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## Addressing the Unforgettable Killer in a Forgetful Mind: A Look into the Advances of Treating Alzheimer's Disease

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*Addressing the Unforgettable Killer in a Forgetful Mind: A Look into the Advances of*

*Treating Alzheimer's Disease*

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The world's population is getting older. Modern science has ensured that people are living longer and healthier lives. However, as the world ages, there is a looming epidemic of Alzheimer's disease promising to surface at any time. Currently, there are almost 30 million cases of Alzheimer's disease worldwide, and that number is only increasing. It is predicted that by 2050, that number will quadruple, and that 1 out of every 85 people will be living with Alzheimer's (Brookmeyer, Johnson, Ziegler-Graham & Arrighi, 2007). This disease kills about 100,000 people each year, which makes it the fourth leading cause of adult death (Lehne, 2007). It is also the second most feared illness, after cancer (*The Alzheimer's Project*, 2009). Advances in therapeutic measures, preventive measures, and research are giving hope to controlling the disease. Even small delays in the onset of Alzheimer's will significantly reduce the global burdens of the disease. As Robert J. Hodes, MD, the Director of National Institute on Aging, NIH states, "If we fail to cure or prevent Alzheimer's disease in the years and decades to come, we will be facing an enormous increase of human suffering, as well as the financial and societal impact that will occur" (*The Alzheimer's Project*, 2009). If the progression and onset of Alzheimer's could be reduced by a meager one year due to advances, there would be nearly 9.2 million fewer cases by 2050 (Brookmeyer et al., 2007).

Within our nation, it affects more than 5.3 million people, and as the baby-boom generation begins to retire and grow older, that number is estimated to more than double to over 11 million by 2040 (Alzheimer's Association, 2009). Currently, 1 out of 8 people over the age of 65 suffers from Alzheimer's, and that number doubles for every 5 year interval older than 65. The cost of both direct and indirect treatment and care of patients

suffering with Alzheimer's is huge, at \$138 billion yearly. By having a better understanding of the disease—its symptoms, pathologies and etiology—there is a greater chance to slow, stop, reverse, or prevent the disease (Lau & Brodney, 2007)

Alzheimer's disease, which was first understood by German researcher Alois Alzheimer in 1906, is the most common form of dementia. It is an irreversible, progressive brain disease that slowly destroys brain functions, including memory, thinking skills, and even the ability to carry out simple tasks (*The Alzheimer's Project*, 2009). Though the cause of Alzheimer's is far from being completely understood, it has been discovered that all people that suffer from Alzheimer's share three common characteristics—an abundance of amyloid plaques and neurofibrillary tangles, and a loss of connections between neurons in the brain, which seem to ultimately result in Alzheimer's (*The Alzheimer's Project*, 2009).

These plaques and tangles begin to accumulate as many as ten to twenty years before symptoms of Alzheimer's appear. Tangles develop deep in the brain in the entorhinal cortex and plaques form in the spaces between the brain's nerve cells. Plaques are made up mostly of insoluble deposits of a toxic protein peptide, or fragment, called beta-amyloid, which stick together in small aggregates, or oligomers, and eventually turn into plaques. This seemingly toxic effect of the beta-amyloids is a serious area of research (National Institute on Aging, 2009). Beta-amyloid has also shown to release free radicals that injure cells, disrupt potassium channels, and it may form channels in the cell membrane that allow excessive entry of calcium. Increase beta-amyloid levels can also cause permanent blood vessel injury, which could ultimately lead to neurons not

receiving blood flow to survive, and thus dying off (Lehne, 2007). Scientists have been able to develop transgenic animal models of Alzheimer's, or animals that have been specially bred to develop Alzheimer's disease characteristics, like beta-amyloid plaques. Research has allowed scientists to carry out preliminary tests in humans of potential therapies to remove beta-amyloid, stop the formation of beta-amyloid, or break it down before it can cause any harm (National Institute on Aging, 2009).

