ALZHEIMER'S DISEASE COOPERATIVE STUDY

Fill in the GAP

For Participants in the Gammaglobulin Alzheimer's Partnership

Summer 2011

Alzheimer's Prevention Initiative

Alzheimer's disease is quickly reaching crisis levels. The Alzheimer's Prevention Initiative (API) intends to help find answers.

Led by Eric Reiman, MD, and Pierre Tariot, MD, from the Banner Alzheimer's Institute, in collaboration with the Arizona Alzheimer's Consortium and other academic, scientific and industry partners around the world, the Alzheimer's Prevention Initiative aims to:

- Evaluate some of the most promising Alzheimer's treatments in prevention trials as soon as possible.
- Provide necessary evidence that evaluates promising risk-reducing and prevention treatments using brain imaging and other biomarkers that demonstrate a treatment's effect on these on Alzheimer's disease.
- Evaluate anti-amyloid treatments before the onset of symptoms, when the treatment is likely to have its most profound effect—and thus provide the best test yet of this approach to the treatment of Alzheimer's.
- Give those people at highest risk of Alzheimer's symptoms access to the most promising treatments in prevention trials

Alzheimer's Prevention Initiative researchers plan to conduct prevention trials in cognitively normal people who, based on their age and genetic background, are at the highest risk of developing memory and thinkingdifficulties Current plans are underway to study the following:

- An extraordinary extended family of 5,000 people from Medellin, Colombia, about a third of whom carry a rare misspelling of a gene called PS1 that causes them to develop Alzheimer's symptoms, starting at the average age of 45. (This work will be performed in collaboration with Dr. Francisco Lopera and his colleagues in Colombia.)
- People with one or two copies of a more common gene, called APOE4, found in approximately one-fourth of the population, that greatly increases their risk of developing Alzheimer's symptoms at older ages. (This work will be performed in the United States.)

They are in the process of developing a U.S.-based Alzheimer's Prevention Registry. For more information and updates about their global Alzheimer's Prevention Initiative go to:

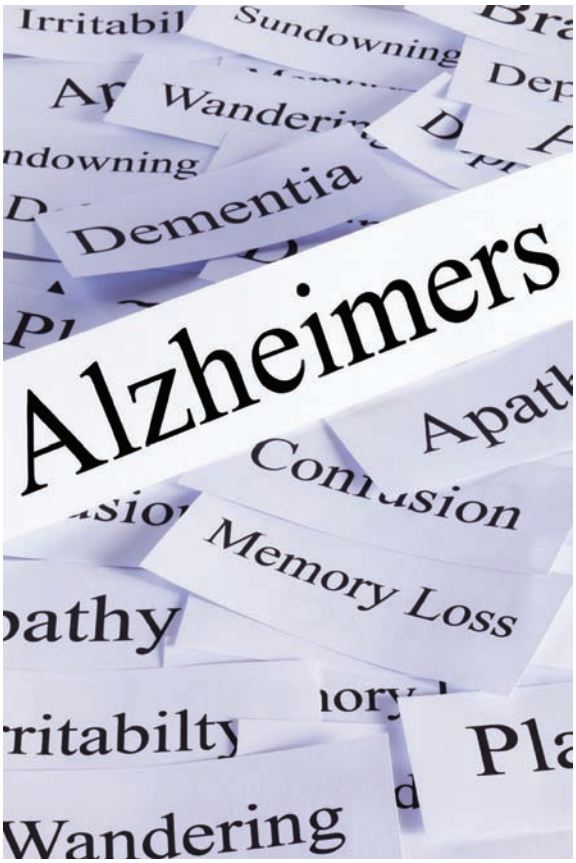
http://tinyurl.com/4nmhf6p

Or you may call (602) 839-5000 or (888) STOP-ALZ (toll free).

IN THIS ISSUE:

What's the Difference Between Alzheimer's and Dementia?

