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Perspective

Scientific Truth or False Hope? Understanding Alzheimer's Disease from an Aging Perspective

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Abstract. In this paper, we argue that the current official definition for Alzheimer's disease is misleading, since it defines senile dementia (SD), a long-known incurable senile/geriatric condition, as a discrete/curable disease. This overly optimistic definition was incepted in the 1970s amid the public's fear of the upcoming SD crisis and desperate hope for a cure. Scientifically, however, it has overturned Alois Alzheimer's age-based concept for disease classification—the essence of modern Geriatric Medicine and the National Institute of Aging. Thus, the current definition for SD, though socially and politically appealing, would be scientifically flawed. As an authoritative study guideline, it has caused profound and far-reaching confusions in research by misleading attention to the presumptive pathogenic/erroneous factors as drug targets for "silver bullets". Such well-intentioned studies would generate numerous data, but render SD a scientific and logical enigma. In this context we discuss: 1) why and how senile conditions including SD differ from discrete diseases by origin, thus also by study paradigm and intervention strategy; 2) why senile conditions may not be explained by abnormal/pathogenic factors, but logically should be explained by "normal" elements in life, perhaps advanced aging plus risk factors; and 3) why the "amyloid-β toxicity" controversy, a simple scientific issue, has lasted for so long. Finally, we ask: can scientific inquiry preserve its integrity and objectivity under social pressure? It appears that these fundamental questions warrant serious attention if the scientific nature of SD is to be eventually understood.
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INTRODUCTION

Alzheimer's disease (AD) is a devastating illness which victimizes families and devours social resources, thereby constituting an unprecedented threat to the healthcare systems of modern society. As an important medical and socio-economic subject, it has been intensively studied for over three decades. During this period, many state-of-the-art technologies have been employed and numerous research advances claimed, however, its pathogenic cause has remained mysterious [1, 2], rendering AD a startling scientific puzzle of the century. It is thus critical for researchers to keep an open mind to the basic and long-held assump-

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tions that have been taken for granted. Over the last decade, one of us has revisited some of these assumptions on the basis of scientific principles and has raised questions about them in a series of theoretical papers [3–5]. In this paper, we continue this theoretical inquiry to seek the scientific truth of the disease by first taking a closer look at its inception.

SENILE DEMENTIA OR "AD"? THE NAME MATTERS

The term "Alzheimer's disease" was originally used for a 51-year-old female dementia patient reported by Alois Alzheimer in 1906. Her symptoms and pathology were found to be similar to those of senile dementia (SD, characterized by plaques and tangles) or senility, a long-known incurable condition. However, because of the patient's unusually young age, the medical community believed that the case could not be explained by senility so warranting a new name. Thus, it became known as AD or presenile dementia (PSD), a name that defined it as a discrete/curable disease but completely distinct from SD by age [6, 7] (i.e., AD/PSD $\neq$ SD).

Although some discussion lingered on (Alzheimer himself was sometimes unsure about the classification) [7], this definition was generally accepted by the medical community worldwide for the following 70 years, during which only PSD, not SD, was coined by Alzheimer's name. Thus, a medical dictionary at the time typically defined AD as "a rare disease in which there is mental deterioration similar to senility, but the disease occurs in middle age" [8]. Unfortunately, many historic accounts today overly emphasize Alzheimer's descriptions of plaques or tangles, but do not explain the inception of PSD, an age-based terminology.

However, this age-based definition was abandoned in the 1970s, because some scientists argued that AD/PSD and SD should be redefined as "a single disease" based on their "similar symptoms and pathology" [9]. In other words, they believed that disease classification should not be based on patient's age, but solely on symptoms and pathological features (i.e., plaques and tangles). This would mean that Alzheimer and his colleagues were wrong and that SD, too, is a discrete/curable disease, i.e., AD/PSD = SD. By offering such an optimistic and scientist-supported perception to a desperate illness, the new definition has been enthusiastically and almost universally received, especially in Western society, and has become an authoritative guideline for research in government initiatives [9–11]. As such, "AD" has been inconspicuously transformed from a rare disease into a social pandemic.

But, is it correct, scientifically? Why have the two opposing concepts, AD/PSD $\neq$ SD and AD/PSD = SD, both been accepted worldwide (albeit at different times)? This amazing puzzle has never been clarified, and thus may be the root cause for many controversies today (Fig. 1).

For example, according to the new definition, PSD = SD, the two medical entities would share a common pathogenic cause. However, 35 years later, while such a cause for PSD has been essentially found (in the form of three mutant genes) [1], the cause for SD has remained totally elusive. This unexpected outcome thus alerts us that PSD and SD may not be a "single disease", after all, and would call into question the theoretical basis for modern AD research.