Tangles are abnormal collections of twisted protein threads found inside nerve cells. The main protein that makes up tangles is called tau. Healthy brain neurons have microtubules that are structures to support the neurons and help transport nutrients and other cellular components from the cell body to the axon. Tau binds to the microtubules and seems to stabilize them, but in Alzheimer's patients, there is an abnormally large number of phosphate molecules attached to tau, which results in hyperphosphorylation, and tau separates from the microtubules and reattaches to other tau threads. These tau threads come together and form tangles within the cell, and can cause the microtubules to fail and the neuron to essentially collapse, leaving it unable to communicate any longer (National Institute on Aging, 2009).

The more plaques and tangles that are present, the poorer neurons work until they eventually lose their ability to function and communicate with each other and die. The plaques are mostly formed around the hippocampus region of the brain, which is where memories are formed. This means that the neurons of this area are killed off first (National Institute on Aging, 2009). Shortly after hitting the hippocampus, degeneration spreads to the cerebral cortex, which is central to speech, perception, reasoning and other

higher functions. This is when the Alzheimer's sufferer begins to lose short-term memory, and struggling with language and reasoning (Lehne, 2007). By the time severe Alzheimer's has hit, plaques and tangles are spread throughout the brain and the brain tissue is significantly smaller (National Institute on Aging, 2009). The disease eventually destroys enough of the brain function to cause death (Lehne, 2007).

Patients with advanced Alzheimer's also suffer from low acetylcholine (ACh) levels—usually about 90% below normal. It is normal for some ACh drop with aging, but the levels decrease much more in Alzheimer's patients. This loss of ACh is significant because ACh is an important transmitter in the hippocampus and the cerebral cortex, which is where most of the brain degeneration takes place, and ACh also important for forming memories (Lehne, 2007).

Currently, there is no cure for Alzheimer's disease, though recent research is giving hope that someday there will be measures to at least delay the onset of Alzheimer's, slow its progress, or prevent the disease completely. Alzheimer's is a complex disease, meaning it is affected and caused by several different factors, including genetic makeup, environment, life history, and lifestyle—some of which are risk factors that can be controlled, while others cannot. The greatest risk factor currently known is age, which is something that cannot be controlled. The risk of Alzheimer's developing doubles every five years after the age of 65, and the number of people 65 and older is growing fast with the aging population (*Can Alzheimer's Disease be Prevented?*, 2009).

Genetics is another risk factor that cannot currently be controlled, but is a promising area for research. It is an essential step in developing drugs, prevention

strategies, and treatments for the disease. Scientists have found genetic links to the two forms of Alzheimer's disease—early-onset and late-onset Alzheimer's. Early-onset Alzheimer's affects people ranging in age from 30 to 60, but is very rare—it counts for only about 5 percent of Alzheimer's cases. This form of the disease is caused by mutations in certain genes, and if a parent has any of these mutations, their child has a 50-50 chance of inheriting the gene and developing Alzheimer's (National Institute on Aging, 2009). Dr. Schellenberg, the director of Alzheimer's Disease Genetics Consortium, discovered one of the three genetic mutations known to cause early-onset Alzheimer's (*The Alzheimer's Project*, 2009).

More commonly seen is late-onset Alzheimer's, which develops after the age of 60. Researchers have found that three alleles of the gene apolipoprotein E (APOE) can influence the risk of Alzheimer's, either positively or negatively. APOE ε2 may provide some protection against Alzheimer's, though this allele rarely occurs. APOE ε3, which is the most common allele, does not increase or decrease the risk of developing the disease. Finally, APOE ε4, which occurs in about 25 to 30 percent of the population, also occurs in about 40 percent of people that have late-onset Alzheimer's, and has shown that it increases risk by lowering the age of onset (National Institute on Aging, 2009). APOE ε4 may also promote formation of plaques, because it binds quickly and tightly to beta-amyloid and making it insoluble, which could promote deposition of beta-amyloid in plaque (Lehne, 2007). APOE research, especially APOE ε4 research, is a vital area to gain understanding in, as it will help researchers discover some of the blurry areas of the disease. It will answer some questions about the basic mechanisms of the disease, like

what makes the disease process begin; it will help researchers determine how the susceptibility genes for Alzheimer's disease interact with other genes, the environment, or lifestyle factors to influence the risk of developing Alzheimer's; it will help identify people who are at high risk for Alzheimer's so that it can be controlled greater, and the research of APOE will all researchers to focus on prevention and treatment approaches (National Institute on Aging, 2009).

