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Rivera: Alzheimer's: A Tale of Two Diseases

Prof. Pierce

Senior Thesis

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Alzheimer's: A Tale of Two Diseases

Alzheimer's disease (AD) is unique in that multiple paths can lead to its manifestation. There are numerous risk factors that increase the susceptibility to AD and a vast number of combinations may lead to its acquisition. Additionally, the underlying mechanism by which the illness manifests itself could possibly differ amongst varying patients. It is my contention that early on-set Alzheimer's can be categorized as a unique illness in respect to late on-set AD, due to vastly different etiologies, although symptoms are similar. It will be demonstrated that early on-set AD is largely a genetically based etiology with little that can be done for prevention. Late on-set AD tends to be due to chronic environmental factors which preventative measures could have stifled. In addition, just as there is a need to have fuller characterization of Dementia, I will defend the position that AD treatment will benefit from more precise categorization as well as raise the ethical repercussions that follow. Lastly, the position for maintaining the illness under the singular name AD will also be considered for its pros and its ethical consequences.

Somewhat tangentially, but important nonetheless, is the importance of noting that this paper in no fashion will take the position that genetics and the environment do not play roles in both illnesses, but rather it will be articulate that they play roles of unique and varying degree in each.

AD was discovered by Alois Alzheimer but named by Dr. Kraepelin in the 8th edition of his Handbook of Psychiatry (Maurer K.; Maurer U., 2003). Dr. Alzheimer was a German psychiatrist as well as neuropathologist who came to be interested in lab work for senile illnesses

(Engstrom, E.J. 2007). The original specimens on which Dr. Alzheimer had based his original conclusions on were reanalyzed, amidst some controversy over AD, in the late 90's. The reanalysis revealed Alois Alzheimer to be correct in his characterization of AD in his historical patient. The patient, 56-year-old Johann F., was observed to have the AD related apolipoprotein allele epsilon-3 (Graeber, M., Kösel, S., Egensperger, R. et al, 1997). Dr. Alzheimer came to be reaffirmed as the discoverer of the illness and the field began to move even further in its characterization of the disease. Alzheimer's disease diagnoses have been update since their inception, now having three separate medical characterizations. Amongst the three are the dementia stage, the symptomatic pre-dementia phase, and lastly the asymptomatic preclinical phase. Historically, AD was thought to have a synonymous presentation of symptoms and underlying pathology. This was later discovered to not be the case, through further AD research it has become evident that underlying pathology can be asymptomatic; essentially observed through diffuse amyloid plaques being present with no manifested AD symptoms. Such scenarios led to the updating of the NIA-Reagan Institute criteria for the diagnoses of AD. Neuropathologically, AD has always been diagnosed through observation of at least a moderate amount of neuritic plaques in the neocortex containing Beta-amyloid, and regional distribution of neurofibrillary tangles, through the use of a low-power microscope. Over the years, AD diagnoses became more nuanced with a scale amended to diagnoses in 1984 to denote severity of impairment due to the illness. Additionally, over the time common comorbidities of AD with other cognitive illnesses (i.e. Lewy body disease) came to also be acknowledged. Presently, the most widely studied biomarkers of AD are AB accumulation now observed through PET imaging, neuronal degeneration, tau deposits (usually elevated in the CSF), as well neurofibrillary tangles (Jack, C. et al. 2011).

Notably, the most common form of Dementia is Alzheimer's disease with a 3.9% global prevalence amongst people older than 60, as of 2014. While Dementia is mostly known as a general cognitive decline, AD differs in that it is accompanied by a much more acute loss of cognition and memory. Additionally, AD physiologically presents with beta-amyloid plaques, NFT's, and a host of other characteristics (Ng, K., Ng, A., Assam, P., Heng, E., Kandiah, N., 2014). The term Dementia conservatively includes AD, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia (Kawamura, T., Umemura, T., Hotta, N., 2012). Dementia can however, be broadened to include Parkinson's disease, Creutzfeldt-Jakob disease, Huntington's disease, and Wernicke-Korsakoff Syndrome, (<http://www.alz.org/dementia/types-of-dementia.asp>) and is somewhat commonly done so in some branches of medicine. As more information is divulged it becomes more and more evident that specificity in the world of dementia is crucial. Each particular type of dementia has a unique underlying etiology with a distinctive pathology. The cognitive impairment of AD is most likely due to the synergistic effects of several factors. Amongst these various disease factors are beta-amyloids building up and elongated unbranched protein fibrils as critical factors (Riek, R., Eisenberg, D. S., 2016). As diffuse beta amyloid aggregate into senile plaques researchers took it unto themselves to make sense of why. It turns out that it is possibly due to a lack of perfusion in the brain, as observed in a study of patients with critical stenosis. 15 out of 20 patients studied showed plaque deposits, most often in the depths of the gyri. (Armstrong, 2013). However, brain perfusion is but one of several possible etiological agents. There are several possible etiological agents for Alzheimer's, which generally fall within two categories: genetic or environmental. Genetic marker examples include mutations in the PSEN gene while, environmental factors include examples like insulin

