

Historic Conference Inspires Optimism

International Scientists Share Pivotal Research

Alzheimer's disease garnered headlines in major media outlets worldwide in July. Sparking this coverage were the exciting studies announced during the *Pivotal Research* program of World Alzheimer Congress 2000—the largest event ever on Alzheimer's disease, attracting nearly 5,000 attendees worldwide.

In *Pivotal Research*, some 3,000 scientists immersed themselves in topics on virtually every aspect of Alzheimer's and similar neurodegenerative disorders. Program faculty included Virginia M.-Y. Lee, PhD, and her husband John Q. Trojanowski, MD, PhD, who in 1998 received the Alzheimer's Association's first \$1 million Pioneer Award for Alzheimer's Disease Research. Said Lee, "*Pivotal Research* may be a watershed—marking the dividing line between studying Alzheimer's disease and really treating it."

In one presentation that attracted wide attention, Dale Schenk, PhD, of Elan Pharmaceuticals, reported encouraging preliminary results from the company's Phase I clinical trials of its "Alzheimer vaccine." In development under the investigational name AN-1792, the vaccine is a synthetic form of the protein fragment beta amyloid 42 ($A\beta_{42}$). This fragment makes up most of the amyloid plaques that are a hallmark Alzheimer abnormality. Schenk and his colleagues reasoned that inoculation with $A\beta_{42}$ might stimulate the immune system to recognize and attack the pathological accumulations. The team's first promising results, reported in July 1999 in the journal *Nature*, showed that injections of AN-1792 prevented formation of plaques in the brains of young mice genetically altered to produce human amyloid. Inoculation also reduced the number of existing plaques in older mice.

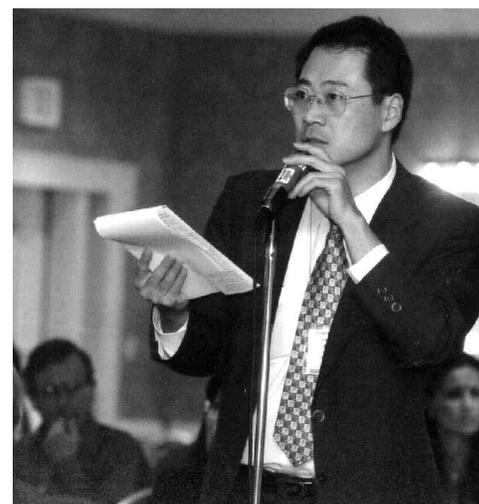
Elan is now conducting Phase I trials in the United States and the United Kingdom to assess the vaccine's safety and tolerability in human recipients. The U.K. trial will enroll 75 to 80 participants with mild to moderate Alzheimer's, who will each receive three doses in increasing strengths. In the just-completed U.S. study, researchers administered a single dose in one of three strengths to 24 participants with mild to moderate Alzheimer's.

Although results are not yet final, initial evidence suggests that the vaccine is safe and well tolerated. One concern, says Schenk, is that by provoking a reaction to one of the body's own proteins, AN-1792 could stimulate an autoimmune reaction in which the body mobilizes a wholesale assault on its own tissues. Autoimmune reactions underlie such conditions as allergies, rheumatoid arthritis, and juvenile diabetes. But Schenk says that the fact that $A\beta_{42}$ accumulates outside cells somewhat reduces the likelihood of an autoimmune response, and so far there is no evidence that one is occurring.

Another key question is whether

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The world's top Alzheimer scientists exchange and debate research findings presented at World Alzheimer Congress 2000 in July.



Memory gardens are designed with wide paths, nontoxic and fragrant plants, and a circular walkway with one entrance to prevent wandering.

Memory Gardens Stimulating for People with Alzheimer's

On a sultry, summer day in Macon, Georgia, the Alzheimer's Memory Garden looks like a typical beautiful public garden. But in some subtle ways, it is not. Designed specifically with the safety and needs of the person with Alzheimer's disease in mind, the memory garden is one of eight public therapeutic gardens created as part of the American Society of Landscape Architect's Alzheimer's Garden Project.

