Riley McManus

Dear Civitas Committee,

My name is Riley McManus and I am from Wayne, Nebraska. I am sending you my senior research paper as my Civitas application. It is the culmination of hours of research and hard work. Hard work is a value I will bring to your honor program. I have always had a stubborn personality when it comes to any challenge. I had wrestled for the last six years and in the summers worked on my family's farm. Both of these have taught me how far hard work can take me. Also, I have learned discipline, and from discipline I have structured my morals and values. As my mom tells it, I have been an odd child since I could walk and talk. If I decided something was wrong I just didn't do it. She told me morals shaped my decisions early in my life. It is still that way today. I don't drink or party or anything like that; I decided long ago that those activities won't help me reach my goals. Peer pressure can be strong, but I have never really been tempted. I think strong values like hard work, discipline, and morality will help me do great things in the Civitas program. I hope to hear from you soon.

Sincerely,
Riley McManus

Physiological Problems Associated with Stage 1 Alzheimer's

People misplaces their keys every now and then, loses the TV remote, or even forgets something important like their glasses at home, but sometimes these can be the very early symptoms of a hidden monster waiting in our minds. Alzheimer's disease is a degenerative mental illness that usually affects the elderly over 65. According to Julia Frank, author of *Alzheimer's Disease: The Silent Epidemic*, "Alzheimer's is a progressive disease, beginning with minor symptoms that may seem unimportant, such as Sarah's losing her glasses or forgetting ingredients in a recipe. Over a period of years, however, the symptoms become increasingly worse until the victim of the disease is robbed of all ability to function normally" (15). Sarah, a grandmother later diagnosed with Alzheimer's, had seemingly benign symptoms that evolved into the characteristic helplessness of Alzheimer's patients. Alzheimer's is often split into three or four stages depending on which source one consults. Elaine Landau writes in *Alzheimer's Disease: A Forgotten Life* that "The first stage of Alzheimer's disease is largely characterized by memory loss concerning recent circumstance or events" (43). Many of the psychological symptoms of Alzheimer's are very well known because they are so obvious. Some of the most common are memory loss, confusion, and mood swings. These symptoms are the ones that most often affect the family and friends of the victim as the Alzheimer's patient loses all control of his self and surroundings. As the disease progresses, these symptoms become more and more pronounced. In later stages, basic bodily functions become impossible and what started as confusion has now progressed into a complete separation from reality. According to Landau this entire process from diagnosis to death can take as little as five years, but the disease can be drawn out as long as 17 horrible years (43). As the brain deteriorates, four main physiological

problems become apparent. The physiological problems that affect the brain because of stage 1 Alzheimer's are plaques, tangles, lesions, and atrophy.

Plaques are often the first physiological symptom to be recognized. These plaques, known as amyloid plaques, build up in the neuralgia, the extra cellular-material that surrounds the neurons, of the brain from other proteins. One of these proteins that builds up is the beta amyloid protein. The word amyloid is defined by Bryan C. Hains in *Brain Disorders* as "small protein fragments that are normally produced by all cells" (7). These beta amyloid proteins often play important roles in different cellular processes in the body, but in Alzheimer's patients these beta amyloid plaques clump together and form useless masses in the brain. *Alzheimer's Disease,* written by Edward Willett, states that amyloid plaques are "formed from another protein called amyloid precursor protein, or APP. Cells use enzymes called secretases on their surface to make beta amyloid out of APP" (30). For some reason, the brain of a person with Alzheimer's is unable to deal with the threat that a buildup of beta amyloid proteins poses. Scientists are not sure why the amyloids are even allowed to build up in the first place. One theory is that the chemistry of the brain changes because "[n]ormally, beta amyloid protein dissolves after it drifts away from the nerve cell that formed it, but when an abnormal secretase 'ships' the APP to a different location, it forms up into insoluble clumps called fibrils. These fibrils cluster together with other fibrils, eventually creating the plaques seen in Alzheimer's patients" (Willett 31). These floating bits of protein should naturally dissipate into the surrounding cellular material, but for whatever reason they continue to build up until dense fibrils are formed. These alone cause very few problems and are still manageable by the brain. As time progresses, these fibrils form the plaques that become the real problem later in the disease. Therefore, the simple beta amyloid protein becomes the mass that has become known as a hallmark for Alzheimer's disease.

