New Direction in Delaying or Preventing Alzheimer’s Disease: The TOMMORROW Study*

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If Alzheimer’s disease (AD) research has taught us anything over the last 30 years, it is this: the disease is extraordinarily complicated. We have come to understand that a number of fundamental cellular mechanisms go awry early in the disease, beginning likely in midlife before symptoms are apparent. Ultimately, over a period of decades, two proteins (amyloid and tau) begin to accumulate abnormally resulting in toxicity and cell death. We are now able to diagnose AD earlier in the course of the disease, but finding a treatment, to either cure or prevent the disease, has proven much more elusive. We now believe that an important key to success is in starting targeted treatment early before significant cell injury has occurred. Identifying people at this silent stage of disease is tricky. It requires a strategy to identify people who are at risk of developing the disease within a few years.

A number of exciting drug prevention trials are starting this year with the same fundamental approach in mind: start early, identify normal individuals at high risk of AD, and try promising therapeutics in this group. The first of the studies to launch is the TOMMORROW study, a novel clinical trial designed to delay the onset of AD symptoms. The TOMMORROW study has its roots right here in the Triangle, conceived by an investigative team within the Joseph and Kathleen Bryan Alzheimer’s Disease Research Center (Bryan ADRC) at Duke University.

The story begins with a genetic discovery in 2009 when a team of scientists led by Allen Roses, MD identified a gene called TOMM40, (this gene is where the TOMMORROW study gets its odd spelling), that interacts with APOE, another AD gene, to influence the timing of symptom onset in AD. In the 1990’s, the Duke team had identified APOE as a major risk gene for AD. Combining both APOE and TOMM40 gene status, the team was able to predict risk of AD in nearly 97% of the individuals studied. This means combined information may offer a way to reliably identify individuals at high risk for AD, appropriate for a clinical trial to delay the onset of their symptoms.

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Every once in a while a person gets extraordinarily lucky. That was me, 27 years ago when I landed at the Duke Aging Center. Little did I know that the Aging Center would give me the knowledge, tools, skillset, and support to launch a career in clinical research focused on physical activity and aging. I have been equally blessed that the Aging Center and the Durham VA Geriatric Research, Education and Clinical Center have longstanding collaborative working relationships. This allowed me to direct an ongoing clinical exercise program for older Veterans, called Gerofit, while at the same time launch several clinical trials aimed at improving physical functioning in older adults through the Aging Center’s Claude D. Pepper Older Americans Independence Center. It has been and continues to be both an honor and a delight to come to work each day.

Over the years, we have shown that it’s never too late to start exercise; that you can experience a positive gain in health benefit, both physical and mental, with exercise; and that you can delay normal age-related declines by remaining physically active. We have collaborated on several landmark studies of exercise and dietary lifestyle directed at older cancer survivors and developed extensive expertise in the development of home-based exercise interventions that we have delivered to diverse groups of older adults (stroke patients, intensive care survivors, older adults at high functional risk, and overweight pre-diabetics) who stand to benefit from being physically active. This year we received $835,000 to implement the Gerofit program at 4 VA Medical Centers across the country!

The most exciting thing about being part of the Aging Center is that you get to collaborate with all sorts of wonderful people. This past year I have focused more on acute and transitions of care and have had the opportunity to work with young investigators implementing a walking program for hospitalized older adults and a walking program for older adults transitioning between hospitalization and early discharge. Both of these programs have demonstrated remarkable maintenance of physical function during the vulnerable periods of hospitalization and discharge with substantial potential for cost savings to the health care system.

I have also been working with a group of geriatricians, surgeons and anesthesiologists who have an interest in improving the outcomes of the older surgical candidate. The literature suggests that while old age is a risk factor for poor outcomes following surgery, low physical fitness and poor physical function are even stronger predictors of risk than age. One of the strongest predictors of functional risk for surgical outcomes is based on a simple test (the Timed-Up and Go Test (Tug) in which a person is asked to rise from a chair, walk around a cone that is ten feet away and return to sitting. A TUG score of 15 seconds or more is a strong predictor of post-operative discharge to an institution. In our preliminary research in this area we observed a decrease from 23 seconds to 14 seconds (39% improvement) in just under 3 weeks of exercise training in an 82-year old man meeting objective criteria for intermediate frailty. We also documented 16% and 21% improvement in chair stands and 6-minute walk distance in an older woman with only 3 weeks of exercise training between the diagnosis of cancer and abdominal oncology surgery.

