



PATHWAYS

Moving Toward a Cure

Spring 2007

Message from the Director

The University of Pittsburgh Alzheimer Disease Research Center (ADRC) is grateful that many of you attended the center's 20th Anniversary Celebration in September 2006 and were able to learn about the many advances and initiatives in Alzheimer's disease (AD). As many of you know, the number of AD cases will increase markedly over the next 20 years. This epidemic of AD is a product of two factors: (1) the incidence and prevalence of AD increases with increasing age, and (2) the large population of baby boomers will live longer than any prior generation.

In addition to adding a sense of urgency to the development of new medications, the prospect of so many new cases has led to the development of different strategies in the battle against AD. For people who already have AD, we are trying to develop better treatments for both the cognitive decline and the behavioral symptoms that emerge during the disease. In 2006, a study published in the *New England Journal of Medicine* showed that the newer medications for controlling behavioral disruptions (hallucinations, delusions, and other psychotic behaviors) were not as

powerful as researchers had hoped they would be. Side effects were also an issue for all of the medications, so clinical judgment about when and how to use them is now emphasized more than ever. Educating physicians about how to treat patients with complicated AD is a central aim of the ADRC.

A significant number of medications aimed at slowing down the progression of AD are in national and international clinical trials, and the University of Pittsburgh ADRC is participating in several of these. Over the next year and a half, the first of these disease-modifying medication trials will come to completion, and we will know if our first efforts to target amyloid protein were successful.

In our next newsletter, I will update you on the trials that will be completed in 2007 or 2008 and discuss both lifestyle changes and therapeutic trials that we hope will prevent or delay the onset of AD.



Steven T. DeKosky, MD
Director

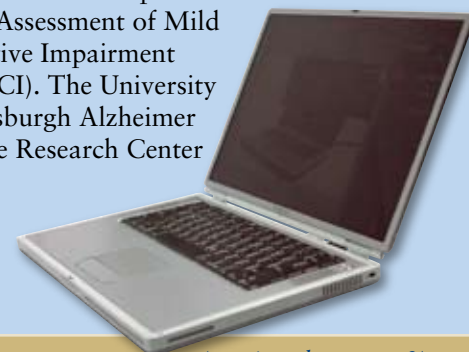
New Test Assesses Cognition and Memory

—Judith A. Saxton, PhD

The majority of older Americans receive their health care solely within the general practice setting. However, most primary care physicians (PCPs) do not routinely screen for or document the presence of cognitive decline in their older patients, although they may suspect or recognize it.

The reasons for this are complex and include lack of time; lack of training or skill in cognitive assessment; and lack of an easy-to-use, reliable screening instrument. Identifying cognitive impairment at the doctor's office would permit earlier referrals for diagnostic workups as well as earlier and more appropriate treatments, which would result in better outcomes for the patients. Such identification will become increasingly more important as new medications are developed for Alzheimer's disease and other disorders.

Judith Saxton, PhD, and her colleagues at the University of Pittsburgh and Psychology Software Tools, a Pittsburgh-based company, have received funding from the National Institute on Aging to conduct a study investigating the usefulness of a self-administered, user-friendly computer assessment of cognitive impairment known as the Computer-based Assessment of Mild Cognitive Impairment (CAMCI). The University of Pittsburgh Alzheimer Disease Research Center



(continued on page 3)

Volunteers Needed for Clinical Trials

A clinical trial is a research study in human volunteers to answer specific health questions. It is a safe and fast way to find treatments that work in people as well as ways to improve health.

If you are interested in participating in any of the following studies, see contact information below the chart.