resistance. The discovery that early onset AD is mostly a genetically based phenomenon, while late onset AD tends to differ in its origin makes a strong point to revisit how we think of AD.

Case for early on-set being mostly genetically based

Genetic factors seem to be central to the pathology underlying early onset AD. It has been shown that “rare mutations in three genes – APP, PSEN1, and PSEN2 – are associated with 1% of AD and other frequent genetic variants such as APOE-E4 can account for up to 20% of total cases of the disease” (Sanchez-Mut, J.V., Graff, J., 2015). The statistics still leave at least, assuming no overlap between mutations, that 79% of AD has a non-genetically linked etiology. To begin with mutations of amyloid precursor protein (APP), the mutation can lead to a greater susceptibility of beta-amyloid build up and coincidentally, lack of its clearance (Armstrong, 2013). A variety of AB peptides are formed as a result of secretase cleavage of APP, the most common peptide being AB₄₂. The amyloid Cascade Hypothesis (ACH) proposes that the deposition of AB peptide acts as the initial pathological event in AD, leading to the formation of senile plaques (SP) and neurofibrillary tangles (NFT), summing up in cell death and dementia. Both SP and NFT acquire several additional proteins during their formation, such as Apo E, ubiquitin, and their complement. The ACH theory has found support in experiments with transgenic mice expressing elevated levels of APP resulting in AB deposition, synaptic loss, and gliosis (Armstrong, 2013). The first objection ACH theory receives from critics is the fact that SP and NFT may prove to be reactive products that result from cellular neurodegeneration, rather than being the cause itself. However, it is important to note that inflammation of the microglia is caused by overload of SP’s and NFT’s around the neurons to the point of toxicity. Therefore, there is still some merit to the discussion between accepting the theory or not, at least in respect

to the degree of ambiguity that persists. The second objection to the theory is how ACH is not a generally accepted mechanism to explain how AB deposition leads to NFT. The presence of tau is necessary for AD pathology, thus its subsequent lack of mention in the ACH model seems to denote an incomplete explanation.

Moreover, the Presenilin (PSEN) gene mutation has been greatly associated with an increased likelihood for early-onset AD. Interestingly enough, the most common type of FAD has been linked to mutations of the PSEN genes (Armstrong, 2013). Additionally, another genetic marker identified for AD is an allelic variation in apolipoprotein (Apo E). This epsilon 4 allele is a major risk factor in late-onset AD, having a 2-3 time increase in frequency within the individual with AD (Armstrong, 2013). Of note, is the fact that people with diabetes are reported to have a significantly low incidence of the APOE epsilon 4 allele but diabetes itself still proves to be a risk factor for AD (Farris, W., et. al., 2002). Some controversy has arisen on the topic of the APO E allele and its AD association due to an opposing study finding no significant support for E318G acting as a risk factor for AD in the APOEε4 carriers (Hippen, et.al. 2016). Additionally, the chromosomal locus 12q13, the region that encompasses the vitamin D receptor (VDR) gene has been implicated as risk factor for AD (Armstrong, 2013).

