

STUDENTJAMA), has functioned as a refreshing space for an exchange of the ideas of future physicians. In these pages, students have considered spiritual assessment of patients, the global HIV/AIDS pandemic, and their own experience of medical education. They have reflected on the nature of healing and spoken to the issues at the core of caring for patients.

The Editorial announcing the end of *STUDENTJAMA* addressed the emerging emphasis on evidence over opinion. To remove *STUDENTJAMA* from the journal in the interest of “incorporat[ing] high-quality articles” misses the function of the section. Students, of course, will rarely publish research of the type and quality demanded by the pages of *JAMA*, but what students bring is as important. Students write and speak of the ideals of medicine, of their hope for the best patient care, of their struggles to forge new identities as healers. And in the process of exchanging ideas over the pages of *JAMA*, we believe that medical students offer our senior colleagues a chance to reflect on their own work as a physician.

For a generation, *JAMA* saw these attributes as central to its mission. Indeed, they align well with 3 of *JAMA*'s 9 objectives: to foster responsible and balanced debate on issues that affect medicine and health care, to anticipate important issues and trends in medicine and health care, and to inform readers about nonclinical aspects of medicine and public health, including the political, philosophic, ethical, legal, environmental, economic, historical, and cultural.²

Medical students will benefit from *JAMA*'s development of an elective in medical journalism and enriched manuscript review for student research submissions. These enhancements are appropriate and important, but they in no way speak to the void left by removing a student section from *JAMA*. We regret this decision.

Brian Palmer, MD, MS, MPH
pres@www.amsa.org
National President
American Medical Student Association
Reston, Va

Yvette Martin
Chair, Organization of Student Representatives
Association of American Medical Colleges
Washington, DC

1. DeAngelis CD, Fontanarosa PB. *JAMA* and medical students: new opportunities. *JAMA*. 2004;291:2872.

2. The key and critical objectives of *JAMA*. *JAMA*. 2004;292:36.

In Reply: We appreciate the recognition by Dr Palmer and Ms Martin that our decision to incorporate articles by medical students into *JAMA* with those of all other authors addresses the “emerging emphasis on evidence over opinion.” However, our encouraging submission of evidence-based manuscripts (as we do evidence-based practice) from all authors does not eliminate our continued interest in publishing well-thought-out opinion articles. We encourage submission of such manuscripts from any *JAMA* reader, including medical students, and will continue to publish special communications, commentaries, A Piece of My Mind, and poetry.

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We believe that, with a little extra assistance, medical students can and will be able to publish all types of articles in *JAMA*. Since publication of our editorial, we have accepted 2 research papers in which medical students are the first author. In addition, we have had a number of inquiries and submissions from medical students, as well as inquiries about the medical student elective in medical journalism.

We ask Palmer and Martin to have patience and let the evidence prove which is the more beneficial method for medical students to have a forum for their work.

Catherine D. DeAngelis, MD, MPH
Editor-in-Chief
Phil B. Fontanarosa, MD
Executive Deputy Editor
JAMA

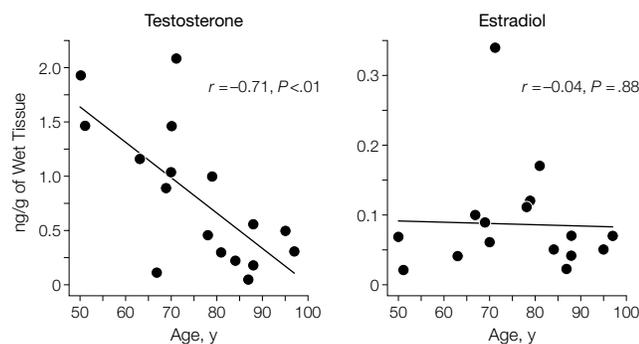
RESEARCH LETTER

Age-Related Testosterone Depletion and the Development of Alzheimer Disease

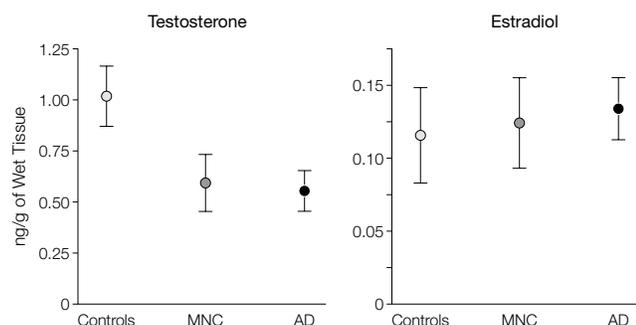
To the Editor: Normal male aging is associated with declines in serum levels of the sex steroid hormone testosterone, which contributes to a range of disorders including osteoporosis and sarcopenia.¹ Unknown is how this relationship applies to age-related disorders in the brain, an androgen-responsive tissue. We hypothesize that testosterone levels in the brain are depleted as a normal consequence of male aging and that low brain levels of testosterone increase the risk of developing Alzheimer disease (AD). Recent data suggest a correspondence between reduced serum levels of testosterone and the clinical diagnosis of AD.^{2,3} However, it is unclear whether testosterone depletion contributes to or results from the disease process. To investigate this issue, testosterone and estradiol levels were analyzed in postmortem brain tissue of elderly men and compared with their neuropathological diagnoses.

