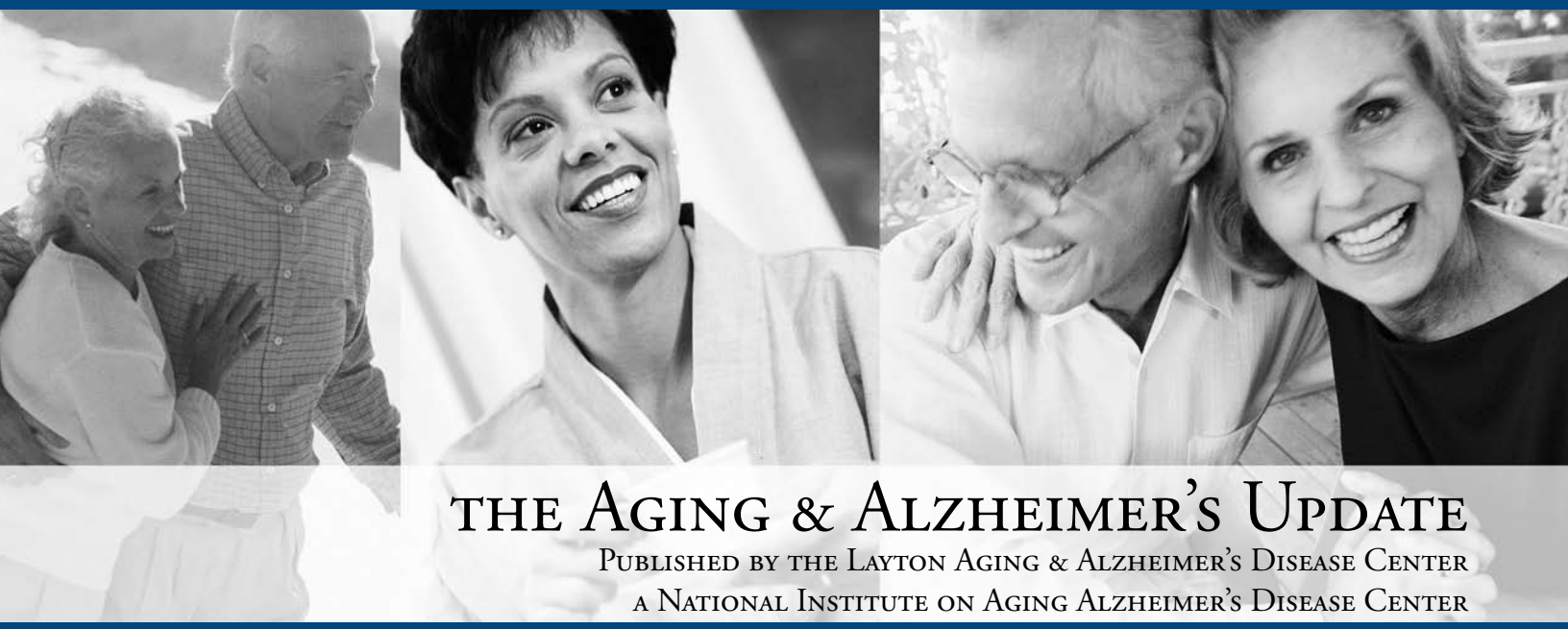
OREGON HEALTH & SCIENCE UNIVERSITY



THE AGING & ALZHEIMER'S UPDATE
PUBLISHED BY THE LAYTON AGING & ALZHEIMER'S DISEASE CENTER
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APRIL 2006

Preventing Alzheimer's Disease: How can we move the search forward?

Dr. Joseph Quinn, Associate Professor and Associate Director, Clinical Core, Oregon Alzheimer's Disease Center

When experts talk about Alzheimer's disease in community lectures, people sometimes express frustration that we haven't yet solved the mystery of how to prevent Alzheimer's disease. Researchers talk about theories and "risk factors" and prevention strategies that might be effective, but we have yet to solve this seemingly intractable puzzle. While many indirect studies hint at how we should proceed on this quest, almost no studies have actually put these theories and strategies to a definitive test.

Here's why: Imagine you could study a thousand people at risk of Alzheimer's disease simply because they are getting older. And say those people were about 60 years old, and they agreed to be assigned to either the treatment or a placebo. And say they were all model patients, who took their pills as they were told and conscientiously returned for their visits, and a year later you checked everyone out to see if the treatment worked. After one year, so few people would have actually developed Alzheimer's disease in either treatment or placebo group that, even if you had chosen a truly effective treatment, you wouldn't be able to tell if it worked. You could continue your study for another year or more, but even at 5 years, there would be so few cases of Alzheimer's showing up that you could not determine if your treatment worked.