"The goal of the Alzheimer's Garden Project is to provide a safe, nurturing outdoor sanctuary where people with Alzheimer's disease can interact with nature, walk, picnic, and enjoy other outside activities," says Mary Gatti, executive director of the Central Georgia Chapter. Betsy Brawley, a former national board member of the Alzheimer's Association, and Jack Carman, a landscape architect, spearheaded the project. Studies have shown that the outdoor environment can enhance the ability of a person with Alzheimer's disease to function mentally and physically.

Dedicated in July 1999 and located on a half-acre plot in Macon's oldest and largest park, the garden has one entrance and a circular walkway—instead of a network of paths—to prevent the person with Alzheimer's from wandering. The walkway is slip-resistant and wide enough for a wheelchair or for two people to walk side by side. Benches along the walkway are placed some distance from trees to reduce shadows, which can frighten Alzheimer patients. The garden's hundreds of plants and herbs are nontoxic, and some plants, such as gardenia and jasmine, were chosen for their distinctive aromas that stimulate the memory. The garden also features bird feeders, a birdbath, and wind chimes. Alzheimer patients and their caregivers have to walk only a few feet from a parking lot to the garden, which also is close to a restroom.

Cox Communications, Nickelodeon Big Help, Habitat for Humanity, and other organizations, including city and county agencies, and the local master gardener club donated either funds, garden materials, or volunteers toward the project. #

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For more information on Alzheimer's disease and the Association or to be placed on the *Advances* mailing list, call (800) 272-3900. Information is also available via the Internet at <http://www.alz.org>.

Letters should be addressed to Michele Pellissier, Editor. Faxes can be sent to (312) 335-1110 and e-mail to michele.pellissier@alz.org. *Advances* does not publish unsolicited poems or short stories or accept advertisements.

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‘Validation Method’ Offers Significant Benefits to People With Alzheimer’s Disease and Their Caregivers

Until recently, it was common for most caregivers to try to stop the person with Alzheimer’s disease who constantly pounds his hand into his fist or to correct the individual who insists that it’s 1939 and Roosevelt is president.

But two experts reported at World Alzheimer Congress 2000 that there are significant benefits to allowing these types of behaviors to continue and to viewing them as means of communication. Referred to as the “validation method,” this concept, pioneered by Naomi Feil, MSW, ACSW, more than 20 years ago, is experiencing a surge in popularity across the country.

According to Rita Altman, RN, of Country Meadows Retirement Communities in Hershey, Pennsylvania, traditionally caregivers attempted to redirect or distract unconventional behavior. “It was much easier to put a Band-Aid on the problem,” said Altman. “In the past, if a person repeatedly asked to see his mother who has been deceased for 30 years,

we may have tried to change the subject or tell him that his mother is running an errand and will be back soon. But everyone has an inner wisdom. Even those in advanced stages of Alzheimer’s disease know when someone is lying to them,” she explained. “Through validation, Feil has taught us that the caregiver might instead encourage the person with Alzheimer’s disease to talk about his mother. By listening and interacting with empathy, the caregiver can validate the person’s feelings and help him express the feelings he may be having trouble communicating,” Altman said.

The validation method links behaviors with unmet human needs. “All human beings have three basic needs: to express themselves, to be loved or feel secure, and to be productive or useful. People with Alzheimer’s disease often must look to untraditional means to express and fulfill these needs. The man who constantly pounds his fists into his hand may have been a successful carpenter earlier in life. Validation helps us understand that he is reliving that work behavior

and finding a purpose,” said Altman.

According to Altman, there are significant benefits to both caregivers and patients through the use of validation. People with whom the validation method is used:

- Display more social control
- Increase their verbal and nonverbal communication
- Cry, pace, or hit less often
- Experience reduced levels of anxiety
- Establish dignity

For caregivers, the validation method helps reduce frustration and burnout, and in health care facilities, has decreased employee turnover where validation therapy is used.

“Validation can be a useful communications tool for family caregivers and health care professionals alike,” said Sam Fazio, director of education and training for the Alzheimer’s Association. “When done correctly and with compassion, this method can be a very positive and rewarding experience for all involved.” *ff*

Estrogen and Alzheimer's: Examining the Evidence

Studies exploring the benefits and risks of hormone replacement therapy—including whether it may delay or prevent Alzheimer's—have yielded conflicting and confusing results. Recognizing the importance of resolving this confusion, the National Institutes of Health launched Women's Health Initiative (WHI) in 1991. WHI has enrolled more than 161,000 women in investigations that seek to clarify the risks and benefits of hormone replacement therapy (HRT) and answer other important questions about women's health.