Thus far, the testing for APOE is limited. There is a blood test that can mark what APOE allele a person has, but there is nothing available to predict who will develop Alzheimer's, since it is not guaranteed that a person with APOE  $\epsilon$ 4 will develop Alzheimer's. Some researchers are skeptical is what can actually be discovered by screening for this gene, and do not believe that it will allow for a completely accurate prediction of Alzheimer's, but along with others tests for more risk-factor genes, it may eventually be of use. Currently, the APOE gene is being looked at in people that may be at risk for Alzheimer's, and scientists are looking for early brain changes and comparing effectiveness of treatments for people with different alleles. This may be an area that if effective ways to treat and prevent Alzheimer's become available, the testing and screening for this gene may come in handy (National Institute on Aging, 2009).

It is estimated that at least six other genetic risk factors are present in the development and progress of Alzheimer's, and research is constantly being conducted to pinpoint what other genes are responsible. This is being done using a new approach called a genome-wide association study, which is a global effort to identify all possible susceptibility genes for Alzheimer's, and Dr. Schellenberg is a part of this study. This

process uses ground-breaking technology where DNA is put on tiny chips that have between 500,000 and 1 million spots that look at the many areas of a person's DNA, the DNA is rapidly scanned and checked for genetic variations that are associated with Alzheimer's (*The Alzheimer's Project*, 2009). This breakthrough technology has led to the discovery of another likely gene that is involved in the development of Alzheimer's, SORL1, which seems to impact the levels of beta-amyloid in the brain. When the gene is active at low levels or abnormally, then there may be a harmful increase in levels of beta-amyloid (National Institute on Aging, 2009). Research is still coming up with genetic candidates to focus on for drug testing and progress towards combating Alzheimer's disease (*The Alzheimer's Project*, 2009).

In hopes to conquer this research, The National Institute on Aging has created two large research programs—the Alzheimer's Disease Genetics Study, and the Alzheimer's Disease Genetics Consortium, which collect and analyze blood samples and other biological information of Alzheimer's patients and non-Alzheimer's patients so that research may be completed and questions can hopefully be answered. The NIA also supports the National Cell Repository for Alzheimer's Disease, where clinical information and DNA can be stored and accessed by researchers. These programs allow for data to be shared and researchers to work together to develop new technologies and methods for Alzheimer's progress (National Institute on Aging, 2009).

Besides age and genetics, other risk factors include environment and lifestyle factors. Exercise and diet have shown to be influential in the development of Alzheimer's disease, and the control of chronic diseases like diabetes may play a role in

the delay or prevention of Alzheimer's. Recent studies have shown that good overall health may help lower the chances of developing many diseases, including Alzheimer's (*Can Alzheimer's Disease be Prevented?*, 2009). One study was completed by Dr. Cotman, who looked at the growth and neurotrophic factors of transgenic mice. He discovered that the protein, brain-derived neurotrophic factor (BDNF), protects animal brains against aging and is increased with exercise. BDNF increases in transgenic mice that exercise, which increases growth factors in the brain—leading to building of new neurons and synapses, and improves vascular function. BDNF helps with thinking, learning, and memory skills, and Dr. Cotman is now researching if it can also slow Alzheimer's disease (*The Alzheimer's Project*, 2009).

