http://www.technologyreview.com/featured-story/429494/the-dementia-plague/
Technology Review
October 5, 2012

The Dementia Plague

As the world's population of older people rapidly grows in the coming years, Alzheimer's and other forms of dementia will become a health-care disaster.

STEPHEN S. HALL
Friday, October 5, 2012

William Utermohlen—*Blue Skies* (detail), 1995

Galerie Beckel Odille Boïcos

- Dementia: The Self-Portraits of William Utermohlen

Evelyn C. Granieri is that rarest of 21st-century doctors: she still makes house calls. On a warm Thursday morning toward the end of August, the New York–based geriatrician, outfitted in a tailored white suit and high heels, rang a doorbell at a seven-story red-brick apartment building in the Riverdale section of the Bronx and was buzzed in.

"You look gorgeous!" the doctor exclaimed when she greeted her patient, a 99-year-old woman with white hair and a wry smile, in the dining room of her apartment. In an hour-long conversation, Mrs. K (as we'll call her) recalled, in moving and sometimes mischievous detail, growing up in Poland, where soldiers on horseback took her brother away; coming to America on a ship and working in her parents' grocery story in Queens; and dealing with male colleagues in the real-estate business when they got "fresh." But when Granieri asked how old Mrs. K was when she got married, she looked puzzled.

WHY IT MATTERS

We have no effective treatments for dementia, a huge health crisis facing the world. The annual cost of care in the United States alone could reach $1 trillion by 2050.

"I can't remember," she said after a pause. A cloud passed over her face. "Was I married? To whom?" A framed photograph on a nearby table memorialized her 50th wedding anniversary.

Spirited and funny, her personality intact even as her memory deteriorates, Mrs. K is one of more than five million Americans with dementia. Far from the gleaming research centers where scientists parse the subtle biochemical changes associated with Alzheimer's disease and other forms of the condition, clinicians like Granieri, chief of the Division of Geriatric Medicine and Aging at Columbia University Medical Center, confront its devastating reality every day. And, often, they talk to relatives of patients. As Granieri and two interns probed Mrs. K's memory with small talk and measured her blood pressure, a niece called from Manhattan to see how her aunt was doing.

Almost every dementia patient has worried family members huddled in the background, and almost every story about dementia includes a moment when loved ones plead with the doctor for something—any medicine, any intervention, anything—to forestall a relentless process that strips away identity, personality, and ultimately the basic ability to think.

Unfortunately, Evelyn Granieri is the wrong person to ask. In 2010 she served on a high-level panel of experts that assessed every possible dementia intervention, from expensive cholinesterase-inhibiting drugs to cognitive exercises like crossword puzzles, for the National Institutes of Health; it found no evidence that any of the interventions could prevent the onslaught of Alzheimer's.

She can—with immense compassion, but equally immense conviction—explain the reality for now and the immediate future: "There really is nothing." Dementia is a chronic, progressive, terminal disease, she says. "You don't get better, ever."

These conversations have always been difficult for doctors and families alike, but perhaps never more so than in the past year, when public reports about dementia research have bounced between optimism and gloom. In the fall of 2011, financial analysts were giddily projecting a global Alzheimer's market of $14 billion a year by 2020 and touting a new generation of drugs known as monoclonal antibodies that were in advanced human trials.

A year later, the prospect for the drugs no longer looked so positive. This past August, the giant drug makers Pfizer and Johnson & Johnson suspended advanced clinical trials of one of the monoclonals because it showed no effect in patients with mild to moderate Alzheimer's. A few weeks later, another leading pharmaceutical manufacturer, Eli Lilly, announced inconclusive results for a monoclonal drug it too was testing against the protein deposits called amyloid plaques that are characteristically found in the brains of Alzheimer's patients. The disheartening results prompted some critics to start writing epitaphs for the prevailing hypothesis about the disease—that these amyloid deposits are causing the cognitive impairment.

