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A Critique of the 2018 National Institute on Aging's. Research Framework: Toward a biological definition of Alzheimer's disease

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Abstract

Shame on the National Institute on Aging (NIA) for sponsoring a new way of defining Alzheimer's disease based on biomarkers (plaques and tangles). 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 Alzheimer's disease related biology. Every person over 25 years of age had Alzheimer's disease biomarkers. The new framework sponsored by the NIA makes every older person liable for a diagnosis of Alzheimer's disease. The legal implications were not even considered. The pharmaceutical connections of most researchers involved brings into question the intent of this framework. This article details the scientific argument against using biology as the only indicator of the disease while ignoring the clinical aspects. The conclusion advocates for a careful reassessment of an emerging eugenics movement where biological markers are becoming more readily relied on when the science supporting these indicators remains incomplete.

Introduction

After more than a century of research the National Institute on Aging and the Alzheimer's Association (NIA-AA) are yet again reverting to the original definition of Alzheimer's disease. A definition which Emil Kraepelin—Alois Alzheimer's supervisor—hastily formalized as a "new disease" in 1911. The recycled definition, published in 2018, is the NIA-AA's Research Framework: Toward a biological definition of Alzheimer's disease and was headed by Clifford Jack (referred to from now on as the Framework) [1].

The Framework relies on the plaques and tangles as the signature of Alzheimer's disease, while overall neurological damage defines the severity of Alzheimer's disease. This time around, in contrast to the 2011 Guidelines [2] the Framework ignores the clinical features of the disease. This is important because for the first time the clinical aspect of the disease—what we think of as Alzheimer's disease, which is how it is expressed through loss of memory, changes in mental capacities and even mood and personality changes—will be ignored in preference to its biological clues. By doing so the authors usher in a new dawn of disease classification. This new biological definition is based on three types of information: [A] amyloid beta deposition, [T] pathologic tau, and [N] neurodegeneration, referred to as the AT(N) [see note below for a more detailed description].

With eight different AT(N) biomarker types this Framework is un-wieldy in its confusion. But the confusion is not in its complexity but in its logic. The authors make the illogical and unsubstantiated claim that "A biological rather than a syndromal definition of AD [Alzheimer's disease] is a logical step toward greater understanding of the mechanisms underlying its clinical expression." (p.536)]1]. That Alzheimer's disease can only be diagnosed through these biological markers (biomarkers) while by ignoring the real disease which is its clinical expression they lose their reference outcome. , they defined the disease but not what is not-pathological. The authors argue that the clinical and neuropathological features of the disease are "…two very different entities…" (p.536) [1] and that "…cognitive symptoms are not an ideal way to define AD [Alzheimer's disease]" (p538) [1]. As a vehicle for scientific exploration, understanding and ultimately cure of Alzheimer's disease, the Framework ignores science, obfuscates methodology, and fudges outcomes in order to drive through an agenda based on pharmaceutical (in contrast to scientific) considerations. There are serious repercussions from this approach but it is a lack of scientific rigor that will eventually expose this approach for what it is, a sham. This paper exposes the lack of scientific methodology utilized by the NIA-AA in reaching their conclusion.

A clinical disease—a disease that is experienced or has observed consequences—is now being argued to be exclusively a biological disease. But Alzheimer's disease is only important because it is a clinical disease. If all who have the biomarkers do not express the disease than there will be no interest in a search for a cure. It is of no consequence what the biology is if the disease is not experienced or observed. By reversing this truism, that the biology is more important than the outcome of the disease, the authors are transforming how we look at health and disease. A transformation that the authors of the Framework

concede is a "…a profound shift in thinking." (p.538.) [1] The profound shift is also found in the lack of scientific method employed. Yet the authors protect this radicalism "…dementia is not a "disease" but rather is a syndrome composed of signs and symptoms that can be caused by multiple diseases, one of which is AD" (p.538) [1]. They admit that what they are studying can be one of many causes of Alzheimer's disease and "The fact that most dementia is multifactorial presents a challenge both for diagnosis and treatment." (p.545) [1]. We are guaranteed no scientific road map for a cure in this Framework. The authors also acknowledge that we do not know how to start: "Cut points must be determined, and age norming biomarker cut points is controversial." (p.550) [1]. "The distinction between normal aging and age-related disease has been debated for decades…and we do not presume to settle this here." (p.550) [1]. Again, the Framework provides no structure for research on the real issues of aging, despite mounting evidence that dementia is not part of the normal aging process [3]. We still do not have a framework for studying diseases related to aging as pathology rather than as aging. For a research framework the authors were remiss when it came to dictating "The committee avoided taking a proscriptive approach to these methodologic issues under the assumption that this was best left to expert work groups and individual research centers." (p.551) [1]. But research centers do not determine these methodological issues, their sole objective in their research company—whether private or university-based laboratories—is to gain funding or monetize a cure.