DHA Omega-3 Fatty Acid	Huperzine A	Pittsburgh Compound-B (PiB)
<p>Description This study will determine whether supplements of Docosahexaenoic acid (DHA), an Omega-3 fatty acid, can slow the progression of cognitive and functional decline over an 18-month period in patients with mild to moderate AD. A subgroup will have the option to participate in the lumbar puncture substudy.</p>	<p>Description The primary function of this study is to determine whether treatment with the Chinese herb Huperzine A improves cognitive function in individuals diagnosed with AD.</p>	<p>Description This study will use positron-emission tomography (PET) imaging to determine how amyloid changes across stages of severity in AD and whether amyloid is present in elderly individuals without memory problems.</p>
<p>Study Length 18 months</p>	<p>Study Length 6–12 months</p>	<p>Study Length Varies</p>
<p>Study Requirements 50 years of age or older Diagnosis of probable AD Fluency in English A reliable study partner</p>	<p>Study Requirements 55 years of age or older Diagnosis of probable AD Fluency in English A reliable study partner Not currently taking a cholinesterase inhibitor (i.e., Aricept, Razadyne, or Exelon)</p>	<p>Study Requirements 30 years of age or older Healthy individuals Diagnosis of probable AD Diagnosis of mild cognitive impairment (MCI)</p>
<p>Compensation Participants will receive \$200 for undergoing the optional lumbar puncture.</p>	<p>Optional Extension Phase Participants will be invited to continue Huperzine A treatment for an additional six months.</p>	<p>Compensation Up to \$200 per year</p>

For information about the DHA or Huperzine A studies, contact MaryAnn Oakley at 412-692-2721 or oakleym@upmc.edu. For information about the PiB study, contact Claire McConaha at 412-692-2727 or cwm15@pitt.edu.

Caregiver Study Seeks Volunteers

If you are a caregiver and would like to participate in the following study, please contact MaryAnn Oakley at 412-692-2721 or oakleym@upmc.edu for more information.

Self-Management and Resource Training (SMART) Study:

Description

This study is designed to determine if an educational self-management program strengthens the personal resources (physical and/or mental) of men and women living with a spouse who has mild memory problems.

Study Length

Three months

Study Requirements

Spouse or living partner of an individual diagnosed with mild cognitive impairment (MCI)



Testimonial from Study Volunteer

“I like the professionalism of it. Everything is very well planned. Staff members try very hard to please me and everyone is so congenial. Everyone is made so comfortable. It all seemed very natural. My overall experience has been very pleasant. Staff members are very, very nice. They have escorted me to all of the different stations and never left me alone, wondering what was next.”

—Sue Lockett

Sue has been an Alzheimer Outreach Center control subject since May 13, 2003, and currently participates in the Alzheimer Disease Neuroimaging Study (ADNI).

(continued from page 1)

is one of the participants in the study of CAMCI.

CAMCI is designed to identify the earliest signs of cognitive impairment in older persons. The availability of a reliable computer test such as CAMCI has a number of advantages:

