



Fill in the GAP

FOR PARTICIPANTS IN THE GAMMAGLOBULIN ALZHEIMER'S PARTNERSHIP

Winter 2012



LETTER FROM THE STUDY LEADER

Norman Relkin, MD, Ph.D
Weill Cornell Medical College, New York

Dear GAP Study Participants,

2012 not only marks the end of the Mayan calendar - it will be a landmark year for Alzheimer's disease (AD) research as well. Three major Phase 3 studies of immune treatments for AD will be completed in 2012. This includes the studies of Bapineuzumab, Solanezumab and the GAP study of IGIV in which you are participating.

GAP enrolled its first participant in December, 2008. In November 2011, the study reached an important milestone when the first 120 participants completed 18 months of study treatment. A group of independent experts that make up the study's DSMB (Data Safety Monitoring Board) examined results from these 120 completers to determine whether it was justified to continue the study.

I'm happy to report that the DSMB recommended that the study continue without modification. In itself, this result does not prove that IGIV treatment is beneficial for AD. The only way to tell is to complete the entire study in all the enrolled participants. The DSMB recommendation indicates that there is at least a chance of success and a sufficient safety record to justify going forward with the study. We expect all those enrolled to complete the planned infusions by December 2012. Results of this landmark

clinical study will be made available soon thereafter.

Your continued commitment to the GAP study does not go unnoticed. Each of you is now critical to its successful completion. I speak for the entire GAP team in saying we are extremely grateful for your continuing participation. It means a lot to everyone who is hoping for new and better treatments for Alzheimer's disease.

*You are
the heroes
of AD
research*

For those of us working toward a cure for AD, one of our biggest hurdles is finding volunteers who complete studies like GAP. I can't stress how important it is to see the study through to completion. This is the only way we will advance AD research at the pace needed to be successful against this epidemic.

In this election year, I encourage you to lend your voice and raise awareness of the importance of clinical trials in the fight against AD. To continue the momentum, we must spread the word that everyone can contribute to AD research. No medical degree required.

You are the heroes of AD research. I will write to you again later in the year.

Sincerely,
Norman Relkin MD, Ph.D

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The Caregiver

Elisabeth Paine, whose husband John is a participant in an AD study, offers her perspectives on being a caregiver-partner.

My Name is Elisabeth Paine. My husband John was diagnosed with Alzheimer's about three years ago. He was 65 and I was 50. The three words I would use to describe the John I married 11 years ago would be intelligent, competent and independent. If you asked me to name the three things Alzheimer's steals, I would say intelligence, competence and independence.

I don't think there is any other disease as cruel.

Alzheimer's is heartbreaking. I can see this disease eating away at him. I can see that his brain is becoming more disordered and I can see how hard he is fighting against the chaos. Sometimes the reality of this disease is all too clear to him and his voice breaks as he tries to tell me his fears. This disease is exhausting. It is Kafkaesque. Nothing is the same day to day. It bounces around. John may lose a skill one day and regain it the next. You can never get a fix on it. If you think you have something under control, the next minute you don't.

I am constantly learning, analyzing, strategizing, trying to make our life work for John and for me. I work hard to reduce his frustrations and maximize his successes. John is maybe a third of the way into the disease. In these first few years here are some of the things I have found particularly hard.

First, very early on I lost him as an intellectual companion. Carrying

on a real conversation requires a person to be mentally nimble, to keep multiple balls in the air. We can talk about things but that is very different from discussing them. I miss him. Second, in many ways I've lost him as a partner in



John and Elisabeth

our life. Decision-making is a complex activity. He can't help me with the sort of decisions partners usually share. There is no one for me to bounce things off of. Nor can he plan anything. Third, there are many things about our life, decisions I make, that I just don't tell him about. I found this very hard – learning to keep things from him, sometimes even lying. His judgment is not reliable and it is less stressful to both of us to just not involve him. Still, I feel guilty. I feel like I am violating the trust in our marriage.

I have a husband but have lost my partner. Sometimes it is a lonely place.

He can still do many daily things. He dresses himself without any problem and often takes his meds without a reminder. He no longer drives but several days a week either a friend or a paid driver takes him on his morning circuit to get breakfast and go to the gym. He can do a few errands with help. Notes help but he may not remember he has a note. He still mows the lawn and brings in wood for the stove. I worry about him getting lost so he wears a small GPS unit on his belt and I carry a smartphone so I can track him on the internet at any time. He has no trouble making or receiving calls on his cell phone so we stay in touch.

