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REVIEWS

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A century of confusion in researching Alzheimer's disease

Mario D. Garrett*[1,2], Ramón Valle[1]

[1] School of Social Work, San Diego State University, California, USA
[2] Department of Psychology, Boğaziçi University, Istanbul, Turkey

ABSTRACT

More than a century ago Alois Alzheimer published a case study that later evolved into the Amyloid Cascade hypothesis—which assumes that increasing proliferation of plaques and tangles in the brain cause dementia. However, studies involving the removal of plaques—amyloid-β—in patients' brains resulted in worse cognitive performance, suggesting that plaques cannot solely be the disease. The search then focused on tau misfolded protein. But the evidence is uncertain. This paper suggests a critical history approach to understanding this confusion in Alzheimer's disease research. Confusion is related to variability in expression of the disease, inaccuracy of clinical diagnostic tools, the relationship to other diseases, and the increasing neurological variance among older adults. The final verdict is that there is an unclear relationship between the biology and the expression of the disease. Alzheimer's disease may in fact be the expression of another, yet unknown, disease. An often overlooked component in Alzheimer's disease is white matter in the brain. Although found to be negatively related to dementia and positively related to learning, white matter remains unexamined in most current research. Historical evidence suggests that this was not the case a century ago. This paper is grounded in historical observations that Alois Alzheimer and his contemporaries identified these criticisms a hundred years ago. By ignoring these criticisms today, we have ended in a research *cul de sac*. This paper argues for greater specificity of the definition of Alzheimer's disease and a broadening of the research focus to include the possible role of epigenetic changes, variance within older ages and brain plasticity. Only by broadening the scope of research and addressing this confusion directly can we move out of this research *cul de sac* and move closer to a cure.

Key Words: Alzheimer's disease, Plasticity, Neurogenesis, White matter

1. INTRODUCTION

This paper is a critical history of Alzheimer's disease—examining historical observations in order to understand intentions of early researchers—aiming to provide a more comprehensive understanding of the disease. The paper focuses on political factors that elevated Alois Alzheimer's findings to a new disease. Findings that later contributed—with input from many significant researchers[1]—into the Amyloid Cascade hypothesis of 1992,[2] which was later enshrined in 2011 as the guidelines for Alzheimer's disease by the U.S. National Institute on Aging. This development came at a cost of ignoring researchers' early ambivalence to these findings. Currently, research continues to ignore the role of brain plasticity and variability among older adults, in favor of biological determinism. But such reliance on biological determinism has created both clinical as well as neurobiolog-

*Correspondence: Mario D. Garrett; Email: drmariusgarrett@gmail.com; Address: School of Social Work, San Diego State University, California, 92182. USA.

ical confusion that we find ourselves in today. The goal of this paper is to ascertain the original meaning of Alzheimer's disease in its original historical context. By reconstructing the political climate which defined Alzheimer's disease as a definitive neurobiological disease we might understand the real meaning of why a new disease was created. Even at the inception of the disease, Alois Alzheimer himself had second thoughts: "The question therefore arises as to whether the cases of disease which I considered peculiar are sufficiently different clinically or histologically to be distinguished from senile dementia or whether they should be included under that rubric." (p. 72).[3] Within three years, Emil Kraepelin—Alois Alzheimer's supervisor and director of the clinic in Munich—christened the disease by including Alzheimer's paper in the eighth edition of his book *Psychiatrie* and calling it Alzheimer's disease.[4, 5] In agreement with Alzheimer, Kraepelin observed that: "The clinical interpretation of this Alzheimer's disease is still confused." (p. 77).[6] If there was confusion then, it remains with us today. By examining how the historical context made it possible for the disease to be adopted so readily, we might better understand this confusion in research and in clinical practice today.

In 1901, at the age of 51, Auguste Deter was admitted to the state asylum in Frankfurt, Germany. She was suffering from cognitive and language deficits, auditory hallucinations, delusions, paranoia and aggressive behavior.[7] Alois Alzheimer, examined her, and when she died five years later—from septicemia and bedsores[8]—her brain was sent to him for examination. Alzheimer's breakthrough was the observation of dense plaques and tangles in the brain of a "young" patient. This initial observation led to the Amyloid Cascade hypothesis[2]—positing that the accumulation of the amyloid-β peptide in the brain is Alzheimer's disease signature pathology.[9] As a result, most Alzheimer's disease treatments tested on humans are drugs aimed at removing amyloid-β. However, after decades of testing, the Amyloid Cascade hypothesis has received negative outcomes in clinical trials on humans.[10] The great success of some of these drugs at removing plaques from the brains of Alzheimer's disease patients is offset by the patients' poor performance on cognitive testing.[11–13] If the removal of the neuropathology does not reverse the disease, then Alzheimer's disease must be an expression of as yet, an unknown disease. The search has now moved from plaques to tangles—*tau* misfolded proteins, mirroring Oskar Fisher's century old assertion—although the outcomes from these clinical studies are still unclear and definitely not simple.[14] This changing target and the inconsistency of outcomes remains a primary source of confusion in Alzheimer's disease research. Even existing medication—based on completely different neurobiological principles—have marginal