TWO FAMILIES OF HUMAN DISEASES DIVIDED BY AGE

Indeed, why did Alzheimer and his colleagues distinguish PSD from SD – two very similar conditions with only a few years of age difference – as distinct medical entities in the first place? More profoundly, should disease classification be based on symptoms and pathology only, or patient's age first?

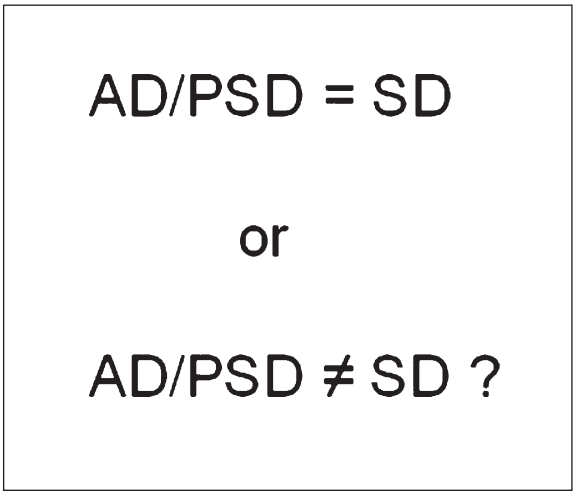

Fig. 1. An amazing conceptual puzzle of the century. The two opposing concepts, one by Alzheimer and his colleagues, the other by current policymakers, are however both widely accepted by the world (albeit in different times), thereby making it perhaps the most intriguing conceptual puzzle of the century. It is also the starting point of many controversies today. Can it be resolved?

Table 1
Two families of human diseases divided by age

	Discrete diseases	Senile/Geriatric conditions
Example	AIDS, polio, Down's, ALS, prion's, presenile hearing and vision loss, PSD	Senile hearing/vision loss, muscle atrophy, atherosclerosis, osteoporosis, Parkinson's, SD
Occurrence	Any age, mostly <age 60	>age 60, fully age-penetrating
Origin	Pathogenic or erroneous factor (single)	Advanced aging exacerbated by risk factors (multiple)
Prevalence	Usually rare or low	High, up to >50% of elderly
Analogy	Car accident or breakdown	Eventual failure of very old car or parts
Study paradigm	Find and inhibit the pathogenic factor	Extending organs' lifespan by protecting them and targeting risk factors
Goal	Cure or eradication	Delay or prevent to a certain extent

We know that conditions occurring in old age can differ from other, discrete diseases. For example, hearing loss in the elderly differs from a similar condition in the young – even though they share similar symptoms and pathology – because one is a result of aging, while the other is a discrete/curable disease that must be caused by a pathogenic/erroneous factor (e.g., pathogens, mutant genes, and toxins). Similarly, vision loss, atherosclerosis, and osteoporosis are also discrete diseases when occurring in the young, but are senile conditions when affecting the elderly.

Thus, human diseases can be divided into two basic families by age (Table 1). Using an analogy, discrete diseases can be likened to car accidents/breakdowns: unpredictable in nature, caused by a mechanical/human error, and fixable, whereas senile conditions would be like the eventual failure of old cars: predictable, multifactorial, and irreversible, but which can be delayed.

Perhaps it was this common sense notion that allowed Alois Alzheimer and his colleagues to unambiguously distinguish PSD from SD and the medical community worldwide to accept it for 70 years. Can this concept be obsolete today? It is not only valid but also the essence for the establishment of modern Geriatric Medicine and the National Institute of Aging (NIA) [7, 12]. Thus, as a rule, human diseases are first categorized by age, and then sub-classified by symptoms and pathology. This rule has perhaps been taken for granted for so long that it has been forgotten, thus allowing the current definition for AD, socially and politically appealing, but scientifically flawed, to emerge.

It is well-known today that discrete diseases are caused by intrinsic or extrinsic pathogenic agents (usually a single one in each case), which lead to symptoms through a linear, cause-effect mechanism (i.e., necessary and sufficient), thus are curable by targeting the single culprit (Fig. 2). This doctrine, ever since Pasteur and Koch's era, has been guiding medical science to brilliant victories over the last century. At the same time, "diseases are caused by pathogenic factors" has become a law of medicine.