"The field is in a precarious place right now," says Barry D. Greenberg, director of strategy for the Toronto Dementia Research Alliance, "because tens of billions of dollars have been invested in the development of new treatments, and nothing—not a single disease-modifying agent—has been identified." Granieri often sets off on her house calls from her second-floor office at Allen Hospital—literally the last building in Manhattan, on the northernmost tip of Broadway. That may sound like an out-of-the-way outpost in medicine's battle against dementia, but in reality it sits at ground zero for the looming medical and societal catastrophe. The hospital's catchment area includes upper Manhattan and parts of the Bronx, one of the three densest concentrations of nursing home facilities in the entire United States, according to Granieri. "Here we sit, right in an epicenter," she says.

The epicenter is a contentious place these days. Frontline clinicians like Granieri are increasingly frustrated with the narrowness of dementia research. In the patients they treat every day, they see a disease that is complicated and insidious, often with multiple causes and murky diagnostic distinctions. In contrast, they see a research enterprise focused on several favorite hypotheses, and they see a drug industry that has profited handsomely from expensive, marginally effective treatments sought by desperate families.

Academic and pharmaceutical researchers, meanwhile, continue to throw money at the dementia problem—but finally, they insist, with better aim and much shrewder treatment strategies. They have begun to assemble a list of diagnostic markers that they believe may reliably indicate the first signs of Alzheimer's disease 10 or 15 years before symptoms appear, and they are gearing up to test new drugs that can be given to healthy patients, in an attempt to block the buildup of amyloid long before dementia's onset. Indeed, to hear researchers tell it, this summer's highly publicized clinical-trial failures are already ancient history. They are finally doing the right kind of science and hope to get the right kinds of answers, the first glimpses of which may appear in the next several years.

As Granieri and other physicians who treat dementia patients know, the stakes could scarcely be higher.

http://www.technologyreview.com/featured-story/429494/the-dementia-plague/2/

The Dementia Plague

(Page 2 of 3)

STEPHEN S. HALL

Friday, October 5, 2012

When he learned in 1995 that he had Alzheimer's disease, William Utermohlen, an American artist living in London, immediately began work on an ambitious series of self-portraits. The resulting body of work serves as a unique artistic, medical, and personal record of one man's struggle with dementia. (See the self-portrait series in more detail here.)

Galerie Beckel Odille Boïcos

Tangled Connections

In October 1986, one year after his grandmother Sadie died of dementia in a New York City nursing home, Barry Greenberg cloned a gene he thought would be key in the battle against Alzheimer's disease. Ever since the German physician Alois Alzheimer first described the pathological hallmarks of his namesake disease in 1906, scientists have focused on two prominent physiological features that snarl the brains of dementia patients: plaques of the gummy protein amyloid beta, which build up outside brain cells, and hairy tangles of protein inside neurons (these tangles are now known to be misshapen versions of a normal protein called tau).

Greenberg, then working at a West Coast startup called California Biotechnology, had found the gene for amyloid precursor protein, which tells the body how to make the protein that ends up as the amyloid plaques. He excitedly called his father with the good news, and his father replied, "That's wonderful, son. Now what's left to be done?"

A quarter-century later, after stops at five pharmaceutical companies and countless twists and turns in the research saga, Greenberg can tell the anecdote with a chuckle, but the larger story is no laughing matter. He has seen this emerging medical disaster as a bench scientist, as a pharmaceutical-industry insider, and now as a coördinator of clinical research and drug development for an alliance of Canadian hospitals and memory clinics associated with the University of Toronto, which serve some 7,000 dementia patients a year.

In a recent talk to a lay audience on Prince Edward Island, he spoke about his grandmother's illness and then dropped the hammer. "The scope of the looming medical-care disaster," he said, "is beyond comparison with anything that has been faced during the entire history of humanity."

The latest global demographic analysis, from a World Health Organization report issued earlier this year, paints the dimensions of that slow-motion catastrophe in quick strokes. An estimated 36 million people worldwide currently suffer from dementia; experts predict the number will double, to approximately 70 million, by 2030 and triple by 2050. (China, India, and Latin America in particular face daunting medico-economic crises.)

Since the prevalence of the disease doubles with every five-year age increment after 65, projections for 2050 put the total global population at risk for dementia (people 65 or older) at two billion. The calculus is as grim as it is simple: as more people live longer, more slide into dementia. Care for those patients currently costs $100 billion a year in the United States, with a projected cost over the next 40 years of $20 trillion; by 2050, the cost to U.S. society is projected to be $1 trillion a year.