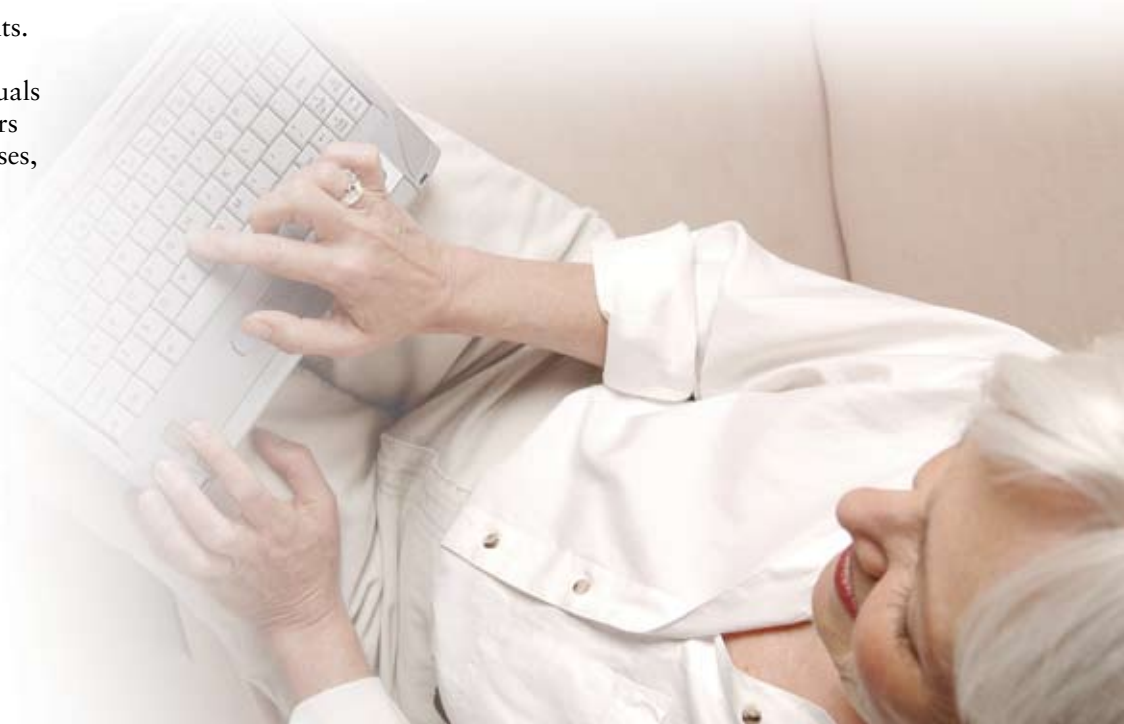
- it allows for a quick assessment of cognitive function that can be completed in the doctor’s examination room while the patient is waiting for the doctor to arrive,
- the specific tests are based on currently accepted mental status assessments and criteria for mild cognitive impairment, and
- the results can be viewed instantly on the computer screen, and a copy of the report can be printed out for the medical chart.

There are also some limitations, the most serious being a lack of computer experience in older patients. Although this may be a drawback, evidence suggests that older individuals are increasingly relying on computers for communication, making purchases, and searching for information.

- Companies such as Apple, Microsoft Corp., and Intel Corp. have programs targeting senior citizens, and recent reports indicate that more than 30 percent of all seniors currently own computers and use them for writing letters, playing games, and managing finances.
- AARP cites more than 2 million members who use the computer.
- Within the not-too-distant future, as the baby boom generation ages, more and more senior citizens will have had routine experience with computers in the workplace and at home.
- Almost all older individuals have experience using automated teller machines (ATMs) at banks and touch-tone telephones; CAMCI uses a touch-screen notepad computer that is no more complex than using an ATM or touch-tone phone.

More than 200 individuals over the age of 65 have already completed the study, and preliminary results suggest that the computerized battery is both sensitive and specific to mild cognitive impairment.

Saxton and her colleagues hope that providing information about older patients’ cognitive abilities will allow PCPs to adapt treatment plans to ensure optimum outcomes. Modifying and adapting clinical management to take cognitive difficulties into account will increase the chances of effective management and improve older patients’ overall quality of life.



Autopsy Program Comforts Families, Furthers Research

— Ronald L. Hamilton, MD

The Neuropathology and Genetics Core, sometimes referred to as the brain bank, has been an integral part of the Alzheimer Disease Research Center (ADRC) since its inception more than two decades ago. While the brain bank serves as an invaluable repository for donated tissues that are used for Alzheimer's disease (AD) research, it also helps to pinpoint the final diagnosis for patients with neurodegenerative diseases.

A definitive diagnosis can be a great comfort to a family and can eliminate unnecessary uncertainty each time the family history is reviewed. Years of experience in AD research have enabled ADRC clinical investigators to be more than 95 percent accurate within their clinical diagnoses of AD. However, there are other types of dementia that can sometimes be clinically similar to AD, including dementia with Lewy bodies; the frontotemporal dementias; and, more rarely, Creutzfeldt-Jakob disease.

It is not uncommon for AD pathology to be accompanied by other pathological changes that may have an important impact on the dementia syndrome—such as infarcts (strokes), Lewy bodies, or mesial temporal sclerosis (a scarring and loss of nerve cells in the hippocampus, a structure that is very important in memory). Autopsy confirmation of the clinical diagnosis of AD and other coexisting neuropathological changes is essential to improving our ability to design and evaluate clinical studies of AD, including therapeutic trials. Careful characterization of the pathological changes in various areas of the brain can then be correlated with clinical and radiological data to better understand the neurodegenerative processes.

