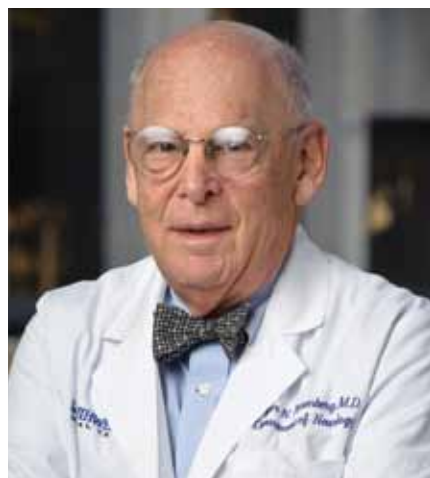


Alzheimer's

D I S E A S E C E N T E R N E W S

FROM THE DIRECTOR | *Roger N. Rosenberg, M.D.*



Scientists have made remarkable advances toward developing effective therapies for Alzheimer's disease in the past year. There is a broad consensus now that amyloid and its most toxic form, Aβ42, is directly responsible in part for the dementia of Alzheimer's disease.

Researchers in Iceland associated with the company deCODE Genetics have just reported that a rare mutation in the amyloid gene is sufficient to impair the conversion of the less toxic form of amyloid to its more toxic form. As a result, no one with this mutation developed Alzheimer's disease. Their findings provide compelling data in support of amyloid being necessary to cause memory and cognitive loss, leading to the dementia recognized as Alzheimer's disease. These and other data provide convincing evidence that amyloid is not just a marker of the disease, but central to its development.

At this year's Alzheimer's Association International Conference, Dr. Norman Relkin of Weill Cornell Medical College reported on the results of long-term, three-year stabilization of Alzheimer's disease symptoms with IGIV (intravenous immunoglobulin). In a Phase 2 clinical trial, he reported no decline among four patients in cognition, activities of daily living, memory, and mood compared to non-treated control subjects with Alzheimer's disease.

Dr. Mary Quiceno of our Alzheimer's Disease Center was a co-investigator in the subsequent Phase 3 study, providing patient data in support of these exciting results. She is currently recruiting trial participants for a second Phase 3 study to determine if IGIV will be of benefit on a larger scale.

This clinical trial represents the first positive data of therapy providing patient stabilization and strongly suggests that IGIV provides an anti-amyloid antibody that prevents amyloid accumulation. The patients treated had mild to moderate Alzheimer's disease and it is believed that if they had been treated even earlier, they potentially would have seen even greater improvement.

The National Institute on Aging is planning three additional anti-amyloid clinical trials. The Anti-Amyloid Treatment of Asymptomatic Alzheimer's Disease (A4), with Dr. Reisa A. Sperling of Harvard Medical School as the principal investigator, is designed to start a monoclonal anti-amyloid

antibody clinical trial emphasizing asymptomatic persons showing an accumulation of amyloid in their brains using positron emission tomography-amyloid brain imaging.

The Dominantly Inherited Alzheimer Network-Therapeutic Trials Unit, with Dr. Randall Bateman of Washington University School of Medicine as the principal investigator, is preparing to initiate prevention trials in people with a genetic mutation that can indicate they definitely will develop the disease at an early age because of an aggressive accumulation of brain amyloid. Thus, anti-amyloid therapy can be employed at a very early stage of the disease process.

The Alzheimer's Prevention Initiative also is designed to test an anti-amyloid antibody in genetically affected persons who will develop the disease at an early age based on a genetic marker. Dr. Eric Reiman of the Banner Alzheimer's Institute in Phoenix is the principal investigator. This study involves a large Colombian family with this genetic mutation. The anti-amyloid monoclonal

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A FAMILY'S FIGHT

Alzheimer's disease claimed Joanne Bara's mother. Then it came for her dad.