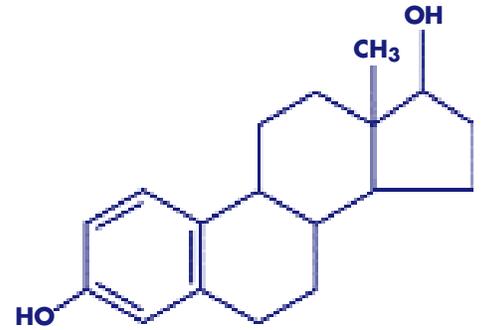
In WHI's HRT trial, more than 27,000 women have been randomly assigned to receive HRT or a placebo (inactive treatment). The

study is double-blinded—neither researchers nor participants know who is assigned to each group. In the active treatment group, women who have had a hysterectomy receive estrogen and those who still have a uterus receive estrogen combined with progestin. (Treatment with estrogen alone is associated with an increased risk of cancer of the uterus, and addition of progestin is thought to reduce that risk.) Participants will be followed for 8 to 12 years to determine whether HRT reduces the risk of heart disease and bone fractures without increasing risk of breast or uterine cancer.

The Women's Health Initiative Memory Study (WHIMS), an ancillary investigation of the HRT study, will explore the intriguing possibility that replacement estrogen may help preserve mental function as women age. Several small studies have offered tantalizing hints that women taking HRT experience a reduced risk and delayed onset of dementia. However, these small studies were all observational—researchers drew conclusions by examining participants' preexisting behaviors rather than by randomizing them to an active treatment or placebo.

Funded by Wyeth-Ayerst Laboratories, WHIMS has enrolled 7,500 HRT study participants who will undergo annual screening with a "mini-mental" examination. Women who score below a designated cutoff will receive more thorough testing. By comparing the incidence of dementia that develops in women receiving HRT and women receiving a placebo, the researchers expect to clarify the role of hormone therapy in preventing dementia.

According to Laura Coker, PhD, about 450 WHIMS participants so far have scored below the screening cutoff and undergone more detailed evaluation. Coker is assistant professor in the Department of Public Health Science's Section on Social Science and Health Policy at Wake Forest University Baptist Medical Center, the coordinating center of the WHIMS study. Coker observes, "As in other clinical trials involving people with



dementia, WHIMS will rely heavily on caregivers to provide transportation and act as informants for women who become impaired as the study progresses. We investigators are continually inspired to see how study participants, their friends, and their caregivers will give of their time to shed light on these issues that are so important to all women." Results of WHIMS are expected in 2005.

Another study called PREPARE (PREventing Postmenopausal Memory Loss and Alzheimer's with Replacement Estrogens) is investigating whether HRT can prevent or delay Alzheimer's in women with a parent, sibling, or child affected by the disease. If you would like more information about PREPARE, which is still recruiting participants, please call (800) 272-3900 to request an Alzheimer's Association fact sheet. You may also contact PREPARE directly by calling toll free (877) DELAY-AD or by visiting the Web site at <http://delay-ad.org>.

Estrogen has also attracted interest as a potential treatment for Alzheimer's. However, a study published by Ruth A. Mulnard and her colleagues in the February 23, 2000, issue of the *Journal of the American Medical Association* provided strong evidence that estrogen does not improve memory, reasoning, or judgment for women who already

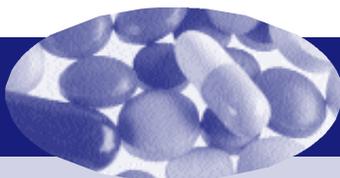
have mild to moderate Alzheimer's. Coker says, "Although this study was small, it was well-designed and its conclusions were clear—the active treatment group experienced no benefit. Many experts consider these results definitive." But Coker cautions that the outcome need not diminish interest in estrogen as prevention—

in many diseases, preventive strategies are entirely distinct from effective treatments. Ongoing research is also investigating estrogen as a potential enhancement to other Alzheimer drugs. A clinical trial sponsored by Pfizer, the manufacturer of donepezil (Aricept®), is exploring whether combined treatment with estrogen and

donepezil may offer greater benefit to women with mild to moderate Alzheimer's than treatment with donepezil alone.

