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OBM Geriatrics

Review

Curing Alzheimer's Disease: Myriad Causes and Myriad Cures Await

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Academic Editor: Ladislav Volicer

Special Issue: Behavioral Symptoms of Dementia

OBM Geriatrics
2019, volume 3, issue 3
doi:10.21926/obm.geriatr.1903063

Received: June 12, 2019
Accepted: July 11, 2019
Published: July 16, 2019

Abstract

Simplifying the cause of Alzheimer's disease has lulled the public into believing that the search for a cure is within reach. The disease has captured the attention of researchers worldwide, catapulting the disease as the third most funded research interest (after cancer and HIV). But after a century of pharmacological failures in stopping or slowing the disease, there is a need to examine how the simplified cause evolved and to explore alternate approaches to understanding Alzheimer's disease. Going beyond the narrow definition established by the U.S. National Institute of Aging's Framework alternate understandings of dementia are emerging. New opportunities exist for cures for specific types of Alzheimer's disease. We are also gaining a better definition of aging. Although we remain ignorant of what aging is we are learning that attempting a piecemeal approach to curing one disease—Alzheimer's disease—however significant, does not promote our understanding of aging. Because Alzheimer's disease is very rare in isolation without other neurological diseases, all evidence points to aging as biologically engineered obsolescence. A simplified view of Alzheimer's disease restricts this neuropathological reality. Hiding under the catchall Alzheimer's disease and holding clinicians back from exploring these specific diseases and curative measures that await.

Keywords
Alzheimer's; engineered obsolescence; critique; co-morbidities; framework; theory; LATE; misfolded protein

1. Introduction

When Auguste Deter died, the first patient identified with Alzheimer's disease (AD), she did not die of the disease but of bedsores. Infections from bedsores are easily preventable. While her legacy was the baptism of Alzheimer's disease, her personal tragedy and mortality proved secondary to the overwhelming interest in Alzheimer's disease. Today the disease still overshadows the personal needs of people living with dementia in terms of their daily care needs. People living with advanced dementia often experience inadequate pain control, increased hospitalization, and fewer palliative care interventions compared to those with cancer [1]. The pharmacological industry itself is aware of this skewed interest by admitting that "…there is a shortage of geriatricians to care for the country's aging population, patients are commonly misdiagnosed, there continue to be long wait times to see neurologists, racial disparities persist, and many patients are never told of their diagnosis by their doctor" [2].

AD funding has focused nearly exclusively on finding a cure. The consequence has been twofold; overlooking other needs of the individual and dimming interest in other maladies such as depression, arthritis and stroke, among many others. Despite growing evidence that reducing risk factors, through such simple lifestyle changes as increased physical activity contribute to delaying the onset of dementia [3] most funding remains focused on finding a cure [4, 5]. AD has extracted most of the funding in health care research to the detriment of other mental health needs of older individuals.

Out of all dementias AD reigns as the most popular dementia diagnosis by clinicians [5]. There are many other type of dementias including: vascular dementia, Lewy body dementia, frontotemporal dementia; normal pressure hydrocephalus; Parkinson's disease dementia; and Creutzfeldt–Jakob disease [6]. These join other rarer dementias including: CADASIL; Fabry disease; Fragile X tremor ataxia syndrome; Gaucher disease; Kufs disease; Limbic encephalitis; McLeod syndrome (neuroacanthocytosis); Neurosyphilis; Niemann–Pick disease Type C; Spinocerebellar ataxia; Whipple disease; and Wilson disease [7, 8]. Focusing solely on Alzheimer's disease, when all of these diseases are related does not make scientific sense. Especially since AD is often misdiagnosed and it is rarely experienced in isolation from other neurological disorders [9].

Historically, AD sole criterion was that it was a young-person disease distinguishing it from senile (old-person) dementia. Alois Alzheimer's supervisor Emil Kraepelin aspired to define the new disease as a "real" disease and not due to old age [10]. The plaques (amyloid plaques formed from amyloid beta Aβ peptides) and tangles (neurofibrillary tangles of hyperphosphorylated tau protein) affected younger brains and therefore must be a disease not senility (of old age.) Even Alzheimer questioned whether these biomarkers "…are sufficiently different clinically or histologically to be distinguished from senile dementia or whether they should be included under that rubric." [11]. Ageism contributed to making a young person's disease more important than generic senile (older persons') dementia, and ageism still plays a role today. Margaret Gatz and

Cynthia Pearson introduced the concept of "professional ageism" specifically in AD [12]. They argue that AD is continuing with this form of ageism through the targeted media focus on scary stories resulting in the public overestimating how common it is among older adults and in over-diagnoses by clinicians. The intensely lurid media representation not only fails to address the ageist misinformation surrounding dementia reporting, but it also likely aggravates the stress and depression frequently experienced by people living with dementia and their caregivers [13]. The only outcomes are fear and anxiety, further fuelling the frantic search to find a cure. The two go hand-in-hand.