Case for late on-set being mostly environmentally based

The majority of AD illnesses have by and large had stronger environmental ties than genetic. While several genetic alterations have been associated with AD, research has shown the vast majority of AD cases to not have strong genetic underpinnings rather they are considered as a consequence of non-genetic factors (Sanchez-Mut, J.V., Graff, J., 2015). A major aspect of AD

pathology has come to widely be thought of as due to faulty beta-amyloid metabolism, be it from overproduction or poor clearance. Research has suggested that familial, early-onset AD is characterized more so by overproduction of AB₄₂, while late-onset AD is characterized by a faulty AB clearance mechanism. Genetically, late-onset AD is associated with e4 allele of the apolipoprotein E gene, a major risk factor for issues involved with AB trafficking (Jack, C. et al. 2011). While the non-genetic factors in which epigenetics are thought to play a role are diabetes mellitus, hypertension, obesity, physical activity, depression, smoking as well as low educational attainment, amongst others (Sanchez-Mut, J.V., Graff, J., 2015). A possible environmental/epigenetic theory has risen stating in its Latent Early life Associated Regulation (LEARn) model that a series of harmful events from gestation to old age may accumulate as epigenetic markers possibly inducing or accelerating AD manifestation. However, epigenetic correlation has yet to be proven as causal and as such, the question remains between whether epigenetic modifications are driving the chromatin behavior or if they are just a consequence of the other processes happening nearby (Sanchez-Mut, J.V., Graff, J., 2015).

Moreover, amongst all the researched possible environmental causal agents of AD perhaps none can match Aluminum in the amount of interest and controversy it has received. Aluminum has become one of the most researched possible environmental etiological agents for AD. It is important to note that there is no known physiological role for Al within the body (Nayak, 2001). Additionally, Al is the most abundant neurotoxic metals on the planet. Only small amounts of Al are needed to produce neurotoxicity in the human body, which can be satisfied through small dosing in dietary Al intake. Experimental evidence has repeatedly demonstrated that chronic Al intoxication reproduces neuropathological hallmarks of AD (Tomljenovic, 2011). However, the efficacy of such experiments have been questioned as well as

their reproducibility. Already damaged brains may be susceptible to the accumulation of Al, muddying the significance of many studies because much research has been conducted in the already AD effected brain. On the other hand, most studies have however, shown enhanced amounts of Al in the AD brain. But as with most controversial topics there are opposing studies and this one exposed high concentrations of Al to patients with renal failure resulting in no cellular NFT development. Acute Al doses have, however been shown to be neurotoxic (Armstrong, 2013). Perhaps Al plays a role in the degree of aggression manifested by AD? A study showed that red blood cell aggregation increased significantly in Aluminum Trichloride-induced Alzheimer's disease (Chen, et. al. 2013). Such a study has possible implications on AD being concordant with vascular dementia due to red blood cell clotting. Additionally, studies have researched whether Al having passed through the blood brain barrier may cause an immune response perhaps leading to an autoimmune response that manifests into AD or at the very least plays a partial causative role (Armstrong, 2013). Of course claims are easier to make than defend and as such further research is necessitated. Topics requiring more research are the organ-specific variations in Al toxicity as well as the kinetics of Al in these varied environments (Nayak, 2001). Lastly, it is important to examine any possible modifying effects other elements within the body may have on Al or vice versa (Frisardi, 2010).

Another possible etiological agent that has been considered is a direct physical injury causing tissue damage. Such an event could result in Hydrocephalus ex-vacuo, a buildup of cerebrospinal fluid (CSF). Not only would the original injury then result in tissue damage but the increase in pressure would continue to have an injurious effect. Additionally, inflammatory cytokines could spread amplifying the original injury. Survivors of head injuries tend to demonstrate what may be an acute phase response to neuronal injury, of overexpression of APP

leading to deposition of AB. Formation of pathological proteins as a result of head injury may be one method by which AD pathology develops and it would propagate via cell to cell transfer through tubulin tracks (Armstrong, 2013).

Malnutrition has also been considered as a possible etiological agent. Development of NFT has been hypothesized to be due to chronic nutritional deficiencies of Ca and Mg. The problem with malnutrition as an etiological agent, however is that malnutrition could prove to be a mere consequence of the disease that resulted from the mental state of the patient. Direct dietary experiments have been conducted to test the hypothesis of malnutrition's role in causing AD. In one experiment, rabbits were fed with high levels of dietary cholesterol which resulted in the induction of AB deposits which accumulated and aggregated. Additionally, a human family carrying a mutation of APP gene (APP71) carriers, which results in a protein change of Valine to Glycine, were shown to have a greater B12 deficiency as compared to non-carrier family members. B12 deficiency could then be theorized to cause a reduction of monoamine transmitters and subsequently a reduction in cholinergic activity (Armstrong, 2013).