For a fact sheet about the donepezil-estrogen study, which is also still recruiting, please contact the Association at (800) 272-3900. **ff**

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Drug Updates

Janssen Pharmaceutica announced in July that the company's new Alzheimer drug galantamine (Reminyl®), approved by Sweden in March, had won approval in the rest of the European Union (EU) as well as Iceland and Norway under EU's pharmaceutical reciprocity agreement. The company predicts EU availability by late 2000. Galantamine was submitted for U.S. approval in late 1999, received an "approvable" letter in August 2000, and could be cleared for U.S. use this year. The drug increases action of the neurotransmitter acetylcholine in the brain in two ways—by inhibiting acetylcholinesterase, an enzyme that breaks it down, and by stimulating certain nerve cell receptors to respond more strongly to it.

Also in July at World Alzheimer Congress 2000, Elan Corporation announced initial favorable results of a Phase I clinical trial of its investigational "Alzheimer vaccine," AN-1792. Preliminary analysis of a U.S. study in 24 people suggests that the vaccine is safe and well tolerated. A second Phase I trial is under way in the United Kingdom. In animal studies published in a July 1999 issue of *Nature*, AN-1792 prevented amyloid plaques from forming and reduced numbers of existing plaques in the brains of mice genetically engineered to mimic the human plaque formation that characterizes Alzheimer's. If final Phase I results hold up, Phase II trials of AN-1792's effectiveness in human subjects could begin by late 2001.

Ongoing Phase II trials are assessing the effectiveness of leteprinim potassium (also known as AIT-082 and Neotrofin®) in repairing and regenerating nerve cells in people with mild to moderate Alzheimer's. In preclinical studies, leteprinim showed promise in restoring nerve function in animal models of aging, memory decline, and brain and spinal cord injury. Phase I data indicated that the drug is safe and well tolerated. Phase II results are due in late 2000, and a large multicenter Phase III study could begin as early as mid-2001.

Ongoing Clinical Drug Studies

Drug studies currently recruiting participants with Alzheimer's disease include:

- Donepezil (Aricept®) and Estrogen
- Melatonin
- Estrogen

A study recruiting individuals with mild cognitive impairment:

- Memory Impairment Study

To obtain information about these studies, contact your local chapter or call (800) 272-3900 and ask for the "drug fact sheets."



End-of-Life Care

MAKING INFORMED CHOICES

Starting September 10, a four-part television series about end-of-life issues will debut on public broadcasting stations nationwide. Hosted by journalist Bill Moyers, *On Our Own Terms: Moyers on Dying* will focus on overcoming fear of death, managing physical and psychosocial pain, controlling how and where we die, and looking at how new models of improved care could be incorporated into the medical system.

For the past year, Moyers and his staff have been spreading the word about the series to generate discussion about dying. Now that many baby boomers are caring for their parents and have had to turn their attention to end-of-life care, the issue has worked its way into the social psyche. “We are just culturally waking up to the ability to talk about dying,” says Daniel Tobin, MD, palliative care physician and director of the Life Institute/Veterans Administration Healthcare Network in Albany, New York. “It’s the last social taboo—children talking to their parents about dying.”

Adds Julie Johnson, program director for the Oregon Trail Chapter of the Alzheimer’s Association: “Boomers want to be empowered with the information to make choices so that they

can have control over the end of their lives and those of their parents.”

So far, 68 Alzheimer’s Association chapters are using the series’ companion discussion guides to generate discussion among their support groups around end-of-life issues, a subject that many families have yet to come to grips with. “Alzheimer families are moving into uncharted territory, and many are unprepared for the dramatic changes in care at the end of life,” Johnson says. “Our chapter offers a class, and we teach members how to advocate for their loved one’s health because decisions have to be made regarding who is going to provide end-of-life care.”