Methods. Brain tissue from men who had provided informed consent was collected at autopsy by repositories associated with Alzheimer's Disease Research Centers at University of Southern California; University of California, Irvine; University of California, San Diego; and Duke University. Tissue was collected between 1997 and 2003, with postmortem delay less than 8 hours (mean delay = 4.6 hours). Subjects with conditions associated with altered testosterone levels (eg, end-stage renal disease, liver disease, alcoholism, and diabetes) were excluded from the study. Included subjects satisfied 1 of the following neuropathological diagnoses: (1) neuropathologically normal (controls) (Braak stage 0-1 without evidence of other degenerative changes, and lacking a clinical history of cognitive impairment; n = 17), (2) AD (Braak stage 5-6 with neuropathological diagnosis of AD in the absence of other neuropathology; n = 19), and (3) mild neuropathological changes (Braak stage 2-3 in the absence of discrete neuropathology; n = 9). No subjects were neuropathologically diagnosed with Braak stage

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Figure 1. Brain Levels of Testosterone and Estradiol in Elderly Men

The estradiol comparison shows only 16 data markers as there are 2 subjects aged 70 years with the same estradiol value (0.06 ng).

Figure 2. Brain Levels of Testosterone and Estradiol in Men, by Neuropathological Diagnosis

Left, Testosterone levels in age-matched control subjects (controls), subjects with mild neurological changes (MNC), and subjects with Alzheimer disease (AD). Right, Estradiol levels in age-matched controls, subjects with MNC, and subjects with AD. For testosterone levels, $P < .05$ is the comparison of age-matched controls vs subjects with MNC and of age-matched controls vs subjects with AD by t test following analysis of covariance with age as a covariate. Error bars indicate SEM.

4. Testosterone and estradiol levels were measured by radioimmunoassay of homogenates of brain samples from the mid-frontal gyrus following organic extraction and celite column partition chromatography.⁴ Hormone levels expressed as hormone weight per wet tissue weight were statistically compared using analysis of covariance with age as the covariate. This study was performed with institutional review board approval from the University of Southern California.

Results. We observed that brain levels of testosterone but not estradiol (FIGURE 1) were inversely correlated with age in men aged 50 to 97 years who were diagnosed as neuropathologically normal. To investigate whether this depletion of brain testosterone may be a risk factor for the development of AD, we compared hormone levels among elderly men who exhibited no neuropathology, mild neuropathological changes, or moderate to severe AD. Men in the 3 groups were of similar age, ranging from 60 to 80 years with mean (SD) ages of 70.9 (5.3), 72.9 (5.7), and 72.0 (6.5) years, respectively, using analysis of variance

($F = 0.002$, $P = .97$). We found that brain levels of testosterone but not estradiol (FIGURE 2) are significantly lower in AD subjects compared with the control subjects. We found that brain levels of testosterone are also significantly reduced in men with mild neuropathology consistent with early stage AD (Figure 2).

Comment. Brain levels of testosterone significantly decrease with age in men who lack any evidence of neuropathology, suggesting that neural androgen depletion is a normal consequence of aging. In comparison with the control subjects, men with AD exhibit significantly lower testosterone levels in the brain. In contrast, the data suggest that estrogen levels in the male brain are affected by neither advancing age nor AD diagnosis. Notably, testosterone depletion likely precedes and thus may contribute to rather than result from the development of AD, since low brain testosterone is observed in men with early indications of AD neuropathology. Although it remains possible that low testosterone may reflect an unmeasured correlate of AD rather than be a contributing factor, we controlled for established causes of low testosterone by our exclusion criteria and statistical adjustment. How testosterone depletion may contribute to AD development is unknown. However, we have recently reported that androgen depletion in male rodents increases brain levels of β -amyloid,⁵ the protein implicated as a causal factor in AD pathogenesis, and decreases neuronal survival upon exposure to toxic insult.⁶ Collectively, these findings suggest that normal, age-related testosterone depletion in the male brain may impair beneficial neural actions of androgens and thereby act as a risk factor for the development of AD.

Emily R. Rosario, MS
Neuroscience Graduate Program

Lilly Chang, MD
Frank Z. Stanczyk, PhD
Department of Obstetrics and Gynecology
Keck School of Medicine

Christian J. Pike, PhD
cjpik@usc.edu
Andrus Gerontology Center
University of Southern California
Los Angeles

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- Morley JE. Androgens and aging. *Maturitas*. 2001;38:61-73.
- Hogervorst E, Lehmann DJ, Warden DR, McBroom J, Smith AD. Apolipoprotein E epsilon4 and testosterone interact in the risk of Alzheimer's disease in men. *Int J Geriatr Psychiatry*. 2002;17:938-940.
- Hogervorst E, Williams J, Budge M, Barnetson L, Combrinck M, Smith AD. Serum total testosterone is lower in men with Alzheimer's disease. *Neuroendocrinol Lett*. 2001;22:163-168.
- Goebelsmann U, Bernstein GS, Gale JA, et al. Serum gonadotropin, testosterone, estradiol, and estrone levels prior to and following bilateral vasectomy. In: Lepow IH, Crozier R, eds. *Vasectomy: Immunologic and Pathophysiologic Effects in Animals and Man*. New York, NY: Academic Press; 1979:165.
- Ramsden M, Nyborg AC, Murphy MP, et al. Androgens regulate beta-amyloid levels in male rat brain. *J Neurochem*. 2003;87:1052-1055.
- Ramsden M, Shin TM, Pike CJ. Androgens modulate neuronal vulnerability to kainate lesion. *Neuroscience*. 2003;122:573-578.