That biology contributes to and is part of the process of Alzheimer's disease is not contested. But to argue that the biological markers of the disease, its neuropathology—is purely the disease contradicts a wealth of evidence. The Framework is more of a research policy rather than a scientific paper and it is therefore of limited scientific merit. It was published even though biomarkers density and cutoff points through "universal standards have not yet been established." (p.551) [1].

The Framework's proposition is premature and flawed. It ensures that all older adults be diagnosed with Alzheimer's disease. Older adults that do not have plaques and tangles in their brains do not exist. As a result, older adults are automatically branded as suffering Alzheimer's disease which makes this new approach ageist. Such sensitivities are overwhelmed by the hubris of the authors when they admit that "Up to 60% of CU [cognitive unimpaired/normal] individuals over age 80 years have AD [Alzheimer's disease] neuropathologic changes at autopsy or by biomarkers…Thus, using a clinical diagnosis of 'AD' to ascertain absence of disease is associated with an error rate exceeding 50% in the elderly." (p.552) [1]. A false positive rate of 50% where it is acknowledged that "However, it is increasingly recognized that neurodegeneration/ injury, even in classic AD [Alzheimer's disease] brain regions, also occurs in non-AD conditions. This is particularly so in elderly individuals where comorbidities are common." (p.539) [1]. The same Framework conceded a high rate of false negatives, when ten to thirty percent of autopsies of individuals with Alzheimer's disease do not show these biomarkers, while among Alzheimer's disease patients around thirty percent have normal amyloid PET or CSF Ab42 results [1]. Fifty percent false positive and false negatives does not form a solid foundation to develop a purely biomarker theory of Alzheimer's disease. These are the same odds as a coin toss.

One study that demolishes the validity of this Framework is the study conducted in 2011 by Heiko Braak and his colleagues from the University of Ulm, in Germany. They looked at 2,332 brains of people that died from various causes from different hospitals that also included children. This is the first time that children's brains were studied for dementia. From this study only 10 brains showed a complete lack of plaques and tangles (less than half one percent) [4]. All of these non-Alzheimer's disease cases were found in the brains of people aged 23 years and younger. By the Framework's criteria, all adults have Alzheimer's disease. Such criterion makes no scientific or clinical sense. In research defining all adults as suffering a disease limits the capacity to differentiate what you are studying.

In addition, there is also a statistical problem to add to the biological problem. Older adults tend to have more neurological variances then younger adult populations. Such variance become greater among the older population—known as heteroscedasticity. Making a specific diagnosis becomes increasingly more difficult among older populations. For neurologists, separating Alzheimer's disease from other co-existing neurological diseases becomes very difficult and impossible in many cases. Dementia among older adults might have outward behavioral similarities, but the inward neurological causes can be very different because there are so many other neurological pathologies present. For example, it is rare with older adults that a brain disease occurs in isolation from other type of (non-cognitive) diseases such as depression [5], and anxiety [6]. While multiple comorbidities exist, isolating the disease includes both a clinical problem as well as a neurological one [7]. As a result, many dementias are misdiagnosed [8,9,10].

Explaining why a U.S. federal agency—the National Institute on Aging (NIA), established to address the health needs of older adults—is pushing an approach that will wrongly identify Alzheimer's disease among all of its constituents, older adults, attests to the overwhelming power of external influences. The pharmacological industry, and the relationships it has with most of the authors of this Framework, seems to be subverting the NIA's primary and sole task—protecting older adults. A cursory look at the business affiliation of some of the primary authors of the Framework identifies hundreds of cases of conflicts of interest [11].

There are both political as well as methodological/statistical deficits in the Framework, and to understand both it is important to understand the context, why such conscious mistakes are propagated.

History

Summarizing research on dementia remains challenging because there is an abundance of research being produced across many technical disciplines. Driven exclusively by funding, whether private pharmacological investments or federal and (international) states funding, research is mostly directed at monetizing a cure, with some notable minor exceptions. Details of such work, some more impressive than others, divert researchers from an overview of the general understanding of the research itself. In 2017, Gill Livingston and her colleagues in reviewing dementia prevention, intervention, and care report that "…around 35% of dementia is attributable to a combination of these nine risk factors; early education up to age 11 or 12, hypertension, obesity, hearing loss and later-life depression, diabetes, physical inactivity, smoking and social isolation." (p.14) [12]. At the same time they argue that in comparison, eliminating the main genetic correlate (Apolipoprotein E) will only result in a 7% reduction in incidence. There is a resistance in acknowledging that what will truly cure, or at least delay Alzheimer's disease is preventive care and lifestyle choices. That pharmacological interests benefit from this resistance is not by chance.