All of this hyper-interest in AD is at the cost of other dementias and other mental health issues at older age, especially depression. From an insignificant disease that hardly anyone knew [14, 15] AD became a "major killer" overnight. This transformation came about through a political rather than through a scientific discovery [16]. The person responsible for this hyper-focus on AD was Robert Katzman. Katzman's resume was impressive; a founding director of the NIA-funded Shiley-Marcos AD Research Center at UCSD; original member of the U.S. National Institute on Aging's National Advisory Council on Aging; and founder of the Alzheimer's Association. Despite this prestige, by his own admission, his most important contribution was the publication of a landmark 3-page non-peer-reviewed editorial entitled: The Prevalence and Malignancy of Alzheimer's Disease, a Major Killer [17]. Euphemistically the article asserts that senile dementia is the same as AD. But by asserting that senile late onset AD was caused by a disease, theoretically he positioned aging as a disease. AD was accelerated aging. He knew the tectonic shift he accomplished and the funding interest that this would generate.

Katzman needed to make AD a pandemic in order to gain congressional support and funding for the newly established U.S. National Institute on Aging (NIA) and its banner disease despite asserting that "Alzheimer's is not just a disease of old age." [18]. Before this tectonic shift, AD was however a specialized disorder with only a few thousand patients. So few in fact, that Katzman himself could not determine their numbers, "Precise epidemiological information is not available concerning the prevalence of Alzheimer disease in the United States." [17]. But by combining the large number of older patients living with senile dementia with those younger patients suffering from AD, Katzman persuaded congress and the scientific community that AD is the sixth highest killer in the U.S. and something needed to be done.

2. Confusion in Research

By comingling these clinical diseases together—AD and senile dementia—research in AD became unfocused and confused [19]. Over four decades later this confusion can be gauged by the unrelenting and consistent failure of pharmacological interventions to stop or slow the disease. Recently nearly all trials for pharmacological intervention for AD have been halted. These include: Biogen and Eisai's aducanumab; Pfizer and Johnson & Johnson's bapineuzumab; Eli Lilly & Co.'s solanezumab; Roche's Genentech's crenezumab; Merck & Co.'s verubecestat (patients saw a worsening of symptoms). Currently the only intervention being tested, with public funding from NIA, is Biogen's and Eisai's Clarity AD study (with BAN2401) and BACE inhibitor (elenbecestat). The prize of uncovering an inoculation against amyloid plaques and tau tangles that promotes cognition is receding further away. Meanwhile current medication focusing on cholinesterase and glutamate inhibitors has limited and short-lived outcomes with potentially sever side effects.

Neurologists are not sure what they are trying to cure if not to eliminate plaques and tangles. Although intuitively we all know what dementia and AD looks like, clinically it remains an elusive disease to differentiate.

With four different criteria for differentiating dementias one study evaluating a sample of 167 older adult patients admitted to hospital with probable dementia found that the concordance was very poor with only 5 cases meeting the criteria for Vascular Dementia on all diagnostic guidelines [20]. Another study similarly found agreement in only 20 out of 1,879 dementia cases [21]. While a third study concurred in 31 out of 107 patients [22]. To get around this challenge, the latest approach by the NIA is to ignore the clinical features completely and to focus on the neuropathology [23]. The new research NIA-Framework, in contradiction to the earlier 2011 guidelines [24] disregards the four stages of the disease—pre-clinical, Mild Cognitive Impairment, dementia and severe dementia in favor of the biology. According to the NIA-Framework there are only three type of biological information that determines Alzheimer's disease: (A) amyloid beta deposition, (T) pathologic tau, and (N) neurodegeneration (severity). For a clinical disease, this approach was unheard of in the medical field. A literature review shows that there is broad support for a correlation between these biomarkers and dementia [25]. However this new AT (N) definition relies exclusively on the presence of these biological markers to define the disease and not on any clinical evidence. As a result, the NIA signed onto a tautology, a circular argument; AD is defined by its biology and biology defines AD. This definition cannot be refuted and therefore not surprisingly has already encountered severe scientific challenges [10, 26, 27]. Clifford Jack one of the main authors of the NIA-Framework recently in acknowledging these problems of definition, concludes by suggesting that "Our language must help us, not mislead us" but then goes to suggest that policy discussions and therefore funds can accept a clinical definition while neuroscientists use a biological one [28] even though the two definitions remain distinct and irreconcilable.