An even more sobering perspective on the problem comes from a small unpublished pilot study that Granieri and her colleagues at Columbia recently undertook. They did a standard cognitive evaluation of every person 70 or older who was admitted to Allen Hospital for any reason—heart problems, pain, diabetes, breathing difficulties. The results stunned them. "In this hospital, of patients 70 years of age or older, 90 percent have cognitive impairment of some kind, which is much higher than we anticipated," she says.

Not only is dementia distressingly widespread, but the complex overlap of symptoms and possible causes makes addressing the problem broader and trickier than just treating Alzheimer's. The emerging reality, which has become increasingly apparent with better brain imaging, is that the majority of cases among the elderly are so-called "mixed dementias"; the cognitive impairment is due to a combination of vascular problems, such as mini-strokes in discrete parts of the brain, and the more classic Alzheimer's pattern of amyloid plaques.

Large-scale international studies in the past three years have shown, according to a recent scientific summary, that dementias caused by blood-vessel lesions in the brain, including vascular dementia

and mixed dementia, "together comprise the most common forms of dementia at autopsy in community-based studies."

Sharon Brangman, a physician who finished a term as chair of the board of the American Geriatrics Society earlier this year, especially welcomes the message that Alzheimer's in particular, and dementia in general, is much more complex than the focused research of the last 20 years would suggest. "When you've lost something, and you've looked in all the obvious places and you still haven't found it, you need to start looking in other places," she says.

"Not everyone with Alzheimer's has the same clinical presentation, and there's more to dementia than Alzheimer's disease. We have a broad disease category that people can enter from multiple avenues. But we are attacking dementia now from only one narrow entry point. It's going to be more complicated than that. **Right now, we have a one-size-fits-all approach to dementia."**

In order to come up with more effective drugs, scientists need to understand exactly how each kind of dementia develops and how to attack that specific disease process. Much of the research has so far focused on Alzheimer's disease. And yet the basic biology of even that most well-studied form of dementia remains fuzzy. Are the amyloid plaques the key pathological factor, as a large body of research suggests, or is it the thickets of aberrant proteins known as tau tangles, which appear in dementia patients after the plaques do? If amyloid leads to tau tangles, how are they related?

Or, as an alternative hypothesis suggests, is dementia somehow connected to impaired processing of blood sugar? (This possibility was endorsed by the NIH's recent decision to support a University of Washington clinical trial of a nasal insulin spray.) Or does the actual cause of Alzheimer's have something to do with an imbalance of metal ions in brain cells, which is the animating idea behind advanced clinical trials by an Australian biotech company?

The persistence of so many hypotheses suggests that neither clear-cut evidence nor consensus for one theory of disease has yet emerged. "I think you have to continue to look at these hypotheses," says Granieri, "but they *are* hypotheses, and [researchers] have to be honest about that."

FEATURED STORY // BIOMEDICINE

HTTP://WWW.TECHNOLOGYREVIEW.COM/FEATURED-STORY/429494/THE-DEMENTIA-PLAGUE/3/

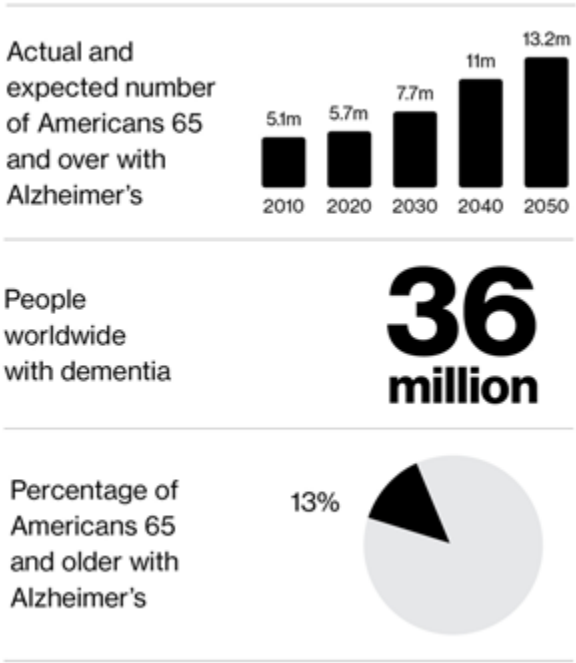
The Dementia Plague

(Page 3 of 3)