clinical efficacy.[15] It seems that we have reached a research and clinical *cul de sac*.

A hundred years ago, Alzheimer was aware of these nuances when he observed that: "There is then no tenable reason to consider these cases as caused by a specific disease process." (p. 94).[3] And his conclusion clearly suggests that these are symptoms or "...an accompanying feature" and not a separate disease (p. 92).[3] Despite this interpretation, and while the cause of the disease remains unknown, public research funds—almost without exception-are focused on the identification of genetic, pharmacological and neurobiological biomarkers. The failure to identify a cause has led researchers to address late onset dementia as sporadic—arising or occurring randomly with no known cause. Despite many studies, because of poor methodological designs, the disease remains idiopathic, without known cause.[16] Overall, more than four in five patients with Alzheimer's disease appear to have sporadic episodes, with onset after 65 years of age[17]—refuting the single reason for defining Alzheimer's disease more than a century ago, that of early—age onset. Alzheimer reports this sole distinction twice in his paper "...because senile dementia was out of the question since the patient was only 56 years of age" and then again (with a different age) "Senile dementia was never considered because of the onset at the age of 54 ..." (p. 77).[3] Seemingly there is no behavioral difference between early- and late-onset Alzheimer's disease[18]—other than ongoing headaches, as reported by some of the familial patients in the Medallin Columbia early-onset study.[19]

1.1 Historical and cultural roots of confusion

In the early decades of the 1900s, three new methodologies were allowing different interpretations of the phenomena of mental illness: (1) histological staining techniques were developed to differentiate different cell types in the brain; (2) psychoanalytic interviewing techniques started looking into the subconscious mind; and (3) experimental methodologies were discovering how learning inappropriate responses have long-lasting behavioral effects. These new methodologies facilitated the separation between psychiatry, psychology and psychoanalysis. With psychiatry adopting neurobiology as its methodology.

These methodologies fell into two dominant philosophies of the early 1900s. On one hand researchers argued that genetic/biological differences in humans can determine their mental and behavioral capacities[20]—a philosophy championed by psychiatry. In contrast, the nurture/learning philosophy—advocating that social interaction shape how we feel and behave—was endorsed by psychoanalyses and psychology. The intellectual father of modern psychiatry, Emil

Kraepelin—who coined Alzheimer's disease in 1911, believed that there exists a genetic, biological and neuronal basis for behavior. In contrast, both Sigmund Freud and his protégée Carl Jung were proposing that upbringing and the unconscious influence behavior. While Wilhelm Wundt—the father of experimental psychology, who mentored Kraepelin—believed that feelings, images and thoughts determine both positive and negative behaviors. Kraepelin perceived a direct threat from the nurture/learning philosophy, resulting in his pursuit to prove that cognitive problems had a genetic and biological basis, but not a psychological one.[21] This perceived threat promoted Kraepelin's quest for biomarkers in Alzheimer's disease, a legacy that remains with us today.

An additional pressure existed for Kraepelin. The rivalry between Kraepelin's Royal Psychiatric Clinic based in Munich, Germany—where Alois Alzheimer worked—and the German University Clinic in Prague directed by the Czech neurologist and psychiatrist Arnold Pick with his protégée Oskar Fisher.[5] The Prague clinic had already defined Pick's disease and Pick's Bodies as forms of prefrontal dementia, and had already defined dementia praexia (premature dementia) as early as 1891, but without the histological evidence that Alois Alzheimer provided. In addition, Oskar Fisher, independently, had identified the plaques, which at the time were known as "Fisher Plaques." Fischer and others at the time also identified a type of dementia referred to as presbyophrenia. Presbyophrenia is synonymous with Alzheimer's disease—early onset dementia. In agreement with Kraepelin, Fischer was of the opinion that presbyophrenia and simple senile (late-onset) dementia were two different diseases. As a result of these advances, the Prague clinic was ahead of the game and Kreplein was aware of this advantage. Although Emil Kraepelin and Eugen Bleuler had already separated schizophrenia from senile dementia, Kraepelin needed a disease to separate senile dementia from its earlier expression that Pick had identified as dementia praexia. And this is where Alois Alzheimer's histological observations come into play.