There remains much to be done in the exercise world. Every day brings new opportunities and the Aging Center is the perfect place to have them come to fruition.
EDITORIAL*
Warning: Ageism May Be Hazardous To Your Health*

By Erdman Palmore, PhD

We have known for some time that most people admit to various forms of ageist behaviors, such as sending greeting cards that make fun of old people or telling jokes about old people. More seriously, numerous studies have found widespread age discrimination in the work place, from compulsory retirement to refusal to promote.

However, only recently has research shown that ageism may be “hazardous to your health.” For example, Becca Levy, PhD, and her colleagues at Yale University found that people ages 18 to 49 with negative stereotypes about older adults had twice the risk of heart attack 30 years later compared to those with positive attitudes.

In another study, she and her colleagues found that persons over age 70 with negative stereotypes of aging were much less likely to fully recover from severe disability than those with positive views.

Ageism can also affect memory performance. Participants in the Baltimore Longitudinal Study of Aging who held negative stereotypes about aging had a 30 percent greater decline in memory 40 years later than those with more positive views.

Hopefully, as we learn more about aging and communicate this information to the public, we can reduce the ignorance and prejudice that cause ageism.

* Partially based on “Ageism: Alive and Kicking” by Tina Adler in the Observer, September 2013. The opinions in this editorial are those of the author and do not necessarily reflect policy of the Duke Center for the Study of Aging.

New Direction in Delaying or Preventing Alzheimer’s Disease: The TOMMORROW Study*, continued

Around the same time, other scientists found that a type of drug used to treat diabetes was also effective in improving memory and function in areas of the brain affected by AD in humans. In animals, the drug reduced amyloid deposition in the brain. Intriguingly, these positive effects were seen with very low doses of the drugs, nearly 55 times lower than the dose used in diabetes. The drug used in these studies, pioglitazone, is commonly prescribed for Type II Diabetes, so the safety profile is well known. And the very low dose needed in order to have a brain protective effect, helps to reduce potential safety concerns. Perhaps one of the most exciting features of this class of drugs for AD is that they appear to influence a number of cellular processes damaged early in the disease. This offers hope that if begun early in the disease process, the compound may have an effect in slowing down the disease.

The investigators working on the TOMM40 discovery entered into an alliance with Takeda pharmaceutical company which manufactures the compound pioglitazone. At the end of August this year, the study officially launched in the U.S. Over the next 2 years, 50 sites across Europe and the U.S., including a site at Duke and one in Kannapolis NC, will enroll and treat over 5800 cognitively normal adults (ages 65-83), many of whom are at increased risk of AD due to their genetics. At the end of 5 years, we will have an answer as to whether we have successfully delayed the early symptoms of this horrible disease.

Those interested in being a part of the TOMMORROW Study or any of our other prevention studies can contact us by phone (1-866-444-2372) or visit our website (https://adrc.mc.duke.edu/).

Be a part of the solution and join us in the search to find a cure for AD. For today is the TOMMORROW we dreamed of yesterday.

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Dzens of the Duke Center faculty and fellows presented their research at the Annual Scientific Meeting of the Gerontological Society of America in New Orleans, LA, on November 20-24, 2013.

C. Chei, D.B. Matchar, X. Shi, Z. Yin, and Y. Zeng, presented a paper on “Vitamin D Deficiency is Associated with Cognitive Impairment in Chinese Elderly: A Result from the Chinese Longitudinal Healthy Longevity Survey.” They concluded that among Chinese elderly, low plasma vitamin D levels were associated with increased odds of cognitive impairment.

N. Dimitrieva was first author of a paper on “Impact of Demographics-Based Differential Item Functioning on Depressive Symptoms among Older Adults.” They concluded that there was measurement equivalence across demographic factors in the four selected studies.

Q. Feng and Y. Zeng presented a poster on “Trends in Disability in the Older Adult May Vary under Different Measurements: An illustration in the Chinese Elderly Population from 2002 to 2008.” They concluded that the improvement in the observed ADL and IADL could be largely due to changes in the living environment instead of the intrinsic improvement of body function.