End-of-life care issues for the Alzheimer patient

One frustration for families caring for someone with Alzheimer’s is determining if that individual is at the end stage of the disease. People are often confused about what end stage dementia looks like because it can vary depending upon the person, says Melanie Chavin, program director for the Greater Chicagoland Chapter.

For the Alzheimer patient, the end-life stage is no longer compared to that of an individual with an acute

condition, such as cancer. Caregivers often need to know what questions to ask the doctor, treatments to administer, and the consequences of those treatments. “The individual loses weight, often is not responsive, and requires more around-the-clock care,” Johnson says.

The end stage of the disease is characterized by a loss of virtually all cognitive and functional capabilities, says Emile Franssen, MD, associate medical director of the Aging and Dementia Research and Treatment Center at New York University. On the basis of ongoing research, Franssen is convinced that this state in Alzheimer patients is not necessarily the outcome of the disease process, but that it results in part from the effects of deconditioning and sensory and emotional deprivation. The key to slowing the progression to this state is to keep the patient functional in all stages of the disease. “This deterioration can be slowed through physical, mental, and emotional stimulation,” he says.

Because the person may no longer be able to communicate, caregivers have to be adept at assessing whether the individual is in pain. This is not only an issue for familial caregivers but for

professionals as well. “Many Alzheimer patients have untreated pain,” says Jan Dougherty, project director for the Arizona Chapter. “Comorbid conditions can be a source of some of the pain.”

Professional and familial caregivers can look to clues, such as facial expressions or how the body is placed, to determine if the person is in pain or discomfort, Dougherty says. “If someone has been sleeping or lying in the same position for two hours, it’s likely that they are experiencing some discomfort.”

such as tube feeding, can worsen the patient’s condition,” she says. “You have to be patient with the person with Alzheimer’s and try different ways of feeding until one works.”

Hospice services are underutilized. By the time, the individual reaches the end stage, their families are mentally, physically, and financially taxed. Many will opt to place their loved ones in a nursing home, unaware that hospice can be a suitable alternative, says Marks, whose chapter has had a relationship with a local hospice for nine years. The emphasis of hospice is

them. Physicians sometimes are reluctant because hospice primarily accepts those individuals who will die within six months, and it can be difficult to determine if the Alzheimer patient has entered the late stages of the disease. Furthermore, interventions can prolong the individual’s life in the late stages. For people with Alzheimer’s, it can sometimes be difficult to determine how long they will live in the late stage of the disease. “The end-of-life stage is longer, so the current hospice model does not fit the course of dementia,” Johnson says. “With hospice, sometimes individuals with Alzheimer’s will get care in the last two weeks that they needed in the last year.”

“ALZHEIMER FAMILIES ARE MOVING INTO UNCHARTED TERRITORY, AND MANY ARE UNPREPARED FOR THE DRAMATIC CHANGES IN CARE AT THE END OF LIFE”

—JULIE JOHNSON
ALZHEIMER’S ASSOCIATION

Sometimes Alzheimer patients are in unnecessary pain because professionals are reluctant to administer medication for fear of giving too much, even though the individual is about to die. “Why would you worry that someone who is about to die will become addicted?” Dougherty asks. “The focus should shift to making that person comfortable during their remaining days of life.”

Because the patient can no longer swallow, hospitals may resort to tube feeding when slow spoon feeding would work better,” says Jean Marks, associate executive director of the New York Chapter. “Interventions,

to provide palliative care or keep the patient physically, mentally, and emotionally comfortable until death. Medicare also covers hospice care.

“If it’s a good hospice, the staff will pay a huge amount of attention to the patient and keep trying to provide comfort,” Marks says. “Sometimes when well-trained hospice staff go into the home, they educate the family caregiver about good care, and this can lead to improvements in the patient’s health.”

In some instances, families may not be aware of hospice because their loved one’s physician may not refer

Still, some hospices are taking steps to adapt their model to the Alzheimer patient, and physicians are working to develop a list of factors to determine if the individual with Alzheimer’s has entered the late stage. Several years ago, the New York City Chapter worked with some physicians and staff of the Jacob Perlow Hospice of the Beth Israel Medical Center to develop prognosticators for determining end-stage Alzheimer’s.