1.2 The resulting confusion in diagnosis

Although Alzheimer's disease is presumed to be very specific neurobiological disease, this is not the case in clinical settings.[22] Physicians and mental health professionals are still struggling to diagnose Alzheimer's disease correctly.[23] The reliability of clinical diagnosis of Alzheimer's disease dementia remains low, being confused with other neurological diseases such as Creutzfeldt-Jakob disease,[24] Lewy Body dementia,[25, 26] and Vascular dementia, which causes the highest incidence of misdiagnosis.[27] In addition to other neurological diseases that confound diagnoses, there

are clinical complications such as anxiety,[28] low education, cultural variability and the main cause of misdiagnoses, depression.[29, 30] It is rare for a brain disease in older adults to occur in isolation from depression[31] and anxiety.[28] The available diagnostic tools are too crude to differentiate these confounds since they measure severity rather than specific deficits.

In addition to the 2011 updated National Institute on Aging/Alzheimer's Association guidelines, other detailed criteria exist for the diagnosis of dementia. Criteria have been published by the Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC), 1992; Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM–V), 2014; International Classification of Diseases, 11th revision (ICD–11), 1994–2017; and National Institute of Neurological Disorders and Stroke–*Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (NINDS-AIREN), 1993. However, these criteria show poor consistency.

Researchers evaluating these different criteria on a sample of 167 older adult patients who were admitted to a hospital with probable dementia, found that the criteria are not specific enough to differentiate multiple types of dementia, multiple causes may exist that result in similar symptoms.[27] They also suggest that there are other brain diseases, primarily white matter lesions, whose cause and identification remain unknown. Similar results were found[32] reporting agreement in only 20 out of 1,879 dementia cases and 31 out of 107 patients.[33] It is only recently that the lack of reliability in these diagnostic tools has received clinical attention.[34]

Evidence also exists that the expression of different neurological diseases is not distinct enough. In neuropathological studies, dementia with Lewy bodies and Alzheimer's disease pathology commonly coexist,[35] and can include reversible conditions,[36] resulting in a spectrum of clinical expression that fall within hypothetically extremes of reversible deficit, Alzheimer's disease and Dementia with Lewy bodies.[37] As such there seems to be a continuum, rather than a difference in kind, between Alzheimer's disease and vascular dementia.[38, 39] In addition to this neurological diffusion, there exist the further complication of the diagnostic setting. Despite references to biomarkers in the literature, the clinical setting is a social exchange with social and cultural expectations—stereotypes—affecting the reporting and interpretation of behavior. Stereotypes play a significant role in diagnosis. Physicians are significantly more likely to diagnose an older adult with memory issues as having "dementia" when there is an expectation beforehand.[40] Of particular interest to clinicians—other than the anxiety and stigma of incurring

the dementia label, monetary costs associated with follow-up testing, or medications prescribed needlessly—is how the diagnosis, in turn, changes the behavior and memory of older adults.[41, 42] The relationship becomes a self-fulfilling prophesy wherein the patient conforms to the diagnosis, even when the diagnosis is incorrect and unjustified.[43]

The resilience of the Amyloid Cascading hypothesis, in the face of growing research discontent, can be seen when the NIA guidelines argued that the hypothesis will work if they can catch the plaques at an earlier stage of the disease.[44] To enable this approach, the definition of Alzheimer's disease was changed to include a pre-clinical stage that is not yet expressed—creating a "prodromal" stage.[44] While the previous (1984) guidelines only recognized two stages—early and late Alzheimer's dementia—the new guidelines propose that Alzheimer's disease progresses on a continuum with four stages.[44] The first is an early, pre-clinical stage with no symptoms,[45] followed by a middle stage of mild cognitive impairment,[46] and finally two stages of mild and severe Alzheimer's disease.[47] The authors were candid about their intentions in stating that "...These recommendations are solely intended for research purposes and do not have any clinical implications at this time" (p. 280).[48] But the social implications are hard to dispel[49] since dementia is the most frequently expressed fear after cancer.[50] By broadening the definition of Alzheimer's disease to include an invisible stage is worrisome to a public already fearful of the disease and further erodes the specificity of a clinical disease. This opened the possibility of defining a clinical disease deprived of clinical evidence.[51]