Social engagement and mentally stimulating activities, along with a nutritious diet and exercise, can also help in keeping both the body and mind healthy (National Institute on Aging, 2009). An ability to withstand the Alzheimer's pathology is called cognitive reserve. A study was done on two people that both died of Alzheimer's. One woman, in her seventies, showed many signs of dementia, and an older woman in her nineties showed very few. After their autopsies were complete, they showed the same amounts of plaques on their brain. It was as if one was seemingly protected from the symptoms of Alzheimer's disease. The difference? The one that did not show much cognitive loss had a social network ten times larger than the younger, and showed to be less likely to be distressed. She worked hard to stimulate her mind and stay active and healthy. Engaging and cognitively stimulating activities seem to maintain the brain better, even when Alzheimer's is present (*The Alzheimer's Project*, 2009).

Some risk factors can be prevented, but others are inevitable, so research is being done to find more preventative measures or treatments for Alzheimer's disease. Currently, there is no cure for Alzheimer's. However, there are some treatments that focus on helping Alzheimer's sufferers to maintain mental function, delay or slow symptoms, and manage behavioral issues related to the disease (*The Alzheimer's Project*, 2009). So far, the treatments for Alzheimer's are mostly for symptomatic therapy—simply improving the quality of life rather than combating the actual disease. However, because Alzheimer's disease is progressive, the efficacies of these treatments are limited. A patient who is suffering from Alzheimer's who begins a treatment regime may experience improvements for a while, but the symptoms may come back or continue to worsen over time. Then there are also therapies that attempt to slow or halt the progression of the disease, though these therapies provide no symptomatic relief. The patients would still appreciate the lack of increasing symptoms, but no immediate relief. This means that researchers desire to combine symptomatic relief with the therapies that delay the disease for optimum efficacy (Lau & Brodney, 2007). Some evidence shows that some therapeutic approaches can be mixed, like chronic treatment with beta-amyloid antibodies that provide disease modifying effects in APP transgenic mice and acute treatment improved cognitive functions. Both symptomatic and disease modifying approaches are imperative for improving Alzheimer's patients health (Lau & Brodney, 2007).

Currently, only five medications to treat Alzheimer's have been approved by the FDA, and these drugs do not stop the disease process, but only help the symptoms for a few months to a few years (*The Alzheimer's Project*, 2009). The treatments for cognitive

symptoms—the symptoms related to memory, language skills, judgment, thought processes, etc.—include cholinesterase inhibitors and memantine. Cholinesterase inhibitors prevent the breakdown of ACh, which is a chemical messenger needed for learning and remembering. Cholinesterase inhibitors keep ACh levels high, which improves the communication between neurons by enhancing the transmission by central cholinergic neurons that have not yet been destroyed. The drugs are usually able to delay the worsening of symptoms for 6 to 12 months in about half of the people that use them (Alzheimer's Association, 2009). They are intended for patients with mild to moderate symptoms, and only have modest and short-lasting improvements, though they still provide some relief. Four of the approved medications for Alzheimer's are cholinesterase inhibitors, though only three of which are recommended—donepezil, galantamine, and rivastigmine (Lehne, 2007). The other drug that is used for the cognitive symptoms of Alzheimer's is memantine, which regulates the activity of glutamate, which is another chemical messenger involved with learning and memory. This drug is similar to cholinesterase inhibitors, as it temporarily delays worsening symptoms for some people (Alzheimer's Association, 2009). This drug, unlike cholinesterase inhibitors, is intended for people that suffer from moderate to severe Alzheimer's disease, because higher doses are better tolerated (Lehne, 2007).

There are also treatments that help with behavioral and psychiatric aspects of the disease, which are the symptoms that affect how the patient feels and acts. The initial treatment of the behavioral issues is by using the non-drug approach, which is to provide the Alzheimer's sufferer with a comfortable and known living environment as to ease any

anxiety, and to try and understand the cause of any behavioral issue so that the catalyst can be avoided in the future (Alzheimer's Association, 2009). These techniques may help, but the caregiver and patient may need more. Some medications are available and effective, but must be used carefully and usually work best when combined with non-drug approaches. Some of these medications are antidepressants, anxiety, sleep-aids, and antipsychotic drugs in extreme cases (Alzheimer's Association, 2009).