Alzheimer's attacks much more than memory. His sense of time is way off. If something happened this morning, he probably thinks it happened yesterday. Last November he emptied the woodstove one morning. By afternoon he thought that the ashes had been cooling for several days and threw them onto a brush pile in the field. Fortunately it was a wet and windless day because unbeknownst to either of us we probably had 10 foot flames burning 50 feet from our barn. By the time I discovered it only a smoldering circle was left.

Alzheimer's attacks spatial intelligence. He runs the dish

washer half empty because it looks full to him. He may forget to actually run it and unload and put away the dirty dishes. I've learned to check and to start meal prep early because many things will be in unexpected places. Alzheimer's compromises the senses, eventually scrambling them completely. John confuses damp and cold. He does the laundry but has trouble telling if clothes are dry or not. He folds them beautifully, but often damp. I've grown accustomed to smelling slightly moldy. This summer he would hang the laundry outside but couldn't fit a full load onto the clothesline because of his spatial difficulties. The trees and lawn furniture ended up festooned with drying clothes!

I had to take over our personal and business finances several years ago. This disease strikes very hard at his pride and ego. Although he loves me and trusts me, it is still hard for him to give over more and more control of our lives to me.

Our life has already changed dramatically, but here's the kicker: If you met him somewhere and talked to him for half an hour, you would never guess he has Alzheimer's. You might think him a little scatterlogical with a quirky sense of humor but you would never think Alzheimer's. This is typical and makes it very easy for family members to indulge in denial – "Dad seems just fine to me." They can convince themselves that it is fine to go on with their own uninterrupted lives because the primary caregiver doesn't need help. It makes it easy for us caregivers to be neglected.

Here is the other kicker: this is just the beginning for John and me. It is going to get much, much

more difficult. And that is pretty scary. This is not a child who I have authority over, who I can just tell what to do. This is a man who is 6' 2" and outweighs me by almost 100 pounds. He can't see many of his own limitations – sort of like a drunk person who thinks they are fine to drive. Because of the Alzheimer's his reality is different from mine but it is just as real to him as mine is to me. Increasingly I will have to cajole, manipulate and trick him

*Here's the kicker:
If you met him
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into doing things he doesn't want to do. Already logic doesn't always work. Arguing definitely doesn't work. I've learned to apologize for things I didn't do or say. I eat crow a lot.

As John loses the ability to do things, I have more and more to do. My days are increasingly both more busy and more tedious. Already I fight fatigue and like most caregivers struggle to keep depression at bay. Meanwhile, I am his anchor in life and he needs and wants me more and more. As Alzheimer's progresses many patients want to be literally within touching distance of their caregiver 24/7.

I am a strong introvert and I like and need my space. But I may have to learn to do without it.

Finances scare me. We have no long-term care insurance and John will need to be on MaineCare eventually. First we will have to spend down our assets. My 401k and IRA will go. Probably sometime in my 60s I will be a widow and I may be a rather poor one.

Despite all this, I have a lot to be grateful for. I have it easy compared to others I know. John has accepted this disease with extraordinary grace. He tries very hard to be cooperative. Both his sons are supportive. We have great friends. I'm very grateful that when John was diagnosed I was in a position to retire and unlike most Alzheimer's spouses my age I'm not trying to do this while working full time.

We still have a lot of laughter in our life. John has always been a master of the bad joke and this talent is unimpaired. He puns a lot, I think in sheer celebration that he can still do it, although I have to say that some of them are getting pretty obscure.

Last week John stopped me in the living room, put his arms around me and asked, "Do you still love me?" I answered, "Of course I love you. You're my own sweet Johnny." "Even with the Alzheimer's?" he asked. "Even with the Alzheimer's, John. We're a team. You never have to worry about that." After a moment, he said, "You have no idea how long it has taken me to get up the courage to ask you that."

That was last week and I wonder if he still remembers.

- Elisabeth Paine

The Silent Epidemic That Became The Disease Of The Century: George Glenner's Promise To Keep

By Joy Glenner

Public awareness of Alzheimer's disease began in the spring of 1974 when the National Institute on Aging (NIA) was created by Congress with the signature of President Richard Nixon. Alzheimer's disease, once an unknown disease, was no longer the silent epidemic. As our aging population continues to grow older, caring for the special needs of Alzheimer's/dementia individuals will severely test the moral fabric of our society with one of the most extraordinary demographic changes in history. Currently there are over 5.4 million Americans diagnosed with Alzheimer's disease.