1.3 The present paradigm is sowing neurological confusion

As a neurobiological proposition, the Amyloid Cascade hypothesis is difficult to validate. Alzheimer himself argued "...how difficult it is to define diseases solely with respect to their clinical features, especially in the case of those mental disorders which are caused by an organic disease process. An identical disease process will be able to cause extraordinarily different clinical features because of differences in its localization, and in the sequence and extent of cortical revolvement, which may be diffuse or localized and moreover possibly localized in many different ways." (p. 94).[3] Contemporary neurobiological research is verifying Alzheimer's insight.

In a study of autopsied brains from 49 confirmed Alzheimer's disease patients diagnosed according to three sets of published pathological criteria, researchers found a correlation between the density of tangles in frontal and parietal lobes and cognitive deficit, whereas no correlation existed between

density of amyloid plaques and cognitive deficit.[52, 53] One possible reason why older adults might have the neuropathology of Alzheimer's disease and yet not show any symptoms might be because the neuropathology is not exclusively the plaques and neurofibrillary tangles but an overall reduction of neurons in the brain.[54] In agreement, scores on the mini-mental state correlate with grey matter density reduction.[55] Other studies similarly show that this grey matter deficit is also accompanied by white matter deficit, where more than half of the patients diagnosed with Alzheimer's disease exhibit white matter abnormalities.[56] The two-way communication between neurons and non-neural cells—glial cells—is essential for axonal conduction, synaptic transmission, and information processing.[57] On the basis of these studies, it is therefore not surprising to find that abnormalities of cerebral white matter are also present in a majority of patients with Alzheimer's disease.[58] This association was identified by Alzheimer when he wrote that: "In addition, Weigert's glial stain preparation shows another unusual finding. One can often see glial fibres, which appear coiled. This appearance does not seem to me to be without general interest: (1) ...the glia are trying to enclose and support the Corpora amylacea; (2) because they may perhaps shed some light on the physical conditions leading to the development of glial fibres (Homburger)." (p. 86).[3]

1.4 The present paradigm is ignoring brain plasticity

Only by ignoring this early ambivalence, did the Amyloid Cascade hypothesis become dominant. To maintain its dominance this approach continues ignoring research in brain plasticity and disease variability. But by doing so this tactic results in clinical and neurobiological confusion (see Figure 1).

The brain is an ever-evolving, changing organ.[59] Neurological studies have shown how learning among taxi drivers changes their brain structure,[60] especially their white matter.[61, 62] White matter is important because these glial cells have been closely tied to learning and to Alzheimer's disease from its inception (p. 3).[63] Because white matter is more malleable than the slower growing neurons, white matter may be important indicators for learning and brain plasticity.[64] Such neurological changes have also been observed among older adults[65] even after suffering a stroke.[66] Numerous studies have measured brain volumes of professional pianists, reporting a correlation between the hours a musician played and the density of their white matter.[67] To the degree that white matter architecture differs between musicians and non-musicians.[68] In fact, most type of learning brings about changes in white matter,[69] as found with playing golf,[70] playing board games,[71] as well as meditation.[72] Such