After enormous resources invested over the last 100 years to research Alzheimer's disease—and providing the sole impetus for the establishment of the U.S. National Institute on Aging (NIA)—we are nowhere closer to understanding Alzheimer's disease. Nor does anyone have any semblance of how to stop and cure the disease [13,14]. Research remains disorganized, clinicians remain confused, and the public has become increasingly worried [15]. Although there are many potential alternate approaches to developing research guidelines on Alzheimer's disease [16-21] the NIA is reverting back again to the original definition of the disease. Historical evidence informs us that it was wrong then, and scientific evidence informs us that it remains wrong today.

A century ago Alois Alzheimer published a case study where he identified plaques and tangles in the brain of a young woman of 51 years. This was not a new observation, nor was it unique. It was known that most people with dementia had the same neuropathology, including the majority with senile (relating to old age) dementia. This was such a non-event that Alzheimer's initial attempt at publishing these observations in 1906 failed because it was not scientifically noteworthy, and it took a year for these observations to be published [22]. However, three years after this initial observation Emil Kraepelin—Alzheimer's supervisor at the Munich clinic—included the observation of plaques and tangles in "young" patients as "Alzheimer's disease" in the eighth edition of his book Psychiatrie. Against the overwhelming evidence from the scientific community, a new disease was created.

We cannot know Kraepelin's motive for such a hurried and ill-informed decision. However, the fact that his neurological clinic in Munich was in competition with the one in Prague likely played a role. The Prague clinic was headed by the much more accomplished Arnold Pick, who already had published more than 350 scientific papers and a textbook of neuropathology [23]. More importantly, Arnold Pick already identified Pick's disease and Pick bodies in dementia as a result of buildup of tau proteins (unknown at the time). In contrast, Kraepelin and Alzheimer had no academic imprint yet in this area. Pick's Prague clinic also included the highly accomplished neurologist Oskar Fischer who was the first to identify Amyloid Beta plaques which became known as Fisher Plaques. Both Fischer and Alzheimer had published observations that identified plaques and tangles, both using the same methodology of reduced silver staining technique developed in 1902 by Max Bielschowsky [24]. At a time leading up to 1918—when the Weimar Republic was declared, ushering in the emerging Nazi movement—the Jewish Fischer and Pick in concert with all other contemporary researchers, argued that Alzheimer's disease was not a new disease. Politically Pick and Fischer were on the wrong side of emerging nationalism and an anti-Semitic swell. It could be argued that politics outplayed science. By enshrining Alzheimer's disease as a new disease—in contradiction to the overwhelming scientific evidence against a new disease—Kraepelin established a political aspect of Alzheimer's disease and gained kudos for his newly established 1917 Munich clinic (now named Max Planck Institute for Psychiatry in Munich) to the detriment of the Prague clinic.

Fast forward in time and the second political event that falsely promoted the uniqueness of this disease came about with the creation of the U.S. National Institute on Aging. In 1974 Public Law 93-296 established the National Institute on Aging and in 1976 Robert (Bob) Butler was appointed its first director. The political theatre behind the scene revealed the true purpose of the NIA. Despite Butler's interest in age inequity—having published a 1969 paper that defined "ageism" and then in 1976 publishing a Pulitzer-winning book Why Survive?: Being Old in America—Butler's focus was always on neurological diseases. Butler confessed: ''I decided that we had to make it [Alzheimer's disease] a household word…And I call it the health politics of anguish.'' (p. 82) [25]. By using Alzheimer's disease to promote NIA's mission, Alzheimer's disease again became political. This involved a radical change. NIA's founding members realized that politically, they needed something more than 'diseases of older adults' to validate their new institute to Congress. President Nixon at the time in rejecting the first proposal for the establishment of the NIA must have agreed with Congress that "we are not in the business of curing aging." Congress saw diseases of older adults as inevitable, one that required care rather than cure. Dementia was also ill-defined, broad, and too diffuse a term to get Congress excited. In response and playing the "health politics of anguish" the founders of the NIA ingeniously focused on Alzheimer's disease. Thanks to Kraepelin, Alzheimer's disease could be approached as a biologically-determined disease—a real disease.

