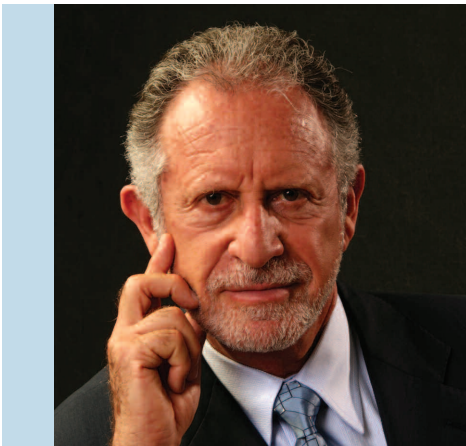


From the EDITOR

Memory, Menopause and Hormones— Conclusions from the NAMS 2008 HT Position Statement



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A pioneer in Women's Health issues and menopause research, in 1967 he established the Groote Schuur Menopause Research Clinic in Cape Town, the world's first such clinic. He was one of the three original founders of the International Menopause Society in 1976, of which he is Honorary Past President, and founded the North American Menopause Society in 1989.

He is the recipient of numerous national and international awards and research grants, and is still an active investigator with multiple grants. Dr. Utian has written over 200 papers related to the reproductive system in women and has authored five books on menopause and its effects on women. He is editor of *Menopause: The Journal of The North American Menopause Society*.

"Am I losing my mind?" "My memory is failing!" How often do you hear a question or statement like these during your day in the office? Incongruously, despite the popular perception that memory is a victim of menopause and the result of estrogen deficiency, surveys of women transitioning menopause at the usual age spectrum of 45 to 55 years overwhelmingly confirm that their greatest fear regarding menopause and hormone therapy (HT) is breast cancer. Nevertheless, wait a decade or two, survey the same population about their greatest concern after age 65, and their answer is now most likely to be fear of memory loss and Alzheimer's disease (AD).

Many of us will recall that as recently as 10 years ago there was increasing optimism that replacement of the female sex steroids estrogen and progesterone, as well as testosterone, in women beyond menopause could be the key to maintenance or recovery of memory. Then came studies like the Women's Health Initiative Memory Study (WHIMS) to dampen expectations and sow confusion. Unfortunately, the entire subject of memory, cognition and processes and diseases affecting them is extremely complex and cannot be explained away by one simple mechanism or clarified by any one research study.

The issue of memory, cognition and the pathologic aspects thereof was one of the health-related effects carefully considered by the committee of experts convened by The North American Menopause Society (NAMS) as the 2008 Panelists on HT and menopause. Their assignment was to attempt to digest the existing scientific literature into a set of clinical recommendations.¹ I can do no better than to freely extract from the

latest NAMS HT Position Statement, for which I served as Chairman of the Panel.¹

The Panelists commenced by defining the term “cognition” as a group of mental processes by which knowledge is acquired or used, encompassing such mental skills as concentration, learning and memory, language, spatial abilities, judgment and reasoning. They recognized that cognitive abilities change throughout life and, that with advancing age, performance tends to decline on many, but not all, cognitive tests.

The NAMS Panel concluded that although memory complaints are common in midlife, findings from well-characterized cohorts suggest that natural menopause has little effect on memory performance or other areas of cognitive function.

They further concluded that limited, short-term clinical trial data involving younger postmenopausal women suggest that estrogen-progestogen therapy (EPT) does not have a substantial impact on cognition after natural menopause. As inferred from very small short-term clinical trials, estrogen therapy (ET) initiated promptly after bilateral oophorectomy may improve verbal memory. Several observational studies report no association between age at menopause and AD. However, a case-control study found that bilateral oophorectomy before menopause was associated with an elevated risk of cognitive impairment or dementia, and this risk increased with younger age at oophorectomy.

For postmenopausal women over age 60, NAMS noted that findings from several large well-designed clinical trials indicate that ET/EPT does not improve memory or other cognitive abilities. One trial within the WHI—the WHIMS—of women age 65 to 79 reported an increase in dementia incidence with ET and EPT use. The estimate of dementia cases attributed to HT was 12 per 10,000 persons per year of ET use and 23 per 10,000 persons per year of EPT use. It is not clear whether progestogen supplementation is associated with greater impairment, as the ET and HT groups from WHIMS are not strictly comparable. Of course, the WHIMS trial applied, by design, to women over age 65 starting hormones for the first time—an unusual situation in clinical practice, and with results that obviously cannot be extrap-

olated to the younger perimenopausal or early menopausal woman.

By way of contrast, the NAMS Panelists noted that a number of observational studies have reported associations between HT use and reduced risk of developing AD. HT exposure in observational studies is more likely to involve use by

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younger women closer to the age of menopause than by women eligible for the WHIMS trial. Speculatively, this difference implies an early window during which HT use might reduce AD risk. However, recall bias and the healthy-user bias may account for protective associations in the observational studies, many of which are difficult to interpret because of fairly small numbers of study participants. The window of opportunity perspective is supported by limited evidence, but no clinical trial data address long-term cognitive consequences of ET/EPT exposure during the menopause transition and early postmenopause. For women with AD, limited clinical results suggest that ET has no substantial effect on dementia symptoms or progression.

