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Editorial

The Mobius Circle of Alzheimer Research

Jack C. de la Torre*

Professor of Psychology (Adjunct), University of Texas, Austin, Texas 78712, USA

Corresponding author

de la Torre JC, Professor of Psychology, Department of Psychology, University of Texas, Austin, Texas 78712, USA, Tel: 760-703-0585; Fax: 623-876-5378; E-mail: jcdelatorre@comcast.net

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Abstract

The amyloid cascade hypothesis or Abeta hypothesis for short, has dominated Alzheimer's disease (AD) research for over two decades. This hypothesis argues that the excessive overproduction of Abeta peptide is responsible for causing the neurodegenerative and cognitive pathology seen in AD due to the excessive formation of amyloid-containing plaques in the brain. The Abeta hypothesis further extrapolates that Interventions aimed at reducing Abeta burden in the brain would be expected to alleviate both the neuropathological deposits and the cognitive deterioration of AD. However, several dozen human clinical trials using immunotherapies against Abeta plaques have failed to either slow down, reverse or otherwise alter the clinical course of this diementia. One clinical trial achieved complete amyloid plaque removal from the brains of patients with AD, but progressive neurodgeneration and cognitive loss was not prevented or alleviated. In view of the overwhelming evidence against the Abeta hypothesis and the critical need to help patients from developing AD, it is proposed that prevention of vascular risk factors to AD will significantly lower the growing prevalence of this disorder. A brief plan for the prevention of AD is outlined.

Corrections in science are not only inevitable but necessary. Scientific progrees can not be made when a bad theory is allowed to fester endlessly. Most scientists are aware that their vision of a problem can be shaped by their assumptions. When the facts do not fit the theory, it is time to move on, not hang-on to uncooperative facts by inventing other worthless facts that spiral into the original mistaken conclusion. Alzheimer's disease (AD) is a disorder characterized by progressive cognitive deterioration, brain amyloid plaques, neurofibrillary tangles, and marked neuronal loss. Two types of AD are recognized, sporadic AD which affects about 95% of all cases reported and familial AD (FAD), an early-onset form affecting about 5% of all cases. AD research in the United States and many other parts of the world, has symbolically involved a process that obediently follows the twisted pathway of a Mobius strip, forming a one-sided circle. Like the Mobius strip, Alzheimer research has largely conformed to a limited boundary which due to its one-sided surface, allows no room for different pathways or topological growth. By now, it should strike most scientists working in the field of Alzheimer research and to millions of people not yet diagnosed with Alzheimer dementia, as singularly baffling that a trackless progress has been documented in the last 100 years to prevent, reverse or otherwise alter the course or prognosis of this disorder. This glacial clinical progress is all the more shocking in view that over 85,000 scientific papers have been published on the topic of AD in the last 20 years. Although there are probably countless petty reasons for the lack of clinical progress in a disorder that was originally described in 1907 [1], the main reason, in our judgment, is the overriding direction, dominant stranglehold and empirical commitment of a single research line that has generated literally tens of thousands of studies to the point where pragmatic intervention and patient well-being have significantly been neutralized.

That main research line that has created the Mobius strip into a self-serving merry-go-round for the past two decades is the amyloid cascade hypothesis or Abeta hypothesis for short. This hypothesis states that the overproduction of amyloid beta peptide (Abeta) is responsible for causing AD through the deposition of amyloid-containing plaques in the brain [2]. More than 20,000 papers published on AD in the last two decades deal mainly with the biochemistry and genetics of Abeta, often using a variety of transgenic mice models made to over-express amyloid deposition to simulate early-onset AD. Despite the robust amyloid deposition observed in the transgenic mice over-expressing human amyloid precursor protein and presenilins, no neuronal loss is reported [3].