Too often, patients and their family members are told by their doctors that the patient has been diagnosed with "a little bit of dementia." They leave the doctor's visit with a feeling of relief that at least they don't have Alzheimer's disease (AD). There is great confusion about the difference between "dementia" and "AD." The confusion is felt on the part of patients, family members, the media, and even healthcare providers. This article provides information to reduce the confusion by defining and describing these two common and often poorly understood terms.



"Dementia" is a term that has replaced a more out-of-date word, "senility," to refer to cognitive changes with advanced age. Dementia includes a group of symptoms, the most prominent of which is memory difficulties with additional problems in at least one other area of cognitive functioning, including language, attention, problem solving, spatial skills, judgment, planning, or organization. These cognitive problems are a noticeable change compared to the person's cognitive functioning earlier in life and are severe enough to get in the way of normal daily living, such as social and occupational activities.

A good analogy to the term dementia is "fever." Fever refers to an elevated temperature, indicating that a person is sick. But, it doesn't give any information about what is causing the sickness. In the same way, dementia means that there is something wrong with a person's brain, but it doesn't provide any information about what is causing the memory or cognitive difficulties. Dementia is not a disease; it is the clinical presentation or symptoms of a disease.

There are many possible causes of dementia. Some causes are reversible, such as certain thyroid conditions or vitamin deficiencies. If these underlying problems are identified and treated, then the dementia reverses and the person can return to normal functioning. However, most causes of dementia are not reversible. Rather, they are degenerative diseases of the brain that get worse over time. The most common cause of dementia is AD, accounting for as many as 70-80% of all cases of dementia. Approximately 5.3 million Americans currently live with AD. As people get older, the prevalence of AD increases with approximately 50% of people age 85 and older having the disease. It is important to note, however, that, although AD is extremely common in later years of life, it is not part of normal aging. For that matter, dementia is not part of normal aging. If someone has dementia (due to whatever underlying cause) it represents an important problem in need of appropriate diagnosis and treatment by a well-trained healthcare provider who specializes in degenerative diseases.

In a nutshell, dementia is a symptom, and AD is the cause of the symptom. When someone is told they have dementia, it means that they have significant memory problems as well as other cognitive difficulties, and that these

problems are severe enough to get in the way of daily living. Most of the time, dementia is caused by the specific brain disease, AD. However, some uncommon degenerative causes of dementia include vascular dementia (also referred to as multi-infarct dementia), frontotemporal dementia, Lewy Body disease, and chronic traumatic encephalopathy. Contrary to what some people may think, dementia is not a less severe problem, with AD being a more severe problem. There is not a continuum with dementia on one side and AD at the extreme. Rather, there can be early or mild stages of AD, which then progress to moderate and severe stages of the disease.

One reason for the confusion about dementia and AD is that it is not possible to diagnose AD with 100% accuracy while someone is alive. Rather, AD can only truly be diagnosed after death, upon autopsy when the brain tissue is carefully examined by a specialized doctor referred to as a neuropathologist. During life, a patient can be diagnosed with "probable AD." This term is used by doctors and researchers to indicate that, based on the person's symptoms, the course of the symptoms, and the results of various tests, it is very likely that the person will show pathological features of AD when the brain tissue is examined following death. In specialty memory clinics and research programs, such as the BU ADC, the accuracy of a probable AD diagnosis can be excellent. And, with the results of exciting new research, such as that being conducted at the BU ADC, the accuracy of AD diagnosis during life is getting better and better.

This contribution was made by Dr. Robert Stern, Director of the BU ADC Clinical Core.

A Potential AD Blood Test

Michael S. Rafii, MD, PhD
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Using a new technology that relies on thousands of synthetic molecules to fish for disease-specific antibodies, researchers have developed a potential method for detecting Alzheimer's disease with a simple blood test. The same methodology might lead to blood tests for many important diseases, according to the report published by Thomas Kodadek's group at the Scripps Research Institute in the January 7th issue of the journal Cell.

The new method relies on the notion that many diseases lead to the production of modified proteins. At some point, the adaptive immune system might begin to recognize those proteins as foreign and mount a response. If tests could be developed to recognize those disease-specific proteins or the antibodies that recognize them, it could be the basis for early diagnosis. But in most cases, researchers have had little luck identifying those abnormal proteins.