I. Iwata, M.A. Greiner, L.G. Qualls, H. White, S.L. Moloney, T. Sullivan, B. Burke, and S. Setoguchi, presented a paper on “Clinical Prediction Rule for One Year Nursing Home Placement among High Risk Older Adults.” They concluded that this prediction rule allows health care providers to estimate baseline risk of nursing home placement and to tailor care among high-risk older adults.

K. Lee, B. Wu, and B. Plassman presented a paper on “Cognitive Function and Dental Care Utilization among Older Adults.” They concluded that individuals with dementia were significantly less likely to visit the dentist regularly than cognitively normal individuals. (See also Wu and Plassman papers.)

L. K. Manning presented a paper on “Understanding and Enhancing Resilience in Later Life: A Qualitative

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Analysis." She concluded that having and cultivating resilience is crucial for aging well.

B.G. Matchar, A. Kane, L.H.Kohn, M.A. McWilliams, J. Schwartz, and L.P. Gwyther presented a poster on “Outcomes and Impact: A Community Partnership Extends an Evidence-Based Early-Stage Alzheimer’s Group.” They concluded that there were beneficial outcomes in several domains including increased self-confidence, communication, and social engagement, as well as decreased stigma.

M. Peterson, S. Hastings, M. Morey, M. Pearson, L. Bateman and K. Caves presented a symposium on “Stride@Home: A VA Non-institutionalized Care Demonstration Program.” They concluded that Stride@Home is an innovative clinical demonstration program that is a potentially cost-saving alternative to institutionalized care for older Veterans at risk for rehospitalization.

B. Plassman, K. Lee, and B. Wu presented a paper on “Drilling Down on the Association between Oral Health and Cognitive Impairment.” They concluded that cognitively impaired individuals had poorer oral health; and that interventions focused on compensating for specific cognitive deficits may increase the benefits for those with cognitive impairments.

K. A. Porter, M.B. Aselage, T. L. Yap, K. Corazzini, C. Colon-Emeric, and R.A. Anderson presented a paper on “Innovation in Treatment Fidelity: Measuring Receipt of Treatment Using Individualized Mapping.” They concluded that the Individualized mapping process 1) reinforces participants’ use of interaction skills, and 2) provides a measure of intervention content mastery and uptake.

K. Shipp presented a paper on “Exercise for Rehabilitation after Osteoporotic Fracture.” She concluded that for hip fractures both home and community-based interventions of progressive resistance training improve strength, balance, fast walking speed, and physical performance.

N. Sperber, C.I. Voils, N.B. Coe, K. Konetzka, J. Boles, C.H. Van Houven presented a paper on “How Do Family Dynamics Influence Long-Term Care Insurance Purchase Decisions?” They concluded that to achieve greater insurance coverage, policymakers and insurers should consider desire for choice when designing policies and products.

B. Wu, G. Fillenbaum, B. Plassman, L. Guo, and L. Quin presented a paper on “Association between Oral Health and Cognitive Status Review of Longitudinal Studies.” They concluded that while some association between dental and cognitive state might exist, the findings were inconsistent across the studies. Standardization of procedures is desirable to produce useful information.

Also L.P. Gwyther was the discussant for the symposium on “Cognitive Impairment and Oral Health in Older Adults.”
By Nancy Lelle-Michel, MSN, CDE, Janet Nicollerat, MSN, CDE, and Ellen Davis, MS, CDE*

The literature abounds regarding the efficacy of Continuous Glucose Monitoring (CGM) for people with Type 1 diabetes, although it primarily focuses on use in pediatric and adolescent populations. There is a lack of evidenced based research addressing CGM use in elders. The increased longevity in this group raises the risk for complications such as severe hypoglycemia.

Although Self Blood Glucose Monitoring (SBGM) has been the foundation for diabetes management, the advent of CGM technology has provided patients and clinicians with essential data to facilitate pattern management designed to avoid hypoglycemia and ketoacidosis.

The main advantage of CGM is that it reveals peaks and lows in blood glucose levels that SBGM by finger sticks may miss. (see Graphics) This is especially important for older patients. We at the Duke School of Nursing are trying to encourage older diabetes patients to use CGM instead of finger sticks.
We have four visiting scholars from China at the Center this year: Wang Zhi Zhong, Xibing Zhu, Zhang Xianling, and Xiujie Zhu.