There was one problem with this approach: by definition, Alzheimer's disease was primarily a disease of younger people

and not a disease of older adults. There were very few patients suffering from Alzheimer's disease in the 1970s. In fact, Richard Katzman himself reports that cases were so few that "Precise epidemiological information [on Alzheimer's disease] is not available…" (p.378) [26]. It was becoming apparent that most patients with clinically defined senile dementia—onset of disease after 65 years—have very similar pathological changes in their brains as patients with Alzheimer's disease [15,27]. A century of criticism, arguing that senile dementia and Alzheimer's disease are one and the same thing, was suddenly being recognized [28]. It became politically expedient now to ignore what Kraepelin and Alzheimer argued for, and to admit that Alzheimer's disease is not uniquely different from senile dementia. Katzman [29] already started eroding the distinction between dementia and Alzheimer's disease and, as a result, the two constructs were merged. However, rather than changing the name of Alzheimer's disease to senile dementia—because the establishment of the NIA relied on the banner of a neurological disease—the name Alzheimer's disease was retained and broadened significantly to include senile dementia [26,30]. This proved extremely beneficial in the politics of anguish. An editorial by Robert Katzman in the April 1976 Archives of Neurology altered the balance [26]. In the short two-page article (plus references), Katzman made the argument for subsuming senile dementia under Alzheimer's disease. It was not peer-reviewed, again a political rather than a scientific discussion. Katzman's political conjectures projected Alzheimer's disease as being the fourth or fifth most common cause of death in the United States. Overnight Alzheimer's disease "became" a national public health issue. As Kraepelin "created" Alzheimer's disease, Katzman "transformed" the disease into a public health menace.

Hubris plays a role again, Robert Katzman was not shy in acknowledging the importance of usurping senile dementia: "I think there's no question that that's my major contribution. Of the 115 papers I've written, that two-page editorial is clearly the most important." [25]. Now, the fate of Alzheimer's disease became intricately woven with the promotion of the NIA. The creation of the NIA depended on Alzheimer's disease gaining prominence and national attention. Without the banner of a disease, Congress was not going to fund research on aging. The ageist attitude was—and remains to this day—that aging is not important by itself. The founding fathers of the NIA knew that they needed constituents to bring the mission of the NIA to Congress, and that meant using Alzheimer's disease as a lure. All they had to do was to persuade the general public that Alzheimer's disease research was not only a national priority—as well as the NIA's—but that it was their priority as well. The growth of locally-based Alzheimer's associations was essential in order to bring public pressure on local and national representatives to support NIA's mission. This required a symbiotic relationship between the NIA and Alzheimer's Associations—one that has endured to this day. With all of this political activity, science was overlooked.

It took more than eighty years for a quasi-theory to be developed to explain Alzheimer's disease. The Amyloid Cascade hypothesis [31] proposed that the accumulation of two misfolded proteins—amyloid-β peptide and tau tangles in the brain—was Alzheimer's disease signature pathology [32]. Even by 1992, it was dead on arrival, existing evidence at the time already refuted this hypothesis, and researchers working in the field knew this.

Deposition of amyloid (A4) protein deposits were (variably) present in 66% autopsies on adults over 65 years of age with progressive supranuclear palsy, 57% with Parkinson's disease, 40% with Huntington's chorea and in elderly patients with frontal lobe dementia [33,34]. A signature biomarker that is shared by other diseases is not a signature but a rubber stamp. By 1990 researchers were arguing that the "Amyloid deposition in elderly persons may thus relate more to certain aspects of ageing and genetics than to AD [Alzheimer's disease], per se." (p.68) [33]. Two years later, despite these stark anomalies, the Amyloid Cascade hypothesis become hallowed knowledge and formed the basis for nearly all of the neurological work in Alzheimer's disease. It even resulted in the genetic creation of special (transgenic) mice whose brain is contaminated with amyloid plaques and tau tangles that form the basis for testing of all pharmacological interventions.

Repeating History

Based on the amyloid cascade hypothesis [31], active immunization against amyloid-β42 peptide was proposed as a treatment. But so far, all types of 'amyloid' trials have failed.

In the active amyloid-β42 immunization clinical trial by Elan Pharmaceuticals (AN1792), researchers were successful at clearing the amyloid-β42 that formed the plaques. The immunization trials show that amyloid can be cleared from the brain, seen as a revolution, the "holy grail" one that the Framework is resurrecting. The problem is that cognition was not improved [35-37]. In fact, longer term follow-up revealed continuing cognitive decline despite removal of plaques [38].