But for end-of-life care to improve for the Alzheimer patient, education needs to be done across the board—among families and health care professionals. “We need to train people to understand how to be more sensitive to the needs of the individual with Alzheimer’s,” says Sue Hamm, executive director of the Southwest Georgia Chapter. **#**

People with Alzheimer's and Caregiver Connect through Web Communities

Do you feel as if you are going through this disease alone? You don't have to anymore. Two Alzheimer communities on the Alzheimer's Association Web site can help you connect with people who are going through the same things you are.

If you have Alzheimer's, go to the People with Alzheimer's community at <http://www.alz.org/people/share/>. You can talk with other people who have the disease and are facing similar situations. Participants in the community are discussing a variety of issues including early-onset Alzheimer's, genetics of the disease, and feelings related to dealing with the disease.

"Many of us with early-stage Alzheimer's find special value in writing as a form of creative self-expression and communication because it does not depend on speed and short-term memory," says Morris Friedell, diagnosed with Alzheimer's disease in 1998 at the age of 58. "It's great that the Alzheimer's Association has set up a Community Circle for people with Alzheimer's on its Web site. I'm hopeful that more and more patients will participate."

A separate community is available for caregivers wishing to share their experiences, learn, and receive support from others. The Web community for caregivers can be found at



<http://www.alz.org/caregiver/share/>. Caregivers in the community are discussing a variety of topics, including long-distance caregiving, financial fears, legal issues, and activities for people with Alzheimer's disease. **#**



Register On-Line for Memory Walk

Helping Alzheimer families in your community just became easier. You can now register or donate on-line for your local chapter's Memory Walk on the Alzheimer's Association's Web site.

First go to the page <http://www.alz.org/whatsnew/memwalk.htm> and select the name of your local chapter, or type in your zip code to locate the chapter nearest you. You will then see a list of walk sites, dates, start times, walk distances, registration fees (where applicable), incentive/prize information, and a brief event descriptions. If you wish to register on-line, you will have to approve the waiver and then provide your name, address, and credit card information. You can also register for Memory Walk by calling your local chapter or (800) 272-3900.

Memory Walk, held every fall, is the largest national event aimed at raising money to fund vital programs and services such as help lines, support groups, and educational events. In 1999 more than 150,000 walkers participated in Memory Walk nationwide, raising \$17.5 million. **#**

What Do You Do When a Loved One Won't Go to the Doctor?

Convincing someone to seek a diagnosis of Alzheimer's is one of the most difficult challenges that families can face. The person experiencing memory loss may become defensive or withdrawal socially in order to "cover up" what is happening. Spouses often help hide a loved one's symptoms from family members as well.

We want to hear from you!

- Do you have helpful tips for convincing someone who may have Alzheimer's to seek a diagnosis?
- How have you handled a situation where a spouse or caregiver is covering up a loved one's memory problem?

- If you are experiencing memory problems, what is preventing you from seeking help?

Your experiences will be incorporated into the next issue of *Advances*. Send your feedback via e-mail to michele.pellissier@alz.org or via mail to:

Michele Pellissier
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Alzheimer's Association Position on Driving and Alzheimer's Disease

The Alzheimer's Association is concerned about the safety of persons with Alzheimer's disease and those around them but does not believe a diagnosis of Alzheimer's disease automatically means a person is incapable of driving.

The Association does not favor a requirement in California that physicians inform motor vehicle authorities when a person is diagnosed with Alzheimer's disease. The Association is concerned that an automatic link between a diagnosis of Alzheimer's and loss of driving privileges could discourage people from seeking a diagnosis and

hinder effective treatment and care early in the disease process.

The Alzheimer's Association supports the statement by the American Academy of Neurology that people with mild Alzheimer's disease should be discouraged from driving but that the final determination should be made with full involvement of the person with the disease, the caregiver, and the health care provider. If there are still some doubts as to the person's ability to drive safely, the Academy suggests that he or she could be referred to a qualified driving evaluation process.



The Association supports the development of further research to design tests that will better determine driving capabilities of individuals with cognitive impairments. **ff**

Q & A presents answers to your research or caregiving questions from leading professionals in the field of Alzheimer's disease. In this issue, a physician and a genetic counselor discuss Alzheimer genetics.