**Wang Zhi Zhong** earned a masters degree in prevention medicine from Ningxia Medical School (2005) and a PhD degree in epidemiology and medical statistics from the Fourth Military Medical University (2009) of China. Currently he is an associate professor in the School of Public Health of Ningxia Medical University. His main research interests and experiences focus on mental health and services in minority populations of western China. Wang has received grants from the Chinese National Natural Science Fund (NNSF) to study the prevalence of mental disorders and their predictors in Hui migrants in Ningxia; and as a Co-Principal Investigator for a study titled, “Epidemiological investigation and health system interventions for mental health in rural western China,” which was supported by the China Medical Board (CMB) in 2011. He will be working with Harold Koenig, MD, in his research here.

**Visiting Scholar Xianling Zhang** is a Ph.D candidate at the Institute of Population Research of Chinese People’s University. She will be working on an “Analysis and Projections of Offspring Resources of Care Givers for Old Parents and Youngsters’ Responsibility for Caregiving.” Along with the rapid development of population aging, research on care-giving to the elderly becomes an increasingly important issue. However, at present there are few projection studies in this field. She plans to conduct this research under the guidance of Prof. Yi Zeng at the Duke Aging Center during her visit from end of Aug. 2013 to the end of Aug. 2014. Her research is in the context of rapid population aging and large changes in intergenerational living arrangement in China. She is also interested in the impacts of care-giving for old parents on youngsters. She will apply the ProFamy extended cohort-component method in this research, using the newest Chinese population census and survey data. In addition to doing research, she is auditing demographic, sociological and international health related courses and participating in related academic seminars.

**Xibing Zhu** is a Ph.D. student from the School of Social and Behavioral Sciences, Nanjing University, Nanjing, China. During her visit (from Oct. 2, 2013 to Jan. 2, 2014) at Duke Aging Center, she will participate in population aging and demography related academic seminars. She will conduct the project “Effects of Family Planning Program on Population Aging in China”, which is an important part of her doctoral dissertation. She will explore the relation between the family planning program and healthy aging. She will explore how the past and present Chinese family planning affects population aging. She will also develop a prediction model to investigate how changes in family planning programs in the future may positively affect healthy aging in China.

**Dr. Xiujie Zhu** is an Associate Professor and Deputy Director of the Center for Gender and Development Research, Hohai University, Nanjing, China. She will be a visiting scholar at the Duke Aging Center from August, 2013, to August, 2014. She plans to do research on the “Quality of Death among Chinese Elderly,” based on the data from a few waves of Chinese Longitudinal Healthy Longevity Survey (CLHLS). She seeks to explore the factors which make a difference in the quality of death among Chinese elderly. With supervisions from Prof. Yi Zeng and Prof. Linda George, she plans to conduct comparative analysis on males vs. females, oldest-old aged 80+ vs. young-old aged 65-79, rural vs. urban, etc. Using multivariate regression analysis, the study strives to understand the continually changing interrelations between aging people and their socioeconomic environment and how these relationships shape the situation and quality of death among elderly. Through involvement in modification and promotion of policy and intervention programs, the study strives for enhancing the well-being of elderly and their families. In addition, she will audit some courses and actively participate in related academic seminars.

Welcome to you all, and good luck with your research!
Deborah T. Gold, PhD, and Keith E. Whitfield, PhD, Senior Fellows at the Center on Aging are spearheading the Gerontological Society of America’s (GSA) project to jumpstart new activities and pilot innovative means for mentoring.

“Mentoring has always been central to scholars in aging but few financial resources have been available to support mentoring activities,” said Gold, an associate professor of psychiatry & behavioral sciences. “The founders of The Mentoring Effect include many former and current leaders of GSA who believe in supporting mentoring to insure an outstanding future for the Society.”

Both Gold and Whitfield are recipients of the Distinguished Mentorship in Gerontology Award. Whitefield is professor of psychology and neuroscience.

More information about making contributions to The Mentoring Effect can be found on GSA’s website at www.geron.org/giveback.
February 27–March 2, 2014:

“Aging in America.” Annual Conference of the American Society on Aging at San Diego, CA. Contact: asaging.org/aia

April 3–6, 2014:

May 15–17, 2014:

November 5–9, 2014: