

Advances

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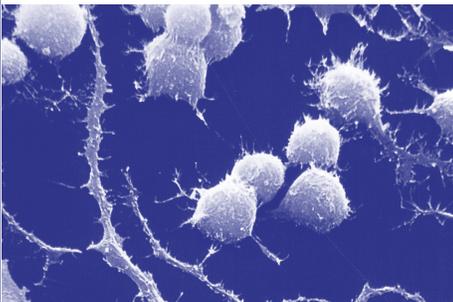
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Early-Onset Alzheimer's Disease *Fighting Back...Speaking Out*

"Suddenly, the lights went out."

That is how John Wagenaar of George, Iowa, recalled the moment that early-onset Alzheimer's unmistakably manifested itself. As he had done every day for 11 years, Wagenaar had gone to his job at a manufacturing plant...and had somehow gotten lost in the plant's new addition. The incident occurred after weeks of growing concern among family and friends about Wagenaar's memory, concentration, and health.

"I spent that night under observation [for a stroke] in the local hospital," Wagenaar said. "The next day I went to a larger hospital in Sioux City. I saw a neurologist and had a CAT scan and other tests."

A few days later came the unexpected news: Wagenaar had Alzheimer's disease.

The year was 1998. John Wagenaar was 60 years old.

Alzheimer's is not just a disease of old age. Early-onset Alzheimer's, which accounts for up to 10 percent of Alzheimer's cases, affects an estimated 400,000 people under the age of 65—some in their 40s and 50s.

Because of their relatively young age, early-onset individuals can face a variety

of financial challenges, including:

- Loss of income and insurance coverage when employment ends,
- Reduction in or loss of retirement benefits due to early retirement,
- Delay in eligibility for Medicare and disability benefits,
- Increase in family expenses due to treatment and care for an affected individual, or
- A spouse being required to work or increase hours to help support the family.

During the 13th Annual Alzheimer's Association Public Policy Forum in Washington, D.C., March 30-April 3, individuals affected by early-onset Alzheimer's and their caregivers joined forces with chapter associates and met with their U.S. senators and representatives to seek remedies—including a

[CONTINUED ON PAGE 11]



John Wagenaar testifies about his life with early-onset Alzheimer's before a Senate Appropriations Committee in Washington, D.C.

Frontotemporal Dementia

Another Piece in the Neurodegenerative Puzzle

Alzheimer's disease is the most common of the dementias, a group of gradually progressive conditions that erode memory, the ability to reason and make judgments, awareness of time and place, and other mental abilities. In the spring 2001 *Advances*, we discussed dementia with Lewy bodies, the second most common such condition. Frontotemporal dementia (FTD), the third most common type, is a relatively new category. It encompasses a group of disorders that cause deterioration and shrinkage in the front and side areas of the brain.

Neuropsychiatrist Arnold Pick recognized the first type of FTD in the early 1890s when he noted dramatic shrinkage in frontal and temporal brain regions during autopsies of some people with a dementia that profoundly disrupted their ability to use language. In later examinations of Pick's tissue samples, pioneer neuropathologist Alois Alzheimer—who first identified Alzheimer's disease—observed that the shrunken brain regions showed similar microscopic changes. Some nerve cells looked swollen or “ballooned,” while others contained spherical abnormalities. Over time, the swollen cells became known as Pick's cells, the tiny spheres became Pick's bodies, and the disorder itself became Pick's disease.

As scientists gained greater knowledge of brain pathology, they observed that some cases of frontotemporal degeneration lacked Pick's cells or bodies. During the 1970s and 1980s, new diag-

nostic imaging technologies revealed that frontotemporal degeneration could account for a wide variety of symptoms besides language difficulties. Imaging studies also suggested that frontotemporal disease is more common than originally thought, representing up to 20 percent of dementia cases.

Frontotemporal disease is more common than originally thought, representing up to 20 percent of dementia cases.

All of these factors—reduced emphasis on Pick's abnormalities, varied symptoms, and newly recognized frequency—contributed to a bewildering proliferation of names for frontotemporal disorders. To counter the confusion, experts adopted the term frontotemporal dementia (FTD) to encompass all the disorders that result from gradual deterioration of the frontal and temporal lobes (regions). In current medical practice, the terms Pick's disease, FTD, and “frontotemporal lobar degeneration” (FTLD) are often used interchangeably.

Characteristic symptoms of FTD

In addition to being less common than Alzheimer's, FTD tends to appear

somewhat earlier in life. Although the disorder may occur in people from 30 to 75 years old, most cases are diagnosed in people in their 40s, 50s, and 60s. Incidence seems to peak around 55 to 65 years of age, then decline.

Because it tends to strike similar brain regions, FTD can sometimes—although not always—produce fairly distinct symptoms. The frontal and temporal lobes are the center of many important brain functions, including language skills; the ability to focus attention; the capacity to organize and understand one's behavior; and the ability to make plans and decisions, solve problems, and control impulses. Early indications of FTD often involve alterations in personality, mood, and conduct. Affected individuals may experience a decline in social skills and manners or engage in unusual verbal, physical, or sexual behavior. Initial symptoms may also involve uncharacteristic apathy, indifference, and an unwillingness to talk. Weight gain due to dramatic overeating is another common symptom. People may repeat motions compulsively or collect and hoard objects. Affected individuals may neglect hygiene and resist encouragement to attend to themselves. Another key feature is that people with FTD lack awareness or concern that their behavior has changed.

Because the first symptoms tend to affect personality and behavior, doctors may initially misdiagnose FTD as a psychiatric disorder. Correct identifica-

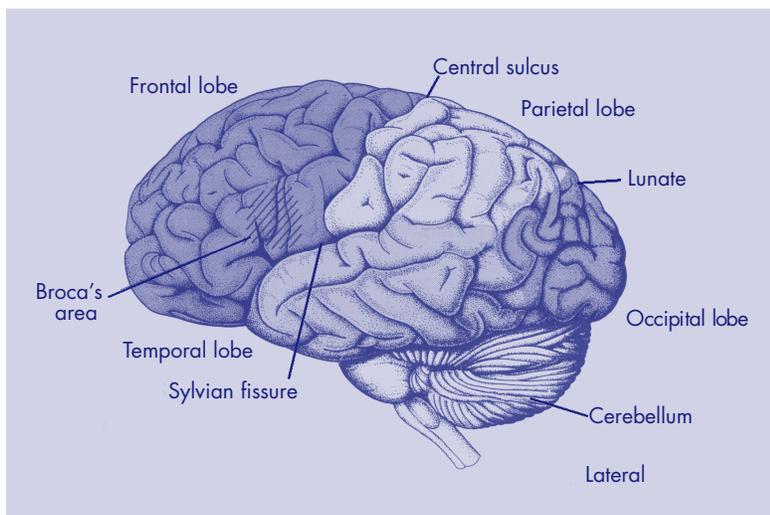
tion requires a thorough physical examination and a careful interview with family members. FTD may have a strong genetic component—many affected individuals report a history of other relatives with dementia. Scientists have already linked particular forms of FTD to abnormalities on chromosomes 17 and 3.

Imaging tests play a key diagnostic role by revealing the characteristic shrinkage in the brain's frontal and temporal lobes. Common procedures include magnetic resonance imaging (MRI), positron emission tomography (PET), computed tomography (CT), and single photon emission computed tomography (SPECT).

As FTD progresses, it takes an increasing toll on mental abilities, and begins to affect memory and other functions that were initially less disrupted than in Alzheimer's and some other dementias. In later stages, people often develop such movement disorders as unsteadiness, rigidity, slowness, twitches, muscle weakness, or difficulty swallowing. People in the final stages of FTD eventually cannot care for themselves. FTD may last from 3 to 17 years, with an average duration of about 8 years.

Treatment options for FTD

Current treatment aims to relieve some of FTD's troubling symptoms—there is not yet any way to stop or reverse the underlying brain deterioration. Antidepressants in the category of selective serotonin reuptake inhibitors (SSRIs) may offer some relief from apathy and depression, and also help reduce food cravings, loss of impulse control, and compulsive activity. Doctors may prescribe antipsychotics—medications that can alleviate extremely unrealistic or disorganized



thinking—in an effort to treat hallucinations, delusions, and aggression. Cholinesterase inhibitors—the chief class of drugs currently used to treat memory symptoms in Alzheimer's—do not help in FTD. These drugs temporarily increase supplies of the messenger chemical acetylcholine available to failing nerves, but FTD does not affect nerves in the acetylcholine communication system.

Goals for the future

Scientists continue their efforts to understand the array of symptoms and pathological changes involved in various forms of FTD. Research has revealed that Pick's bodies are composed of an abnormal form of tau protein—the same protein that makes up tangles, one of the hallmark abnormalities of Alzheimer's disease. Another recent discovery has shown that many—but not all—of the individuals with the form of FTD linked to chromosome 17 have mutations in the gene that codes production of tau. Insights into the relationships among FTD, Alzheimer's, and other dementias may eventually provide important clues in the effort to unravel the mystery of these complex disorders. ♦

Advances

Are you a working caregiver?

WE WANT TO HEAR FROM YOU!

- What problems have you faced balancing work and caregiving responsibilities?
- How have you creatively solved these problems?
- What do you advise other caregivers in the same situation?
- What do you think should be done to help working caregivers?

Send your feedback, no later than July 16, by e-mail to barbara.harfmann@alz.org or by mail to 919 North Michigan Avenue, Suite 1100, Chicago, Illinois, 60611-1676.

The Genetics of Early-Onset Alzheimer's

Clues to Alzheimer Pathology

Most cases of early-onset Alzheimer's disease are known as the familial form of the disease. This means that a causal factor can be passed from one generation to the next. Because certain families have had long histories of early-onset Alzheimer's, researchers had a logical place to begin searching for genes associated with the disease. Since the 1980s, when this effort began, scientists have identified three gene mutations that play a causal role in early-onset familial Alzheimer's disease.