The Abeta hypothesis is primarily based on three linked assumptions, briefly stated: (1) early-onset or familial Alzheimer's disease (FAD) is driven by genetic missense mutations of the amyloid precursor protein (APP) and of presenilins (PS1 and PS2) in chromosomes 1, 14, and 21 which generate excessive production of $Abeta_{42,}$ a presumed toxic peptide that causes FAD; (2) by extrapolation, the abnormal process responsible for the overprduction of amyloid beta in FAD mimics the pathophysiology of the non-genetic form and consequently causes sporadic AD; (3) clearance or abolishment of such amyloid beta-containing plaques in Alzheimer brain will improve cognition and favorably alter the neurodegenerative progression of this disease [4]. This

syllogistic argument leans on its major premise that FAD is caused by toxic Abeta accumulation, which even if one accepts as valid, and this is debatable, [3,5-7] it does not follow that the genetic and non-genetic forms of AD express the same pathology since they don't share the aberrant genes supposedly responsible for FAD. Without such evidence, the major premise that the genetic cause of AD is also the cause of sporadic AD, would not appear to provide the needed degree of support for that conclusion and instead introduces an error in deductive reasoning. It is curious consequently, that although FAD accounts for less than 2% of all cases of AD, most basic research in AD uses rodent models expressing the human-mutated APP found in FAD. This important point can be stated another way. The notion that FAD and sporadic AD share the same pathologic cause, first asserts that gene mutations in chromosomes 1,14 and 21 produce excess amyloid brain deposits which cause FAD dementia.

Basically, if the Abeta argument is to make any sense, the dementia that develops in sporadic AD should also show the same gene mutations because without such mutations there would be no FAD. However, there is no evidence that gene mutations are involved in sporadic AD. If only this much information were available to describe the Abeta hypothesis, it would have been enough for most investigators to turn away from this proposal in search of other research opportunities. However, this paradox was put on hold as several pharmaceutical companies expressed a financial interest in mining the Abeta hypothesis, prompting many investigators to hang on and study the problem deeper. Since the Abeta promoters knew that no gene mutations of chromosomes 1,14 and 21 have ever been found in sporadic AD, they concluded, with pharmaceutical help, that the excess formation of Abeta must be due to other sources, the gist of which form the basis for over 20,000 scientific papers in the last two decades. Collectively, these papers have yet to pin down the exact pathologic process involved in sporadic AD.

Since it is axiomatic that most scientists with an intellectual or financial stake in a theory tend to ignore the facts that may undercut their views, it is not surprising that the Abeta hypothesis has survived this long. To survive, the Abeta hypothesis has creatively morphed into a 9-headed Hydra whose heads, like the mythical monster, can regrow after being cut-off. Thus, each time sharp evidence cuts off one of its heads, the monster hypothesis survives by quickly growing another head. In this fashion, the Abeta hypothesis may lose lots of heads in the long run but continues to grow replacement heads as quickly as they are severed.

At this point, the reader may ponder as to why make such a big deal about who is right or wrong in following this or that research line. If this counter-argument to the Abeta hypothesis were about selling bubble gum or men's perfume, unconcern might be understandable. Unfortunately, the topic of AD and its possible cause, or treatment, or its prevention, is primarily about people's health and well-being. As such, the dreadful misery AD causes the afflicted and the hardships that fall on its care-takers, should energize scientists and clinicians to seek interventions that will significantly reduce or ideally eliminate this formidable disorder. The clinical evidence in support of the Abeta hypothesis is dismally weak. One factor which strenghtens or weakens any theory is the amount of verifiable evidence available to support it [8]. Often, positive animal experimentation is sufficient to warrant human clinical trials after which it can be determined whether the experimental intervention is safe and effective. The dictum that scientific theories can be made or broken by experimentation is a well-known adage in research. Experimentation using the scientific method *requires the elimination of a hypothesis* if experiments or clinical trials repeatedly contradict its hypothetical predictions. This axiom has been defied by the Abeta hypothesis repeatedly. After an avalanche of scientific papers and several dozen clinical trials that resulted in zero advantage to patients at risk or those carrying an AD diagnosis, it is fair to question the credibility of the Abeta hypotheisis. For example, the Abeta hypothesis predicted that reducing or clearing amyloid beta-containing plaques from AD brains should improve cognitive function and slow down or arrest the progressive pathologic process. Repeated clinical trials showed neither prediction occurred. These clinical trials included active and passive Abeta immunotherapies of such drugs as Neurochem's AlzheMed [tramiprosate], Myriad Genetics's flurizan [tarenflurbil], Elan's AN-1792 and 301, Pfizer's bapineuzimab and Lilly's solanezumab [9-13].

