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At More Risk for Alzheimer's?

Scientists are studying how genes and gender interact in Alzheimer's disease

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Now and again we all forget where we left our glasses or what we hurried into the kitchen to retrieve. As we get older, these events seem to increase in frequency. But Alzheimer's disease is more than mere forgetfulness. It is a degenerative disease of the brain that causes cognitive dysfunction, behavioral changes and dementia.

The disease, which affects an estimated four million Americans, eventually robs its victims of their memories and their ability to reason. And Alzheimer's appears to affect women more frequently than men.

The finding that women might have an increased susceptibility, particularly women with a certain genetic background, has begun to provide crucial clues about the underlying biology of the disease and new insight into its prevention and treatment. Further, a number of small clinical and epidemiological studies have shown that estrogen replacement therapy appears to help protect postmenopausal women from Alzheimer's. By exploring how estrogen affects the development and activity of the brain, researchers may uncover new ways to protect people at risk for developing Alzheimer's disease.

Since the turn of this century, life expectancy has been steadily increasing. By 2030, some nine million Americans will be 85 or older. Unfortunately, as a greater proportion of the population survives past 85, the number of people with Alzheimer's disease will rise. The prevalence of the disease increases dramatically after age 65, rising from 4 to 6 percent at 65 to 15 to 20 percent at 75 and 30 to 40 percent at 85.

This century has seen dramatic increases in the life expectancy of women compared with that of men. With an elevation of women's social status and the elimination of many of the risks of pregnancy, women are surviving as many as three to 10 years longer than men. Because women are living longer, they are at greater risk for developing Alzheimer's disease—a situation that is reflected in the higher prevalence rates in women.

Yet studies examining the incidence of Alzheimer's—how many people are diagnosed a year—offer conflicting results. Some show higher rates for women; others find no difference. Researchers think the disparity in these incidence studies might reflect the fact that the disease is caused by multiple genes interacting with different environmental influences.

The major risk factors associated with Alzheimer's disease include age, genetic predisposition and gender. But the idea that gender on its own may increase a person's risk is still controversial. A few preliminary studies suggest, however, that gender may interact with one's genetic predisposition

Remembering: Looking at old family photographs stimulates memories for those in the early stages of Alzheimer's disease. A retired psychotherapist, Sarita Stein, 86, stopped seeing patients when she realized she could not remember everything they had told her the previous week.

Coping: Elizabeth Mudd, 71, who runs a small bed-and-breakfast in her home, uses a whiteboard to jog her memory and carries everywhere a small book—full of lists, names, appointments.

somehow to influence the age of onset of the disease. In cases of familial Alzheimer's disease, women are at a higher risk than men of the same age. And they appear to experience an earlier onset. These results suggest that gender may be a risk factor in familial cases of Alzheimer's, and gender may influence the course of the disease, especially in the presence of certain genes.

Over the past few years, researchers have found that mutations or different forms of a particular gene may occur more frequently in people with Alzheimer's than in the general population. In 1992 Alan D. Roses and his collaborators at Duke University found such a relation between one form of the gene for apolipoprotein E (ApoE) on chromosome 19 and an increased risk for late-onset Alzheimer's. This finding established the *APOE* gene as a susceptibility gene for the disease.

The *APOE* gene comes in three varieties, called *APOE2*, *APOE3* and *APOE4*. Roses and his colleagues demonstrated a relation between the average age of onset and the number of *APOE4* copies a person inherits. People who have two copies of *APOE4* tend to get Alzheimer's at an earlier age—sometimes 20 years earlier—than those who have no copies.

But Haydeh Payami and her associates at the Oregon Health Sciences University recently found that the effect of inheriting one copy of *APOE4* differs depending on gender. For men, individuals with two copies of *APOE4* were at the highest risk for developing Alzheimer's, and men possessing one copy, or no copies, had a lower risk. But for women, having one copy of *APOE4* appears to be as bad as having two copies—both genetic situations cause an earlier onset of the disease. If scientists can learn how *APOE4* affects the age of onset, or how gender influences that mechanism, they may be closer to developing interventions that can delay the disease.

Sex and the Brain

Alzheimer's disease is characterized by a progressive decline in memory, orientation, language and communication skills, and the ability to reason. The destruction of critical brain regions starts 20 to 40 years before symptoms are clinically detectable. Ultimately, the disease leads to the loss of increasing numbers of neurons, especially in the hippocampus and cortex—parts of the brain that help to code memories and process information. As increasing numbers of cells in these critical brain regions die, short-term memory fails, and the ability to do familiar tasks begins to decline.

In the late 1970s Barbara B. Sherwin, now at McGill University, first linked a loss of estrogen with memory problems in a group of women who had had their ovaries removed. At the time, few people recognized that estrogen—the hormone that activates and regulates the female reproductive system—may have a number of effects in the human brain, quite apart from its role in reproduction. Then, in the mid-1980s, Howard M. Fillet of the Mount Sinai School of Medicine conducted the first study on the effects of estrogen on cognition in humans. He found that after six weeks of estrogen treatment, three of seven women with Alzheimer's showed significant improvement in attention, orientation, mood and social interactions.