By Jeff Carlton

Joanne Bara knows too well the indignities and indiscriminate nature of Alzheimer's disease. It robbed her of both parents, first taking her mom and then her dad.

Her mother, Myra Quig, died in 2006 at age 74, having spent nearly 15 years in the grip of dementia. A few months after his wife's death and after years of devoted caregiving, Ms. Bara's father, Donald Quig, also was diagnosed with Alzheimer's. He died in 2010 at age 78.

"We knew something was going on with my dad, but we at first thought it was from the stress of taking care of mom," Ms. Bara said. "It was hard to believe it was happening to him, too."

Watching her parents' struggle was enough to convince Ms. Bara to participate in a UT Southwestern Medical Center research study at the Alzheimer's Disease Center. In all, Ms. Bara and her parents have

a connection with the Center dating back more than a dozen years.

She is one of the participants the Center follows in a long-term, longitudinal study called the Neurobiology of Aging. The data collected is available to all UTSW researchers for use in any number of studies, said Kristin Martin-Cook, Clinical Research Coordinator in the Alzheimer's Disease Center.

Ms. Bara's parents also took advantage of Alzheimer's Disease Center resources. Mrs. Quig was in one of the first mild cognitive impairment studies ever done, comparing the effects of a high dose of vitamin E and Aricept to Aricept and a placebo. Mr. Quig was a regular participant in the caregiver support group at the Alzheimer's Disease Center until he, too, succumbed to the disease.

In the case of her parents, Ms. Bara watched as her sweet-natured mother transformed into a virtual stranger. Mrs. Quig became scared, angry, and combative, requiring full-time supervision, her daughter said.

The disease had the opposite effect on her father, a stern and sometimes unemotional figure who became "very sweet, very huggy, very 'I love you,'" Ms. Bara said.

"My mom was really tortured by the disease," she said. "With my father, it was almost like he relaxed a bit."

Ms. Bara, a former UT Southwestern employee who now works for a company that makes lasers for eye surgeries, said she took part in the

research study out of a desire to advance the science of Alzheimer's treatment. Her hard-earned personal knowledge about what the disease can do to a family, however, makes this battle a personal one.

"My mom was really tortured by the disease," she said. "With my father, it was almost like he relaxed a bit."

"People often look at obvious signs of Alzheimer's and pooh-pooh them as signs of normal aging," she said. "But if they get a really good baseline on me early on, the minute I start showing a little decline, I might be able to do something about it. People need to understand how important it is to get involved in studies and be aware of what the possibilities are." *



'A NEED TO KNOW'

A Q&A with new faculty member Dr. Benjamin Williams



Dr. Benjamin Williams, who joined the Alzheimer's Disease Center faculty in July, took a circuitous route to specializing in memory disorders. He earned a doctorate before he got his medical degree, first specializing in marine biology and the motor control systems of invertebrates.

But a career change to medicine, and a challenging three-year residency at the University of California – San Diego, cemented his interest in Alzheimer's disease. Dr. Williams, Associate Professor of Neurology and Neurotherapeutics, comes to UT Southwestern Medical Center from Lubbock, where he was a solo practitioner with a part-time appointment at Texas Tech. He has spent more than two decades treating patients.

Q: How did you end up specializing in Alzheimer's disease and memory disorders?

Dr. Williams: My training program at UCSD was a real hotbed for Alzheimer's research. And when I

went into private practice, it was obvious that there was a real need for people with memory disorder problems.

Q: You've been a clinician for more than 20 years. What was it like treating Alzheimer's disease when you first started?

Dr. Williams: It wasn't that long ago that people would think, 'Mom is getting senile and there is nothing you can do about it.' Primary care doctors didn't do any kind of cognitive screening. Then the drug companies and researchers took a disease in which there was very little

interest and brought it from the dark closet out into the light. But to this day, the medications have fallen far short of what we want and need, which is very disappointing. Still, there is a service performed by being able to tell an individual, 'Yes, I really believe you have this disease.' People can make plans. Families can understand what is going on. People have a need to know.