In one trial using Elan's AN1792, immunisation with $Abeta_{42}$ resulted in virtually complete amyloid plaque removal in patients with Alzheimer's disease, but despite this, progressive neurodgeneration was not prevented or alleviated [9]. In another trial, bapineuzimab was retested in AD patients and after 78 weeks, no significant differences in the rate of cognitive decline were found when compared to placebo-treated controls. Nearly 10% of bapineuzimab-treated patients developed vasogenic edema during the trial. Thus, these trials not only failed to improve cognition or alter neurodegenerative progression of AD but some of these studies had to be stopped because patients taking the anti-Abeta treatments developed severe adverse events [14]. One major concern about the Abeta hypothesis is the design of clinical trials to address answers rather than assumptions and as such, evidence is gathered to prove these answers or justify their failure. This is antithetical to the scientific process. Nevertheless, some investigators dismiss the idea that repeated clinical failures that have tested the Abeta hypothesis should not be taken seriously until an extra 5 years of retesting anti-Abeta therapy is performed and in the event that clinical failures continue, the testers should then "re-organize their mindset" [15]. This mindset has not yet affected the pharmaceutical technocrats and investigators involved in the clinical design of these trials. The tactic after each negative trial included a scramble to offer possible reasons for the failure followed by the resetting of new trials using either identical or me-too copies of the anti-Abeta treatments. The pharmaceuticals involved in this deception are, to paraphrase H.L. Mencken, swathing the ugly facts in bandages of soft illusion.

Thus, the continued re-invention of these anti-Abeta compounds are presently being retested on other AD patients in several on-going trials. Why do these pharmaceuticals persist in clinically re-testing the same failed concept over and over again and expecting a different result? In the case of the Abeta hypothesis, the answer is, money. Pharmaceutical industry executives have learned the calculus of profit and made that their

corporate mantra while in the process, any groundings of human decency or concern for human suffering have been side-stepped or ignored.

Curiously, the pharmaceuticals involved in these anti-Abeta treatments claim they spend hundreds of millions of dollars as an investment to target a multi-billion dollar industry. However, the facts are these: 1) A number of studies have indicated that substantial Abeta burden can be found in cognitively intact older people even though the plaque and tangle distribution, density and topographical progression of these 'hallmark' deposits is the same as that seen in symptomatic AD patients [16-20]. 2) Two neuroimaging studies have confirmed that the amount of plaque deposition in cognitively normal and AD brain is similar In a large community-based necropsy study of elderly patients' brains aged 70-103 years, 33% of normal, non-demented individuals showed similar Abeta plaque densities and deposition as those with AD [21]. More recently, a second study showed that 33-65 % of cognitively normal persons who underwent (11)C-Pittsburgh Compound B (PiB) scans (a technique that detects Abeta brain deposits) had similar high PiB binding as patients diagnosed with AD [22]. 3) Abeta plaque formation in AD brain is a downstream pathologic event [23], a finding which explains why significant Abeta brain accumulation does not appear to be associated with worse cognitive function [24]. 4) Virtual clearing of amyloid plaques from human brain with anti-Abeta immunization does not prevent progressive neurodegeneration or the advancing cognitive loss typical of AD [9]. Thus, amyloid deposition, does not correlate with the neurodegenerative process that includes neuronal, synaptic and metabolic loss, nor to the severity of dementia, and its pharmacotherapeutic elimination from brain does not improve any of the features that characterize AD. The clinical evidence thus far has revealed that the cause of AD by Abeta overproduction in the brain has not been demonstrated. It is clear that a paradigm shift is needed to remove the cobwebs that the Abeta hypothesis has created over the years to stifle Alzheimer research progress. What would a paradigm shift bring about? There is now considerable evidence that several dozen vascular risk factors to AD substantially reduce cerebral perfusion and pose a strategic target for the prevention of AD [25-32]. Some of these preventable vascular risk factors to AD include cardiovascular disease, dyslipidemia, atherosclerosis, hypertension, and cerebrovascular disorders which primarily afflict the elderly population [33,34,35]. These vascular risk factors are readily detected by routine laboratory tests at the primary care level and when found positive, can be referred to AD specialists for early treatment and follow-up for long-term changes.

If the onset of AD is to be significantly prevented or controlled, early identification and detection of offending risk factors in both healthy and mildly symptomatic individuals followed by a plan of application for appropiate intervention or management is imperative [36]. Identification, detection and treatment of vascular risk factors to AD will also ensure their control and prevention. This approach will not only result in a better health outlook for the patient but also significantly lower the growing prevalence of this mind-shattering disorder.

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