Moreover, AD has also been considered to be greatly affected by aging, and prove to possibly be an exacerbation of aging. With the present state of technology people are simply living much longer lives now when compared to the past. Currently life expectancy has risen in the United States to roughly 78.8 – 78.9 years according to an NPR piece (Rob Stein, 2016). Age may be the culprit in making the present moment have dementia as the fifth leading cause of death in “high-income countries” (Elie Dolgin, How To Defeat Dementia: The three things that could help prevent a meltdown in health-care systems worldwide). Research has shown that myelin loss is secondary to neuronal degeneration, this finding is suggestive of an age related loss of myelin. In addition, the loss of cells in the locus caeruleus (LC) diminishes the amount of

noradrenaline provided to the cortex via terminal varicosities. Noradrenaline is an integral stimulative factor in activating microglia to suppress production of Amyloid Beta plaques (Armstrong, 2013). With the reduction in noradrenaline AB plaques are free to aggregate and if medicine already pushes people to live to the brink of the body's capacity then in accordance with the age theory, AD is bound to occur.

Infectious agents have also been implicated as a possible etiological agent that may very well culminate in full manifestation of AD. The virus herpes simplex (HSV) may do so by leading to antibody movement into the cerebral spinal fluid (CSF), inducing abnormal protein formation resulting in Plaque formation as well as NFT and possibly full on AD manifestation. Marked structural and biochemical alterations have been observed in regions associated with olfaction, i.e. olfactory bulb and EC (Armstrong, 2013). HSV1 infection is thought to induce AD-like tau phosphorylation at several sites. The virus is has been observed to activate glycogen synthase kinase 3B and protein kinase A, the enzymes that cause phosphorylation at several sites that can result in neurofibrillary tangles (Wozniak, Frost, and Itzhaki, 2009).

Moreover, a defective endosomal sorting and/or trafficking as well as lysosomal dysfunction are thought to be other possible physiological pathologies researched under AD interest. They have been implicated by AD research to be possible etiologies or at the very least important symptoms to note, particularly as a site for therapy. As a possible etiological cause, researchers theorize that AB accumulates due to a dysfunction in the late autophagy stages of the pathways. The defunct pathways would lead to an inefficient clearance of autophagic vacuoles, resulting in progressive build up and illness manifestation (Peric & Annaert, 2015).

**Historical degenerative anatomical pathways that have been of interest in AD
research.**

The degeneration of anatomical pathways is significant and as such must be touched upon when speaking on the topic of AD. The Cholinergic pathway is one of the pathways historically scrutinized by AD research scientists. AD is characterized by a profound degeneration of cortically projecting cholinergic neurons of the basal forebrain as well as an associated depletion of cortical cholinergic activity. Interestingly enough, it seems that the degeneration of the cholinergic pathway is exacerbated when the patient also has trisomy 21 (Grothe, et.al. 2014). Several post-mortem studies have shown significant loss of acetylcholine in the AD patient's brain. Additionally, 50 to 70% reductions in choline acetyltransferase (CAT) as well as reductions in acetylcholinesterase (late in the disease) were found. The fact that some of this data comes post-mortem means that the data cannot be taken at face value due to the significant changes that tend to occur at the extremes of life. Undoubtedly, degeneration of the cholinergic system occurs in AD. However, multiple neurotransmitter deficits are common in AD. Thus researchers believe there must be an underlying issue causing AD manifestation and the deterioration of this pathway (Armstrong, 2013). An interesting note to make is how ethanolic extracts of *Phyllanthus emblica* (EEPA) ripe fruits have shown positive effects on the brain via antioxidant mechanisms which decrease acetylcholinesterase activity in rats, this may serve as a possible treatment for AD or at least a treatment for the deterioration specific site of Cholinergic pathway (Uddin, 2016).

The cortico-cortical pathway is another anatomical pathway that has been researched to determine its role as a possible major factor in the AD pathology. The pathway in the AD brain is characterized by loss of synaptophysin reactivity in the cortex, which relates to synapse loss in

the temporal lobe. Additionally, decrease in the synaptic marker SP6 has been observed in all regions of the AD brain. NFT was also observed in the cell bodies that give rise to the cortico-cortical pathways. It is theorized that a possible mode of disease spread could be in an orthograde or retrograde fashion. Studies have reported that tau and AB could exit cells via exocytosis and enter new cell via endocytosis, essentially traveling via a cellular highway. Protein transfer has also been shown to be able to occur in a much more direct manner, via tunneling nanotubes (TNT). With such a diverse and wide spread mechanism of protein travel it may prove the case that only stifling AD's point of origin rather than its spread could prove feasible. Moreover, another systemic point of interest in AD is mitochondrial metabolic dysfunction. This organelle based theory has also be implicated as a possible etiological agent to consider when studying AD. Early change in AD is characterized by swollen and distorted mitochondria, accompanied by cerebral metabolic decline. Such a finding led to the hypothesis being formed and labeled the Mitochondrial Cascade Hypothesis (MCH) (Armstrong, 2013).