Q: Are there Alzheimer's prevention strategies that you tell your patients?

Dr. Williams: There is some evidence that physical activity helps. That would be aerobic activity, and more frequent than most people want to hear about it. Also, eat a healthy, Mediterranean diet that includes fish and omega-3 fatty acids; control vascular risk factors such as blood pressure, cholesterol, and diabetes; pay good attention to your primary care doctor; and keep your brain engaged.

Q: What are some tips to keep your mind engaged?

Dr. Williams: If you don't use it, you will tend to lose it. So anything that makes you sit down, pay attention, and concentrate is helpful: crossword puzzles, Sudoku, picture puzzles. Games are great, as long as they are games of some skill. I always joke that a basic card game like slapjack probably is not adequate.

Q: Where are we now in terms of treatment and research?

Dr. Williams: This is a serious disease and people have a real struggle ahead of them. There's momentum in the world of Alzheimer's research, and hopefully some of these ongoing trials will reveal something that will keep the momentum going. *

"If you don't use it, you will tend to lose it. So anything that makes you sit down, pay attention, and concentrate is helpful."

Research Studies

CLINICAL TRIALS

To learn more about studies under way or find out when new studies are added, visit www.utsouthwestern.edu/adc or call the UT Southwestern Memory Research Unit at **214-648-9376**.

IGIV (INTRAVENOUS IMMUNOGLOBULIN)

This 18-month study needs people with mild to moderate Alzheimer's disease between 55 and 89 years of age. The trial's researchers will investigate the effectiveness of IGIV infusions in possibly stopping or reversing Alzheimer's disease. Participants will undergo magnetic resonance imaging (MRI) and receive infusions by IV (intravenous route) every two weeks for a total of 36 infusions, most of which will be done at home by a home health agency. Trial participation also requires that a study partner accompanies the subject for each visit. Call Charlotte Isah at **214-648-9310** for more information.

RESVERATROL

This placebo-controlled trial (participants may or may not be receiving actual drug) requires 10 in-clinic visits over a period of 52 weeks. Eligible persons must have a diagnosis of mild to moderate Alzheimer's disease, be 50 years of age or older, and have a study partner attend all in-clinic visits. Resveratrol, a substance found in red grapes, red wine, and chocolate, may have anti-aging effects. The study investigators hope to learn whether daily doses of pure resveratrol can delay or affect memory loss and functioning. All trial participants must undergo a spinal tap and volumetric magnetic resonance imaging (VMRI). For more information, call Jackie Rabb at **214-648-9358**.

EXERCISE

People with mild cognitive impairment who do not currently adhere to a regular fitness program are needed for a one-year study that will compare individually tailored, supervised aerobic exercise training with flexibility and stretching training. The trial researchers will investigate the effects of exercise on cognitive and cardiovascular health, as well as changes in proteins known to damage and/or protect the brain. Call Kristin Martin-Cook, **214-648-9368** or Lauren Baikie, **214-345-4629**, for information.

COGNITIVE TRAINING FOR MILD MEMORY COMPLAINTS

People aged 60 or older who are in overall good health but who are noticing more "senior moments" or have been diagnosed with mild

cognitive impairment are needed for a study evaluating the effects of cognitive training on brain function. A brief cognitive screening will be given to determine eligibility for the study. Those who qualify will receive eight cognitive training sessions, study-related assessments, an electroencephalogram to measure brain waves, and follow-up testing. For more information, call Kristin Martin-Cook, **214-648-9368**, or Audette Rackley, **214-905-3007**.

OBSERVATIONAL AND BIOMARKER DEVELOPMENT STUDIES

While these studies do not require or offer a new treatment, they are the foundation for future research and therapeutic trials.