As soon as the brain finally recognizes the plaques as a threat, it releases some of its greatest defenses to fight the building plaques. One of the first things the brain does is the body's basic response to any invader: inflammation. "In Alzheimer's patients these plaques cause inflammation, just like an infection would. Over time, this inflammation, which normally functions to kill viruses and bacteria but does nothing to remove the plaques, destroys brain cells in the vicinity of the plaques" (Willett 31). Inflammation is the body's natural defense against almost every type of injury: a cut, blunt force trauma, or infection. Normally, inflammation functions to seal and quarantine off sections of the body in order to prevent further harm. When the brain has this constant pressure the cells are slowly damaged. Carol Turkington and Joseph R. Harris write in *Understanding Memory* that "The result is a state of chronic inflammation that progressively injures nearby nerve cells" (8). This constant pressure is just the first and often least destructive of the brains responses to the plague build ups. The brain also brings in macrophages to try and clean out the plaques. The macrophages that are brought in are called microglia and they are the central nervous system's main defenders. They try and engulf as much plaque as they can until they take in too much and rupture. As the plaque keeps building up, the brain pumps in more microglia to clean up the ever growing extra cellular material. Finally, the brain sends in oxygen-free radicals, which are cells with poisons locked within them. These cells get close to plaque buildup and rip themselves open and dump their contents on the plaques. This would be great if the plaques were made of living cells, but they are bundles of protein. Soon, as this poison is being spilled out, it leaks into the surrounding cells. All of these defenses are meant to solve the problem, but they just compound it.

Eventually the brain's own defenses leads to damage and necrosis. First, the inflammation damages and weakens all of the cells around the plaques. Then, as macrophages

rush in and burst after filling themselves with plaques, the area is flooded with nonliving cellular material. Finally, the oxygen-free radicals come in and weaken or kill any strong, healthy cells left. One source described this process, "[l]ike tiny garbage collectors, the microglia keep trying the [sic] clear the plaques away, while the oxygen-free radicals try to poison them. Neither works, but both can eventually damage healthy cells" (Willett 31). This process of cells dying unnaturally is called necrosis. All these cells undergoing necrosis cannot just lie around without causing problems. After necrosis the natural course for living material is to begin decaying. This entire process may take years to reach the decay stage, but once necrosis has set in the symptoms are impossible to undo or stop. Even though they normally defend the brain, inflammation, microglia, and oxygen-free radicals end up causing some of the most extensive damage in the brain.

The next physiological symptom most often seen in the brains of Alzheimer's is the neurofibrillary tangle. "While plaques are made of beta amyloid clumps, the tangles are made of another kind of protein called tau" (Turkington and Harris 8). There does seem to be some sort of correlation between plaques and tangles, but studies have not shown yet what that commonality is. Tau protein naturally occurs in the brain's nerve cells, or neurons. These small proteins are necessary because "[t]he internal support structure for nerve cells depends on the normal functioning of tau, which functions like the rungs of a ladder, holding the two parallel branches of axons apart" (Turkington and Harris 8). Healthy tau acts as the cross bars and support beams of one of the brain's most important cell structures. The brain is a wired, interconnected pathway for information to flow, and the dendrites and axons are the facilitators that keep all of these highways running smoothly. Dendrites receive information from chemical neurotransmitters and axons send that information to more dendrites. Tau is what organizes all

of the dendrites and axons so everything is not running into each other. When this protein changes and fails, the consequences are tragic and tangles begin to build up.