Ethical reasoning and considerations for one illness versus two

As is the case with most pursuits of science, how we go about them is laden with much meaning. The organization of Alzheimer's may prove to be no different and depending on how it is done it can potentially lead to greater clarity in publications as well as efficacy in studies. By distinguishing late onset from early onset, prevention may become much more compelling due to the vast prevalence of late onset AD which seems to be mostly caused by life events and choices. The treatment of late on-set AD as a distinct illness would serve to elucidate how prevention is key, and in doing so possibly necessitate legislation that would go against the food industry, i.e.

On the other hand, the solidarity that comes from shared experience is known to lead to normalizing of large diseases, not in the sense that illness is normal but rather in the sense of breaking stigmas associated with the illness of interest. In the same fashion in which cancer was brought into the public light and garnered support, it is possible the same could be done with AD. Such an occurrence would make AD more financially strong making the fight for a cure more feasible. Support could possibly be easier to gain through a unified illness, that way the illness is seen as more prevalent raising more concern and with it greater funding. This is in accordance with the historical example of cancer, a general term encompassing a wide range of illnesses (Mukherjee, S. (2010). *The emperor of all maladies: A biography of cancer*. New York: Scribner). At the current moment \$700 million is spent as annual funding by the NIH for Dementia, as of 2015, which is quite small compared to the \$2 billion for cardiovascular disease and \$5 billion for cancer. Importantly however, more money is being demanded as people begin to speak out more and the illness gets more public attention. (Elie Dolgin, *How To Defeat Dementia: The three things that could help prevent a meltdown in health-care systems worldwide*). Thus, the ethical considerations for the illness to be unified under one term must also be considered. Pairing Dementia and AD, at least amongst the public's eye, could have a positive economic effect for those committed to AD research. Projections for the year 2050 have Dementia effecting roughly 130 million and costing the American tax payers an estimated \$1 trillion per year (Elie Dolgin, *How To Defeat Dementia: The three things that could help prevent a meltdown in health-care systems worldwide*).

According to George Vradenburg, chair and co-founder of the non-profit UsAgainstAlzheimer's, there is a stigma attached to the illness. In addition, the family caregivers tend to be overworked and too exhausted to be motivated enough to speak up. The tables are

turning for the patients, however, with social and political awareness increasing in the past five years (Elie Dolgin, How To Defeat Dementia: The three things that could help prevent a meltdown in health-care systems worldwide). Thinking of AD as a more severe form of Dementia is beneficial, bolstering the urgency to address Dementia economically as well as increasing the empathy for Alzheimer's patients. Robert Egge has an interesting opinion on the future relationship between AD and the public. The chief public policy officer of the Alzheimer's Association, does not believe people will have the choice when it comes to accepting the reality of Dementia. He believes that in just a few short decades, everyone will have a friend or loved one with the disease, essentially forcing the public to pay attention to its existence (Elie Dolgin, How To Defeat Dementia: The three things that could help prevent a meltdown in health-care systems worldwide).

The general ethics of AD

The ethical responsibility to few issues are as clear cut as is treating Alzheimer's as quickly and aggressively as possible. Ethics concerns itself with who we ought to become as individuals and how we ought to act in relationship to others (Panicola, M. R., 2011, Health Care Ethics). How that may be applied to Alzheimer's is clear, by asking ourselves towards what ideal society we want to proceed. Our society is one built on aspirations of complete egalitarianism, and as such we should make decisions to progress towards such a reality. Thus, by answering what our society ought to be, we can determine what to do. AD should be treated as aggressively as Cancer, even though Cancer can take people's youth, Alzheimer's can take people's highly personal and valuable passage/experience towards death away. Furthermore, a society built on equality has far reaching implications, one of them being a right to a humane death and AD is a

relentless foe to the very agency required for such a death to take place. AD leaves a vessel with the driver withered away over the years. Additionally, someone would be hard pressed to find fault in the acknowledgement that we should conduct as much research as possible now in order to mitigate needless future suffering. Also, it should be noted that costs spent now on AD research is money saved down the road in terms of healthcare. Health care costs can be directly from the AD patient or from the family of the individual. The burden of care can prove to be overwhelming and not all people are capable of handling such a scenario. Insufficient coping can lead to a malignant social psychology in the home (Sabat, S. R., 1994, Excess disability and malignant social psychology).

