Public release date: 28-Jan-2004

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Low free testosterone levels linked to Alzheimer's disease in older men

Older men with lower levels of free, or unbound, testosterone circulating in their bloodstreams could be at higher risk of developing Alzheimer's disease (AD) than their peers, according to new research. This prospective observational study is believed to be the first to associate low circulating blood levels of free testosterone with AD years before diagnosis.

The study appears in the January 27, 2004 issue of the journal *Neurology*. This work was conducted by investigators at the National Institute on Aging (NIA), one of the National Institutes of Health, and scientists at other institutions supported by NIA grants.* "Our finding that low free testosterone might be associated with an increased risk of developing of AD is a step forward in helping to understand the possible effects of sex hormones on the aging brain and other parts of the body," said Susan Resnick, Ph.D., an investigator in the NIA's Laboratory of Personality and Cognition and corresponding author of the study.

Dr. Resnick, however, cautions that much more research is needed before scientists can establish a causal relationship between low testosterone and AD. "Even if a relationship between AD and levels of free testosterone in the bloodstream is confirmed, we are very far away from knowing if hormonal therapy or any other intervention could safely prevent AD," she said.

Dr. Resnick, Scott Moffat, Ph.D., and their colleagues evaluated the testosterone levels of 574 men, ages 32 to 87, who participated in the Baltimore Longitudinal Study of Aging (BLSA)**. The investigators examined free and total testosterone levels-measured over an average of 19 years-in relationship to subsequent diagnosis of AD. Based on physical, neurological and neuropsychological exams, 54 of the 574 men were diagnosed with AD.

The research team found that for every 50 percent increase in the free testosterone index in the bloodstream, there was about a 26 percent decrease in the risk of developing AD. Although overall free testosterone levels fell over time, these levels dropped more precipitously in those men who later developed AD. In fact, at the end of the study, men who were diagnosed with AD, on average, had about half the levels of circulating free testosterone as men who didn't develop the disease. In some cases, the drop-offs in free testosterone levels associated with AD were detected up to a decade before diagnosis.

Previously, Dr. Resnick and her colleagues found that older men with high levels of circulating free testosterone have better visual and verbal memory and perform spatial tasks more adeptly than their peers.

"It is quite possible that circulating free testosterone has a broad range of influences on the aging brain," Dr. Resnick said. "The effects of some of these influences-such as the role of testosterone in the development of certain types of memory loss and AD-are just beginning to be explored."

In men, testosterone is produced in the testes, the reproductive glands that also produce sperm. As men age, their testes often produce somewhat less testosterone than they did during adolescence and early adulthood, when production of this hormone peaks. Within the body, testosterone tends to bind with sex hormone binding globulin (SHBG). But some testosterone remains freely circulating in the bloodstream. Unlike the SHBG-bound form of the hormone, free testosterone can circulate into the brain and affect nerve cells. In this study, only reduced levels of free testosterone were associated with AD, Dr. Resnick said.

Other BLSA studies suggest that many men older than 70 have low levels of free testosterone compared to younger men. But while prescription testosterone replacement therapy is available, it may not be advisable for most older men because many effects of hormone therapy remain unclear. It is not yet known, for instance, if testosterone replacement increases the risk of prostate cancer, the second leading cause of cancer death among men. In addition, studies suggest that in some men testosterone therapy might trigger excessive red blood cell production. This side effect can thicken blood and increase a man's risk of stroke.

"We still have much to learn," Dr. Resnick said. "For now, testosterone therapy should not be considered an option for older men seeking to reduce their risk of Alzheimer's disease or to improve their memory and cognitive performance in general."

A multi-disciplinary panel, led by the Institute of Medicine (IOM) and supported by the National Institute on Aging (NIA) and the National Cancer Institute, recently evaluated the pros and cons of conducting clinical trials of testosterone replacement therapy in older men to answer many of the lingering questions about the effects of this hormone in the aging body. The NIA is considering the IOM recommendations very carefully and likely will act on the recommendations to begin small-scale clinical trials to determine the efficacy of testosterone in treating symptomatic older men with low testosterone levels. Until carefully designed and monitored clinical trials are conducted, the risks and benefits of testosterone therapy for most men who do not have extreme deficiencies of the hormone will remain largely unknown.

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AD is an irreversible disorder of the brain, robbing those who have it of memory, and eventually, overall mental and physical function, leading to death. For more

information on AD research, two new publications are available from the NIA: 2001-2002 Alzheimer's Disease Progress Report and Alzheimer's Disease: Unraveling the Mystery, which includes a CD-Rom animation of what happens to the brain in AD. These publications may be viewed at NIA's AD-dedicated website www.alzheimers.org, the Institute's Alzheimer's Disease Education and Referral (ADEAR) Center, or by calling ADEAR at 1-800-438-4380.

The NIA, one of 27 Institutes and Centers that constitute the National Institutes of Health, leads Federal efforts to support and conduct basic, clinical, epidemiological, and social research on aging and the special needs of older people. For more information about the NIA, visit the website at http://www.nia.nih.gov/.

* Scott Moffat, Ph.D., formerly of the NIA, is now at Wayne State University, Detroit. Claudia Kawas, M.D., now at the University of California, Irvine, collaborated on this study while at the Johns Hopkins University Alzheimer's Disease Research Center in Baltimore under NIA/NIH grants, AG80325, AG05146, and M01 RR02719. Marc R. Blackman, M.D., collaborated on this study while at Johns Hopkins University; he is clinical director at the NIH's National Center for Complementary and Alternative Medicine. Former NIA investigator S. Mitchell Harman, M.D, Ph.D., is now at the Kronos Longevity Research Institute in Phoenix.

** Launched in 1958, the BLSA is America's longest running scientific examination of human aging. Volunteers receive comprehensive medical, physiological and neuropsychological evaluations every two years at the NIA Gerontology Research Center in Baltimore. The BLSA has measured testosterone levels in its male participants since 1963.

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