Alzheimer's begins changing chemicals and proteins in the body, and one of those proteins is tau. "Tau is a protein found in the nerve cells of the brain. In people with Alzheimer's disease, however, this protein behaves differently – it gathers in tangled filaments in the neurons" (Landau 32). As discussed earlier in this paper, tau is the basic support structure in nerve cells and gives some rigidity to the axons. It is essential to the basic functioning of the brain and without them cells begin to quickly deteriorate. "In cells of patients with Alzheimer's, this parallel structure collapses as the tau protein 'crosspieces' twist into paired helical filaments" (Turkington and Harris 8). These once ordered sets of cell extensions rapidly devolve into tangled bundles of neurons. These tangles fill the inside of nerve cells to the point that the extended axons fall into each other, and without the support of tau become entangle. Imagine millions of hoses being pathways in ones brain and then plugging the ends. Soon the weight of themselves brings them out of structure, and they start to weave together. Untangling just one or two hoses at the beginning of every summer is a bothersome chore, but these tangles become anything but a bother in the brain. Tau does an unnoticed job, but once it fails, the symptoms become unmistakable and impossible to ignore.

After the tau fails and the axons tangle, irreversible brain damage occurs. Axons send information from one cell to another. This constant flow of information helps in the storage of memory so even as cells die the memory is constantly moving into a living cell. As these axons tangle, they become constricted to the point they cannot send information. After the have been tangled they begin to die, almost like they are suffocating. Connections to entire areas of the brain become cutoff and start receiving little or no stimulants. With these vital connections

outward symptoms become apparent. Short-term memory loss, one of the first signs of Alzheimer's, is caused by this fragmentation of the information pathways in the brain. "In addition, Alzheimer's disease alters some brain neurotramitters, the chemical messengers through which nerve cells communicate. Among these is acetylcholine, a neurotransmitter crucial to memory" (Landau 34). Between failing tau and changing brain chemistry, memory becomes impossible as the disease progresses. Learning new things also becomes nearly impossible. A person learns by making connections to past lessons and experiences, but without those lessons and new memories become just a dream to the victim of Alzheimer's. Also, tangles in the frontal lobe of the brain are responsible for many of the emotional changes and mood swings often seen in Alzheimer's patients. Because of the singular failure of the tau protein, unstoppable brain damage begins and often a person's very personality starts to degenerate.

Another characteristic symptom of Alzheimer's disease are lesions. These lesions are actually a combination of the plagues and tangles. As of now, no one knows the exact cause of any of the symptoms of Alzheimer's. "Scientists disagree about whether it's the sticky plaques of beta amyloid in the brain or the tangles of tau protein inside brain nerve fiber that play a more central role in the destruction of brain cells" (Turkington and Harris 8). Since both of these symptoms show up at once, a relationship between the two is not known. Scientist do not know if plaques cause tangles, tangles cause plaques, or if neither affect the other and both are just a byproduct of Alzheimer's disease. This question is not a new one, and according to Turkington and Harris "For nearly a century scientist have wondered which of the brain lesions associated with Alzheimer's causes the disease- the plaque that clutter up the empty spaces between nerve cells or the stringy tangles that erupt from within those cells" (7). Hundreds of thousands of

hours of analysis have been pinpointed on this disease since its "discovery" in 1906 by Alois Alzheimer after an autopsy of a 55 year old with dementia (Turkington and Harris 3), and we still are no closer to the actual cause of this disease. Darkness still shrouds why and how these lesions begin and how they can be stopped.

After the lesions form, they become impossible to treat. This becomes a sobering fact for many Americans with Alzheimer's. Hains writes that "Approximately 10% of Americans over the age of 65, and nearly 50% of those over 85, have Alzheimer's disease" (1). This translates into millions of patients and tens of millions of family members wondering what the treatment options are. Sadly, as of now, there are none. There are certain activities like crosswords and social interaction that can slow down the process of this disease, but there is nothing to stop it. The lesions soon develop into scars within the brain tissue itself. Surgery to remove these scars became the first treatment option early in the study of Alzheimer's. This option was dangerous and ineffective because even if one removes all the scar tissue, that does not stop the production and spread of the lesions. Today new medicines are being tested on Alzheimer's patients. The main problem is that the chemistry in the brain has changed enough that most medicines no longer affect the body as expected. Also, any drug strong enough to dissolve plaques or tangles would probably kill the patient. As Tom McGrath writes in his *Men's Health* article "Can You Catch Alzheimer's?" "Over the past century, the only thing that has prevented the disease from becoming even more widespread and devastating is that most people passed away from something else before they were old enough to develop it" (par. 37). This is a depressing but undeniable fact about the ultimate cure of Alzheimer's. The truth is there is no cure for this disease.