14 comments

STEPHEN S. HALL

Friday, October 5, 2012



Data from Alzheimer's Association and World Health Organization

Demented Mice

One recent afternoon, in a newly renovated 12th-floor research complex in Columbia University's College of Physicians and Surgeons, Alzheimer's researcher Karen Duff inspected several elderly mice sitting in cages on a shelf in her lab. These were, in lab parlance, tau mice. They had been genetically engineered to produce abnormal human tau protein in a very specific part of their brains, the same small place where autopsies have shown that it first appears in human brains. One mouse in particular stood out because of its ragged, ruffled brown fur.

"This one may be a bit demented," Duff said matter-of-factly. "It's a little less well-groomed, and one of the first signs [of dementia] is a rougher fur." If these mice mimicked the pattern of pathology seen in humans with dementia, Duff added, the misshapen protein "would have spread to areas of the brain affected by Alzheimer's disease." The confirmation came a few days later, when technicians sacrificed the animals and mapped tangled bits of malformed tau that had spread throughout their brains**. It is these tangles, according to Duff, that eventually kill the cells that confer memory, perception, cognition.**

The mice on Duff's lab shelf and their experimental brethren have introduced a surprising new wrinkle to the pathology of Alzheimer's. Duff and her colleagues have conducted experiments showing that misshapen tau proteins initially sequestered in the part of the brain where Alzheimer's typically first appears (the entorhinal cortex) somehow were able to spread along nerve circuits and hop across synapses to other parts of the brain long known to be involved in dementia, including the hippocampus. As these abnormal tau proteins spread through the brain, they "usurped" and corrupted the normal tau proteins in affected cells, inducing lethal tangles and killing neurons.

The good news is that this mechanism offers novel opportunities for treatment: attacking abnormal tau as it hops between cells. The Columbia group is already conducting animal tests of a monoclonal antibody designed to intercept tau at precisely this vulnerable point of passage, and Duff says pharmaceutical companies have shown considerable interest in the model.

But the new findings are also a stark reminder of how much researchers still need to learn about Alzheimer's in particular and dementia in general. The scientific literature now describes amyloid as necessary but not sufficient to explain Alzheimer's symptoms, yet despite intense investigation, there is no general agreement on the mechanism linking the two signal features of a brain in the throes of the illness. Scientists still don't know why the amyloid plaques precede the tau tangles by anywhere from 10 to 20 years, and they don't know how the two pathologies are connected. **"We know amyloid protein builds up, but there's a lot of debate if it's the chicken or the egg, if that's the trigger or the result of the disease," says Brangman.**

Even after decades of discussion about the role of amyloid in Alzheimer's disease, researchers concede, the hypothesis that these plaques are key to the illness has not been properly tested. "We haven't tested the right patients at the right time with the right agents," says Greenberg. "The reality is that we haven't done that yet. But the field knows what to do and is doing it now."

Indeed, several ambitious clinical trials—Greenberg considers them the most important trials in the history of Alzheimer's drug discovery—are poised to launch in the next few months, and the results will shape dementia research for years to come. If these so-called prevention trials succeed, they will hold out hope that the usually inevitable course of dementia can be altered. If they fail to modify the course of the disease, however, the implications will be what researchers like Greenberg and Duff call "devastating" and "horrendous."

True Test

Given the magnitude and urgency of the problem, it's no wonder that when Kathleen Sebelius, the U.S. health and human services secretary, announced new NIH funding last February, she told reporters, "We can't wait to act." And yet it's clear to many experts that we probably will wait for an effective Alzheimer's drug—perhaps as long as 10 or 15 years.

The challenge of finding a treatment that will alter the course of dementia is daunting precisely because the process of neural degradation proceeds invisibly for so many years and starts so early.

How early?