Kodadek's team decided to take a different tack. They used a large library of randomly selected, unnatural molecules known as "peptoids" to screen for antibodies found in the bloodstream of animals or patients with specific diseases and not in healthy controls.

Their method uncovered three peptoids that appear to discriminate between healthy and Alzheimer's disease blood samples with high accuracy. Three of them reacted strongly to the blood of six patients with the condition, but not that of 16 healthy individuals used as controls. Although this is encouraging the findings must be corroborated by further studies to demonstrate that antibodies can indicate whether the attack opens a picture for diagnosing the disease.

*** Reddy MM, Wilson R, Wilson J, Connell S, Gocke A, Hynan L, German D, Kodadek T. Identification of candidate IgG biomarkers for Alzheimer's disease via combinatorial library screening. Cell 2011 January 7;144:132-142.*

What Do the Religious Studies Reveal??

An Update on the AD Religious Studies

Since 1993, substantive findings in Alzheimer's Disease (AD) research have come from two longitudinal studies involving monastic orders. Neither the University of Minnesota's Nun Study, nor Rush University's Religious Orders Study, is likely to directly result in a cure for AD. Rather, both studies continue to make breakthroughs in the identification and investigation of potential AD prevention strategies.

To say that the religious study participants are an AD researcher's dream is probably an understatement. The clergy-subjects often live homogeneous lifestyles and are willing to make commitments to ongoing cognitive testing. As a result, the AD religious studies have off- the -charts subject retention rates. Finally, the participants in both studies agreed to donate their brains to the research project after death.

The studys' goals are to try to track cognitive decline during old age and identify risk factors for AD. Researchers gain a rich understanding of how the participants lived their lives — from how much they exercise, to what foods they eat, to what activities they participate in. Later, they examine the condition of their brains, from the physical shape ofthe cerebral cortex, to the accumulation amyloid and other proteins in the brain thought to contribute to AD.

What We've Learned from the Nun Study

Beginning in 1986, a young University of Minnesota epidemiologist initiated a pilot study of the aging process using subjects from a local School Sisters of Notre Dame convent. Results from Dr. John Snowdon's original pilot study immediately attracted the attention of the AD research community. Since that time, the studyhas grown to become one of the foremost clinical research studies in history. The sisters were an unusually rich group of study subjects. Researchers stumbled into a uniform and concise convent recordkeeping system that included work and family histories, socio-economic information, medical records, and historic autobiographies of all study participants.

Dr. Snowdon's Nun Study began in earnest in 1993. Since that time, the study moved with him to the University of Kentucky and back again to the University of Minnesota in 2009, as Dr. Snowdon began his retirement. In 2001, the study made the cover of Time magazine and was the subject of Dr. Snowdon's bestselling book *Aging with Grace: What the Nun Study Teaches Us About Living Healthier, and More Meaningful Lives.*

The research is ongoing and the results continue to impress. Here are some examples of things the religious have taught us date:

- The finding of an apparent correlation between "idea density" and linguistic ability in youth as an indicator of AD later in life.
- The potential relationship between folate levels and AD.
- Identification of the potential impact of undetected stroke and a new emphasis on the relationship between vascular health and AD.
- The relationship between historic head injuries and AD.

Findings from the Rush Religious Orders Study

The longitudal Religious Orders Study, led by David Bennett, MD, at the Rush Alzheimer's Disease Center (ARC) in Chicago, began in 1993. Since the first clinical evaluations in 1994, the National Institutes of Health (NIH) supported study has grown to include over 1,100 Catholic clergy-participants throughout the United States.

The research project is focused on the identification of AD risk factors and exploration of the neurological basis of AD and cognitive impairment. The study is also examining the role that the environment and genetics play in AD and cognitive decline. The clinical data and the volume of tissue from the Religious Orders Study is expected to spawn further examination of the causes and prevention of AD and cognitive decline.