Another approach was related to inflammation response. There was observational evidence that inflammation is part of the disease process. Patients with rheumatoid arthritics who regularly consume non-steroid anti-inflammatory drugs (NSAIDs) had lower rates of Alzheimer's disease [e.g., 39]. However, the anti-inflammatory drug R-flurbuprofen trial conducted by Myriad Genetics was stopped. Although stage two showed some promise, the outcomes in stage three proved non-significant. It was not clear whether the concentration was sufficient (800 mg) and whether the effects of the drug were too diffuse and non-specific. It is not possible to interpret the outcome of the trial in any useful way. More recent studies with NSAIDs on reducing the incidence of Alzheimer's disease have proven inconclusive [40,41]. Best interpretation is that a daily dose of generic ibuprofen reduces the likelihood of Alzheimer's disease.

Both these types of studies did however leave one possible interpretation; that the lack of positive outcomes could be due to the disease already being present and therefore the intervention could not prevent it. Again, the argument being proposed is that there is a need to catch the disease much earlier [42]. The Framework complies with this hypothesis. But there is a problem in logic.

If removing amyloid-β in patients resulted in poorer performance on cognitive testing in human trials [37,43,44] then the plaques cannot be the disease [45]. Therefore, if one of the signature biomarkers of Alzheimer's disease is found not to cause Alzheimer's disease then something else must cause the dementing features that we observe. Boche concludes that; "However, the continuing progression of cognitive decline in AD patients after Abeta immunisation [plaques] may be explained by its lack of apparent effect on tangles [tau]." (p.13) [43]. The results are clear, the amyloid-β42 are precursors to the real disease which is the tau tangles. It could be that there are unknown, or hidden precursors. But the Framework does not address the possibility that Alzheimer's disease is caused by other biomarkers that we perhaps have not yet identified.

The Tau Influence

Given these setbacks, the only way that the Amyloid Cascade hypothesis can survive is through two interpretations. One is that we need to treat the disease at an earlier pre-clinical stage. Secondly, we need to develop safer immunization of amyloid-β42 since this seems to be the precursors to the tau tangles which might be the cause of the clinical disease. But this strategy has not fared well in the past. In 2018, Stefano Cappa with the Institute for Advanced Studies, Pavia Italy remarked that the competing "tau hypothesis" shares most of the conceptual assumptions of the amyloid approach—the idea that the development of Alzheimer's disease could be stopped or delayed by interfering with the biology, in this case the formation of neurofibrillary tangles—pathologic Tau [46].

Despite reservations, resources have been diverted to the next big thing—stopping Tau from becoming a problem in the brain. There are four ways this protein becomes toxic and so far, there are attempts to limit two of these (phosphorylation and glycosylation.) Although these are showing some small effect in animal studies [47] and in reducing risk of Alzheimer's disease [48], so far, the results have been trivial and diffuse [47].

While there are treatments that attempt to immunize, and therefore stop the formation of tau, these therapies have similarly shown some success at clearing the tau but without the desired clinical outcome. It seems that the theory is wrong from the start. The biology—tangles and tau as the neuropathology—might contribute, moderate and/or mediate the disease, but it is unlikely to be the disease itself—despite the Framework's assertions. However, if we are to rely on the objectives of the Framework's stated ambition of clearing the amyloid-β42 and tau tangles, then we have succeeded: Mission Accomplished. Such success can only be accomplished if we remove the clinical outcome in the definition of Alzheimer's disease, thereby ignoring the observation that individuals' dementing behavior does not improve [43].

But judging success on neuropathology and ignoring clinical evidence is superficial. If clearing the amyloid-β42 and tau tangles results in the patient retaining the clinical disease i.e., suffering from memory disorders, personality changes, and impaired reasoning., then we have failed. The public does not want clean brains, they want "abnormal" behavior to go away. Any approach that ignores these realities of success is doomed even if the objectives of the Framework are successful.

The clinical aspect of the disease deserves attention. The Framework specifies that; "…[a] person has an AD [Alzheimer's disease] biomarker profile, we cannot know if the cognitive deficit is attributable to AD alone or to other potential comorbidities in addition…different cognitive stages may be present in the population among people with the same biomarker profile" (p.546) [1]. Not only does the Framework not address the clinical aspect, but it argues against the role of biomarkers in the clinical expression of the disease.