Last July, the Dominantly Inherited Alzheimer's Network, a network of leading academic centers based at Washington University in St. Louis, published surprising findings that detectable changes in amyloid chemistry in patients with a genetic form of Alzheimer's may appear in a person's cerebral spinal fluid up to 25 years before the onset of Alzheimer's symptoms. By the time Alzheimer's patients show up in the neurologist's office with signs of mild or moderate dementia, it is too late.

If the amyloid hypothesis for Alzheimer's is correct, therefore, researchers need to find and treat patients a decade or more before the first signs of cognitive impairment appear. They need a drug that crosses the blood-brain barrier to disrupt the buildup of amyloid. And they need diagnostic tools—the cognitive and neural equivalent of a glucose test for diabetics—to measure changes in amyloid and other biomarkers to determine if the therapies are working. (These same diagnostic markers might also be used to identify patients at risk for Alzheimer's who would benefit from preventive treatment.)

Although progress has been made in finding these markers, their reliability is still uncertain. The Food and Drug Administration could speed up drug approvals on the basis of improvements in them, says Sam Gandy, director of the Mount Sinai Center for Cognitive Health in New York. But everyone will still be "holding their breath" until patients are "well beyond the age at which they would be expected to be at risk of becoming demented."

The group of researchers based at Washington University has assembled a promising tool kit to help them detect the progress of the disease: brain imaging of amyloid deposits, analysis of cerebral spinal fluid, and cognitive tests. But who should the test subjects be? As it turns out, there are several rare genetic forms of Alzheimer's, and these have been the network's longtime research focus.

People who inherit very specific dominant mutations are fated to develop Alzheimer's at a relatively early age, and researchers can calculate when the first symptoms of the disease are likely to appear. The network is now in the final stages of selecting three distinct therapeutic agents that target amyloid, with plans to test them in patients with genetic forms of Alzheimer's.

Randall Bateman, a Washington University physician and researcher, says the aim of the study is to find a drug that will curtail the buildup of amyloid in the brain, much as doctors use statins to reduce the risk of stroke and heart attack by lowering cholesterol levels. Bateman says his research group hopes to launch human tests using the biomarkers by early 2013; he and his colleagues hope to see evidence of effects on these markers after two or three years of treatment rather than waiting 10 or 15 years, when symptoms of dementia would be expected to appear.

The other closely watched trial will be launched—with the NIH's blessing and funding—by the Banner Alzheimer's Institute in Phoenix and Genentech. Most of the patients in this trial also have a genetic

form of the disease. Members of an extended family of some 5,000 people living in the Antioquia region of Colombia are at risk for a very rare mutation; those who are carriers invariably develop an early-onset version of Alzheimer's. The idea is to treat about 300 members of this group with an experimental drug to attack amyloid plaques an estimated 15 years before symptoms would be anticipated.

The drug, licensed by Genentech, is an amyloid-attacking monoclonal antibody called crenezumab. Doctors believe it can safely be injected at a higher dose than other monoclonal drugs. "We believe the higher dose will translate into higher efficacy," says Carole Ho, group medical director for early clinical development at Genentech.

In administering these drugs earlier, to a population genetically susceptible to the disease, Alzheimer's researchers believe they are finally giving the right kind of therapy to the right patients at the right time. And given the stakes, the two prevention trials have sparked high anticipation. "This will be the first true test of the amyloid hypothesis," says Barry Greenberg. "The strategy is sound. So let the data happen."

If the prevention trials succeed, however, there's no guarantee that this version of early intervention will help in most cases of dementia. Clinicians warn that these rare, early-onset, mutation-based forms of the disease account for at most 10 percent of all Alzheimer's cases. As Evelyn Granieri puts it, "This may not even be the Alzheimer's disease that the majority of people get."

The genetic forms of the disease are similar in pathology to the forms most people do get, Ho says. Still, even positive results gleaned from early interim analyses of these trials would come too late for the millions of people who have already begun the slow descent into cognitive decline. "The reality," says Granieri, "is that most people who are around and sentient now are not going to be around for the cure."

All the more reason, according to Greenberg, to adopt "fundamentally different thinking" in dementia research. "The medical-care system is going to be bankrupt by 2050 if we don't figure out a way to delay or treat Alzheimer's disease," he says, and he believes that won't happen without a major public-private international initiative. "The competitive marketplace," he says, "was not conceived to overcome problems of this magnitude."