white matter changes may have lasting and positive effects on other executive functioning extending beyond the original skill.[73, 74] Although white matter can increase in response to learning new tasks, it is also prone to degradation. White matter patterns can therefore provide some explanation for the variance we see among older adults and their expression of dementia.
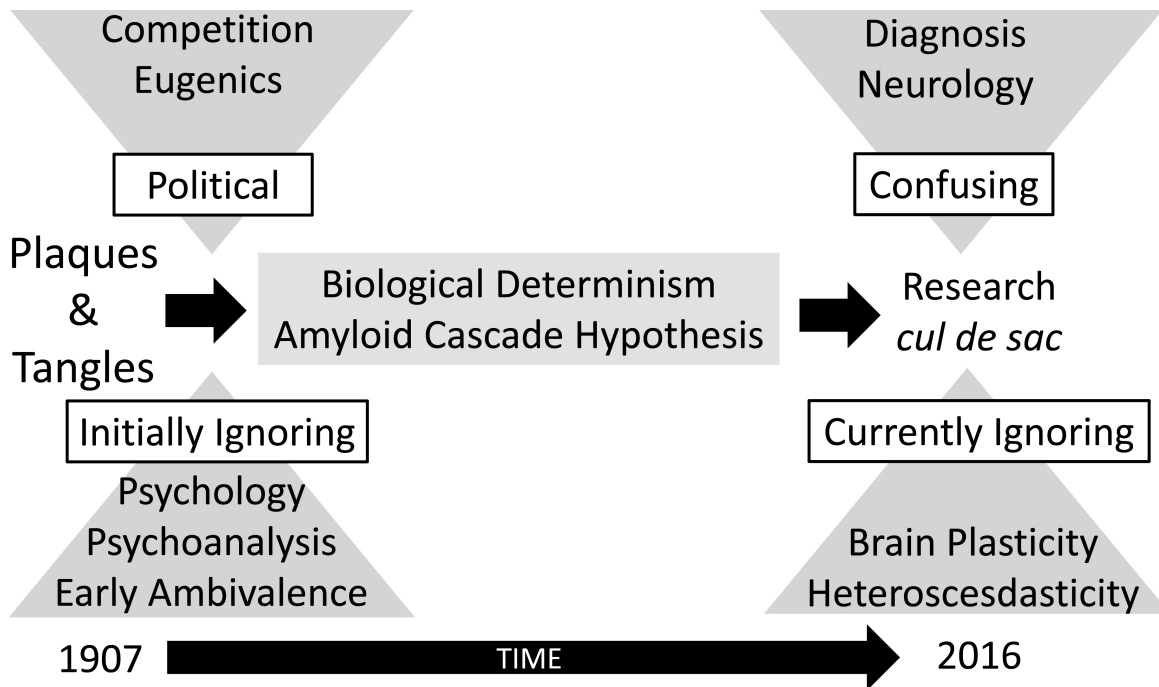

Figure 1. How biomarkers for Alzheimer's disease gained prominence through political pressures, while ignoring contradictory research, resulting in research *cul de sac*.

1.5 Present Approach is Also Ignoring Heteroscedasticity as it Prevails Among Older Adults

Heteroscedasticity—in this context—refers to increasing variance with older age. This diversity and variability increases as a cohort ages—unlike regular variance, which is random, the term for increasing variance along a continuum is specifically termed as heteroscedasticity. This variance was first identified in 2003 with the Nuns' Study when David Snowdon showed that dementia is mediated by education through a process identified as "...cognitive reserve—the capacity of the brain to resist the expression of symptoms in the face of existing neuropathology." (p. 453).[75] The aging process can have both gains and losses,[76] creating a more neurologically diverse population. Older adults have greater variance than younger age cohorts in behavior, memory, morbidity and their level of neuropathology.

Apart from around five percent of early-onset cases, most cases of dementia are senile—pertaining to old age. Alzheimer himself acknowledged this more than a hundred years ago: "Hence there appear to be a variety of intermediate forms between these presenile diseases and the typical cases of senile dementia. As similar cases of disease obvi-

ously occur in the late old age, it is therefore not exclusively a presenile disease, and there are cases of senile dementia which do not differ from these presenile cases with respect to the severity of disease process." (p. 94).[3] Among the oldest-old, when compared to younger people, Alzheimer's disease is more likely to be related to mixed disease pathologies.[77]

Heteroscedasticity might explain why multiple studies have shown that the correlation between Alzheimer's disease neuropathology and its clinical expression declines with age.[78] In part, the loss of association reflects increasing prevalence of other, non-Alzheimer's disease cerebral pathologies in patients as they age.[79] Interestingly, approximately half of clinically diagnosed demented oldest-old have insufficient neuropathology findings to account for their dementia, while approximately half of individuals without dementia meet the neuropathological criteria for Alzheimer's disease.[80, 81]

2. DISCUSSION

Several major sources of confusion remain in Alzheimer's disease research.[30, 82] The primary confusion comes from the varied causes of cognitive diseases. Isolating the disease remains both a neurobiological as well as a clinical

problem.[83] Resulting in most dementias being misdiagnosed.[84–86] A lack of understanding remains as to whether one disease has different expressions—e.g., Alzheimer's disease, Lewy Body Dementia, Vascular dementia—or whether different diseases can result in the same expression—e.g., Alzheimer's disease caused by either genetics or a vascular disease such as normal pressure hydrocephalus which is reversible. Therefore, it is difficult to make distinct and accurate diagnoses. This is the primary source of confusion. The concept that Alzheimer's disease is not a disease but a syndrome will provide an impetus for more research looking at the process of the disease rather than an exclusive focus on finding biomarkers.