Q: Does having a parent with Alzheimer's increase my chances of developing it? If so, are there tests that clarify my risk?

A: Scientists recognize two types of Alzheimer's disease: familial (multiple family members are affected) and sporadic (only one member has the disease). Experts further distinguish between early-onset Alzheimer's, which strikes between the ages of 30 and early 60s, and late-onset disease, which is diagnosed in people who are at least 65. Early-onset, familial Alzheimer's is strongly hereditary. Late-onset Alzheimer's, the common form, has a subtler inheritance pattern.

The average worldwide lifetime risk of developing any type of Alzheimer's is about 5 percent by age 65, rising to 20 to 40 percent by age 85. Having a parent or sibling with Alzheimer's approximately doubles the average risk. The risk continues to increase as the number of affected relatives rises, and having more than one affected sibling appears to cause the greatest increase.

Risk increases because children, parents, and siblings may share certain genes. Certain forms of genes are "deterministic"—having that form virtually guarantees a certain outcome. Other genes are "susceptibility" genes—they raise the likelihood of an outcome but do not ensure it.

Scientists have so far identified four genes that influence the risk of developing Alzheimer's—one associated with late-onset disease and three with early-onset, familial cases. The late-onset gene, which codes a cholesterol-processing protein called apolipoprotein E (ApoE), is a susceptibility gene that occurs in three significant forms—ApoE-ε4, ApoE-ε3, and ApoE-ε2. Everyone inherits a copy of ApoE from each parent.

People with one copy of ApoE-ε4 have an increased risk of Alzheimer's, and people with two are at even greater risk. However, not everyone with two copies develops Alzheimer's, and many people with the disease have none. Experts believe that several other unidentified genes also

influence the likelihood of developing Alzheimer's disease. Environmental factors may also be involved.

The three genes implicated in early-onset, familial Alzheimer's code proteins called presenilin 1, presenilin 2, and amyloid precursor protein. The forms of these genes that lead to Alzheimer's are deterministic—virtually everyone who has them develops the disease. If a parent has one of the known mutations (changes) in these genes, each child has a 50 percent chance of inheriting the mutation.

Tests are available that can determine whether a person carries ApoE-ε4 or one of the early-onset, familial mutations, and many people with affected relatives wonder if they should be tested. Most experts do not recommend testing for ApoE-ε4 because ApoE status is not predictive. Having one or two copies of ApoE-ε4 suggests an increased risk—but not a certainty—of developing Alzheimer's, and lacking ApoE-ε4 does not protect against it.

Most experts also agree that genetic testing may make more sense for people in families affected by early-onset, familial Alzheimer's. Researchers recommend that testing occur at a major academic center and that individuals receive genetic counseling as part of the process. Genetic counselors help people explore emotional and legal implications as well as scientific and technical issues before testing proceeds; after testing is completed, they explain and interpret results and help people accept the outcome.

Richard Mayeux, MD, MSc, is Gertrude H. Sergievsky Professor of Neurology, Psychiatry, and Public Health and the co-director of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University. Jennifer Williamson, MS, is a certified genetic counselor at the Taub Institute. #

Send us your questions...

If you have a question you'd like to ask about Alzheimer research or care, please mail it to: Alzheimer's Association, 919 North Michigan Avenue, Suite 1100, Chicago, Illinois 60611-1676, Attn: Michele Pellissier, or send e-mail to: michele.pellissier@alz.org.

[HISTORIC CONFERENCE CONT'D
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prevention or reduction of amyloid deposits will improve mental function. Scientists do not yet know whether plaques are a cause or result of Alzheimer's. Several studies reported at *Pivotal Research* suggest that vaccination with A β ₄₂ may, in fact, improve memory in aging amyloid-producing mice. Schenk says that if final Phase I results hold up, Phase II trials to assess effectiveness in human subjects could begin by late 2001. For a fact sheet about AN-1792, contact the Alzheimer's Association's information and referral line at (800) 272-3900.