Following the lead of the International Working Group (IWG) in collaboration with the NIA-AA, there is already a movement at improving the existing Guidelines of 2011 [2] and defining a more accurate clinical diagnosis of Alzheimer's disease [48]. This is a better approach. The initial Guidelines, although not without criticism [e.g., 16,49], proposed that Alzheimer's disease progresses on a continuum with three stages [2]. The first is an early, pre-clinical stage with no symptoms [50], followed by a middle stage of mild cognitive impairment [51], followed by a final stage of Alzheimer's dementia [52]. An additional update focusses on the criteria for identifying Alzheimer's related changes at autopsy [53]. These further improvements on the original guidelines were concerned with the clinical application of their work. Importantly they were aware of how Alzheimer's disease can have atypical forms, mixed diseases, and can have a preclinical presence.

By ignoring all of these aspects of the disease, ignoring the scientific literature that negate the simplicity of the Amyloid Cascade hypothesis and the similarly ill-fated tau-cascade hypothesis, and focusing purely on the neuropathology—regardless of the clinical aspects—the Framework is attempting not just to define a new diagnosis of Alzheimer's disease. It is trying to reengineer how we define disease itself.

Nosology

How we classify diseases has always relied on their clinical expression, but it is changing. In 2008 the National Institute of Mental Health (NIMH) introduced Research Domain Criteria (RDoC), a new classification of diseases—nosology. It was especially promoted by the NIMH then director Thomas Insel, who has now migrated to Google Life Sciences which in the Google empire has become a full-fledged member of Mountain

View's Alphabet Inc., and taken on a new name: Verily, a for profit health company.

The RDoC came into its own with the publication of the 2013 DSM-5—Diagnostic and Statistical Manual of Mental Disorders. DSM-5 is the definitive reference for diagnosing psychiatric disease sponsored by the American Psychiatric Association. This latest version heralded a radical diagnostic departure by moving towards more dimensionality of disease (no longer binary), relying on more biological indicators and an emphasis on pharmacological outcomes. The implicit assumption in DSM-5 and explicitly stated in RDoC is that behavioral/mental/clinical disorders are manifestations of biological/neurological disorders. Bad behaviors are nothing more than biological expressions. Fixing the biology will fix the problems. Thomas Insel himself argued that the explicit emphasis of RDoC is to "yield new and better targets for treatment." [54]. While demoting the importance of understanding the disease, it elevates the search for a cure. An illogical approach, it undermines the scientific method in favor of a panacea, one that accommodates an economic imperative.

A backlash of criticism ensued [e.g., 55-57]. but despite evidence against this approach, RDoC gained legitimacy. RDoC's biological determinism was promoted by the success of how easy it was for the public and scientists to believe that Alzheimer's disease was determined by a simple cause, a biological malfunction. The history of Alzheimer's disease laid the foundation for a new way of biological determinism that has not been seen since the height of the eugenics movement in 1923 when the American Eugenics Society was founded. But this emphasis on biology is misplaced. There is no evidence that biology exclusively determines Alzheimer's disease.

Eugenics Versus Science

In May 2016, in a short eight-page report in Nature Biotechnology, Rong Chen, Stephen Friend and Eric Schadt from the Icahn School of Medicine at Mount Sinai, New York, and their colleagues reversed our idea about genetic determinism. This small revolution proved to be radical because by association, this also unhinges biological determinism—the belief that biology determines all your traits [58].

What Chen and his colleagues did was to apply scientific method to examining commonly held beliefs about genetic diseases. Usually genetic investigations focus on a group with a disease and then identifying genes that are different in this group from the rest of the (control) population and singling-out a gene that "caused" this difference. Sometimes geneticists get lucky and find only one gene that is different between the two groups. In such circumstances this single gene follows Mendelian laws in how it affects people. Using this methodology, scientists have subsequently identified 584 Mendelian diseases: where one gene causes a specific disease. For the first time the validity of this assumption was being tested. The results were unexpected and revolutionary.

Rong Chen and his colleagues screened for 874 genes among 589,306 individuals. They identified 15,597 individuals who had genes for debilitating diseases but they did not express the disease—they were genetically infected but did not show it. After rigorous elimination of candidates for various technical and theoretical reasons, 13 individuals had genetic disorders for: cystic fibrosis, Smith-Lemli-Opitz syndrome, familial dysautonomia, epidermolysis bullosa simplex, Pfeiffer syndrome, autoimmune polyendocrinopathy syndrome, acampomelic campomelic dysplasia and atelosteogenesis. For over fifty years it was believed throughout the scientific community that having one of these genes results in a debilitating disease. But for these lucky 13 adults were completely normal. They did not express the disease. This single paper heralds the death of biological determinism [58]. What this informs us is that Mendelian genetics alone does not determine the disease, they are instead mediated or moderated by something other than Mendelian genetic. We know very little about what can moderate and mediate this process.