George G. Glenner, M.D., FCAP, graduated from the Johns Hopkins University School of Medicine with honors in 1953. George became a board certified pathologist after studying and teaching forensic medicine at the Harvard School of Legal Medicine and his completion of the study of anatomical pathology at Boston Hospital. He was the Laboratory Chief of Molecular Pathology at the NIH Institute of Allergy, Molecular and Infectious Disease for 26 years before he became a faculty member in 1981 in the department of pathology at the University of California, San Diego (UCSD).

George was invited to serve on the charter executive board of the National Alzheimer's Association as well as serving on the Medical Scientific Board. I became a member of the committee of the National Alzheimer's Association's Family Services Programs. We met



George G. Glenner, MD

four times a year in various cities where our study groups wrote training and educational material; we became advocates in testifying in federal and state legislative hearings on the urgent need to establish funding for implementation of family respite care services. The high morbidity and mortality rate of family caregivers was alarming. I became the founding Chairman of the Board of the San Diego Chapter of the National Alzheimer's Association, and George was the chapter's Medical Advisor. Almost overnight the new, small group became over two hundred members. We faced hopeless, fought to drop "less," and found hope. Alzheimer's disease was no longer *the silent epidemic* – this was the beginning of our mission: No family ever had to face Alzheimer's disease alone again.

The Call That Changed Our Lives

George Glenner established the nation's first Alzheimer's Disease

Autopsy and Brain Bank in 1981 at UCSD. Human tissue was urgently needed for his own scientific research as well as making brain tissue with patient histories available to qualified scientists around the world to study the little known malady. Frequently we spent our evenings in George's lab in the Basic Science Building on the UCSD campus, in La Jolla, CA. The call that impacted our lives was a frantic Brain Bank call at 1:00 a.m. in the morning by a distraught family caregiver that was a potential murder/suicide that changed our lives forever. The caller was preparing to take the life of his wife who was severely afflicted with Alzheimer's disease and then turn the gun on himself. I had the call traced as George spoke quietly to the overwrought man until the sheriff arrived where he found the caller with a loaded gun in his hand as he stood next to his feeble wife's bed. Once the crisis had been stabilized, George turned to me and quietly said, "What are you doing tomorrow? It's time to take care of the living while scientists pursue the answer to this dehumanizing disease that robs the mind of its victims while it breaks the hearts of their families." Our lives were changed forever that night.

1982 – Sharing the Caring is Born

In less than six months, with the grand total of \$35,000 and a lot of faith, the first Alzheimer's Family Center opened its doors in a rented cottage in the Hillcrest area. To all involved in creating the center, it was a monument to the future.

Within a few weeks following that traumatic phone call for help, George had organized a board of directors, medical advisory board and honorary board of directors that worked feverishly to produce a mission, by-laws and business plan. It was a talented and multifaceted group; a diverse blend of knowledge, skills and experiences at high levels in medicine and health care; public policy, business, finance, social services, marketing and volunteerism. The Glenner legacy of touching lives through *Sharing the Caring* was born.

Programs and services for treating both the patient and their family caregiver evolved. This model had never been developed – we literally wrote the book on specialized care for advanced dementia and incontinent patients in a home-like environment combining social activities and skilled nursing care. Our vision was to provide eight hours of care per day with therapeutic activities producing a loving and successful day for the patient and relief for their stressed family.

Ironically, the long awaited opening day for the first patients was on October 22, 1982, the same day George and I had been invited to be present in the Oval Office of the White House with President Ronald Reagan when he signed H.R. 4996, the U.S. Congressional proclamation that we had petitioned San Diego freshman Congressman Bill Lowery to sponsor, naming Thanksgiving Week, November 1982 as National Alzheimer's Disease Week. President Reagan was most interested in learning more about the disease as he shared with us, "my mother died in a nursing home at age 96 and she didn't know who I was and I

was told that she was senile." The President asked George many questions about senility . . . was senility Alzheimer's disease? George responded to the President that "senility was not a disease, rather a plethora of insults that occur anywhere in the body and cause the confusion, serious memory lapses and the deterioration of personality and intellect that are routinely dismissed as inevitable in old age." He described Alzheimer's disease as a disorder that destroys certain vital cells of the brain, and he further explained that the cost of care produces an untold burden on family caregivers. The President turned to me and asked, "Are you also a doctor?" I responded, "No, Mr. President, I am here to represent the families who provide over eighty percent of the care for their loved ones, and to thank you for proclaiming National Alzheimer's Disease Awareness Week. The President shook my hand as he kindly said, "Then I must be one of your families."