Stephen S. Hall's latest book is *Wisdom: From Philosophy to Neuroscience* (Vintage). His last story for *Technology Review* was "The Genome's Dark Matter." End

http://www.technologyreview.com/news/428480/an-alzheimers-warning-25-years-before-symptoms/?mod=related

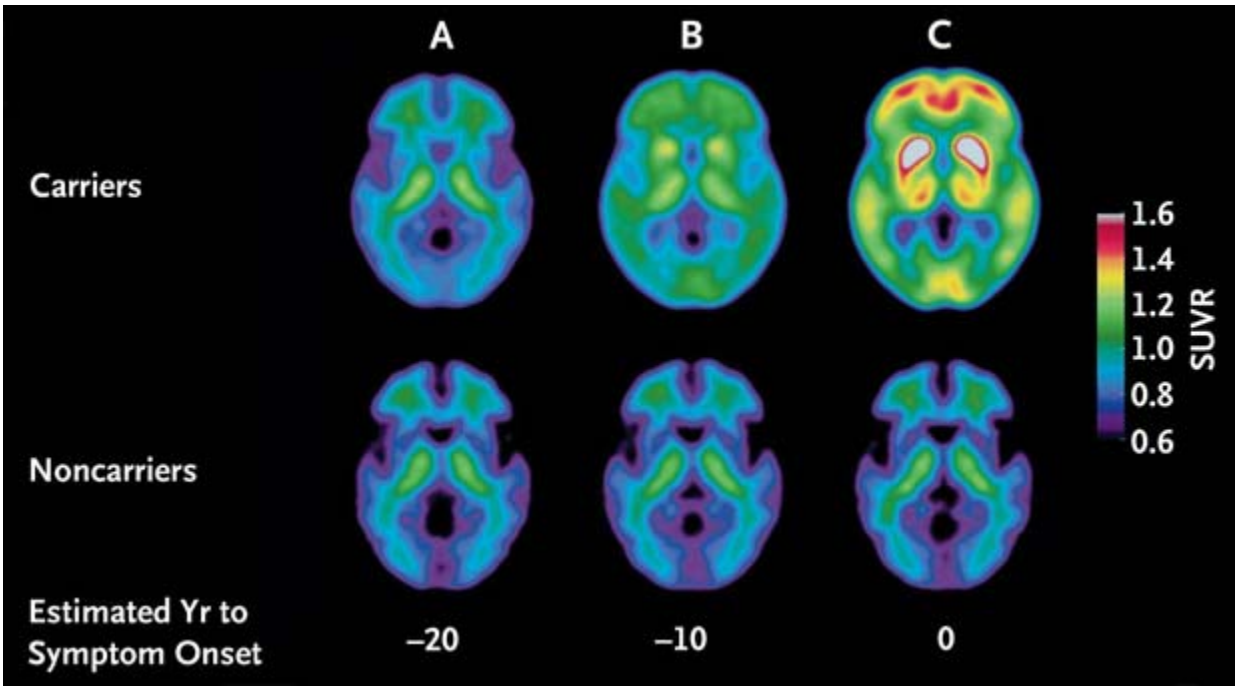
Technology Review
July 11, 2012

An Alzheimer's Warning 25 Years Before Symptoms Show

The rise and fall of certain proteins can indicate dementia's onset decades before the appearance of symptoms.

KAREN WEINTRAUB

Wednesday, July 11, 2012



Early onset: Brain scans show evidence of Alzheimer's disease 20 years before symptoms arise (far left), 10 years before (middle), and after the onset of symptoms (right). Beta amyloid, a protein associated with the disease, is more visible in people who develop the disease (top row) than in those who don't. The more color in the scan, the more beta amyloid is present in the brain.

The first detectable signs of Alzheimer's disease occur as long as a quarter century before symptoms like memory loss become noticeable, according to a detailed chronology of molecular changes to the brain and spinal fluid of people who later developed the brain disease.

The research, published today in the *New England Journal of Medicine*, provides a timeline of the subtle changes that begin in victims' brains and, importantly, can be detected years ahead of time by MRI exams, blood analyses, or other tests.