The Framework usurps the RDoC mission. But despite the change in name, the aim similarly equates biomarkers with disease. But as we have discussed, science contradicts this assumption. The NIA-AA Framework relies exclusively on biological markers even though "None of the biomarkers are as sensitive as direct examination of tissue at autopsy." (p.544) [1]. The reliability of the tools we have to measure these biomarkers are questionable; "a negative amyloid PET scan should not be equated with the complete absence of Ab [amyloid-β42] in the brain or even with absent or sparse neuritic plaques [tau tangles]…pathologic tau that can be present in the brain below the in vivo tau PET detectable threshold is unknown at this time." (p.544) [1]. The tools we have are unreliable, but even more worrisome, they lack validity—they are not scientifically useful. We have to judge how sensible it is to choose neurological degradation to define severity when "the number of neurons or neuronal processes that must be lost to detect atrophy on MRI or hypometabolism on FDG PET is not known." (p. 544) [1]. These anomalies, identified in the Framework, might placate critics but they also succeed in highlighting the lack of robustness of the theory they are proposing. Even if we accept that this aim is to focus on cure, how reliable is this approach to help cure Alzheimer's disease when these biomarkers are known to relate to (cause?) other diseases.

The AT(N) biomarkers are not an exclusive signature of Alzheimer's disease alone. "In any individual, the proportion of observed neurodegeneration/injury that can be attributed to AD [Alzheimer's disease] versus other possible comorbid conditions (most of which have no extant biomarker) is unknown." (p. 543) [1]. These admissions reveal serious scientific flaws that expose this Framework to failure. There is also no connection between these biomarkers, as the authors confess: "The AT(N) biomarker system does not imply a specific order of events nor does it imply causality." (p. 541) [1]. And even though the authors refrain from using the clinical expression, their only means of

validating the disease is through its clinical expression: "The rate of cognitive decline is significantly greater for cognitively impaired and CU [cognitively unimpaired] individuals who have abnormalities in both an amyloid biomarker and a second biomarker type (which could be CSF T-tau or P-tau, atrophy, or hypometabolism) in comparison to individuals who have neither or only one of these biomarker abnormalities." (p.541-2) [1]. There is not one study that can prove that "…biomarkers predict greater likelihood of and more rapid cognitive decline" (p.542) [1]. It is likely, but the science has not been done, and science cannot be presumed.

Ignoring Science

The disclaimer is that this framework is "…for research purposes only…" Defining a research framework through an international publication under the auspices of a U.S. National Institutes is unnecessary. A research directive can easily have been issued through a Request for Proposal directive. As with the 2011 guidelines [2], again issued by the NIA-AA, the effect was that the then newly proposed clinical continuum—pre-clinical/Mild Cognitive Impairment/Alzheimer's disease—was adopted by clinicians throughout. Given the research importance, the Framework will similarly be haphazardly and unevenly adopted across the clinical field. Such duplicity remains worrisome. A true research framework would approach it through scientific methods, not by self-serving selection of cherry-picked facts.

A scientific study would establish the following: What are the correlates of dementia (both biological and psychological/clinical.) Other "mis-folded" proteins are present in brains, some 34 proteins can mis-fold, why focus on just two? If Alzheimer's disease is an amyloid problem why not look at this under amyloidosis instead of separately (i.e., Parkinson's disease)? Why are some mis-folded proteins useful in viral and bacterial protection? A longitudinal study of chemical changes in the brain. with particular attention to the effect of physical and psychological trauma to the brain, needs to be conducted to establish parameters of study. A theory must include all of these parameters. If there is a focus on just two biomarkers, the amyloid-β42 and the tau neuritic tangles, then how many people (of all ages) have these biomarkers, what is the tipping point and what is the cut-off point where it is clinically expressed through dementia or/and another clinical disease? How and why do these misfolded proteins misfold?

But the main failure of the Framework is its lack of scientific insight. The brain is the most complex entity in the universe, no other system or organ is as complex. Valid competing explanations for dementia invariably treat the brain as a complex system, and therefore any disease is expressed through the breakdown of complex systems. For example, in older people there are changes in resilience, reduction in body temperature, hormone changes (especially for women) all of which affect the blood-brain-barrier and other biological systems that protect the brain from infections. With reduced resilience, the brain receives an onslaught of bacterial, fungal, viral, metal, and other invasions with which the brain experiences difficulty in coping. The plaques and the tangles in this scenario might easily be responses to such an attack. The Framework's exclusive focus on these biomarkers does not elucidate these many different dynamic processes. Science first needs a theory. Observations are not made in a vacuum.