Identifying these genes is in itself an important step in Alzheimer research, but determining what proteins the genes encode and how those proteins function in healthy and diseased brains will help researchers reveal the molecular processes that are fundamental to Alzheimer's disease. A brief look at ongoing research focusing on two of these genes reveals progress as well as hurdles in the path of explaining the complexities of Alzheimer's.

Investigating suspect genes

In 1995, researchers identified two genes known as the presenilin genes after conducting genetic screening tests on families with histories of early-onset Alzheimer's.

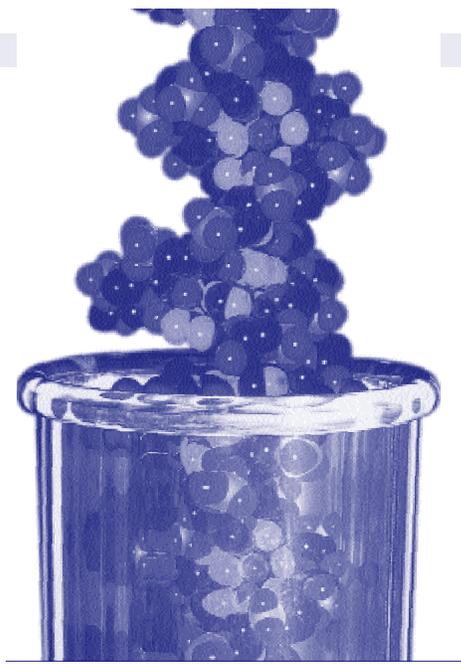
These genes provide instructions for the production of proteins called presenilin-1 and presenilin-2. Mutations of

the presenilin-1 gene, located on chromosome 14, may be responsible for 70 to 80 percent of all cases of early-onset familial Alzheimer's. Mutations of the presenilin-2 gene, located on chromosome 1, may account for up to 20 percent of familial cases.

Researchers suspected that presenilin proteins play an important role in Alzheimer pathology because mutations of the presenilin genes are associated with increased production of beta-amyloid protein fragments (A β). A β is the primary component of amyloid plaques, abnormal structures that accumulate in brains affected by Alzheimer's disease. Although the role of plaques in Alzheimer's is unknown, evidence suggests that they may contribute to the degeneration of brain cells.

The link between presenilin gene mutations and increased production of A β is being diligently researched. Scientists have learned that A β is clipped from a parent molecule by enzymes in a two-step process. While the activities of the enzymes were known, their identities and the genes that encoded them remained a mystery. Researchers referred to the mystery enzyme activity as beta-secretase (β -secretase) and gamma-secretase (γ -secretase).

In 1999, scientists reported on the identity of a likely candidate for β -secretase,



Since the 1980s, when this effort began, scientists have identified three gene mutations that play a causal role in early-onset familial Alzheimer's disease.

a protein most often identified by the acronym BACE. And in 2000, researchers offered compelling evidence that the presenilin proteins were, in fact, responsible for β -secretase activity. This evidence was a milestone in defining Alzheimer pathology, but many questions remained. Are other proteins involved in the production of A β ? What do presenilin proteins do in a healthy brain and how do mutations affect protein activity? Can scientists develop pharmaceutical treatments that target these proteins without disrupting other essential processes in the brain?

Researchers are investigating these questions on many fronts, and the Alzheimer's Association is providing

research grants to support these endeavors. Two research grant recipients who are contributing to this growing body of knowledge about presenilins are highlighted in the following paragraphs. Their work is helping the research community to construct a more complete picture of the role these proteins play in early-onset Alzheimer's and to understand molecular processes that may contribute to all forms of the disease.

SPOTLIGHT ON RESEARCH

John Hardy, PhD

In 1999, the Alzheimer's Association granted a two-year, \$200,000 Zenith Fellows Award to John Hardy, PhD, of the Mayo Clinic in Jacksonville, Florida. Hardy's research group is investigating whether the mutation of a presenilin gene results in a gain or loss of a protein's function. In other words, although the mutated genes are associated with increased levels of A β , it is not clear whether the mutations result in "overactive" or "underactive" proteins. This question is further complicated because researchers have observed at least 40 different mutated versions of the presenilin genes, and every mutation may not affect protein activity similarly.

In investigations with certain mutated versions of presenilin-1 genes, Hardy's group found evidence that mutations result in a loss of protein function. The researchers also observed that the loss of function caused an increase in a form of A β that is more likely to form plaques. Through ongoing work on the outcomes of mutated presenilin genes, they hope to discover how to target presenilin-1 for therapeutic interventions.

SPOTLIGHT ON RESEARCH

Jie Shen, PhD

Jie Shen, PhD, of Brigham and Women's Hospital in Boston, Massachusetts, received a three-year, \$180,000 research grant in 1999 to fund her group's investigation of both the normal and altered function of presenilin-1. Shen and her colleagues have studied mice that were genetically altered not to produce presenilin-1. The researchers observed that these mice did not develop normal brain cells. The evidence suggested that the protein is important in early stages of brain development when cells are becoming more specialized to carry out a particular brain function.