Currently, the most exciting work coming out of the Religious Orders Study is related to cognitive reserve. The ongoing research looks at how the sum of life experiences may impact the development of AD. Specifically, researchers are evaluating how a lifetime of physical, mental and emotional health may result in a cognitive reserve that offsets the development of AD.

The study is funded through 2011 and Dr. Bennett and the Rush ADC are expected to continue the study for, at least, another five years. To date, published results have included:

- Evidence for an association between cognitive stimulation and lesser cognitive decline.
- Presentation of data suggesting a link between diabetes, undetected stroke, and increased risk of AD.
- A potential link between the loss of body mass over time and AD.

Walking and the Risk of Cognitive Decline

By Michael S. Rafii, MD, PhD
Associate Medical Director, Alzheimer's Disease Cooperative Study

Researchers from the University of Pittsburgh analyzed the relationship between walking and brain structure in 426 people: 299 cognitively healthy adults, 83 people with MCI, and 44 people with Alzheimer's dementia. The researchers monitored how far each of the patients walked in a week. After 10 years, all patients underwent 3-D MRI exams to identify changes in brain volume.

When they entered the study in 1989-1990, participants were asked how many city blocks they walked in an average week, whether for exercise, chores, or any other reason. Follow-up questionnaires every three years showed that the number of blocks walked remained steady over time. In addition, participants were given a brief test of cognitive skills at various times throughout the study, with the final one five years after the second MRI scan.

As shown by MRI, brain volume was preserved in healthy adults who walked at least 72 city blocks, or 6 miles, per week. Cognitive exam scores showed walking six miles a week was associated with a 50% decline in Alzheimer's risk over 13 years. Walking more than 72 blocks a week offered no additional benefit. Cognitively impaired people needed to walk at least 58 city blocks, or approximately 5 miles, per week to maintain brain volume and slow cognitive decline. Over 10 years, scores on the 30-point cognitive test dropped by an average of five points in cognitively impaired patients who were sedentary, compared with one point in those who walked 5 miles per week.

The relationship between walking and preserved brain volume persisted even after the analysis was adjusted to take into account other risk factors for dementia, including age, gender, and high blood pressure.

The findings showed across the board that greater amounts of physical activity were associated with greater brain volume.

**Raji CA, et al "Physical activity and brain structure in healthy aging and cognitive impairment" RSNA 2010.*

Does Bilingualism Delay the Onset of Alzheimer's Disease?

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On a recent trip to Canada I was asked by friends and family about the latest news that hit the Canadian print media, "Could being bilingual actually prevent the onset of Alzheimer's disease?"

According to investigators from the Rotman Research Institute at Baycrest in Toronto, the answer appears to be, "Possibly…. yes". Cross sectional data was reported from a group of 211 Alzheimer's disease patients who received care at the Baycrest clinic in Toronto, Canada. As is typical for most visits to a memory clinic, information regarding age of onset of cognitive problems, information about occupation, education, and language history were taken. Other information obtained unique to this group was fluency in English and other languages, place of birth, and date of immigration to Canada. To be classified as "bilingual" a person had to have spent the majority of his/her life (at least from early adulthood) regularly using at least two languages. A total of 102 patients were classified as bilingual (60 women) and 109 were monolingual (60 women). The bilingual patients included speakers of 23 first languages of which the five most common were Yiddish (n= 24), Polish (n= 12), Italian (n= 11), Hungarian (n=9) and French (n= 7).

In simple statistics that compared groups, persons who were monolingual presented with memory complaints at a younger age- 72.6 y (SD=10) compared to 77.7y (SD=7.9) in those who were bilingual. This main finding suggested that the "onset of the dementia" process was delayed by 5.1 years in those patients who spoke more than one language. In order to see if any differences occurred within the monolingual and bilingual groups that could possibly explain these findings, the investigators conducted further analyses, that looked at the duration of time between symptom onset and "clinic appointment", immigrant status, years of education, and potential gender effects in both groups.