More damning is that by publishing the Framework, the NIA ignores the neurological reality of older people—older people being ostensibly the focus of the National Institute on "Aging." With older people the correlation between AD neuropathology and its clinical expression declines with age [29]. Since there are increasing prevalence of brain pathologies in older patients [30], older people are neuropathologically more complex than the NIA-Framework concedes in their theory.

3. Neuropathologies are Common in Normal Aging

At the turn of the 20th century, at the time that Alois Alzheimer was performing his clinical work, it was assumed that if you live long enough you would ultimately get senile dementia. In a way that same prediction remains true today, since with age the frequency and severity of neuropathologies increase. Many neuropathologies might have no immediate clinical expression as with silent strokes that cause no obvious outcomes despite neuronal damage. Some older adults have substantial plaques and tangles without any clinical burden [31]. A third of clinically diagnosed demented older adults [32] and half clinically-diagnosed demented oldest-old have insufficient neuropathology findings to account for their dementia [33]. In contrast, approximately half of individuals without dementia meet the neuropathological criteria for AD [34]. It is very common to find plaques at autopsy of persons with previously documented normal intellectual functions [35-37]. We expect to find 47 percent of non-demented 65 year olds to have severe

plaques [38] and 32 percent among non-demented 78 year olds [39]. In fact AD biomarkers become irrelevant with older people. Heiko Braak in 2011 after dissecting 2,332 brains ranging in age from 1 to 100 found that only 10 cases had complete absence of plaques and tangles, every person over 25 years of age had them [40]. Even a fifth of normal 26-30 year-olds already had stage-1 neuropathology at autopsy [36]. Plaques are useless biomarkers without a cut-off point, but such a demarcation has eluded neuroscientists because it will likely conflict with clinical reality. There are also other neuropathologies present other than plaques and tangles.

There are many studies that document differing levels of neuropathologies among non-demented older adults [41]. Half of older adults living in the community already have cerebrovascular lesions while a quarter have tangles without Alzheimer's disease [42]. Another misfolded protein called TDP-43 was found in 13 percent of the group while another 15 percent had other neural inflammation, tumors and neuronal trauma [42]. All without exhibiting any cognitive deficits. A third of non-demented older adults have cerebral microinfarcts and a third of those the infarctions are high-level [43]. Up to 75 percent of cognitively normal older adults have various degrees of a cerebral amyloid angiopathy—a type of brain amyloidosis including plaques—while 23 percent had argyrophilic grains composed mainly of tau-protein [44] with a prevalence reaching 31 percent in normally functioning centenarians [45]. One in ten have cerebrovascular lesions (small or large infarctions, lacunes—obstructing a small artery—and white matter lesions) [44]. As high as one in three people with normal cognition have cerebral arteriosclerosis [46]. All of these numerous of neuropathologies exist among people with normal cognitive functioning. Older people have complex neuropathologies.

To focus explicitly on just two misfolded proteins among this array of pathologies in normal older adults is imprudent and fanciful. As a result, for those that are diagnosed with AD, some are likely mis-diagnosed. AD is often confused with other neurological diseases such as Creutzfeldt Jakob disease [47], Lewy Body dementia [48] and vascular dementia that causes the main misdiagnosis [20]. A majority (74%) of subjects who died with Mild Cognitive Impairment did not have AD biomarkers, or other neurological diseases such as Lewy body disease, or hippocampal sclerosis pathologies but they did have cerebrovascular pathology [49]. Vascular disease is the main precursor to dementia and AD and offers some insight into cures. Other non-neurological conditions mimic or exacerbate the clinical expression of dementia but have more psychological causes such as anxiety [50], low education, cultural variability and the main cause of misdiagnoses, depression [51, 52]. It is rare for AD to occur in isolation from depression [53] and anxiety [50]. Diagnostic tools are too crude to differentiate these confounds. AD in isolation from these and other chronic diseases, is rare and among older adults unlikely. In one large study only 0.01 percent of patients had a diagnosis of dementia with no co-morbid conditions [9]. This helps explain why multiple studies have shown that the correlation between plaques and tangles and AD declines with age since there are many other factors that are causing cognitive problems [29].