Research has shown that on occasion, Alzheimer's can be treated with vitamin E, which has shown to delay the loss of ability to carry out activities. This is thought to help because vitamin E is an antioxidant and may protect nerve cells from chemical damage. There are many other alternative therapies rumored to help Alzheimer's. However the efficacy and safety of these therapies, like coenzyme Q10, ginkgo biloba, or omega-3 fatty-acids, is unknown. The FDA does not require supplements to claim any efficacy or safety, along with the purity of the drug. Also, manufacturers of the drugs are not required to report to the FDA any problems that may have appeared because of the use of the supplement, which can have serious interactions with other medications (Alzheimer's Association, 2009).

Though these treatments may help ease the blow of Alzheimer's disease, researchers are religiously searching for new treatments to alter the actual progression of the disease and underlying disease process, along with improving the quality of life for Alzheimer's patients (Alzheimer's Association, 2009).

Because the beta-amyloid plaques seem to be one of the ultimate perpetrator of Alzheimer's disease, most of the efforts for new drugs and research have been targeted at

reducing these plaques within the brain. Scientists have aimed their drugs to either reduce levels within the brain or increasing the clearance (Lau & Brodney, 2007). Beta-amyloid peptides are produced by proteolytic cleavage of their substrate—amyloid precursor protein (APP)—by beta-secretase (BACE1) and  $\gamma$ -secretase. Therefore, scientists are targeting these two proteases for their drugs. Many pharmaceutical companies are working on  $\gamma$ -secretase inhibitors, which are in clinical trials, in order to reduce the products of the plaques. However, a major concern with  $\gamma$ -secretase inhibitors is that it also inhibits signal transduction that is mediated by many other  $\gamma$ -secretase substrates. This creates the challenge of selective inhibition, which it is thought that the most advanced compound of  $\gamma$ -secretase inhibitors, R-flurbiprofen (Flurizan), may be successful in doing, and is in Phase III clinical trials, with second generation drugs closely behind (Lau & Brodney, 2007).

Beta-amyloid production can also be indirectly reduced by enhancing the non-amyloidogenic cleavage mediated by  $\alpha$ -secretase. If other enzyme levels and activity increase, the production of beta-amyloid will decrease. Some of these treatments, like statins and muscarinic M1 agonists are being tested in clinical trials. Statins are also being studied to see whether the inhibitory effects can reduce cholesterol-enriched lipid rafts where amyloidogenic processing of APP occurs (Lau & Brodney, 2007).

Along with decreasing the beta-amyloid production, the plaques can be diminished by increasing the clearance of the brain beta-amyloid. Clearance is regulated by protease degradation, receptor-mediated efflux from brain to blood, and phagocytosis by microgila. The efflux of beta-amyloid from the brain to blood is thought to be

mediated by the lipoprotein receptor-related protein and P-glycoprotein. Researchers are trying to work on these proteins as potential therapies to increase the clearance. These include RAGE inhibitors, which mediates the movement from the blood to the brain, and beta-amyloid immunotherapy, which has not only shown potential for reducing plaques and thus Alzheimer's, but it has also shown to provide acute cognitive improvement (Lau & Brodney, 2007).

Another hallmark of Alzheimer's are the tau tangles found in the brain, which is another key area of research for potential drug therapies. In the cerebrospinal fluid of Alzheimer's patients, tau levels are elevated. It has been shown that in transgenic mice expressing tau, loss of neurons occurs. However, other studies have shown that by removing praline-directed phosphorylation sites on tau abolishes tau toxicities in *Drosophila*, and inhibition of tau kinases improve tau pathologies and helps behavioral functions in mice. Because of these findings, tau kinases are a huge target for drug research. Currently, glycogen synthase kinase 3 inhibitors are in Phase I of clinical trials, and other tau kinases are also being researched (Lau & Brodney, 2007). The problem with tau kinsase inhibitors is selecting the right kinase to target, because there are many, and studies have shown that inhibition of one kinase may preclude phosphorylation by others. Tau immunotherapy is also being looked into, as behavioral deficits in tau transgenic mice seemed to be reversed by immunotherapy. Very few tau therapies are in clinical development, and along with these areas, tau oligomerization, cleavage, and degradation are opportunities for more research, so there is still much hope for development in this arena (Lau & Brodney, 2007).