If you could study people who were at higher risk of Alzheimer's disease, for example older people or people with a family history of Alzheimer's disease, you might have a better chance at telling if the treatment worked—but it would still require thousands of subjects studied for several years-a multimillion dollar proposition. And if the treatment did not work—you would have spent a lot of time and money with nothing to show for it.

So how can we carry out research efficiently to learn how to prevent Alzheimer's disease? One idea is to measure "markers" of the disease

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OHSU

Remember Alzheimer's Disease Research when you do your Oregon taxes!

(Charitable Check-offs at end of form 40)

The Oregon Income Tax Check-Off Alzheimer's Research Fund supports research that will improve our understanding of dementia or that will advance health care treatment or prevention strategies. These funds are made available by Oregonians through the Oregon income tax check-off program.

Applications are evaluated on the basis of scientific merit with priority given to investigators just entering the field of dementia research and to new or innovative projects. Special attention will be paid to projects that foster collaboration. Last year this fund supported studies that investigated spoken language used by cognitively impaired and healthy elders; the potential for the herb, gotu kola, as a treatment for Alzheimer's disease; biochemical mechanisms that may affect brain function in AD, and unobtrusive monitoring of activity in home settings as a new approach to detecting dementia.

The program is administered by the Oregon Partnership for Alzheimer's Research (OPAR), a community-wide research advisory committee of researchers and Alzheimer's disease experts. For information about the Tax Checkoff Alzheimer's Disease Grant Program, contact Linda Boise, Ph.D., at boisel@ohsu.edu or by phone: 503 494-6370.

Preventing Alzheimer's...

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process, rather than rely on the appearance of dementia itself, since the dementia is in many ways the tip of the biological iceberg. The Oregon Alzheimer's Disease Center has been a leader in developing MRI-based measurement of regional brain volumes as one such marker for the last 15 years, and has also been a leader in the development of biochemical markers of disease in cerebrospinal fluid (the fluid which bathes the brain, and which can be safely sampled by "spinal tap.") Our hope has been that we can develop the means to monitor the disease process before it is too late to intervene. After all, treadmill tests detect coronary artery disease before it's too late; mammograms, PSA levels, and colonoscopy detect cancer before it's too late. Why not try to do the same early detection and intervention for Alzheimer's disease?

A study recently launched in a collaboration between the Oregon Alzheimer's Disease Center and the University of Washington will attempt to use "biomarkers" to develop a new method for testing Alzheimer's disease prevention strategies. In this study, patients at risk of Alzheimer's disease by virtue of age greater than 70 and a family history of Alzheimer's disease will be enrolled in a clinical study. Participants will have cerebrospinal fluid collected by lumbar puncture or "spinal tap", and will then be randomly assigned to take either a study medication or placebo. The study medicine is the commonly used anti-inflammatory drug ibuprofen, which is thought to have potential in the prevention of Alzheimer's disease. After taking the study medicine for 6 weeks, subjects will have a second cerebrospinal fluid collection. Biochemical markers of Alzheimer's disease will be measured in samples taken before and after the drug treatment, and the effect of ibuprofen will be compared with the effect of placebo treatment. This will be the first study of the biochemical effects of ibuprofen in the aging brain, and the first biochemically based study of prevention strategies in Alzheimer's disease.

A prevention study using the usual memory tests and functional assessments as endpoints would literally require thousands of patients, several years, and millions of dollars. This study, in contrast, will require less than a hundred subjects and should be completed in less than a year. Regardless of the findings regarding ibuprofen per se, this study will serve as a foundation for future studies of better ways to prevent Alzheimer's disease.

To find out more about the research studies discussed in this newsletter or about other research and clinical trials at the **Layton Aging & Alzheimer's Disease Center**, check our Web site (www.ohsu.edu/research/alzheimers) or call Joyce Lear at 503 494-7615.

Layton Center funding update

The Oregon Brain Aging Study (OBAS) has received a five year Merit Review Award from the Department of Veterans Affairs. Dr. Jeffrey Kaye heads the study, which began in 1989. This longitudinal study has focused on factors associated with healthy brain aging. Its importance lies in its focus on the very old – those 85 and older and the long-term follow up. In this new cycle, questions are directed toward establishing biomarkers of brain aging protection associated with a recently identified phenotype that has been shown to be resistant to cognitive decline among the oldest old. Dr. Kaye and colleagues plan over the next five years to determine how these biomarkers map to rates or trajectories of functional decline prior to the emergence of dementia. Finally, the study ultimately focuses on establishing whether the resistive phenotype of cognitive decline and brain aging is associated with distinct changes in the brain neuropathology.