ADNI 2 (ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE – PHASE 2)

This study builds on the first ADNI studies and will enroll people ages 55 to 90 with no memory problems, mild cognitive impairment, or early Alzheimer's disease. Participants will undergo magnetic resonance imaging (MRI), traditional glucose-based positron emission tomography (PET), new amyloid PET scanning to investigate the formation of beta-amyloid plaque formation, and standard neuropsychological and neurological exams. Participants will be compensated for their time and participation. Call Kristin Martin-Cook, **214-648-9368**.



CORE AND TARCC RESEARCH STUDIES

People with mild cognitive impairment, early Alzheimer's disease, or frontotemporal dementia are needed for observational studies. The studies usually involve one visit a year for neuropsychological testing, neurological exams, brain imaging, and blood sampling. The data collected from these visits are used by many investigators studying the aging brain and disorders of cognitive function. These visits often involve financial compensation. Call Sarah Hoefs, 214-648-0563.

TELENEUROLOGY

People with dementia are needed to participate in a videoconferencing study. Two neurological examina-

tions will be performed by a physician, once in person and once via TV screen. This research may help bring new diagnostic services to rural and underserved populations and aid in the development of new examination procedures for patients who need to be seen by a neurologist but cannot visit a doctor's office due to illness or distance. Call Sarah Hoefs, 214-648-0563.

COMING SOON:

LOAD (LATE-ONSET ALZHEIMER'S DISEASE GENETICS INITIATIVE)

The LOAD study, originally begun in 2002 and closed in 2011, will begin again in the next few months focusing on phone follow-ups of previously enrolled persons and

families. The goal of this national study is to expand upon the scope of information/data gathered from subjects already enrolled in the first phase of LOAD as well as to enroll new large families (with three or more siblings age 60 or older) diagnosed with Alzheimer's disease. For all subjects previously enrolled in the LOAD study, the coordinator will call each person for phone follow-up only. New subjects from previously participating families who are now age 60 or older may also enroll in this study. Call Barb Davis, 214-648-9367. *

FOOD FOR THOUGHT

Dr. Mary Quiceno offers nutritional advice for those worried about Alzheimer's disease



Dr. Mary Quiceno's patients often come to her clinic with bags of vitamins and supplements, wondering whether their diets or vitamin regimens might help delay or prevent the onset of dementia.

While the science isn't yet conclusive, plenty of studies point to the beneficial effects of certain foods and supplements, said Dr. Quiceno, Assistant Professor of Neurology and Neurotherapeutics at UT Southwestern Medical Center. Some of those studies are taking place at the Alzheimer's Disease Center, where Dr. Quiceno is the leader of the Education and Information Core.

- **Resveratrol:** "We are just starting to recruit for a trial looking at resveratrol – a substance found in red grapes, red wine, and dark chocolate – that is believed to have anti-aging effects. It's also available as an over-the-counter supplement," she said. "We will conduct a study of people with Alzheimer's disease-related dementia to see if it has a direct effect on cognition."
- **Mediterranean diet:** "There's evidence to suggest that the Mediterranean diet is beneficial for people who not only want to prevent dementia, but also for people who already have dementia," Dr. Quiceno said. "Certain cold-water fish, nuts, and oils contain omega-3 fatty acids or are good sources of vitamin E and anti-oxidants – all of which are good for your brain's health. The Mediterranean diet is high in omega-3 rich foods."
- **Algal DHA:** "There was a recent study in which this over-the-counter supplement was given to cognitively normal older people who thought their memory wasn't as good as it used to be. Those who took the supplement seemed to benefit," she said.
- **Turmeric:** "Scientists are just starting to study turmeric, which comes as a supplement and also is a spice often found in Indian food," Dr. Quiceno said. "One of turmeric's components is called curcumin, which is thought to have anti-inflammatory, anti-amyloid, and anti-oxidant properties."