On average it took approximately 3.5 years for a patient to present to the clinic for a formal evaluation: 3.8y (SD=2.9) for monolingual patients, and 3.1y (SD=1.9) for bilingual patients. However, monolingual patients presented to the clinic at younger ages (76.5y, SD=10.0) than bilingual patients (80.8y, SD=7.7). Neither immigrant status, years of education, or gender were thought to contribute to the main findings.

This study suggests that bilingualism- a cognitively demanding task – may contribute to the "cognitive reserves" of the brain thus enhancing intellectual functioning in advancing age. Most research in this area, has touted the positive effects of intellectual (i.e., crossword puzzles, playing bridge), physical and social activities as building up "cognitive reserve" and thus promoting overall well being. This study adds to the literature that speaking more than one language can build up "cognitive" reserve which ultimately may delay the onset of Alzheimer's disease. Further work will require study of a larger group of patients over time to assess how bilingualism may affect the changes seen in cognition that occur in patients with Alzheimer's disease.

If you would like to read more on this topic please check out the following articles:

Craik F, Bialystok E, Freedman M. Delaying the onset of Alzheimer's disease- Bilingualism as a form of cognitive reserve. Neurology 2010; 75:1726-1729

Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. Psychol Med 2006; 36: 441-454

Bialystok E, Craik F, Freedman M. . Bilingualism as a protection against the onset of symptoms of dementia. Neuropsychologia 2007; 45:459-464.

HDL and Alzheimer's Disease

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According to researchers at Columbia University, people with high levels of HDL cholesterol (the "good" form), are 60% less likely to develop AD. The researchers followed 1,130 seniors with no history of memory loss or dementia and measured their cholesterol levels every 18 months for four years. When the researchers compared the cholesterol levels of study participants with and without Alzheimer's, they found that those with the highest HDL counts, over 55 mg/dL, had about a 60% reduced risk of developing the disease compared to those whose levels were under 39 mg/dL.

Their findings support the theory that high levels of HDL cholesterol are correlated with lower incidence of AD. The study was published earlier this week in the Archives of Neurology and sheds more light on the interactions between cholesterol and AD.

Apolipoprotein E (apoE), as readers of this blog will recall, participates in the mobilization and distribution of cholesterol among various tissues of the body, including the brain. In humans, there are three common isoforms of apoE: apoE2, apoE3, and apoE4. ApoE4 differs from apoE3, the most common isoform of apoE. A single e4 allele is sufficient to increase the risk of developing atherosclerosis, and also Alzheimer's disease. The e4 allele results in slightly elevated plasma LDL cholesterol levels and a small but significant decrease in plasma HDL levels. HDL is one of the major carriers of protein in and out of the brain, and also binds to beta-amyloid.

This finding further advances the idea that the interplay between cholesterol, cholesterol-carrying proteins such as apoE and HDL, and beta-amyloid may be critical in the development of AD. This study has important strengths. It is a prospective cohort study designed for the diagnosis of cognitive decline that has complete clinical and neuropsychological evaluation at each interval.

Guidelines recommend that men raise HDL levels that are under 40 mg/dL and that women increase HDL numbers under 50 mg/dL. An HDL of 60 mg/dL or higher is optimal.

* *Association of Higher Levels of High-Density Lipoprotein Cholesterol in Elderly Individuals and Lower Risk of Late-Onset Alzheimer Disease. Christiane Reitz et al., Arch Neurol. 2010;67(12):1491-1497.*

Fill in the GAP

A Publication of the Alzheimer's Disease Cooperative Study

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ALZHEIMER'S DISEASE ADCS COOPERATIVE STUDY

BRAIN EXERCISE

Mind Games are a really fun way to exercise the mind. Check out the mind games on the BrainBashers website — **www.brainbashers.com** — good for both caregivers who want to stay sharp and study participants with mild dementia.

Answer quickly. Starting with an empty barrel, which happens first?	What is represented by this BrainBat?	What four related words are merged here:
2/3 full 1/4 empty 1/2 full 3/4 empty	Schubert's Symphon	SWAS PURI UINM NTTU MGER MNER
3/4 empty: since 3/4 empty means 1/4 full.	Schubert's Unfinished Symphony	Spring, summer, autumn and winter