NIA and pharmaceutical companies are working to delay and prevent Alzheimer's through treatment clinical trials. Now that more is understood about the mechanisms and risk factors for the disease, there are more areas of interventions under study—cardiovascular treatments, hormones, type 2 diabetes treatments, antioxidants, omega-3 fatty acids, immunization, cognitive training and exercise, along with others (*Alzheimer's Disease, Unraveling the Mystery*, 2008).

Dr. Craft, a researcher with VA Puget Sound at University of Washington School of Medicine, has made groundbreaking discoveries linking insulin and glucose with Alzheimer's. Insulin has an important role to play in aging of the body and brain; the insulin system is one of the most important predictors of how one will age. Insulin is produced every time food is eaten. It is a peptide, a small protein, and produced in the pancreas in response to glucose, which is the primary fuel for all cells—including brain cells. Glucose needs insulin to be transported into the cell. If insulin cannot allow glucose to get into neurons, they cannot carry out their duties—including thinking, memory, and attention skills. If insulin is not working correctly, and glucose builds up outside the cells, which leads to insulin resistance, which leads to cardiovascular disease, hypertension, small vessel strokes, and diabetes—all of which contribute have shown to Alzheimer's disease (*The Alzheimer's Project*, 2009). With the rise in obesity and sedentary lifestyles, insulin resistance is becoming more prevalent today and beginning earlier in life. Dr. Craft has shown that as insulin increases, beta-amyloid is also increasing, so if preventative measures are taken to keep insulin at bay, Alzheimer's may also be prevented. The best way to treat increase of insulin is exercise—30 minutes of

aerobic exercise a day. Diet is also a big factor, as high-fat, high-sugar foods sky rocket insulin levels and cause it to remain high, rather than returning to a normal, lower level. In a study done by Dr. Craft, participants who consumed low-fat and low-sugar diets showed lower incidence of not only insulin, but also beta-amyloid after only four weeks. So along with a healthy diet and exercise, treatment for diabetes and high insulin may also help treat Alzheimer's patients (*The Alzheimer's Project*, 2009).

Another area of progress being made in Alzheimer's research is the inflammation that occurs with Alzheimer's. Dr. Rogers, with Banner Sun Health Research Institute, along with other scientists, figured that with all the beta-amyloid production in the brain of an Alzheimer's patient, that the brain's immune system must be trying something to get rid of it—inflammation. The body uses inflammation to rid itself of foreign material, which in this case, is beta-amyloid. The brain then initiates an inflammatory attack to try and get rid of all the beta-amyloid, using the cells present in the brain called microglia. Though the brain is trying to be productive with these measures, it seems that it is also causing damage. Though inflammation is often good, as it kills foreign invaders, it can also destroy healthy tissue in the process (*The Alzheimer's Project*, 2009). Over time, it is believed that it kills a lot of brain cells and connectors of brain cells in Alzheimer's patients, because it has been confirmed by thousands of studies that the inflammatory response is ongoing in a brain with Alzheimer's for years. This inflammation is killing neurons, but unfortunately not getting rid of the beta-amyloid. This means that anti-inflammatory medicines, like ibuprofen, though does not help with any of the

Alzheimer's symptoms, may help decrease the risk of getting the disease or to more advanced stages of the disease (*The Alzheimer's Project*, 2009).