In addition to such prospective investigations exploring estrogen's effects, several groups of researchers were conducting retrospective analyses on previous estrogen studies. In the early 1990s Victor Henderson, Annlia Paganini-Hill and their co-workers at the University of Southern California were among the first to report epidemiological evidence suggesting that estrogen may reduce the risk for Alzheimer's disease. In a larger study conducted in 1996, Henderson and his colleagues analyzed data from a population of nearly 9,000 older women. In studying a subset of about 250 women who had died with Alzheimer's disease, the researchers found that the risk for developing Alzheimer's decreased significantly among women who had received estrogen replacement therapy (ERT). And the women who received the highest doses over the longest times were the most protected.

Other epidemiological studies have provided further confirmation of the protective effects of ERT. Richard Mayeux and his collaborators at Columbia University studied 1,124 older women who were free of the clinical symptoms of Alzheimer's. The researchers found that the age of onset for Alzheimer's was significantly delayed in estrogen users compared with nonusers, and the relative risk was significantly reduced. Women who were on ERT for longer than one year had the greatest risk reduction. None of the 23 women who were taking estrogen when they enrolled in the

study had developed Alzheimer's by the time the paper was published.

And as part of the ongoing Baltimore Longitudinal Study of Aging, conducted by the National Institute on Aging, Claudia H. Kawas and her colleagues at Johns Hopkins University have studied 472 women whose health status has been followed for 16 years. They found that women who take estrogen after menopause reduced their risk of developing Alzheimer's disease by 54 percent.

The Estrogen Link

Animal studies are continuing to reveal how estrogen may enhance brain function. Such findings reinforce the results seen in human clinical studies. It appears that estrogen can improve learning and memory by helping to build and maintain the synapses that connect neurons in the brain.

In the 1970s Bruce S. McEwen and his colleagues at the Rockefeller University first reported that estrogen might have a direct effect on the brains of rats. They had found that estrogen boosts the ability of neurons to relay chemical messages by increasing the levels of acetylcholine, a neurotransmitter involved in learning and memory.

A few years later McEwen, Catherine S. Woolley, Elizabeth Gould and their colleagues discovered that estrogen may enhance learning and memory in animals by helping to build and maintain the synapses through which neurons communicate with one another. Synapses are destroyed in the brains of people with Alzheimer's disease, a loss that hampers their ability to learn and remember information. By removing the ovaries from adult female rats, the Rockefeller researchers found that estrogen deprivation causes a loss of synapses in the hippocampus. Treating these rats with estrogen restored their synapses to normal numbers. Perhaps something similar happens in the brains of postmenopausal women who receive ERT.

Another pioneer in this area was Dominique Toran-Allerand of Columbia University. She showed that in developing neurons grown in a culture dish, estrogen stimulates the growth of axons and dendrites, the neuronal structures that form the synaptic connections.

As we learn more about estrogen, we are finding that it can act alone as an important biological signal. But, more significantly, estrogen also appears to work in a cooperative manner with other classes of signaling molecules to stimulate neuronal growth and activity. Toran-Allerand recently reported that in neurons grown in culture, estrogen increases the production of receptors that bind to nerve growth factor, a hormone necessary for neuronal development and activity. The results suggest that estrogen and nerve growth factor may work together to enhance each other's biological activities.

Caretaking: Dorinda Lord cares for Ethel Burns, 87, round-the-clock, helping this former owner of several dress shops maintain her appearance and interest in fashion.

It is becoming abundantly clear that estrogen has many facets. It plays a key role in growth and repair of neurons in the brain. But it also may help protect nerve cells against damage from free radicals and other cellular toxins. James W. Simpkins and his co-workers at the University of Florida have found that estrogen can directly prevent brain cells from being killed by toxins through an unknown mechanism that does not involve either estrogen receptors or nerve growth factor. Other investigators, including Judes Poirier of McGill University, are studying how ApoE, a cholesterol-transporting protein, may affect the regeneration and repair of neurons. Such animal studies are beginning to suggest how estrogen may protect the brain from destruction by Alzheimer's disease.

ERT or No ERT?

Estrogen replacement therapy might not be the answer for everyone. Fortunately, several studies currently under way should help women to make better-informed decisions about ERT as it relates to Alzheimer's and other diseases. One such study—a part of the Women's Health Initiative of the National Institutes of Health—is monitoring the health of 25,000 women, some of whom are receiving ERT plus progestin, which appears to reduce estrogen's cancer risks. In a few years, the study should provide a clear picture of how ERT is altering the course of Alzheimer's. A second clinical study, headed by Ruth A. Mulnard of the University of California at Irvine, is examining the effects of ERT on 120 women with Alzheimer's disease. The results of this study—sponsored by the National Institute on Aging—should be available within a year.

Toran-Allerand adds a note of caution about interpreting the results of these studies. Many, including the NIH's Women's Health Initiative, involve the use of Premarin, an estrogen preparation made by Wyeth-Ayerst using the urine of pregnant mares. In the future, additional studies comparing different forms of estrogen may lead to the development of therapies that are more effective and have fewer side effects.

As we learn more about estrogen and how it enhances the viability of neurons, we hope to be able to exploit this information to develop better treatments for delaying, and perhaps preventing, this devastating disease. SA

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For more information, contact the Alzheimer's Association at 800-272-3900 or at http://www.alz.org on the World Wide Web. Other Web sites are the National Institute on Aging (NIA) at http://www.nih.gov/nia and the National Institute of Mental Health at http://www.nimh.nih.gov To order "Alzheimer's Disease: Unraveling the Mystery," call the NIA's Alzheimer's Disease Education and Referral Center at 800-438-4380.