The researchers also studied mice that had a version of the presenilin-1 gene programmed to operate during development but to shut down in certain regions of the brain later in life. Shen's group observed that when the altered

presenilin-1 genes shut down, the levels of A β declined. They also noted that other important cellular functions—in which presenilins seemed to play a role during brain development—were not altered by the absence of presenilin proteins later in life. This detail is an important clue for researchers in determining whether it is "safe" to target presenilins for Alzheimer therapy.

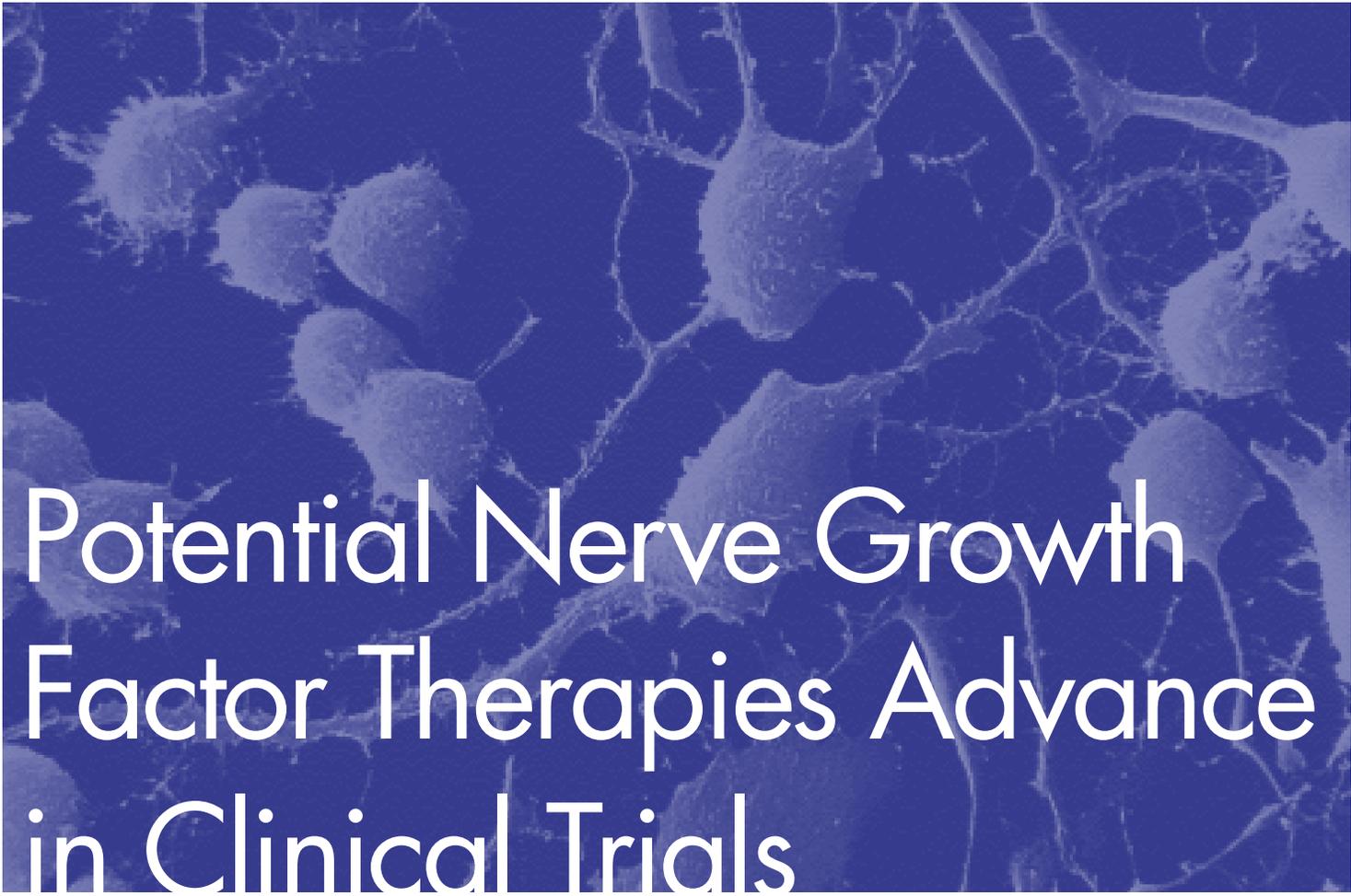
As researchers reveal more about how presenilins contribute to A β production, we will have a clearer understanding of the molecular processes of Alzheimer's. One of the next steps will test compounds that may inhibit presenilin protein activity. These investigations may lead to new drugs that can be tested in the laboratory, in animal studies, and in clinical trials. If this work brings about successful pharmaceutical treatments, we may, in years to come, be able to alter or slow the progression of Alzheimer's disease. ♦

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FDA Approves Fourth Alzheimer Drug

On February 28, 2001, the United States Food and Drug Administration (FDA) approved galantamine hydrobromide (Reminyl®), the fourth drug marketed specifically to treat symptoms of mild to moderate Alzheimer's. In clinical trials comparing galantamine to placebo (inactive treatment), participants receiving galantamine showed better results in measures of thinking and reasoning, daily

functioning, and behavior. Like other approved Alzheimer drugs, galantamine is a cholinesterase inhibitor. This class of drugs temporarily increases the brain's supply of acetylcholine, a nerve messenger chemical that becomes deficient in the Alzheimer brain as cell death progresses. For a fact sheet about galantamine or cholinesterase inhibitors in general, please call the Association's Contact Center at (800) 272-3900.