Apart from other dementias or psychological disorders, there are three main neurological diseases that complicate accurate diagnosis: idiopathic normal-pressure hydrocephalus (iNPH), LATE and hippocampal sclerosis. Between nine and 13 percent of residents in nursing homes and assisted living facilities have iNPH and are likely misdiagnosed with AD [54]. In iNPH cerebrospinal fluid accumulates within the cerebral ventricles in the brain causing pressure and impaction on the surrounding brain tissue. Although both pathologies of AD and iNPH interact and have related pathologies [55] in some cases the clinical outcome caused by iNPH can be reversed. An

alternative interpretation is that iNPH also damages the ependymal, subependymal and choroid plexus cells residing in the ventricles of the brain that control homeostasis and interfere with stem cell production that are crucial in neurogenesis [56].

Other recent examples are emerging of neurological diseases that mimic AD. A new and common neurodegenerative disease was recently christened called LATE (Limbic-predominant Age-related trans-activation response TAR DNA binding Protein-43 [TDP-43] Encephalopathy). TDP-43 discovered in research on HIV in 1995 [57], then in cystic fibrosis in 2001 [58] and later in 2006 in amyotrophic lateral sclerosis and in some cases of frontotemporal lobar degeneration that mimic dementia [59]. Recently it has also been implicated in lateral sclerosis and progressive muscular atrophy [60].

LATE usually also includes plaques and tangles and is reminiscent of senile dementia since it affects older people (hence the name 'age-related'). Although not everybody accepts LATE as a true, specific pathologic entity, it shows how easy it is to differentiate different types of AD. One in five clinical diagnoses of AD are likely to implicate LATE [61] and is present in up to 57 percent of Alzheimer's disease [62]. The uniqueness of this disease is somewhat confounded as it is age determined [62] and hence correlated with generic atrophy in the medial temporal lobes, frontal cortex, and other brain regions [63]. It also concentrates in different parts of the brain as the disease develops [63]. As with the NIA-Framework's definition of AD [23] the lack of clinical validity shadows LATE. Around one in five older adults with normal cognition will have LATE at autopsy, and an abnormally higher rate among Asians maybe because they have longer life expectancy [64]. Although LATE is independently associated with less effective episodic memory while its associations with global cognitive impairment and dementia are difficult to separate.

In 1994 hippocampal neuron loss and gliosis, collectively termed hippocampal sclerosis was discovered that contribute to dementia [65] and mimics AD [66]. Hippocampal sclerosis results from epilepsy, hypoxia, hypoglycaemia, certain infections, and numerous other neurodegenerative conditions [67]. As with LATE, the misfolded protein said to be responsible is again likely to be TDP-43 [68].

With such myriad neuropathologies, some that are silent and have no obvious effects, while other diseases mimic AD—misfolded protein diseases; iNPH; LATE; and hippocampal sclerosis—it is of little wonder therefore that physicians and mental health professionals are still struggling to diagnose AD correctly [69]. Dementias are complex because the neurological realities of older people are complex.

4. Dementias are Complex

The brain is the most complex entity in the universe with over 86 billion neurons and 85 billion-non-neuronal cells (glial cells) [70, 71]. Each neuron might have as many as 38,000 synapses even in older brains (68 to 89 years) and also in brains from severely congenitally cognitively impaired adults [72]. Multiplying the number of synapses to each of the billion neurons, in the cerebral cortex alone adds to more than 1,000 times the number of stars in our galaxy. Each synapse can have as many as 26 different levels of strength of transmission (therefore not binary) [73]. Glial cells also communicate chemically through glutamate and maybe through hundreds of other neurotransmitters [74]. All in all, by one estimation, the total number of synaptic switches in the whole brain approaches 10^20 [Sextillion] that equals to the total number of transistor "switches"

in all of the computer chips on earth today [75]. Overall one human brain compares to the entire global Internet rather than to any single computer [76]. With such complexity neuropathology can act either as a domino effect or alternatively the trauma is subdued for the short-term until there is a tipping point.