There seems to be a significant connection of Alzheimer's disease and cardiovascular disease, as well. Many studies have shown that cardiovascular problems contribute to Alzheimer's. The coronary arteries in an Alzheimer's patient have much more atherosclerosis than healthy people, which causes hypertension, high blood pressure, and causes changes within the heart. The heart then has to work harder in order to pump blood out, because it is working against higher blood pressure. This results in the heart getting bigger, and eventually it fails at pumping all of the blood out of the heart and to the brain (*The Alzheimer's Project*, 2009). Alzheimer patients are twice as likely to have brain arteries that are blocked up by cholesterol. This means that along with higher blood pressure discouraging all the blood to get the brain, there are smaller arteries for blood to flow through as well. One fifth of a human's blood is needed in the brain. If there are injuries of the blood vessels that bring the brain blood, which means there is going to be injury to the brain as well. As people get older, these injuries accumulate and add up, making one more vulnerable to Alzheimer's. The cholesterol deposits on the artery wall also act as a sore, which causes inflammatory cells to hone in on and try to repair. Once the capillaries are inflamed, they are less able to do their normal jobs—which one of these jobs has shown to be delivering excess beta-amyloid out of the brain and into the blood for disposal. Therefore, the removal of beta-amyloid excess cannot be completed, and is built up in the brain—leading to Alzheimer's. The good news in the relationship between Alzheimer's and vascular disease is that there are already treatments in place for

vascular disease—which seem to benefit and prevent Alzheimer’s disease as well. Statin, for instance, is a drug that lowers cholesterol and it shows to decrease the risk of Alzheimer’s disease, and lower the frequency of the disease (*The Alzheimer’s Project*, 2009).

Progress of immunization is a big focus of researchers. Early studies of beta-amyloid immunizations in mice were very successful in reducing deposits of beta-amyloid, and brain performance on memory tests were much improved on preliminary clinical trials in Alzheimer’s patients. Sadly, some participants faced problems of life-threatening brain inflammation, so the study was not completed (can AD be prevented). Even though the trial was halted, the 372 participants were tested for four additional years and 59 of them did respond to the amyloid vaccine by creating antibodies. Later, when some of the participants died, their autopsies showed that the plaques were essentially gone from their brains (*The Alzheimer’s Project*, 2009). Because of such hopeful results, researchers are continuing to work on the vaccine and trying to reduce the bad side effects. Several new vaccine strategies have been permitted by the FDA to be tested for safety in early-stage clinical trials, so there is much hope for a vaccine (*Can Alzheimer’s Disease be Prevented?*, 2009). Also, human antibodies are being trialed, which would be directly inserted into the body rather than the body making them on its own in response to a vaccine. This allows for much more control of how much is produced, and the antibodies will bind to plaques to neutralize them or stimulate clearance (*The Alzheimer’s Project*, 2009).

Hormones are another area of focus in preventing Alzheimer's, specifically estrogen in women. Estrogen considerably declines after menopause, and studies have shown that estrogen may protect the brain. This led to the thought that if women were to take estrogen supplements after menopause, that the brain would continue to be protected from Alzheimer's. However, many studies have shown that estrogen does not successfully slow the progression of Alzheimer's in patients that have already been diagnosed, nor does it treat or prevent Alzheimer's when treatment is begun later in life. Some studies even showed that women over the age of 65 who took estrogen or estrogen with a synthetic progestin were at an increased risk of dementia and Alzheimer's (*Can Alzheimer's Disease be Prevented?*, 2009). Researchers are still hopeful that some form of estrogen will be beneficial, and continue to work on finding that. Some scientists formed estrogen-like molecules called SERMs (selective estrogen-receptor modulators) that focus on consequences of estrogen after menopause, like bone loss. SERMs are thought to have the protection of estrogen without the side effects, like uterine cancer. Researchers are hopeful that these SERMs, like raloxifene, can slow Alzheimer's progression (*Can Alzheimer's Disease be Prevented?*, 2009).