Layton Center neurologist receives grant to study Anti-amyloid therapy for Alzheimer's disease

The Department of Veteran's Affairs has awarded Dr. Joseph Quinn, associate professor of neurology, a Merit Review grant to screen candidate anti-amyloid agents, alone and in combination, in a mouse model of Alzheimer's disease. The agents are things that are already approved for use in human beings as either supplements, over the counter drugs, or investigational drugs, so a positive finding in the mice can lead directly to a clinical trial. Using mice for these studies are also beneficial as a combination therapies can be tested in mice, which is very difficult to do in human subjects.

News from the Alzheimer's Association

Over the past several years, the Alzheimer's Association - Oregon Chapter has faced significant challenges. In 2003, due to a variety of circumstances, the Chapter found itself in a "survival mode." Happily it is now in a growth mode. This past year, the Chapter assisted more than 10,000 individuals, families, and caregivers. In addition to a greatly improved financial position, the Chapter has added new programs, including "Maintain Your Brain," and "Partnering with Your Doctor," and an education and support program for persons with early stage dementia.

On April 11, 2006, The 8th Annual McGinty Memorial Conference on Alzheimer's Disease will be presented for professional and family caregivers by the Alzheimer's Association – Oregon Chapter:

"Making a Difference – One Person at a Time"

Tuesday, April 11, 2006
7:30 a.m. - 4:30 p.m.

CROWNE PLAZA - 14811 KRUSE OAKS DRIVE
LAKE OSWEGO, OREGON

About the Conference
The McGinty Memorial Conference on Alzheimer's disease honors the late Dean McGinty, M.D., a Portland geriatrician, early advocate for the special needs of persons with dementia and a pioneer in the Alzheimer family support movement.

Conference highlights include: Presentations on caring for and communicating with someone with Alzheimer's disease, "Finding New and Better Ways to Treat Alzheimer's," using humor, and other timely topics.

A Panel Presentation:
"Empower Yourself – Get Current, Stay Current" will be facilitated by Roger Anunsen, creator of MemAerobics, a neuroscience researcher, activity program designer, author and speaker. Panel Members: Dr. Pat Gillette, Dr. Jeffrey Kaye, and Vicki Schmall, Ph.D.

To find out more or to obtain a registration form send an email to: judy.mckellar@alz.org or call the Alzheimer's Association at 503 413-7115 or 800 733-0402

OHSU Town Hall Meeting: Bench to Bedside for Alzheimer's Therapies

Jan 28, 2006 – Trish Pruis and Christa Helms

Three years ago, Senator Ron Wyden helped start an annual Town Hall meeting to create a dialogue among researchers, practitioners, and patient advocates on important issues in brain research. This Town Hall event has been a highly successful part of OHSU Brain Awareness season, drawing nearly 300 people. This year's panel was mediated by David Heil, a nationally known health educator, and the theme was the bench-to-bedside process for getting drugs from a research lab to the people that need them. The main emphasis was on drug therapies for Alzheimer's disease (AD).

Panelists represented researchers, Pharmaceutical industry, and the Alzheimer's Association. Three main concerns were highlighted by the panelists: 1) patients and doctors need better information, 2) we need to get drugs to people sooner, and 3) our government needs to make an investment and commitment to battling AD.

Panelists agreed that patients and doctors need to be well informed about the drugs available for AD treatment. It is currently difficult for patients to get understandable information about most drugs. The package inserts, e.g., tend to be technical and difficult for non-scientists to understand. One recommendation was that pharmaceutical companies could improve their public image, and perhaps the efficacy of their medications, by clearly and quickly communicating instructions for using the drugs and possible risks. Another problem discussed was that many doctors are not trained to diagnose AD, so the disease may go unnoticed for some time. With increasing pressure to shorten the amount of time spent with each patient, doctors may not properly match drug treatments, or explain them, to individual patients.