The domino effect is an attractive theory for its simplicity. Where rogue proteins create accumulated devastation. Other than AD in 1911 and the Amyloid Cascade hypothesis that followed [77] the earliest evidence for such a domino effect theory comes from studying prions. Prions are misfolded proteins that cause spongiform encephalopathies colloquially known as "mad cow disease" [78] as well as Creutzfeldt-Jakob Disease and Kuru [79]. Prions are ubiquitous in our foodchain, certain fungi (yeast and Podospora) contribute to prion-like elements in our diet [80]. Nowadays there are 34 protein misfolding-protein-diseases that have been studied including (with the protein responsible); AD (amyloid-β accumulation in extracellular amyloid plaques and hyperphosphorylated tau forming neurofibrillary tangles), Parkinson's disease (α-synuclein), Huntington disease (poly-Q extended huntingtin, TDP-43) amyothropic lateral sclerosis (TDP-43, superoxide dismutase) transmissible spongiform encephalopathy (prion), and type 2 diabetes (islet amyloid polypeptide) [81]. These misfolding-protein-diseases can be induced under experimental conditions by administrating intracranial seeds of misfolded protein [82]. In the natural world, all sporadic cases of misfolding-protein-diseases affecting the brain are largely associated with aging. Suggesting that aging promotes the frequency of protein misfolding and/or diminishes the natural capacity for the brain to deal with these rogue protein [83] In this context it is easy to see why mis-folded proteins in neurodegenerating diseases mutually interact [46]. Comorbidities coexist with AD including cerebrovascular disease, argyrophilic grain disease, TDP-43 proteinopathies, and hippocampal sclerosis, Lewy body disease [84] and tangle-predominant dementia [85].

Since aging is the main correlate of dementia and AD we can conjecture that aging itself acts as the tipping point rather than solely due to misfolding-protein-diseases. Older age correlates with the brain becoming increasingly more challenged to compensate for neuronal trauma.

Older adults have multiple scars from surviving numerous traumas. They have resilience, despite or because of these neuropathologies. In some cases these pathologies have been found to be protective. For example "…a protective function of amyloid-β is supported by all of the available literature…" [86]. Since plaques trap and imprison bacterial pathogens, it remains unclear whether plaques are fighting a real or falsely perceived infection in AD [87]. Also, similar to plaques, argyrophilic grains that form tau misfolded proteins have also been identified as having protective mechanism against spreading of other types of tau misfolded proteins (tauopathies) [88]. It is likely that in the case of AD, and likely for other misfolding-protein-diseases, the misfolded protein might be a mediating process that has an initial protective rather than disease promotion. We can only conjecture at this stage. Dementias are complex. As we age the etiology of dementia becomes complex and multifactorial. Statistically known as heteroscedasticity, dementias among older adults might be caused by greater number of neurological traumas compared at younger ages.

Most late-life neurological diseases are somehow related and connected. Pure solitary diseases are rare among older adults. Neurological studies have confirmed that brain diseases of older adults are complex since there are multiple comorbid pathologies and substantial variation among individuals [47, 49, 89, 90]. In addition to the effects of aging there are also interactions of proteins among themselves and diseases that share common pathways, and unknown genetic and

neurological variations that make single disease study that much more problematic [91]. Among older adults single disease study are near to impossible since neuropathologies are mixed in older age [92]. Mixed brain pathologies increase the odds of dementia to almost ten times higher when compared to patients with no brain pathology [93]. The complexity of neuropathology in older age is highlighted by the finding that among nonagenarians half of all dementias are of unknown etiology [33]. Aging might be the convergence and then the tipping point that overwhelms the brain and impact behavior and functioning. Which might explain why we find so many neurological diseases among older people.

Peter Nelson and his colleagues in reviewing the literature also noted that there are additional neurological changes that occur resulting in clinical dementia but not considered neurological dementias yet. These pathologies include amyloid angiopathy, age-related brain atrophy, synaptic pathology, white matter rarefaction, granulovacuolar degeneration, neuron loss and neuro-inflammation [25]. But since all of these pathologies are related to aging, including AD, there lies the conundrum. Is aging, the tipping point, and therefore a disease? [94]. The easiest solution will be to define aging as a disease [95, 96]. However, other than sensationalizing the issues by aggregating all the effects of aging, such moves further confuses research since nearly all diseases become more prevalent as we age. Conflating diseases will only monetizes elusive cures and further confus scientific objectives. The answer is to further differentiate clinical and neurological diseases and at the same time to study aging as a unique, pervasive and radical phenomenon as Leonard Hayflick has repeatedly suggested [97].