ADRC's brain banking program not only provides a definitive final diagnosis (at no cost to the family if the patient has been followed at ADRC),

it also preserves rapidly frozen samples from more than 25 different areas of the brain in specially designed ultra-low-temperature freezers that are monitored 24 hours a day.

ADRC has provided brain tissues to investigators in the Departments of Psychiatry, Neurology, and Pathology at the University of Pittsburgh as well as many other investigators in the United States and other countries. ADRC does provide some demographic information (age and sex) with the samples, but the data are de-identified so that a person's identity is not revealed.

Brain samples provide the only opportunity to study AD at the molecular level, since animal and cell culture models of AD do not mimic all the complex changes in the disease. Human brain tissue studies remain the gold standard for AD research.

Brain banks are a valuable link in the effort to translate "bench-top" science into clinical practice. The pace of research in AD is accelerating as never before, and many of the discoveries made in the laboratory are beginning to be translated into clinical treatments. We are beginning to unravel the enigma of AD and now, more than ever, it is critical that laboratory findings using tissue culture systems or transgenic animal models are correlated with the actual changes occurring in the human brain.

Removal of the brain at autopsy is done rapidly and in a careful and respectful way, and it allows for an open casket funeral, if desired. Donation of the brain at autopsy not only provides the family with the comfort of a final diagnosis, it also provides them with the knowledge that their loved one has contributed "the last full measure" in the fight for a cure.



Ronald L. Hamilton, MD
Director, Neuropathology and Genetics Core

Autopsy Facts

- An autopsy is performed as soon as possible after the death of the patient. An autopsy performed within 12 hours is preferable; however, there is still immense value in having an autopsy performed up to 24 hours after death.
- Under normal circumstances, only the brain is examined during an ADRC autopsy. The brain autopsy is performed carefully so that it is not noticeable in any way and does not prevent an open casket viewing.
- Upon the patient's death, if a family wishes to have an autopsy performed on their loved one, they may call ADRC at 412-692-2700.
- Regardless of when a family member calls, an ADRC staff member will be available to advise the family of the steps they should take.
- Transportation to and from the autopsy site is most effectively arranged through the funeral director handling the burial, but it can be arranged by ADRC if necessary.
- There is no autopsy cost to the family for a patient who had been a participant at ADRC.

If you have questions or would like further information on the autopsy program at ADRC, please contact us at 412-692-2700.

Understanding Changes in the Brain

— Steven T. DeKosky, MD and Milos D. Ikonovic, PhD

The primary causes of the memory and cognitive deficits in Alzheimer's disease (AD) are not known with certainty, but they involve a combination of structural changes (e.g., loss of nerve cells and their connections, or synapses) and biochemical changes (loss of neurotransmitters, the brain chemical messengers that nerve cells use to communicate with each other). Understanding when and how these changes occur during the course of AD is critical for developing treatments and preventive strategies.

We investigated such structural and biochemical changes in brain tissue samples that were collected during autopsies from members of the Religious Orders Study in Chicago, Ill.—a noble group of nuns, priests, and brothers who are examined (medical and psychological examinations) every year and then donate their brains for Alzheimer's disease research when they die.

We examined subjects with very mild cognitive problems or mild cognitive impairment (MCI) and compared them to normal people and those with mild AD. We found that choline acetyltransferase (ChAT), a brain enzyme that makes acetylcholine (a cholinergic neurotransmitter important in memory), is not lost early in the disease, as previously thought, but is preserved or even elevated in brain regions important in memory and awareness. We see this activity as the brain "fighting back" against the disease. This change was not seen in all brain regions, so not all brain areas are capable of the compensatory response. This may be why cerebral cortical dysfunction appears later in some regions (e.g., the frontal lobes, where we observe this cholinergic "plasticity") than others (the parietal and temporal lobes, where we don't see it). The loss or exhaustion of this response and the loss of synapses leads to clinical AD.