The time it takes to get drugs from the laboratory to the patient was another concern discussed at the Town Hall meeting. Drugs that act on the central nervous system, such as those used to treat Alzheimer's disease, take approximately 13 years to move from the laboratory to the market for patient use. There is great need for funding and legislation to speed the bench-to-bedside process. One suggestion was to apply the "Subpart E" law of 1988 to AD drugs. "Subpart E" is intended to speed availability of new drugs to patients with life-threatening or severely debilitating illnesses by skipping phase III trials. In Phase III trials, the new treatment is compared to current standard therapies; the Food and Drug Administration (FDA) only approves drugs that complete Phase III trials. This course of action would necessitate that pharmaceutical companies provide accurate information regarding safety and side effects to both patients and doctors, so that patients can decide for themselves whether or not to use the newest treatments for AD.

Much of the discussion during the Town Hall centered around the desire to get treatments to where they can really help people with dementing illness. The current attitude prevails that nothing can be done to prevent or alleviate AD, but science moves ever closer to the discoveries that will provide the answers. The consensus at the Town Hall was that research institutions and pharmaceutical companies need funding and a commitment from our government to make it happen. There is much to be learned about Alzheimer's

Speakers/Panelists (from right to left): James Callaway, Ph.D., Senior Vice President Alzheimer's Program, Elan Pharmaceuticals; Dennis Bourdette, M.D., Chairman, OHSU Neurology Department; Judy McKellar, Executive Director, Alzheimer's Association Oregon.

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disease. Understanding how much Alzheimer's disease is controlled by genetics and how much by environmental factors needs be explored. Research leading to treatments and prevention strategies are much needed. In Oregon, Alzheimer's disease is projected to increase by 93% over the next 20 years. Funding AD research now is especially important because we are still at a point where we can work on treatment and prevention before AD explodes on the health care system. As Dennis Bourdette, MD, Chairman of the OHSU Department of Neurology put it, "It is important that all of us become involved in advocating for more funding by the federal government for research on AD. We are facing an epidemic of AD as our population grows older. Federal dollars for biomedical research in general are shrinking. We need to invest now in research towards finding new treatments and a cure if we truly want to conquer AD."

Responding to readers' questions

In our last issue of the Aging & Alzheimer's Update, we invited readers to send us topics they would like to hear more about. Several readers asked us to report on research about the use of herbs in Alzheimer's therapy. In this column, we turn to Dr. Barry Oken, Associate director of the Layton Aging & Alzheimer's Disease Center and director of the Oregon Center for Complementary and Alternative Medicine in Neurological Disorders for an update on research using botanicals for treatment and prevention of Alzheimer disease.

Botanicals are drugs obtained from plants that are sold as dietary supplements. They may contain dozens of biologically active ingredients. Other dietary supplements include single chemicals such as vitamins or other chemicals normally present in the body such as lipoic acid. Pharmaceutical companies have had limited interest in botanical research, in part because of the lack of a patent, so that almost all of the larger U.S. studies have been funded by NIH.

Several botanicals or herbs have been studied at OHSU and other research institutions to determine their effect in Alzheimer disease (AD). The most studied has been ginkgo biloba standard extract. In AD there is a suggestion of a small but statistically significant benefit on cognitive function compared to placebo. There is uncertain data concerning its utility in healthy seniors without Alzheimer's disease. A study at OHSU enrolled 133 healthy seniors over age 84 years who took 240 mg per day of ginkgo biloba standard extract or placebo for four years. All subjects have finished taking their pills. The data is being analyzed and we hope to have some results this spring. Another larger study of ginkgo biloba in healthy seniors is still ongoing at the University of Pittsburgh. Both studies were funded by the NIH-National Center for Complementary and Alternative Medicine.

The herb, Gotu kola (Centella asiatica), is currently being studied at OHSU and elsewhere for its effects in nerve cell models of nervous system injury. It appears to increase axonal growth in these models. Studies have shown that an extract of the herb improves memory and behavior problems in a mouse model of the Alzheimer's disease. Dr. Amala Soumyanath is working to identify the components of the herb that are responsible for its effects on memory. There have been no studies yet in humans with Alzheimer's disease.

Another small study among healthy seniors at OHSU was a trial of Bacopa monniera or placebo. Bacopa monniera is an Ayurvedic herb that commonly grows in marshy areas throughout India and is used in India for memory, epilepsy, and as a mild sedative. As with many studies of botanicals, the number of subjects enrolled was too small to make any major conclusions.

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The Aging & Alzheimer's Update

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OHSU includes the schools of dentistry, medicine, nursing, and science and engineering; OHSU Hospital and Doernbecher Children's Hospital; numerous primary care and specialty clinics; multiple research institutes; and several outreach and community service units.