Conclusion and future of AD

The current opinion of many in the field has turned to the acceptance of AD as a multifactorial disease with the illness best characterized as the culmination of several etiological factors. The toxic medley serves to accelerate aging, leading to a bodily allostatic load. The new baseline of the body is thought to get to such an overwhelming degree that the brain can no longer function properly (Armstrong, 2013). While a large faction of the AD community suspects that AB aggregation is at the heart of the illness, to appropriately test the hypothesis an efficient treatment for its clearance must be put together.

A bright future of treatments and medications fill the future of AD research with hope. Drug 2-hydroxypropyl-beta-cyclodextrin (HP-beta-cyclodextrin), may prove a potentially useful pharmacological tool. The drug's effect comes through a mechanism that lowers cholesterol as well as possibly preventing AB production/oligomerization. Such a drug action may prove

beneficial for AD by tackling the lysosomal issue (Peric & Annaert, 2015). Currently, various drugs in the market are used to treat AD by merely alleviating symptoms, but there is a serious need to treat etiological effects, particularly because AD has a long asymptomatic phase (Rafii and Aisen, 2015). Very recent research aims at doing such a thing. Researchers have observed in animals that hibernate cold shock proteins such as RBM3 that may be of therapeutic value in patients with AD. The mechanism by which proteins re-fold at varying temperatures may prove to be key (Peretti, et.al. 2015).

Additionally, antibody based treatment/medication, i.e. experimental drug solanezumab. This antibody-based medication specifically removes the amyloid-beta proteins which clump to form the sticky plaques. Early trials have shown beneficial (R.S. Doody et al. N. Engl. J. Med. 370, 311-321; 2014; Elie Dolgin, How to Defeat Dementia: The three things that could help prevent a meltdown in health-care systems worldwide). In another study, intravenous administration of blood from young mice into old mice was shown to reverse loss of synaptophysin and calbindin, which are indicators of cognitive decline in people with AD as well as in the transgenic mouse model of the illness (Wyss-Coray, T., Aging, neurodegeneration and brain rejuvenation).

Another critical intervention in the fight against AD is early screening. Early screening via PET imaging using 18F-florbetapir as the agent for imaging allows for an easier estimation of B-amyloid neuritic plaque density within the body. It has been estimated that early intervention that delays AD symptoms by only 5 years is can lead to a significant reduction of patients on the scale of 5.5 million by 2050, in the US alone (Hutton, M., et al., 2016. Therapeutic development for Alzheimer's disease at Eli Lilly and Company). Lastly, an interesting note worth pursuing is how Cancer and AD are proving to set themselves as mutually

exclusive. It would seem that manifestation of one serves to guard against manifestation of the other, by what means may be a beneficial inquiry in leading to cures for both (Catala and Seisdedos, 2014).

Taking the compilation of AD research into account it would seem that there is need for greater clarity in classification of the illness. Perhaps AD should be seen as one disease amongst the public's eye, possibly it should be taken even more broadly. A massive campaign against dementia in general could prove to garner support on the level of cancer. However, meticulous classification of the various nuanced yet unique illnesses must be enforced amongst academia in order to ensure maximal efficacy in research. In addition, although public appeal may be to generalize the illness that fact that the majority of AD come from environmental factors should still be accounted for. This can be done by emphasizing the environmental factors and their interplay with genetic susceptibility, i.e. hinting at epigenetics. Such a push could make for individuals to lead healthier lives, such as Paula Wolfert's mentioned in a New York Times Article. Paula maintains a diet free of carbohydrates and centered on salmon, berries and greens, as well as turmeric extract, cinnamon and eggplant (New York Times. Kim Severson. March 21st, 2017. Her Memory Fading, Paula Wolfert Fights Back With Food). While such an extreme diet may not be committed to by the general public, any beneficial changes to their diets could ease their risk factors as well as stifle AD manifestation into later years.

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