5. Differentiating Dementias

Curing dementias require identifying the many different causes of AD and how it relates to other dementias. AD is not caused in isolation. We are recently witnessing a move towards differentiating AD as the new disease LATE highlights. Historically LATE is senile dementia, reverting back to a century ago when Alois Alzheimer's separated senile dementia from Alzheimer's disease. As a result LATE is contradicting Katzman's conflation of the two diseases and his ploy of 1976 is being rescinded in neurology if not in policy. By christening LATE neuroscientists are pushing back at the simplistic answer that neuropathology affecting cognition is always likely AD. By acknowledging senile dementia again through LATE, we are now becoming more adept at distinguishing dementias through better neurobiological markers. Dementias and AD will become more differentiated as a result of increasing accuracy of emerging methods and techniques. This will lead to more specific diseases, pointing at specific causes and the emergence of targeted cures. Although questions have rightly been voiced about the integrity of defining LATE as a specific neurological disease suggesting that perhaps we should taper our enthusiasm and to see such differentiation not as a panacea but a road map for incrementally understanding complex dementias including the further breakdown of AD.

Because older age presents a convergence of many neuropathologies a better methodological approach would be to study diseases among younger cohorts. Reducing confounds provides clearer research parameters. The epidemiology of young-onset dementia (30-64 years) identifies AD at 30 percent of all cases but 70% are open for intervention especially "…vascular risk factors [that] can…have a role in preventing progression of Alzheimer's disease." [98]. Preventable cases of dementia include some vascular dementia (15 percent), alcohol related dementia (12 percent)

and dementia due to carbon monoxide poisoning (less than 1 percent) [99]. Not only are younger people more likely than older people to have treatable conditions causing their dementia but researching the neurological progression of the disease is much clearer when the disease is not confounded with other neurological diseases. Present day cures include the steroid treatment of cerebral vasculitis and cessation of alcohol consumption along with thiamine replacement in alcohol related dementia [100]. These might seem simplistic, but by focusing on specific diseases science will accumulate knowledge to tackle the difficult task of ultimately understanding neuronal trauma and the role aging plays. Until such time, focusing on AD alone, without investing in understanding aging as the tipping point, results in lost opportunities.

Such emphasis does not distract from basic science, but it should deflect some of the research funds to include a broader and more neurologically diverse research objective. It is incidental that one of the misfolded protein that is now generating much interest in LATE is DTP-43 was identified by researchers working on HIV. A broader use of scientific research funds would promote exploratory science rather than confirmatory science that has lead to a century of failures in Alzheimer's research.

6. Conclusion

Although we cannot explain AD as caused by simple malfunction of two misfolded protein, we can also not assign the cause to old age, even though both are correlates of the disease. As Sherwin Nuland portrayed, diseases in older age are choreographed disorder that eventually splutters into death [101]. When autopsying brains of different ages, Heido Braak found that misfolded protein first show up in the brainstem at much earlier age [40]. The seeds of what we call aging have a lifetime of gestation. We are programmed to age as part of a biologically engineered obsolescence. Biologically engineered obsolescence is not a disease it is our natural state. This explains why among older people we never see AD in isolation and we more likely see it together with other dementias [45, 47] and other neuropathologies [43, 44]. At the end all the biological engineering in planned obsolescence in older age converge so that only 0.01 percent of older patients have a diagnosis of dementia with no co-morbid conditions [9]. Biologically engineered obsolescence differs from a disease. With engineered obsolescence you have to address the engineering of nature (i.e, aging) rather than its mishap as in a disease [97]. Perhaps that is the barrier for moving ahead in studying Alzheimer's disease, it is easier to blame nature rather than to understand it.

Aging remains elusive and presents a complicated subject for neurological study. Aging cannot be studied piecemeal as evidenced by the fact that all neurological diseases interact [26]. The complexity of the brain makes single theory, however plausible, inherently short-sighted.

Although ageism motivated the separation of AD from senile dementia, we are evolving to appreciate the role of aging in neurological disorders. The cure for all of the maladies associated with aging is a long way away but by differentiating dementias the problem becomes more manageable and we learn about the nature of diseases. Science does not beckon to our call it is a method of gaining knowledge, not a method of finding cures. Broadening research funds and having a broader agenda will diversify the knowledge base that will eventually lead to a cure for most of dementias. Perhaps then we will start to understand what aging is and the role it plays in these neurodegenerative diseases. The failed search for the Holy Grail cure for AD, exemplified by

the search for an inoculation against plaques and tangles, has been constructive in teaching us about aging and our biology of planned obsolescence. We need to have broader appreciation of the complexity of neurology in order to expose some of the science behind aging.

Acknowledgments

None.

Author Contributions

The author did all the works.

Funding

No funding was made available for the production of this manuscript.

Competing Interests

The author declares no competing interests.

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