A blue-tinted microscopic image of nerve cells, showing various cell bodies and branching processes, serving as a background for the title.

Potential Nerve Growth Factor Therapies Advance in Clinical Trials

NERVE CELLS PRODUCE NERVE growth factors, proteins that regulate cell maturation during prenatal development and also play an important role in cell survival, repair, and regeneration during adult life. Because of their significance in cell maintenance and repair, these factors have attracted attention as potential treatments in Alzheimer's disease, stroke, spinal cord injury, and other neurodegenerative conditions.

Although nerve growth factors seem to hold therapeutic promise, getting them into the brain poses a special challenge. The factors themselves are too large to cross the blood-brain barrier, a biological shield that restricts passage of potentially dangerous molecules. Two experimental treatments that use different approaches to this problem have recently progressed to new investigational stages.

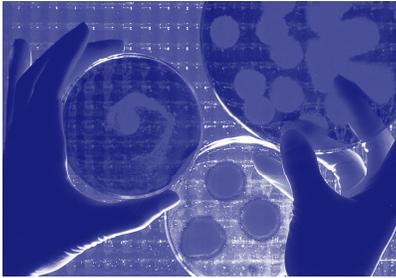
Stimulating production of growth factors

In the first advance, NeoTherapeutics, of Irvine, California, has begun recruiting participants for a new Phase II clinical trial of their experimental drug leteprinin potassium (Neotrofin®). Leteprinin is a small molecule that crosses the blood-brain barrier when taken by mouth as a liquid and, once in the brain, activates genes that produce nerve growth factors. In preclinical trials, leteprinin showed promise in treating animal models for aging, memory decline, and brain and spinal cord injury. Phase I trials enrolling small numbers of people offered preliminary evidence of the drug's safety and tolerability in humans.

In December 2000, NeoTherapeutics released results of a pilot U.S. Phase II trial enrolling 19 individuals with mild to moderate Alzheimer's who received

either a placebo (inactive treatment) or various doses of leteprinin. The researchers found that recipients of 500 or 1,000 milligrams experienced greater improvement in memory and judgment than those who received 150 milligrams. Based on this outcome and results of trials in other countries, NeoTherapeutics plans to focus their next clinical trials on the higher doses.

The new Phase II trial—the largest United States study to date—is enrolling about 500 participants with mild to moderate Alzheimer's at 52 locations nationwide. Although study centers are somewhat concentrated in Florida, there is a site convenient to most major cities. The 24-week protocol will assign 50 percent of participants to receive leteprinin and 50 percent to receive a placebo. Leteprinin recipients will begin treatment at 500 milligrams, escalate their



Researchers found that recipients of leteprinin who received 500 or 1,000 milligrams experienced greater improvement in memory and judgment than those who received 150 milligrams.

dose to 1,000 milligrams, then decrease it again to 500 milligrams if adverse reactions necessitate reduction. These adjustments will take place during the trial's first three weeks, with participants remaining on their assigned dose through the twelfth week. After that, all placebo recipients will switch to leteprinin, while a small percentage of drug recipients will be reassigned to the placebo group. The rest of the active treatment group will continue to receive the drug. No one will be able to continue taking leteprinin after the study's 24-week conclusion.

Individuals interested in enrolling will have to meet certain guidelines regarding their general health. People who are currently taking cholinesterase inhibitors (donepezil, rivastigmine, galantamine, or tacrine) are eligible to apply, but if accepted will have to discontinue those drugs for the duration of the study. The study also restricts use of certain other medications during enrollment.

For more information about the trial or to be considered for participation, please call the NeoTherapeutics clinical trials hotline at (949) 788-6700, extension 300. You may also request details on-line at http://www.neotherapeutics.com/clinical_trials.html. For

a fact sheet about leteprinin, please call the Alzheimer's Association Contact Center at (800) 272-3900.

Implanting genes

In the second milestone, doctors at the University of California at San Diego (UCSD) School of Medicine launched a Phase I gene therapy trial by implanting cells genetically modified to produce nerve growth factor directly into the brain of a 60-year-old woman with mild Alzheimer's. The modified cells were derived from the recipient's skin. She recovered well after the 11-hour operation, but it will take time to learn whether the treatment provided any benefit or if it caused any long-term side effects. The chief purpose of a Phase I trial is to determine if a treatment is safe.

Under the current study design, the Phase I trial will enroll seven additional participants. This initial stage of human testing builds on previous favorable results involving similar procedures on animals. In both monkeys and rats, implantation of modified cells producing nerve growth factor appeared to boost the numbers of functioning nerve cells and prevent cell death. The UCSD research team, led by Mark H. Tuszynski, MD, PhD, receives part of its funding from an Alzheimer's Association

grant. Further information about the trial is available at Tuszynski's laboratory's site on the Internet at http://obsidian.ucsd.edu/~tuszynski/clinical_study.htm. ♦



MEMORY WALK 2001

Take steps this fall to help 4 million Americans with Alzheimer's and their families by joining Memory Walk, the Alzheimer's Association's largest fund-raising event.