A second source of confusion comes from the great variance among older adults' experience with the disease—namely heteroscedasticity. Even among identical twins, this drift can result in one twin experiencing Alzheimer's while the other escapes.[87] This drift is caused by epigenetic changes that can also influence brain plasticity. Variance among individuals increases as they age and will continue to dilute the linear association between a specific disease and its expression. While researchers continue to look for biomarkers, the Alzheimer's Forum has identified more than 1,395 studies working on 695 genes[88] accounting for only up to 0.5 percent of Alzheimer's disease.[89] Genetic studies will never provide the exclusive solution for understanding or curing Alzheimer's disease.

A third source of confusion comes from the fact that clinicians often misdiagnose Alzheimer's disease. There are issues with the diagnostic criteria, made worse by the fact that most older adults experience concurrent multiple morbidities that can mimic or obscure the disease. There is also evidence that some patients acquiesce to the disease label despite being told of the mistaken diagnosis.[90] This in turn results in Alzheimer's disease being over-registered and over-diagnosed,[91] resulting in wasted health care expenditures[92] and undue stress on the family.[93] Despite an awareness of these problems, and steps taken to address them,[94] a rigid adherence to the existing status quo continues to influence the types of research being conducted.

3. CONCLUSION

There is no denying the devastating impact of an illness that destroys the mind, changes behavior, and affects the personhood. The disease affects not just the victim but is affecting the lives of whole families across generations. This emerging pandemic will in turn transform our society. Hopefully this paper will promote a broader approach to studying Alzheimer's disease, allowing for a wider spectrum of scientists to become involved in finding what Alzheimer's is

and subsequently finding a cure. We still do not know what causes Alzheimer's disease or indeed what it is. This confusion is not new, and to this day researchers question whether Alzheimer's disease is "an inevitable part of 'normal' aging, or a bona fide neuropathological disease, entirely different from aging?" (p. 47).[95] It is remarkably similar to questions asked a century ago at the start of Alzheimer's disease research. While "Even today, with technology, research history, and a considerable amount of monetary resources, it is still unclear, for example, how to distinguish the normal from the abnormal in old age or how to explain the appearance of Alzheimer[s]-like plaques and tangles in persons without clinical symptoms." (p.1).[96] The work of researchers who first exposed these inconsistencies[97–100] still remain on the periphery of the discussion and now need to be brought to the center.

The conclusion from these critiques is that clinicians are not diagnosing Alzheimer's disease correctly.[101] Whatever the disease is, Alzheimer's disease is not a simple trigger that starts the profusion of plaques and tangles which then interferes with brain functioning.[16] Alzheimer's disease is likely to have multiple events that can initiate the disease and is likely to have both mediating and moderating factors that promote the disease. It also probably affects individuals differently depending on their resilience and capacity to buffer the disease. As such, the way to change course in research is for funding to expand to cover broader issues other than the search for biomarkers. Funding needs to first address the confusion of diagnostic uncertainty. This will entail training for neurologists and physicians on the many different types of dementia and their possible causes, for patient organizations to focus on better individual-based care, and for the public to understand the many contributing factors of dementia, some of which can be prevented. This is a public health approach to the disease.[102] Ignoring these complexities will have radical social and scientific consequences. Consequences that were prophesied in 1911 when Perusini wrote: "of course, as usually happens when anatomo-pathological datum offers easy enticement, there will be more than one person who, on the basis of these findings will make the most useless and fanciful anatomo-psychic guesses, and those who amuse themselves with anatomically localizing the location of conscience, the will and related matters, would find a good playground, in which the tangles, for instance, might offer the most clear-cut explanation for the disorientation observed in the senile demented patient…" (p. 144).[103] Emerging scientific evidence is exposing the role of the environment, brain plasticity and reserve, the contribution of other diseases and how people with biomarkers for Alzheimer's disease seem to escape its expression. In response to this lack of

theoretical leadership, researchers are ignoring any theoretical underpinnings and applying pragmatic approaches. One such example has shown how lifestyle changes reverses cognitive decline.[104] Other emerging *ad hoc* therapies support a broader public health theory of Alzheimer's disease and support the role of lifestyle changes in countering the effects of Alzheimer's disease.[105] After a century of confusion, broadening our research emphasis—by acknowledging the clinical and neurological confusion and promoting a public health approach—will navigate us out of this Alzheimer's disease research *cul de sac* and provide viable research guidelines for prevention, management and cure.

CONFLICTS OF INTEREST DISCLOSURE
The authors declare no conflict of interest.

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