THE ORIGINS OF ALZHEIMER'S

Fall Forum speaker Dr. Scott Small to discuss where Alzheimer's disease begins

By Jeff Carlton

Alzheimer's disease is a progressive disorder that starts in one region of the brain and then spreads. Pinpointing where and why it begins and determining how it spreads over time are critical to diagnosing and treating the disease.

Dr. Scott Small will address those issues on Oct. 30 at the Fall Public Forum, presented by the Friends of the Alzheimer's Disease Center. His lecture is called "Alzheimer's Disease: Where and Why it Begins, and How it Spreads Over Time."

The lecture will be held at the North Campus' Simmons/Hamon

Fall Public Forum

7 p.m. • Oct. 30

6000 Harry Hines Blvd.

Biomedical Research Building, at 6000 Harry Hines Blvd. Complimentary valet parking will be available.

"The ultimate goal is a cure," said Dr. Small, Professor of Neurology at Columbia University Medical Center's Taub Institute for Research on Alzheimer's Disease and the Aging Brain. "Pinpointing where Alzheimer's disease begins and how it spreads opens up novel therapeutic avenues – either by trying to stop the disease at its 'source' or by blocking its spread from that source."

Dr. Small said his lecture will examine a number of studies indicating that Alzheimer's disease begins in the brain's entorhinal cortex, found in the deepest part of the temporal lobes. In people, this region of the brain is located directly above the upper molars. The cortex is part of the hippocampal circuit, which is involved in the memory process, he said.

The lecture also will look at why the disease seems to originate there and how it seems to spread to other regions of the brain.

"There seem to be unique

features of neurons in the entorhinal cortex that make them particularly vulnerable to Alzheimer's pathology," he said.

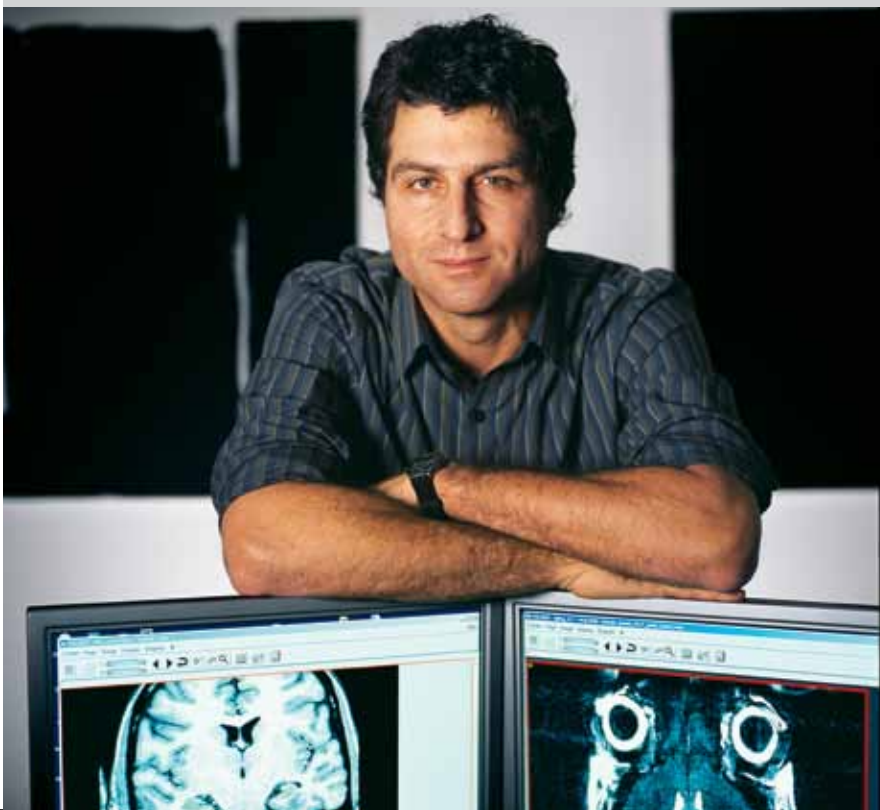
Dr. Small earned his bachelor's degree in psychology from New York University in 1986, graduating from the honors program summa cum laude, receiving the University Award for distinguished honors thesis and the President's Award for academic excellence. He received his medical degree from Columbia in 1992 and then completed a medical internship at UCLA and a neurology residency at Columbia Presbyterian Medical Center.