All funds raised go to local chapters to support community programs and services.

For more information about how to join this fun, inspiring event, call our Contact Center at (800) 272-3900 or log on to: www.alz.org/memorywalk.

Alzheimer's Challenges

Couples' Closest Ties



ALZHEIMER'S EFFECTS ON memory, reasoning, and behavior require caregiving families to make adjustments in virtually every area of their lives. For individuals who are caring for an impaired spouse, some of the most difficult changes involve intimacy and sexuality. Despite Alzheimer's profound impact on intimacy, few couples find information about this aspect of the disease readily available. In a study funded by the Alzheimer's Association, Linda M. Duffy, RN, MS, interviewed 38 people caring for Alzheimer spouses about the disease's effects on their sexual relationships. Although 80 percent of participants reported that their relationship had changed as soon as symptoms appeared, no participant was ever asked about these effects by a health care professional.

Edna L. Ballard, MSW, a psychiatric social worker at the Duke Family Support Program in Durham, North Carolina, has helped many Alzheimer caregivers cope with these sensitive and challenging issues. "Caregivers grieve as they watch their spouses

become shadows of their former selves," she says. "The most painful change brought about by this disease is the eventual disintegration of the characteristics and traits that previously defined the individual's personality and capacity for intimacy."

Finding your own way

In helping couples adapt to the inevitable changes that Alzheimer's brings to an intimate relationship, Ballard assures them that there is no single best approach. "A fundamental concept of all sexual counseling is that couples should feel comfortable with whatever works for them in the context of a loving relationship," she says. "The few studies that have been done about Alzheimer's and sexuality suggest that many couples experience a gradual, mutual fading of sexual interest as the disease progresses. But every couple is unique."

Ballard says that she has seen couples for whom the sexual connection gains in importance as the person with Alzheimer's loses the ability to join in other previously shared activities. In other cases, required role adjustments make it extremely difficult—and sometimes impossible—for a caregiver to retain sexual interest in a spouse. Some caregivers report that sheer exhaustion at the end of a long day robs them of interest in sex or any other physically strenuous activity. Others find that the need to help a spouse with toileting, bathing, and

other daily activities destroys romantic feelings by making them feel more like a parent than a lover.

Sensitive situations

One troubling situation may arise when a female caregiver remains interested in sex with a spouse who becomes a more hasty or less considerate lover than he was before Alzheimer's struck. "It is extremely important to realize that loss of sexual manners occurs as a result of the disease and not because someone has suddenly lost regard for his partner," Ballard cautions. "Alzheimer's erodes the capacity to remember the proper sequence in which to perform activities. Just as someone may try to put his pajamas on over his clothes, he may forget that thoughtful lovemaking involves preliminary stages." One strategy that may help counter such forgetfulness is for women to take a more active role than they may have assumed in the past. "With guidance," says Ballard, "a husband with memory impairment may be more than willing to participate in steps that he may not remember to initiate himself."

Another sensitive situation occurs when a person with Alzheimer's may fail to recognize a partner in intimate moments. Caregivers worry about whether they should consider their partners able to consent to sex under such circumstances. Says Ballard, "I encourage caregivers to be guided by nonverbal as well as verbal signals.

If a partner seems willing and able to enjoy the encounter, sex can provide a unique bond and closeness. The experience of that connection with a loving spouse can be very important even for a person with significant impairment. However, if a partner shows any fear or reluctance, a caregiver should respect that even if the partner does not directly refuse.”

Coping with persistence

A person with Alzheimer’s may also forget that the couple has just had sex and try to initiate another encounter. In some cases, sexual invitations can be repeated many times. According to Ballard, this is another situation with no single solution. “First, it is important for wives to realize that ‘no’ is an acceptable answer to excessively frequent requests. Many women of a certain age feel that it is their duty to make every effort to accommodate their husband’s wishes regardless of their own feelings. Current thinking supports a woman’s right to be guided by her own wishes and needs as well as those of her partner.”

A complicating factor for some caregivers is the worry that saying “no” to a persistent partner may trigger anger and agitation. In Ballard’s experience, some spouses may avoid confrontation through skillful use of delaying tactics. “Distracting your partner may help,” says Ballard. “For example, suggest

waiting until after the next meal, or television show, or some other shared activity. Your partner may have forgotten a request for sex by the time that activity ends.” If requests recur at night and interfere with adequate rest, a caregiver may need to consider sleeping separately to preserve health and energy.

Comfort and reassurance

Ballard and other researchers emphasize that persistent requests for sex may spring from a more general need for human contact and responsiveness. “Sometimes a sexual invitation really expresses a need for reassurance through loving touch,” says Ballard. “It’s crucial to remember that people with Alzheimer’s remain worthy of warmth and respect even though their behavior may be challenging—they may not bathe, they may act self-absorbed or ornery, or otherwise put us off.” By offering frequent pats, hand-holding, help with range-of-motion exercises, or even applications of hand lotion, caregivers may provide enough touch to stave off persistent requests for sexual intimacy.