In other encouraging news, Barry Reisberg, MD, of New York University School of Medicine reported favorable results of a Phase III trial of the drug memantine in people with moderately severe to severe Alzheimer's. According to Reisberg, these are the stages when people develop problems with dressing, bathing, and other daily activities and when behavioral symptoms that often complicate Alzheimer's tend to become significant. As a result, these are also the stages that cause the greatest caregiver burden and represent the points at which families tend to move relatives with Alzheimer's from their homes into assisted living arrangements.

Reisberg described a six-month study in which participants who received 10 mg of memantine twice a day showed significantly slower decline in mental function and behavior than enrollees who received a placebo (inactive treatment). Another Phase III study showing favorable results in Latvian patients with severe Alzheimer's was published in 1999 by Bengt Winblad,

MD, PhD. Memantine acts on the brain's N-methyl-D-aspartate (NMDA) receptors, which are among the structures that respond to glutamate, one of the brain's specialized chemical messengers involved in formation of memories and other nerve functions.

The drug has been approved for over 10 years in Germany, under the trade name Akatinol-Memantine, for treatment of various neurological conditions. According to Reisberg, approval in Germany was based on studies that would not meet current U.S. Food and Drug Administration (FDA) standards. He said that it was "possible" that the agency might consider approval on the basis of a single study because there is no drug specifically for Alzheimer symptoms currently approved for individuals with severe disease. All current Alzheimer treatments are approved for mild to moderate stages. But he cautioned that more typically, at least one additional favorable U.S. Phase III trial would be necessary before FDA would consider approving memantine.

On the basic research front, presenters described progress in creating a genetically modified mouse to serve as a better animal model of Alzheimer's. This model would provide scientists with a living laboratory in which to study Alzheimer biology, pathology, and treatment. Scientists have created mice such as the ones used in the vaccine experiments that form amyloid plaques, but success has been more limited in modifying mice to develop neurofibrillary tangles, the other hallmark Alzheimer abnormality. Scientists have created mice that produce human tau, the protein that deforms to produce tangles, but none of the animals actually

develop those lesions.

At *Pivotal Research*, however, several teams reported progress in creating mice that form tangles. One group succeeded in creating tangle-producers and then, by crossbreeding them with amyloid-producers, created mice that form both plaques and tangles. However, the lesions tend to form in the animals' spinal cords rather than in brain areas typically affected by Alzheimer's. As a result, the mice develop a neurological disorder that paralyzes their hind legs, and the paralysis makes it impossible for them to navigate mazes and perform other physical tests used to assess mental function in rodents.

Another team reported creation of a tau-producing mouse that forms tangles in its brain. Preliminary behavior studies suggest that these mice may also develop memory problems. If scientists can successfully crossbreed this animal with an amyloid-producer, the result might represent a significant advance in the quest for an Alzheimer mouse model.

Responding to excitement generated by these encouraging reports, President Bill Clinton announced on July 16 that \$50 million appropriated over the next five years to the National Institute on Aging would be targeted to Alzheimer research, with emphasis on developing a vaccine. According to the White House press release, "This commitment builds on new research findings reported just this week that provide new optimism for the development of immunological and pharmacological interventions that not only slow the onset of Alzheimer's but possibly prevent it." #

Global Alzheimer Community Meets with Change In Mind

Frasier's David Hyde Pierce and presidential daughter Maureen Reagan applauded the president's appropriation of \$50 million of additional funding for Alzheimer research during World Alzheimer Congress 2000, but urged the government and private sector to do more.

Over the 10-day span nearly 5,000 researchers, physicians, and professional and family caregivers representing 50 countries convened at the congress to network and share information and left with a renewed sense of why their efforts are so important.

At the conclusion of the congress, one

family caregiver addressed attendees. "My mom has Alzheimer's, and my world seemed very small. The congress has been an overwhelming experience because I had no idea this was such a huge global problem. I no longer feel alone, now that I know about all of the work being done around the world. On behalf of Alzheimer families, thank you for caring." *ff*

Above: Maureen Reagan, joined by David Hyde Pierce, proclaimed to congress attendees, "We are an army against Alzheimer's!" during an evening reception.

Below: Congress participants enjoy the "International Showcase," highlighting exciting programs and services of Alzheimer's associations worldwide.



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