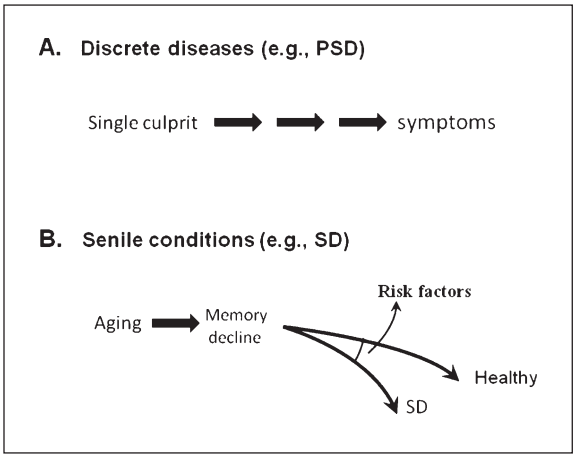

Fig. 2. How the two disease families differ by origin. A) Discrete diseases are caused by (usually single) pathogenic factors, which lead to symptoms through a linear and cause-effect mechanism. B) Senile conditions such as SD start in normal aging, which can be accelerated to excess in some elderly, but not in others. Thus aging can end up in various results. Since the only reason that are known to separate "healthy" from "SD" are risk factors, we consider them important.

However, that law may need to be revisited today, since something Pasteur and Koch did not see has happened. Partly as a result of medical progress, people live much older and so senile conditions have increased exponentially. These conditions differ from discrete diseases by origin, thus also by prevalence, study paradigm, and intervention strategy (Fig. 2 and Table 1). For this reason, medical researchers may not

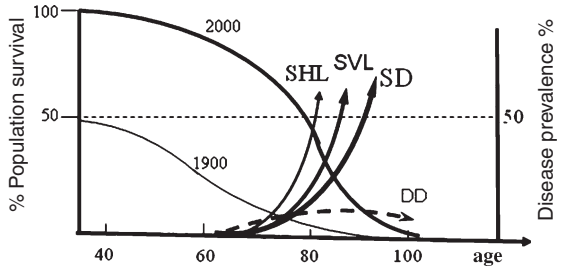

Fig. 3. Fully age-penetration distinguishes senile conditions from discrete diseases. Senile conditions, such as severe hearing loss (SHL), severe vision loss (SVL) or SD, are fully age-penetrating (surpassing the 50% landmark) [12]. This feature definitively distinguishes them from discrete diseases (DD), which are usually in low prevalence. Note that the prolonged life expectancy (1900 versus 2000) results in a dramatic increase of old population and senile conditions.

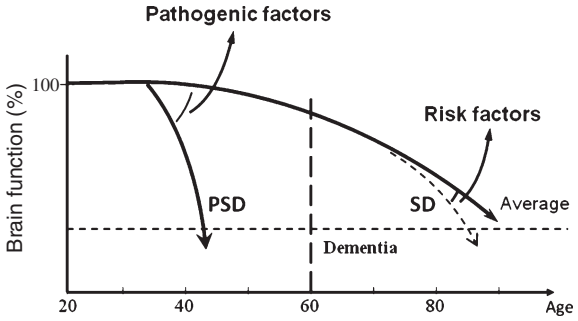

Fig. 4. Why PSD differs from SD by origin. A pathogenic factor must exist to divert, abruptly and decisively, the middle-aged brain to PSD. But, risk factors can suffice to accelerate, slowly and insidiously, the oldest brain into SD – usually a few years ahead of the healthy average. These two types of etiologies are distinguished by patient's age, thus if the keyword *senile* is removed from the disease name, they would be easily confused.

always attribute diseases to pathogenic factors anymore, but must first ask: how old is the patient? The watershed between the two types of disease is commonly thought to occur at age 60 or 65 [12]. Though not absolutely accurate, this borderline must be drawn since it is of considerable guiding value for research and correct in most cases.

For example, by this borderline, SD would differ fundamentally from a group of the so-called "neurodegenerative diseases", such as Huntington's, ALS, Prion disease, and Down's symptoms, even though they share some similarities (Table 1).

Another defining feature of senile conditions is that they are fully age-penetrating, i.e., their prevalence can surpass the 50% landmark in the elderly after a certain age (Fig. 3). This feature can distinguish senile conditions from some discrete diseases that affect elderly, such as AIDS, pneumonia, and even age-related cancers. Such cancers increase with age, but are not fully age-penetrating, and never surpass 50%, indicating that the role of aging is different in them. Thus, senile conditions are not equal to "age-related" diseases, which can be likened to an "accident in an old car".

Whatever disease one studies, the first question always is: what class does it belong to (i.e., is it a genetic, infectious, or senile)? Science starts from classification and strides from a sharp one, but wanders from a fuzzy one.