In 1996, he was selected as Chief Resident of the Department of Neurology. Upon completing a fellowship in neurobehavior in 1998, he joined the Columbia University faculty. Dr. Small's honors include the Herbert Irving award, the Paul Beeson Physician Faculty Scholar Award in aging research, and the McKnight Foundation award in clinical neuroscience.

"I went into medicine to understand how the brain works," he said. "The only way you are going to cure a disease like Alzheimer's is if you understand its fundamental molecular mechanisms."

The Friends of the Alzheimer's Disease Center was established in 1996 to provide financial support for Alzheimer's research at UT Southwestern. All the group's contributions go directly to support Alzheimer's research at UT Southwestern.

Since its founding, the group has raised more than \$1 million for grants to researchers. For information on joining the group, call the Office of Development at 214-648-2344.



antibody crenezumab, developed by Genentech, will be tested to prevent or slow the progression of disease.

If passive immunotherapy with a preformed anti-amyloid antibody is shown to be effective to prevent or slow the progression of disease as hoped for in the design of these clinical trials, then it is possible that active immunization with an anti-amyloid vaccine may have real value. The DNA AB42 vaccine that my colleagues and

I have developed at UT Southwestern continues to undergo the pre-clinical research required by the Food and Drug Administration to obtain an Investigational New Drug License.

That will allow us to begin a Phase 1 clinical trial on asymptomatic persons accumulating amyloid, detected by PET amyloid brain imaging or with studies using cerebrospinal fluid obtained from patients.

These represent extraordinary

advances in understanding the early phases of the disease and in developing new therapeutic strategies that have a high potential to prevent or delay its onset. Alzheimer's disease therapeutics are experiencing significant advances, and UT Southwestern's Alzheimer's Disease Center is contributing to this effort. *

Dr. Rosenberg holds the Abe (Brunky), Morris and William Zale Distinguished Chair in Neurology.

COMMENTARY: A NEW APPROACH

Alzheimer's research needs to shift focus to younger, asymptomatic patients

By Dr. Roger N. Rosenberg and Dr. Reisa A. Sperling

A cardiologist wouldn't wait for a patient to have a heart attack before prescribing a statin drug to lower cholesterol. No oncologist would wait for a tumor to spread before attempting treatment.

Yet when it comes to Alzheimer's disease, which is as fatal as heart attacks and as feared as cancer, that's essentially what we do. It is time for a new approach to Alzheimer's research, one that focuses on new frontiers of discovery.

The scientific community should shift its research focus to therapies that delay or prevent the progression of Alzheimer's disease before dementia robs patients of their minds and memories.

We must encourage and educate our colleagues, the public, and regulatory agencies to realize the potential benefits of early intervention.

In short, we must get better at identifying Alzheimer's disease early and stopping it in its tracks.

Focusing on early intervention therapies may appear to be a simple paradigm shift, but it is possible only because of important developments in recent Alzheimer's disease research.

Through advanced brain imaging techniques and in biochemical studies of cerebrospinal fluid, which surrounds the brain, we can identify people who are most at risk for cognitive loss and Alzheimer's disease before they show any outward symptoms.

Researchers have identified one of the earliest brain changes in Alzheimer's disease: the accumulation of a protein called beta amyloid, detectable with a spinal tap test or brain imaging scan. Low levels of beta amyloid in the cerebrospinal fluid – which also can be detectable via PET brain scans – typically mean the protein is accumulating in the brain. Scientists believe that high amyloid mean that a person is at increased risk for progressing to Alzheimer's dementia.