Based on these considerations, the NAMS expert panel concluded that HT cannot be recommended at any age for the sole or primary indication of preventing cognitive aging or dementia. HT seems to increase the incidence of dementia when initiated in women age 65 and older. Similarly, HT should not be used to enhance cognitive function in younger postmenopausal women with intact ovaries, although very small clinical trials support the use of ET initiated immediately after menopause induced by bilateral oophorectomy. Available data do not adequately address whether HT used soon after menopause increases or decreases later

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50. Pfeifer M, Begerow B, Minne HW, et al. Vitamin D status, trunk muscle strength, body sway, falls, and fractures among 237 postmenopausal women with osteoporosis. *Exp Clin Endocrinol Diabetes* 2001;109:87-92.
51. Lui LY, Stone K, Cauley JA, et al. Bone loss predicts subsequent cognitive decline in older women: the study of osteoporotic fractures. *J Am Geriatr Soc* 2003;51:38-43.
52. Siris ES, Chen YT, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med* 2004;164:1108-12.
53. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280:2077-82.
54. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med* 2001;344:333-40.
55. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med* 1992;327:1637-42.
56. Kiraly SJ, Kiraly MA, Hawe RD, Makhani N. Vitamin D as a neuroactive substance: review. *Scientific World Journal* 2006;6:125-39.
57. Sonnenberg J, Luine VN, Krey LC, Christakos S. 1,25-Dihydroxyvitamin D3 treatment results in increased choline acetyltransferase activity in specific brain nuclei. *Endocrinology* 1986;118:1433-39.
58. Hernan MA, Olek MJ, Ascherio A. Geographic variation of MS incidence in two prospective studies of US women. *Neurology* 1999;53:1711-18.
59. Lux WE, Kurtzke JF. Is Parkinson's disease acquired? Evidence from a geographic comparison with multiple sclerosis. *Neurology* 1987;37:467-71.
60. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004;62:60-5.
61. Kipen E, Helme RD, Wark JD, Flicker L. Bone density, vitamin D nutrition, and parathyroid hormone levels in women with dementia. *J Am Geriatr Soc* 1995;43:1088-91.
62. Sato Y, Asoh T, Ozumi K. High prevalence of vitamin D deficiency and reduced bone mass in elderly women with Alzheimer's disease. *Bone* 1998;23:555-7.
63. Wilkins CH, Sheline YI, Roe CM, et al. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatry* 2006;14:1032-40.
64. Yaffe K, Lindquist K, Penninx BW, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology* 2003;61:76-80.
65. Kuo HK, Lipsitz LA. Cerebral white matter changes and geriatric syndromes: is there a link? *J Gerontol A Biol Sci Med Sci* 2004;59:818-26.
66. Kurella M, Chertow GM, Luan J, Yaffe K. Cognitive impairment in chronic kidney disease. *J Am Geriatr Soc* 2004;52:1863-69.
67. Gloth FM III, Alam W, Hollis B. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. *J Nutr Health Aging* 1999;3:5-7.
68. Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacology (Berl)* 1998;135:319-23.
69. Ferrucci L, Guralnik JM, Studenski S, et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. *J Am Geriatr Soc* 2004; 52:625-34.
70. Bartali B, Semba RD, Frongillo EA, et al. Low micronutrient levels as a predictor of incident disability in older women. *Arch Intern Med* 2006;166:2335-40.
71. Vieth R, Ladak Y, Wallich PG. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *J Clin Endocrinol Metab* 2003; 88:185-91.
72. Kinyamu HK, Gallagher JC, Balhorn KE, et al. Serum vitamin D metabolites and calcium absorption in normal young and elderly free-living women and in women living in nursing homes. *Am J Clin Nutr* 1997;65:790-7.
73. Dawson-Hughes B, Heaney RP, Holick MF, et al. Estimates of optimal vitamin D status. *Osteoporos Int* 2005; 16:713-6.
74. Heaney RP, Davies KM, Chen TC, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 2003; 77:204-10.
75. Lappe JM, Davies KM, Travers-Gustafson D, Heaney RP. Vitamin D status in a rural postmenopausal female population. *J Am Coll Nutr* 2006;25:395-402.
76. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr* 2007;85:6-18.
77. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab* 2004;89:5387-91.

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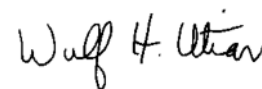
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dementia risk. Limited data do not support the use of HT as treatment for AD.

Clearly, the existing data, despite demonstrating the limitations of current knowledge, open ideas and offer possibilities for further research into the relationships between hormones and cognition. That research is, at present, covering basics of cell culture, the use of artificial neural networks, study of animal biology and behavior, other hormone systems like insulin pathways and gonadotropins, protein metabolism, and attempts to eventually translate this basic scientific endeavor into clinical research studies. While epidemiologic observations help direct some lines of research, such observations cannot, themselves, directly link cause and effect. This raises the necessity for testing multiple steroidal drugs in varying doses, combinations and routes of delivery. Beyond that will be the testing of earlier-generation estrogen agonist-antagonist molecules and, as an area of rapid drug development in a relatively early stage, the potential of testing new and ever better designed molecules. As basic mechanisms of brain cell

metabolism and neural pathways are revealed, the possibility exists for specific ligand receptor products to be developed with planned and precisely targeted activity.

All in all, even though this is an exciting frontier in the new science of brain and memory research, currently HT use does not appear to be the answer to memory loss, and much work lies ahead. Real support is necessary to stimulate and encourage basic science and clinical researchers going forward. We are just scratching the surface of the science and the potential for defeating what is one of the most devastating problems facing humanity; namely, loss of memory and its impact on the individual and the family.



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Reference*

The North American Menopause Society. Estrogen and progestogen use in postmenopausal women: July 2008 position statement of The North American Menopause Society. *Menopause* 2008;15:584-603.

*References to material described are listed in the NAMS statement cited above.