2006 - Alzheimer's 100 Years and Beyond International Celebration

George Glenner was cited at the *Alzheimer's 100 Years and Beyond International Celebration* in Tübingen, Germany in 2006 for his significant isolation and identification in 1984 of the exact amino acid sequence of the beta amyloid protein. George's seminal discovery was termed *the watershed year* by Zavin Khachaturian, Ph.D., the first intramural Director of Alzheimer's Disease Research at the National Institute on Aging. Dr. Khachaturian commented, "George was the quiet scientist who met all obstacles and laid the groundwork in showing the

rest of us the road map to a cure while he provided care for 'the living.'"

The first center was born out of love and necessity in 1982; a major grant from the City of San Diego provided a permanent building for the Hillcrest center in 1986; a second center was established to serve the South Bay area with U.S. Congressional funding in 1994; and the third center opened to provide care in coastal North County with a major grant from the Silverado Senior Community, 2002.

The Alzheimer's Family Centers are formally affiliated (1982-present) with the Regents of the University of California and the UCSD School of Medicine; later a partnership developed with the Shiley-Marcos Alzheimer's Disease Research Center when it was designated as one of the first NIH Alzheimer's Research Centers of Excellence in 1987.

The Alzheimer's Family Centers became *The George G. Glenner Alzheimer's Family Centers, Inc.* in memoriam to the founder who died in 1995.

It has been a privilege to be a part of our early evolution and growth; it has produced a powerful message to all of us about the fragility. . . and the wonder of life. Our Alzheimer's families are infinitely precious to us. They gave us the love and knowledge to treat others as our own. It was a privilege.

George, who loved poetry, always quoted Lord Tennyson:

***The work goes on,
The cause endures,
The hope still lives,
The dream shall never die.***

RESEARCH ROUNDUP



By Michael Rafii, MD, PhD

Director, Memory Disorders Clinic
Associate Medical Core Director
Alzheimer's Disease Cooperative Study
University of California, San Diego

Highlights From the 4th Annual Conference on Clinical Trials in Alzheimer's Disease (CTAD)

Held in San Diego, California, the venue was filled beyond capacity, drawing over 500 researchers from around the world. For the bulk of the meeting, researchers worked on methods they hope will improve future trials' chances of success. Clearly, better drugs are needed to treat AD, and there have been no drugs approved in over a decade. These methodological improvements include using more advanced statistical methods to analyze subject data, and to incorporate biomarkers of disease, including brain amyloid levels and measures of brain atrophy, as part of efficacy measures. In addition, there was much discussion on trial designs that target the disease in the pre-dementia phase of Alzheimer's disease, sometimes referred to as Mild Cognitive Impairment (MCI).

Paul Aisen, MD, the Director of the ADCS at UC San Diego, opened the conference with a discussion of the evolution of AD trials and with a particular emphasis on why recent trials have failed. "The problem is we've tried to move from short acting to disease modifying drugs, and that's what has caused us to stumble," he said. "If interventions are needed before the brain has suffered significant damage and cognitive impairment, clinical trial design will require the detection of

subtle and discreet changes, over long periods of time, and in large numbers of subjects."

There is international consensus that Alzheimer's disease starts some 15 years before symptoms of dementia appear, and new trial designs will need to be based on a biomarker-supported diagnosis of prodromal AD. Prodromal AD, which is the cause of cognitive impairment in roughly half of patients diagnosed with MCI, is basically defined as patients who are not demented but are destined to develop dementia within a few years because they have the earliest signs of AD developing in their brain. Several companies have begun using such designs to treat patients with prodromal AD, before dementia sets in.

Right Drug, Right Target, Right Time

"Ultimately, the challenge ahead requires increasingly sophisticated procedural, scientific and regulatory coordination between and among the private sector, the government and academia. Figuring out primary, secondary and tertiary prevention will require the right target at the right phase and right time" said Aisen.

Nevertheless, Aisen's confidence in collaborative approaches to AD research continues to grow. "Over the last few years I believe that the extent of precompetitive cooperation among companies, coupled with the cooperation among academics internationally, as well as government entities, has

resulted in workable solutions to the difficulties of conducting trials in AD."

Detecting Early Changes

Traditional measures of cognition are not sufficiently sensitive to detect early, preclinical AD. Thus, efforts are underway to develop neuroscience-based cognitive assessments that are sensitive to subtle brain dysfunction. Diana Woodruff-Pak, Ph.D, of Temple University presented data suggesting that assessment of eyeblink conditioning may be useful in detecting early cognitive dysfunction in normal elders.