Studies suggest that inappropriate sexual behaviors—such as undressing in public or requesting sex from strangers—are rare in people with Alzheimer’s. For example, in Duffy’s study of 38 caregiving spouses, only one interviewee reported

public sexual impropriety. One male caregiver and two females reported increased frequency of requests for intercourse. None of the individuals with Alzheimer’s asked spouses to participate in activities that were new to their usual lovemaking behavior. ♦

*These and related issues are discussed in more detail in *Sexuality and the Alzheimer’s Patient* by Edna L. Ballard and Cornelia M. Poer, available from the Duke Family Support Program at (919) 660-7510. The \$10 price includes postage and handling. For information about resources in your community, contact your local chapter of the Alzheimer’s Association at (800) 272-3900.*

“Sometimes a sexual invitation really expresses a need for reassurance through loving touch.”

—Edna L. Ballard, MSW



Q • What is the difference between early-onset and late-onset Alzheimer's disease?

A • The first medical literature about the disorder that we now call Alzheimer's disease was published in 1907. In that research, Alois Alzheimer, a German neuropathologist, described the plaques and neurofibrillary tangles that are now recognized as the hallmarks of the disease. This initial study was based on the autopsy of a woman with dementia who died in her mid-50s. Because the plaques, in particular, had not been identified in autopsies of older people with dementia, the coexisting brain abnormalities were believed to be a sign of a rare disorder that only strikes younger adults. Also, memory loss and dementia in old age were probably thought to be normal at the time. It was not until the 1960s that researchers began to identify these same neuropathologic hallmarks in the majority of dementia cases among older people. Scientists now agree that Alzheimer's is the leading cause of dementia in older adults and that it rarely strikes younger adults.

The terms *early-onset* and *late-onset* are artificial designations rather than forms of the disease. The age that is most often used to distinguish early-onset and late-onset cases is 65, but not all researchers agree on that number. It is accurate to note, however, that the majority of Alzheimer cases occur in individuals over the age of 65 and that the prevalence of the disease increases with age. Alzheimer's affects a small percentage of individuals under the age

of 65, usually people in their 40s, 50s, or early 60s.

Several studies have investigated clinical differences between early-onset and late-onset Alzheimer's, but generally these efforts have shown no substantial difference between the pathology or symptoms in the two groups. There is some evidence, however, that the disease progresses more quickly in early-onset cases than in late-onset cases.

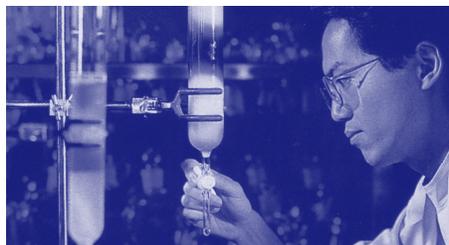
One important fact about age of onset is that inherited forms of the disease usually have an early onset. Many people with early-onset Alzheimer's have inherited a mutated version of one of three genes, located on chromosomes 21, 14, or 1. Virtually any individual who inherits one copy of such a gene will develop Alzheimer's, if he or she lives long enough. While genetic cases usually have an early onset, early-onset cases cannot always be attributed to genetics.

A mutation of the APOE gene on chromosome 19 is associated with a susceptibility to late-onset Alzheimer's. There are several versions of this gene, including APOE- 2, APOE- 3, and APOE- 4. People who inherit one or two copies of APOE- 4 have a greater risk of developing Alzheimer's than people with other forms. This risk factor does not mean that the gene causes the disease. While at greater risk, an individual with two copies of APOE- 4 may never develop Alzheimer's, and only about 50 percent of the people with late-

onset Alzheimer's carry APOE- 4. These genetic differences do not necessarily point to a conclusion that early-onset and late-onset Alzheimer's are distinct diseases. Instead, these differences reveal that the conditions that promote Alzheimer's are varied and complex. There may be more than one path to the disease process that leads to the accumulation of plaques and neurofibrillary tangles that results in the destruction of brain cells.

Perhaps the most important difference between early-onset and late-onset Alzheimer's is the impact age may have on the individual with the disease and on the family. Regardless of when Alzheimer's strikes, it can be devastating. When the individual with the disease is still relatively young, however, the impact may be more complex. A person who develops the disease early in life is likely to be working and may be the primary income provider for the family. He or she may have heavy financial commitments—a child's college tuition or a mortgage—that are often not confronting older individuals with Alzheimer's. The family may also face challenges in providing care, because most services and care facilities are designed primarily for the needs of older people. Although programs, support groups, and care facilities have begun to meet these challenges, the burden of care often associated with Alzheimer's disease is only increased when the disease strikes an individual at an early age. ♦

Rachelle Doody, MD, PhD, is the Effie Marie Cain Professor in Alzheimer's Disease Research and associate director of the Alzheimer's Disease Research Center at Baylor College of Medicine in Houston, Texas.