The development of biomarkers that can track and predict the natural course of the disease is important for carrying out drug studies, in part because changes to these molecules could give early hints that a drug works. Treatments for Alzheimer's have all been unsuccessful so far—in part,

researchers think, because people received drugs only after symptoms had become obvious and their brains were too damaged to recover.

"This is perhaps the most comprehensive picture of what changes, in what order, and by how much," says Randall Bateman, a professor of neurology at Washington University School of Medicine, and the study's first author.

Now, with a roadmap of the disease's signature, Bateman says, doctors will have a better chance of judging whether a treatment is working by looking at interim measures rather than waiting until the disease is full-blown. Bateman is participating in a set of important new studies to see if Alzheimer's can be prevented. The two-year drug trials involve currently healthy patients who carry genes for an early-onset, inherited form of Alzheimer's. The biomarkers will be used to judge whether the medications are helpful at preventing or slowing the course of the disease.

A combination of factors similar to those that lead to heart disease—diabetes, poor diet, lack of exercise—are associated with the development of Alzheimer's, although the disease's root cause is still a matter of scientific debate.

The timeline was constructed from studies of 128 people from families plagued by a rare, inherited form of Alzheimer's in which symptoms emerge in patients still in their 30s, instead of after 65, as is the case with most of the five million Americans with the disease.

According to the study, levels in the spinal fluid of Aβ42, a protein associated with Alzheimer's, begins to decline 25 years before the onset of symptoms; at 15 years before symptoms develop, levels of another protein, called tau, begin to rise, and some brain shrinkage and atrophy is evident; at 10 years out, the brain's consumption of the sugar glucose is discernibly lower, and some memory impairment can be measured.

The researchers created the chronology by measuring the key molecules in volunteers who are healthy, but whose genes predict they will develop Alzheimer's. By learning at what age those volunteers' parents first developed Alzheimer's symptoms, the researchers were able to infer the time span between the molecular changes and the disease's onset.

Family members who did not inherit the Alzheimer's genes showed none of these early signs of the disease, Bateman says, suggesting that the markers really do distinguish between people with early-stage disease and those without. It remains to be seen whether the biomarkers can also predict Alzheimer's disease in the general population.

The Washington University scientists continue to look for more families with the genetic form of Alzheimer's to join its study, which is recruiting families with a history of early-onset Alzheimer's spanning three generations…" End

Agriculture Defense Coalition Notes – October 15, 2012

The world's populations are being exposed to herbicides, pesticides, insecticides, and a whole host of other toxic chemicals and biological weapons since World War I. The intensity of these exposures is increasing worldwide each year…and no studies are being conducted to see if these types of exposures could be the root cause of dementia and Alzheimer's, and a whole host of other problems like autism (the list is a long one and increasing each year).

We only look toward treatment of these types of problems…not toward the cause of them…due to the influence of those that sell these chemicals for profit. If we only look for the cures then we are always behind…trying to catch up with our increasingly toxic world and the impacts that those toxic have on the environment and our health.

The question for all of us is when are we going to wake up…much too late…is my guess.

"…Man, owing to an egoism that is too shortsighted about his own interests, his penchant to take pleasure in all that stands at his disposal, in short, owing to his carelessness about the future and his fellow men, seems to labor at annihilating his means of preservation and even at destroying his own species. By everywhere destroying the great plants that protected the soil, for the procurement of objects that satisfy his craving of the moment, he rapidly brings about the sterility of the soil he inhabits, gives rise to the depletion of springs, keeps away the animals who drew their substance from those springs, and causes large parts of the globe, once quite fertile and populated in every respect, to be barren, sterile, uninhabitable, and deserted. Always disregarding the advice of experience, in order to give himself over to his passions, he is perpetually at war with his fellow men, and destroys them from all sides and under all manner of pretext; with the result that one sees populations that were once thriving, become increasingly impoverished. It would seem that man is destined to exterminate himself after having rendered the globe uninhabitable…"

Jean-Baptiste Pierre Antoine de Monet, Chevalier de la Marck
(1 August 1744 – 18 December 1829), French Naturalist.
Above Quote from: "Système analytique des connaissances positives de l'homme" (1820)