We think these changes involve brain deposition of amyloid-beta peptide (A β), the toxic protein that accumulates in AD. We demonstrated that in MCI (preclinical AD), there are already substantial A β deposits in the brain. Whether this early amyloid pathology is associated with changes in synapse number and ChAT activity levels in selected brain regions in MCI and early AD is the focus of our current research. The insight into how A β accumulation influences and relates to cholinergic and synaptic dysfunction and how they all relate to clinical symptoms during disease initiation and progression, will facilitate development of therapies for different periods of the disease's course. We hope our studies will aid in the definition of the sequence of brain changes underlying cognitive impairment in MCI and early AD and direct us to ways to slow, stop, or prevent the disease.

20th Anniversary a Success

Approximately 165 people attended ADRC's 20th anniversary celebration on September 28, 2006, at the Circuit Center on Pittsburgh's South Side. Administrator Leslie Dunn introduced the program and speakers, and investigators and faculty presented up-to-date research findings.

Director Steven T. DeKosky presented a brief history of Alzheimer's disease research during the last 20 years. William E. Klunk, director of psychiatry, enlightened the audience with his exciting research on Pittsburgh Compound-B. Neuropsychologist Judith A. Saxton explained why pencil-and-paper cognitive testing is important. Psychiatrist Robert A. Sweet presented findings on the behavioral changes in Alzheimer's disease; neuropathologist Ronald L. Hamilton explained the neuropathology/autopsy program; and neuropsychologist James T. Becker discussed imaging of brain volume and its relationship to thinking function.

Attendees asked questions and made comments about their experiences with AD and research. Of the attendees completing program evaluations,

95 percent indicated that this program had significantly improved their knowledge about AD research.



Left to right: Amanda Hunsaker, Judith Saxton, Lori Macedonia, MaryAnn Oakley, Shelley Ferson, Shirley Portis, Donna Simpson, Carolyn Rickard, Thomas Baumgartner, Leslie Dunn, April Kane, and Kathie Savage

In Memoriam



The University of Pittsburgh Alzheimer Disease Research Center thanks the following individuals and companies for their generous donations received August 1, 2006–January 31, 2007.

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In Memory of Louise L. Lantzy

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Erma L. Nicol

Staff Spotlight

Veteran Senior Administrative Assistant

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Your contributions are greatly appreciated and help to support research and education in the area of Alzheimer's disease. You can remember or honor a loved one by using the envelope enclosed with this newsletter to mail in your donation.

December 31 Deadline for Special Tax Benefits for IRA Gifts

If you are at least 70 ½ years old, you may be able to support Alzheimer's disease research with a direct transfer from your IRA or Roth IRA. Your gift of up to \$100,000 would not be counted as taxable income to you and it would be applied against your annual required minimum distribution. However, you must act quickly. This opportunity is scheduled to terminate at the end of 2007. Special rules apply. For more information, please contact Jim Olsen at 412-647-7781.

Topics at Noon Series

Noon-1 p.m.
ADRC Conference Room S439
4 South UPMC Montefiore
3459 Fifth Avenue
Pittsburgh, PA 15213

May 10, 2007

"The Process of Medication-Taking in Persons with Alzheimer's Disease Living in the Community"

Judith A. Erlen, PhD, RN,
Fellow of the American Academy of Nursing, and a professor and doctoral program coordinator in the University of Pittsburgh School of Nursing

Light refreshments will be served. Registration is not required. For more information, call 412-692-2700.

Marlene Paytas has been working at the Alzheimer Disease Research Center (ADRC) for almost 11 years, and she is now the senior administrative assistant.