FIGHTING BACK...SPEAKING OUT

[CONT'D FROM PAGE 1]

doubling of funding for Alzheimer's research—for a crisis situation.

Wagenaar testified before a Senate Appropriations Committee; was featured in a segment on *NBC Nightly News*; and was a panelist at the Forum session *Advocacy: In My Own Voice*. He spoke of the burden Alzheimer's had placed upon his wife of 41 years, Darlene, whose work role has expanded from part time to full time.

The effects of early-onset Alzheimer's may be especially profound for spouses. Most people with Alzheimer's disease continue to live at home even as the disease progresses over an extended period. As a result, a spouse may feel loss because of the changes the disease brings to the marriage, including sexual relations. He or she may take on the lion's share of managing the household and the affected person's care.

That was exactly the case with Bob Nichols, a former prosecuting attorney from Green Bay, Wisconsin, who was diagnosed in 1997 at the age of 65. Nichols participated in the plenary session *Alzheimer Advocacy—A Prescription for Change*. Unable to practice law, Nichols now works for his wife of 41 years, Dennie, who helps to protect the safety and health rights of the elderly.

"Our relationship has changed," Nichols noted. "As the chief family breadwinner and a caregiver, she has had to become more assertive." Still, the father of three notes that he and Dennie are fortunate to have avoided the financial struggles common to others in their situation.

Wagenaar, too, has been fortunate. His employer has allowed him to continue working, and his wife is now employed on the same shift. He continues driving, with Darlene at his side.

The Big Sioux chapter of the Alzheimer's Association was a tremendous help. Said Wagenaar: "One of the [Association] people came to my work to talk to everyone about Alzheimer's disease. They helped my coworkers understand more about the disease and how they could help keep me safe at work." He emphasized another challenge facing younger Alzheimer's individuals. Because of their seemingly healthy appearance, they often find it difficult to obtain an accurate diagnosis. Wagenaar explained that when he first visited his physician, "I was given a complete physical, but the exam didn't find anything wrong with me."

Early-onset Alzheimer's is receiving more attention from various Alzheimer's Association chapters. Early-stage support group programs allow affected persons and their caregivers to meet with others experiencing similar problems. The programs offer emotional support, along with practical information about the disease, daily management, and legal/financial issues.

Individuals affected by early-onset Alzheimer's continue to speak out. During his visits on Capitol Hill, Nichols renewed acquaintances with people he had met during his legal career. His message to all was the same: Immediate doubling of Alzheimer research funding, from \$500 million to \$1 billion, would cost only a fraction of many budget initiatives, but would help keep people out of nursing homes and dramatically alleviate Medicare and Medicaid costs.



Bob Nichols, a former prosecuting attorney who has Alzheimer's, speaks at the Public Policy Forum.

Nichols was following his own advice, given during the plenary session: "Be an advocate, just as I was in the courtroom. Tell your congressperson politely—but forcefully—to listen."

With three children and nine grandchildren, Wagenaar hopes to ensure that no one else in his family is afflicted. He knows that at least three genes have been associated with early-onset familial Alzheimer's. "While I am still able, I will speak out about Alzheimer's disease so that my children, grandchildren, and others can be spared from this devastating disease," he said.

Wagenaar concluded: "We are in a race against time and if we don't find the answers soon, Alzheimer's will be an epidemic." ♦

Association publications Living with Early-Onset Alzheimer's Disease (ED206Z) and Understanding Early-Onset Alzheimer's Disease (ED432G) provide valuable information about coping with early-onset Alzheimer's. To order a copy, please call (800) 272-3900.



New Directions in Alzheimer Care

More than 200 Alzheimer experts will present the latest findings in care and clinical research on July 15-18 at the 10th National Alzheimer's Disease Education Conference in Chicago. This year's conference theme, *New Directions in Alzheimer Care*, will focus on groundbreaking directions in four key areas: meeting society's changing demographic needs as Americans grow older; providing innovative programs and practices to serve the holistic needs of persons with dementia; building and supporting a workforce trained in providing dementia care; and enhancing systems of care so that affected individuals and their families are connected to appropriate services.

The conference includes three plenary sessions and dozens of education sessions geared to each attendee's needs. A poster display will highlight innovative Alzheimer's research and programs taking place nationwide. Participants may also view product and service displays of more than 100 exhibitors.

There will be many opportunities to network, both during the conference and at a new special event, a Lake Michigan boat cruise. During the evening sail, you will be able to enjoy hors d'oeuvres, talk with other attendees, and take in views of Chicago's skyline. While there is no additional fee for the cruise, tickets are required so early registration is necessary.

Back by popular demand, morning and afternoon preconference intensive sessions will be held on **Sunday, July 15**, at a cost of \$75 for each half-day session. Topics include improving long-term care staffing, providing comfort care at the end of life, measuring quality, and ethical dilemmas in Alzheimer's. To ensure participation, registration must be received on-line no later than **Wednesday, June 20**.

The cost of the conference is \$400. Register on-line no later than **Wednesday, June 20** at <http://www.alz.org/newdirections.htm>. After June 20, participants must register on-site for a fee of \$450 per person. ♦

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