Science is a method, based on theory. A theory accomplishes three primary things. First it summarizes all existing information, without ignoring anomalies. It explains all that is observed. Secondly a theory predicts. Thirdly a theory generates hypotheses that are open to testing and refutation. We can test a theory through its many parts. During this stage of testing, the method of science is to test the smallest number of variables against the most discreet outcome. This stage relies on a good methodology and accurate statistics. Most science fails here.

Science is reliant on constant replication in order to ascertain the relationship that we are observing is indeed real (i.e. true). The likelihood that a research finding is indeed true depends on three indicators: the prior probability of it being true (before doing the study), the statistical power of the study, and the level of statistical significance [59,60]. Because most studies do not follow these requirements, focusing instead on statistical significance alone, Ioannidis argues most current published research findings are false [61]. We are creating pseudo-science and building upon an edifice of falsehoods.

This level of unawareness—in sociology referred to as Agnotology, the study of culturally induced ignorance or doubt—is further fueled by attempts to find a cure before understanding what we are trying to cure. Such applied science, however noble, is not science. Science is a method used to understand a phenomenon. It is not predetermined. With the new target to develop a cure for Alzheimer's disease by 2025 [62] we continue to ignore out incomplete understanding of the disease, the many possible causes and complex physiology of the disease, how other existing diseases interact together and the slow progression of the disease occurring in the elderly population [63]. We are kicking the can down the road. We will find ourselves in the same spot in a century from today and we will be reading the same kind of criticism as we are here today.

Conclusion

Arnold Pick saw dementia as ". . . a mosaic of localized partial dementias. . ." (p. 35) [64], Alzheimer's disease is likely caused by a mosaic that includes: viral (HIV/AIDS, herpes simplex virus type I, varicella zoster virus, cytomegalovirus, Epstein-Barr virus), bacteria (syphilis and lyme-disease/borrelia), parasites (toxoplasmosis, cryptococcosis and neurocysticercosis), fungi (Candida glabrata), infections (possibly prions), and vascular (stroke, multiple-infarct dementia, hydrocephalus, injury and brain tumors) [65].

There are processes that promote and delay the infection and the spread of infection. Primarily the Blood-Brain-Barrier [e.g., 66], inflammation [e.g., 67], vascular [e.g., 68], White Matter

[e.g., 69] and many other dynamic processing in the brain. Such models already exist [e.g.,70].

Individual traumas do not constitute a disease. The brain has multiple physiological systems that work in a complex balance that we do not understand fully. There are processes that can promote or delay the spread of infection. Processes that include the Blood-Brain-Barrier [e.g., 66], inflammation [e.g., 67], vascular [e.g., 68], White Matter [e.g., 69] and many other dynamic processing in the brain. Combing such process together in a unified framework already exist [e.g.,70]. The brain is complex and science is nowhere close to understanding its mechanics. Shortchanging science in order to get to a quick fix is demeaning to scientists and defrauds humanity. We will end up in the same position a hundred years from now.

We end with a warning that was made more than 100 years ago. Gaetano Perusini, one of the brilliant researchers working with Alois Alzheimer, offered a warning for our time. What he wrote then, in his day, could easily apply to the Framework we face today. "…[scientists] 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) [71].

Older adults have truly become a playground for a new wave of eugenics. In 2009 in France, such pharmacological conflicts of interest resulted in the guidelines for Alzheimer's disease being withdrawn by their highest court as they "contravened national law on conflicts of interests and the agency's own internal rules." [72]. Ignoring the clinical, sociological, psychological and social context of the disease in preference to the pharmacological. We deserve better from the National Institute on Aging.

Note

A= Biomarkers of Ab plaques in the cortex of the brain. Measured by injecting a radioactive material—ligand—that attaches to the plaques and then imaged using Positron-Emission Tomography-PET. Or measured by low Ab42 in the cerebrospinal fluid (CSF).

T= Biomarkers of fibrillar tau. Measured by injecting a radioactive material—ligand—that attaches to the tau and then imaged using Positron-Emission Tomography-PET. Or measured by elevated phosphorylated tau (P-tau) in the cerebrospinal fluid (CSF).

N=Biomarkers of neurodegeneration or neuronal injury. Measured by elevated phosphorylated tau (P-tau) in the cerebrospinal fluid (CSF). Measuring metabolism in the brain by injecting Fluorodeoxyglucose (FDG) which is a radioactive chemical that is taken up by cells as if it is glucose and then measuring activity with Positron-Emission Tomography-PET. Hypometabolism is not defined. In additional the measure include atrophy as measured by Magnetic Resonance Imaging (MRI). Atrophy is not defined.

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