The current strategy for clinical research trials for new anti-Alzheimer's drugs is to test them on patients already suffering from dementia, which we now recognize as a late stage of the disease. By dementia's onset, the brain is far too damaged to recover.

The Food and Drug Administration has approved no new drug therapies for Alzheimer's disease since 2004, and the three drugs in use are of limited benefit and do not address the disease's basic biology. The pharmaceutical industry has spent billions of dollars over the past decade without discovering effective therapies.

It is daunting to contemplate clinical trials of medications that may have side effects in "normal" asymptomatic patients who happen to be at risk for Alzheimer's disease. The potential benefit, however, could be transformative.

There is desperate need for bold new ideas and therapies. We must be innovative enough to foster discovery

of new drugs as early as possible.

We now recognize at an earlier stage than ever before the patients who are at risk for Alzheimer's. Now we must find better ways to treat them.



its Alzheimer's Disease Center.

Dr. Rosenberg is a Professor of Neurology and Neurotherapeutics at UT Southwestern Medical Center and the Director of



Alzheimer's Research and Treatment at Brigham and Women's Hospital in Boston.

Dr. Sperling is an Associate Professor of Neurology at Harvard Medical School and the Director of the Center for

This commentary originally appeared in the *Houston Chronicle*.

SUPPORT THE QUEST FOR PREVENTION, TREATMENT, AND A CURE



JOIN THE FRIENDS OF THE ALZHEIMER'S DISEASE CENTER

The Friends of the Alzheimer's Disease Center provides crucial support to UT Southwestern Medical Center's most promising and passionate researchers working to unlock the mysteries of Alzheimer's disease.

In addition to funding research through generous annual grants, the Friends sponsor a community-wide public forum every fall and spring, where the latest breakthroughs and best information on Alzheimer's disease are presented by leading experts from UT Southwestern and major medical centers nationwide.

Membership begins at \$500 per year, per individual or couple. Your donation is tax deductible and truly makes a difference in the fight against Alzheimer's disease.

To join the Friends of the Alzheimer's Disease Center, call **214-648-2344** or visit our website at www.utsouthwestern.edu/donatenow. Your support safeguards vital research into enhancing quality of life through early detection and improving the lives of patients and their families who live courageously each day with Alzheimer's disease.

GETTING SERIOUS ABOUT SIGNS OF FORGETFULNESS

Many people who experience "senior moments" call the Alzheimer's Disease Center to ask whether such experiences might be more serious than normal memory changes. This concern is especially true when other family members have developed Alzheimer's disease.

It can be difficult to tell the difference between typical memory glitches and symptoms related to mild cognitive impairment (MCI). A thorough evaluation by a doctor who specializes in cognitive issues and uses objective cognitive tests can differentiate between the two. There are, however, a few key differences to consider:

- Normal memory changes with age may include misplacing things, occasionally forgetting names, forgetting why one walked into a room, taking longer to make decisions, or finding it harder to pay attention to details. Generally, the information forgotten is not significant and eventually recalled.
- MCI, however, affects cognition and short-term memory more significantly. Issues with remembering names or misplacing

items occur more consistently and the information forgotten may be more important. These memory issues also reflect a change from how the person was functioning previously. People may have more problems with word-finding, forgetting to pay bills, missing appointments or events, and needing details repeated to them more often. Still, these changes are subtle and do not affect the person's ability to do routine daily activities.

Research studies suggest that many MCI patients who have memory loss as their primary change eventually progress to Alzheimer's disease. Furthermore, the current focus of cognitive research is on MCI. Researchers want to detect the earliest signs of memory impairment through various imaging techniques, cerebral spinal fluid, and cognitive tests to develop a treatment or medication to stop the continuing brain changes leading to Alzheimer's. Contact us through an email at ADC@utsouthwestern.edu or call our ADC at **214-648-0563** for more information.

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