Acting as a liaison among the clinic, the Alzheimer Outreach Center, and the administration, she coordinates the consensus conference schedule and serves as a receptionist to the clinic by communicating and distributing ADRC information. She also creates weekly patient and clinic schedules, trains and supervises students and volunteers, and oversees the organization of the ADRC patient file room. Her other duties include coordinating all clinic appointments—initial and follow-up—and conducting online scheduling of all radiology scans.

Before coming to work for ADRC, she was a 23-year veteran of the dental field, an office manager, and a surgical implant assistant. Her education started at North Hills Senior High School in Pittsburgh and continued at the Community College of Allegheny County, where she studied to be a dental assistant. Her continuing education has included communications and management programs.

The interaction she has with the patients and their families—and, she adds, with the wonderful staff—is the most rewarding aspect of her job. When she's not enjoying herself on the job, you might find this well-rounded staff member dancing, boating, working on her stained glass projects, antiquing, or spending time with her significant other Tom. She also deeply values her family. Although her two "wonderful, sweet" grandchildren, 2-year-old Ella and 3-month-old Carter, live 10 hours away in Greenville, S.C., she does the best she can to see them as often as possible. She is also grateful to have a wonderful father who is almost 93 years old and still very active and healthy.





University of Pittsburgh

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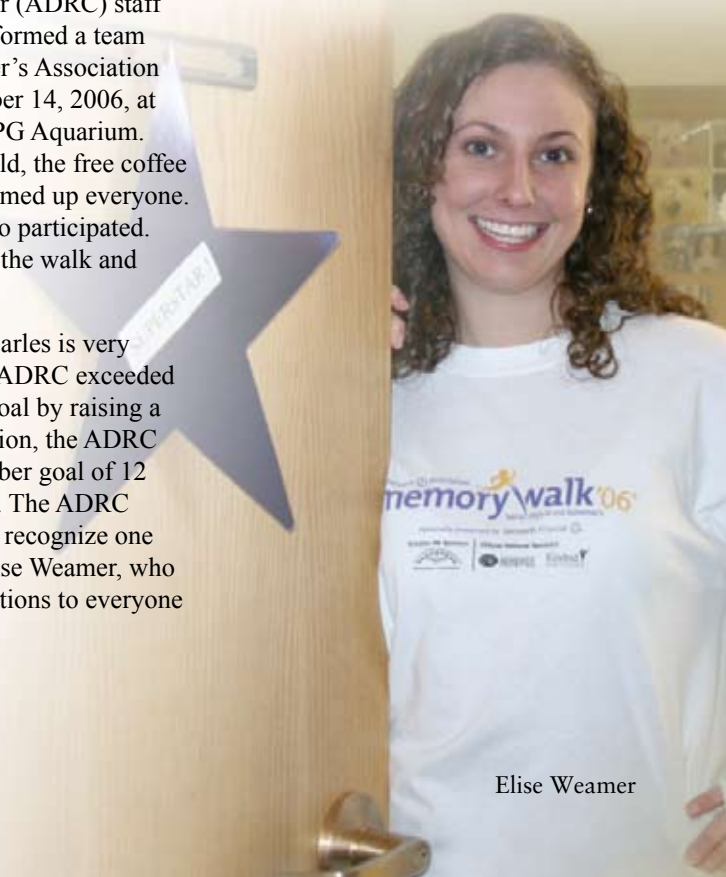
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Memory Walk Exceeds Goal

— Beth Sarles

The University of Pittsburgh Alzheimer Disease Research Center (ADRC) staff and friends once again formed a team for the annual Alzheimer's Association Memory Walk on October 14, 2006, at the Pittsburgh Zoo & PPG Aquarium. Although it was a bit cold, the free coffee and Smiley cookies warmed up everyone. Thanks to all of you who participated. We saw many of you at the walk and enjoyed saying hello.

As team captain, Beth Sarles is very proud to report that the ADRC exceeded its \$2,400 fundraising goal by raising a total of \$3,620! In addition, the ADRC surpassed its team member goal of 12 with a record 21 people. The ADRC would especially like to recognize one of its staff members, Elise Weamer, who raised \$690. Congratulations to everyone who participated.



Elise Weamer