Modern science and technology is a huge part in combating Alzheimer's. Along with the genetic progress for finding the connection with Alzheimer's, other advancements have occurred. Scientists can now visualize plaques by imaging the brains of living individuals. This allows them to explore the ins and outs of the plaques and have a better understanding of the living characteristics. In the past, this was never something that was able to be done—look into the actual tissue of the brain. Autopsies

were the only form of research of the brain that was available. If it was possible to look directly into the tissues of the brain, Alzheimer's could be caught many years before symptoms occurred, so preventive measures and early delay could be put into effect (*Alzheimer's Disease, Unraveling the Mystery*, 2008). This image inside the brain could also help improve early diagnosis, allow monitoring of the disease progression, and see how effectively treatments are working. Though this is not quite possible, scientists are one step closer with the development of a compound called Pittsburgh Compound B (PiB). This compound binds to beta-amyloid plaques in the brain, and then imaged using a positron emission tomography (PET) scan. It has been shown that people with Alzheimer's show more of the PiB in their brains than healthy people. It is being researched to see if the healthy people that do take up more PiB in their brains will later be diagnosed with Alzheimer's down the road (*Alzheimer's Disease, Unraveling the Mystery*, 2008). Studies have shown that about 20 percent of seventy-year-olds show evidence of beta-amyloid plaques, without any symptoms. (*The Alzheimer's Project*, 2009)

The advancements of imaging have allowed for much more research to be completed, as well. Dr. Reisa Sperling, of Harvard University, took advantage of MRI and PET scan technologies and believes that she can now see early signals of problems in the brain. The scans clearly show brain activity and what regions of the brain are engaged when someone is learning something new. She believes that certain areas of the brain that are involved with making and retrieving new memories, like the hippocampal regions, go into overdrive in the very early stages of Alzheimer's, and this is visible on

the MRI and PET scans. She believes that this may be an indication of cognitive decline (*The Alzheimer's Project*, 2009). In a study that she conducted, Dr. Sperling noticed that people with mild memory problems had extremely active hippocampal formation, which she believes that that area of the brain was trying to compensate for the damage done by the advancing Alzheimer's disease. Within two years, about half of the people that showed hyperactivity in Dr. Sperling's study had developed Alzheimer's disease. In a person with full-blown Alzheimer's disease, the scans show little or no activation of the hippocampal formation when the person learns something new and the images show shrinkage or atrophy of the brain. Dr. Sperling is continuing her research to see if there is a correlation between plaque formation and hyperactivity in the hippocampal formation, along with trying to form a definitive link between the hyperactivity and the impending onset of Alzheimer's disease (*The Alzheimer's Project*, 2009).

Along with imaging progressing for detecting Alzheimer's early on, scientists are working hard to discover if anything else will work as biological markers for detecting Alzheimer's. These markers include biological compounds present in blood, urine, or cerebrospinal fluid and could indicate early changes within the brain. Scientists are working more to understand what causes level changes within these markers and how they work, which would allow more understanding about Alzheimer's develops and what initiates the disease. Certain medications can also be tracked using these markers, and can be looked at to see the efficacy and side effects early on in the disease. This may also lead to new prevention strategies (*Can Alzheimer's Disease be Prevented?*, 2009). These markers are also important for patients that are undergoing treatment that is delaying the

disease rather than improving the symptoms, because the patients could easily get discouraged and struggle with compliance since effects are not being seen. However, with markers available, the efficacy of the drug can better be seen by the patients (Lau & Brodney, 2007).

The past twenty-five years have been remarkable in the progress made in understanding Alzheimer's disease and working towards defeating the challenges it brings. However, the process is not near over, as researchers and scientists are still searching for those few medications or vaccinations that can stop this epidemic in its tracks. Something needs to be done, and many people have the passion and ability to do it, though funding and support always seems to be lacking. Everyday is one step closer to having the perfect answer, but for now, the advancements in science, treatment, prevention, and knowledge must continue to improve and help suffering Alzheimer's patients as much as possible.

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