The test is non-invasive, relatively quick, and easy to administer. "It's simple...and studies have shown that the delayed eyeblink conditioning response is severely impaired in mild to moderate AD. This effect is specific to AD. Our hypothesis is that it detects changes in neural circuits and will prove to be useful as an initial screen for prodromal AD in normal population" said Woodruff-Pak.

A group led by Jacob Raber, Ph.D, of the Oregon Health and Science University, developed human versions of spatial navigation and object recognition tests commonly used in animal studies. These behaviors are sensitive to dysfunction in an area of the brain called the entorhinal cortex, which is affected early in AD. Raber's tests, called Memory Island and NINL (novel image, novel location), have both been shown to

Do you have a friend or family member who is interested in participating in an AD research study? If so, information on ADCS research sites conducting this study can be found at www.adcs.org/Studies/IGIV.aspx.

be sensitive for assessing cognitive performance and age-related cognitive decline in preclinical AD. The NINL test has even been shown to detect the subtle cognitive effects in individuals who are ApoE4-positive, which places them at elevated risk of developing AD.

Jeffrey Kaye, Ph.D, director of the Oregon Center for Aging and Technology (ORCATECH) at the Oregon Health and Science University discussed using unobtrusive home based monitoring to capture real-time continuous data for assessment of everyday cognitive change. A variety of sensors can track multiple behaviors and activities, including walking speed, medication adherence, and social activity, all of which are affected in the early stages of AD.

Preclinical AD: What We Know

As clinical trials edge toward prevention among people who are asymptomatic, it will be important to understand what characterizes people in the preclinical stages of AD. According to the recently proposed diagnostic criteria, preclinical AD can be divided into five stages depending on the presence of clinical symptoms, biomarkers of amyloid, and biomarkers of neuronal injury.

Ronald Petersen, MD, Ph.D, presented findings from the Mayo Clinic's Olmsted County Study of Aging, a population-based study of nearly 3000 non-demented elderly people. Complete evaluations on all of the subjects, including tests for subtle signs of cognitive impairment, found that among the

nearly three-quarters of these subjects who were essentially "normal," more than half showed some signs of being on the pathway to AD. Petersen said these data indicate that the new pre-clinical AD criteria are able to identify individuals at very early stages on the AD pathway.

Society for Neuroscience, Washington, DC

With 42,000 members, the Society for Neuroscience's "Neuroscience 2011" meeting remains the largest meeting in the world on fundamental research on the nervous system. Many presentations were made with direct relevance to AD. One included the work of Dr. Gene Alexander from the University of Arizona, who found that physically fit seniors show fewer age-related changes in their brains. The findings further previous data in the AD field and underscore the importance of exercise for maintaining brain health throughout life.

As people age, some regions of the brain—including those responsible for attention and memory functions—begin to lose volume or shrink. To see how physical fitness affects brain aging and age-associated declines in cognition, Alexander and colleagues scanned the brains of 58 men and 65 women (ages 50 to 89 years) and evaluated their performance walking on an inclined treadmill.

The more physically fit a participant was, the fewer age-related brain changes they showed. In particular, exercise endurance and breathing efficiency offered the best combina-

tion of fitness measures in predicting patterns of brain aging. Individuals with higher levels of aerobic fitness also outperformed their less physically fit counterparts on tests measuring memory, executive function, and information processing. Identifying the fitness indices that are the best predictors of brain aging and cognitive performance may help improve exercise-based interventions to promote healthy brain aging.

Another interesting presentation was on how short-term estrogen treatment increases the volume of cortical gray matter in postmenopausal women. The research reveals a potential benefit from short-term hormone replacement therapy. Researchers, led by Paul Newhouse, MD, of Vanderbilt University, imaged the brains of 24 healthy postmenopausal women who took either estrogen or a placebo for three months. After treatment, the women who took estrogen had more gray matter in regions known to be involved in attention, decision-making, and memory.

The findings suggest the brain remains responsive to estrogen treatment even after menopause, and that this responsiveness or plasticity is important for preserving cognitive functioning, especially in the early postmenopausal period. The findings suggest that long-term hormone treatment, shown to have adverse effects on health in postmenopausal women, may be unnecessary for cognitive benefit. Short-term estrogen treatment in normal postmenopausal women is sufficient to increase gray matter in the brain.

Fill in the GAP

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BRAIN EXERCISE

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

www.aarp.org/health/brain-health/brain_games/

BRAIN TEASERS Guess the meaning of...

1	LONG DO	2	WEAR LONG	3	MIND MATTER
		4	T O W N	5	T O U C H

ANSWERS
1. Long Overdue 2. Long Underwear 3. Mind Over Matter 4. Downtown 5. Touchdown