Atrophy is a secondary symptom of Alzheimer's, and it usually first affect the hippocampus. Sonja M. Lillrank, in *Alzheimer's disease and Other Dementias,* writes that "Atrophy means that the cells wither and shrink and ultimately lose their function and die" (47). Most people have heard of muscle atrophy. This occurs when, after a long period of disuse, muscles waste away and become much smaller. The exact same thing can happen in the brain once connections fail and nerve cells stop doing anything. Doctor Jeffrey Browndyke is an assistant professor in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center and is a faculty member at the Joseph and Kathleen Bryan Alzheimer's Disease Research Center at Duke (Landau 9). He explained that "This loss of brain tissue is called cerebral atrophy. There may be general atrophy seen throughout the brain or atrophy only in specific areas of the brain" (Landau 33). Atrophy affects some areas more heavily than others, especially areas with ventricles. Ventricles are spaces within the brain containing brain fluid. The hippocampus happens to have to ventricles and often deteriorates the fastest of any part in the brain. "The hippocampus, which is part of the temporal lobe, is important for learning and short-term and long-term memory" (Lillrank 34). This is why Alzheimer's victims are noted to have memory problems, confusion, and learning problems. At first the symptoms seem slight, like forgetting where the remote is and misplacing glasses. After atrophy set in, these symptoms become more profound as the patient forgets who that person at their front door is and why there is a car in the driveway. It is normal, for instance, to forget wear one's glasses are, but it is not normal to forget that one wears glasses and wonder why one cannot see. The first symptoms of memory loss are often the result of hippocampus atrophy.

The brains in Alzheimer's patients undergo major physical changes because of cerebral atrophy. The most notable change is the size. "The brains of AD patients begin to appear

shrunken as affected areas of the cortex begin to degenerate and collapse" (Hains 6). The brain in Alzheimer's victims is smaller and the wrinkles are deepened and more pronounced. This is why in the later stages this disease steals the identity of the victim. The loss in memory is the symptom most commonly associated with Alzheimer's. "The changes are most likely the result of a reduction in size of areas of the brain that are very important in memory—the hippocampus and a near-by region called the entorhinal cortex" (qtd. In Landau 50). The atrophy also has an effect on other parts of the brain, and this brings with it a whole new host of symptoms. These symptoms are things like separation from reality, mood swings, and depression. Brain scans can often tell an even fuller story about how the brain has been affected by Alzheimer's. "It usually shows that the brain has shrunk somewhat and that there has been a loss of neurons, or nerve cells, from an area considered essential to processing thought" (Landau 32). As more and more nerves start to fail, regular thought patterns are interrupted and often the victims will lash out because of utter frustration. Atrophy is a secondary symptom that causes the primary indications of Alzheimer's disease.

Plaques, tangles, lesions, and atrophy are the four earliest physiological symptoms associated with Alzheimer's disease. In a book written 25 years ago scientists predicted "Based on present statistics, we know that Alzheimer's disease will be much more common in 20 or 30 years than it is today" (Frank 67). As it turns out, they were more than right. Alzheimer's cases have doubled since that book was published, and scientists are still no closer to finding a treatment, let alone a cure. Alzheimer's is a disease for the future, a disease for the next generation to beat. The "baby boomers" are already too late; nothing can be done for them. "Our Parents are getting older. Soon we'll all be affected one way or another by Alzheimer's disease… if we haven't already. [….] People in their 20s, 30s, and 40s are the ones Alzheimer's

is especially going to affect" (McGrath par. 42). The sad truth is that those with Alzheimer's and their families will suffer, but maybe the patient's children, grandchildren, or even great-grandchildren will see the day Alzheimer's is controlled. For now, though, this dream is far away. We can only hope that someday Alzheimer's will also be a fleeting, lost memory.

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