Committee on Aging. Swindlers, hucksters and snake oil salesman: hype and hope marketing anti-aging products to seniors. 107th Congress, 1st session. Washington, DC: Government Printing Office, September 10, 2001.
2. Pierpaoli W, Regelson W. The melatonin miracle: nature's age-reversing, disease-fighting, sex-enhancing hormone. New York: Pocket Books, 1995.
3. Regelson W, Colman C. The superhormone promise. New York: Pocket Books, 1996.
4. Perls TT, Reisman NR, Olshansky SJ. Provision or distribution of growth hormone for "antiaging": clinical and legal issues. *JAMA* 2005;294:2086-90.

TO THE EDITOR: The study by Nair et al. may be misleading. One problem arises from the age of the persons involved in the study. Women older than 60 years rarely have postmenopausal symptoms. In the absence of symptoms, how are the beneficial effects of treatment on the quality of life to be demonstrated? Similarly, one may question the use of testosterone in men older than 60 years.

The principal problem, however, is that Nair et al. treated laboratory values (low values of DHEA and testosterone), not — as is usual medical practice — symptoms. To return to the example of postmenopausal care for women older than 60 years, such an approach could be equated with indiscriminately treating unselected postmenopausal women, all of whom, of course, have low estradiol levels, with estrogen replacement, whether or not they are symptomatic. Whether such an unselected approach to treatment would ever reveal clinical benefits regarding the quality of life is questionable.

That DHEA can indeed positively affect certain physiological processes of aging has been suggested with regard to ovarian function.¹⁻³ Thus, nothing in the study by Nair et al. contradicts the value of further investigation of DHEA in specific conditions of aging.

Norbert Gleicher, M.D.

David Barad, M.D.

Center for Human Reproduction
New York, NY 10021
ngleicher@thechr.com

Drs. Gleicher and Barad are part owners of a pending patent involving the use of DHEA for the improvement of ovarian function in women with diminished ovarian function.

1. Casson PR, Lindsay MS, Pisarska MD, Carson SA, Buster JE. Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: a case series. *Hum Reprod* 2000; 15:2129-32.
2. Barad DH, Gleicher N. Increased oocyte production after treatment with dehydroepiandrosterone. *Fertil Steril* 2005;84: 756.
3. *Idem*. Effect of dehydroepiandrosterone on oocyte and embryo yields, embryo grade and cell number in IVF. *Hum Reprod* 2006;21:2845-9.

THE AUTHORS REPLY: Our conclusion that “additional long-term studies of testosterone are warranted to determine the risk–benefit ratio of higher doses” is in agreement with the view expressed by Page et al.¹ We showed that low-dose testosterone significantly increased testosterone levels but resulted in no physiologically relevant beneficial effects. However, unlike the investigation of DHEA in the study, the investigation of testosterone did not address the potential beneficial effects of replacement therapy that would increase the plasma levels of testosterone in older people to levels found in young people. Standard testosterone replacement in younger men with testicular failure has a profound effect on body composition,² but the response to testosterone therapy in older men with low testosterone levels remains uncertain. Biweekly intramuscular injection of testosterone (at a dose of 200 mg) in older people¹ has been shown to increase peak testosterone levels to values above the normal range in young people³ and improves physical performance.¹ However, because of adverse events, the investigators had to reduce the dose in some subjects.¹ Transdermal administration of testosterone maintained testosterone levels in older people to levels within the normal range for young people for a period of 36 months but had no effect on physical performance,⁴ despite a significant increase in fat-free mass. We agree with Page et al. that there are tantalizing data on the effect of testosterone on bone density. The findings in the studies cited here and in other studies highlight the importance of conducting long-term studies to document ad-

verse events and long-term benefits of restoring testosterone levels in older people to levels seen in young people.

In response to Yasuda and Horie, the HSQ is a measure of perceived but not actual health. On the basis of the HSQ, we cannot state whether the persons in our sample were more or less healthy than the general population. Scores for both the physical and the mental components of the SF-36 questionnaire derived from the HSQ are only minimally different from a score of 50, and our interquartile range includes 50. We agree with Yasuda and Horie that the interaction between testosterone and exercise training in older people remains to be determined and warrants further investigation.

We agree with the comments by Perls about DHEA and the unfortunate rush to hormone therapies to maintain youth, even though no scientific data conclusively support such approaches. In response to Gleicher and Barad, our study specifically addressed whether the long-term administration of DHEA has any beneficial effects in women older than 60 years who have low levels of DHEA. The main outcome measures were objective physiological measurements and responses to the standard HSQ. We did not evaluate the effect of DHEA in women who have postmenopausal symptoms for which estrogen therapy is likely to be more effective than DHEA.

K. Sreekumaran Nair, M.D., Ph.D.

Glenn Smith, Ph.D.

Mayo Clinic
Rochester, MN 55905
nair.sree@mayo.edu

1. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab* 2005;90:1502-10.
2. Brodsky IG, Balagopal P, Nair KS. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men — a clinical research center study. *J Clin Endocrinol Metab* 1996;81:3469-75.
3. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *J Clin Endocrinol Metab* 2004;89:503-10.
4. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84:1966-72.