"ADVANCED AGING PLUS RISK FACTORS" BEST EXPLAIN SD

It should be pointed out that the two defining features, >age 60 and >50%, do not just mean a quantitative trait, they also imply a qualitative or fundamental difference in the medical nature of senile conditions. Because they can affect the majority of elderly, senile conditions may no longer be considered *abnormal/disease* in their common sense (i.e., exceptions from the majority norm) since they have become a statistical *norm* in the elderly and, as such, cannot be explained by abnormal/pathogenic agents. Thus, logically, they would have to be explained by factors that can occur in the majority of the elderly, or "normal" factors. This consideration, therefore, calls for a fundamentally new model for SD.

This new model may also be reached by asking two basic questions. First, what is the root cause of SD? It is well known that the rapid increase of SD in recent years is the result of a demographic change – the elderly used to live to age 60 or 70, but today 80 or 90. Thus, the "extra years" gained in life expectancy, an extraordinary achievement in modern society, is also the root cause for SD. Therefore, *advanced aging* is the first and necessary element in our model (i.e., no aging, no SD).

The second question is: why can many other elderly remain healthy at the same old age? This fact has been taken to suggest that aging is not a critical factor and dementia must be caused by a pathogenic factor [13]. However, while this view is correct for PSD because a middle-age disease must occur by this mechanism (Table 1 and Fig. 4), it is however a conceptual mistake for SD.

The reason is that SD occurs at *advanced age*. At this life stage brain cells are so frail that they are vulnerable to any negative influences, such as a lack of physical and brain exercises, unhealthy diets, social

isolation, and certain genotypes. Though they matter little for the young, these risk factors can accelerate the death of the oldest cells—in the absence of *bona fide* pathogenic factors (Fig. 4). This risk factors-centered model for old cell death, while contrasting to current views, is similar to how mild bone loss is accelerated into clinical osteoporosis, or mild atherosclerosis into heart attack.

Indeed, these risk factors are the only factors found to separate healthy and SD elderly in most cases, so they must also be included in any model for SD. Thus, put together we propose that *advanced aging plus risk factors* best explain most SD cases [4].

This model emphasizes several key points. First and foremost, as stated above, a statistically normal condition should be logically explained by factors that can occur in the majority of the elderly. For a long time, the official guideline has led us to believe that the central question in SD is: which pathogenic factors (e.g., plaques, tangles, or other "erroneous" factors) cause cell death, and how do they do so [13]? This question stems from a "disease" perspective. But, from an aging perspective, the correct central question should be: what factors accelerate brain aging (with its associated plaques, tangles, and other age-related changes) to excess? The latter question leads to our model.

Second, SD is perhaps the most desperate disease in social impact, but not a "disease" in medical nature. If prolonged life expectancy is the root cause, then SD intervention should aim to extend the lifespan of the brain. In addition to targeting lifestyles, this goal may also be achieved by energizing and protecting old neurons with physiological stimulators and functional activators [4, 21]. A recent example is the use of physiological products to protect old bone cells from osteoporosis [22]. This "new" strategy for intervention should be emphasized in SD, as it contrasts with those which aim to "inhibit" various "pathogenic" processes as in discrete diseases (Table 1).

Third, our model may explain why pre-symptomatic predictions of SD by biochemical tests or neuroimaging have not succeeded after so many studies [14]. The multifactorial nature of SD clearly indicates that any meaningful predictions for future SD would have to take into consideration numerous risk-enhancing factors. Some of which can be as subtle as spouse survivorship, psychological status or social connections, yet can play critical roles in SD nonetheless [15–17].

Is there a "causal factor" for SD? The answer may be implicated in current knowledge. The fact that aging is the greatest risk factor for SD implies that probably no other factors can contribute to SD more than aging itself. Also, from its multifactorial nature, it can be inferred that there may not be any single factor that is decisively responsible for most SD cases.

A dreadful disease does not have a cause? This is not anybody's hope, but is true. What causes an old car's death? Generally it is aging, but strictly speaking, aging is not sufficient (some cars can function at the same old age). So, it does not have a necessary and sufficient factor, i.e., a cause. It is a probability that can be influenced by many factors [3].

As a matter of fact, an increasing number of investigators have realized today that aging and risk factors should be the primary targets for study and intervention in SD [18–21]. However, such studies will not produce major progress in society unless a change in public awareness and research funding priorities is made.

CONCEPTUAL DILEMMAS TODAY

Since it has departed from common sense, the current definition for AD would inevitably fall into logical paradoxes. For example, as a discrete disease—defined by symptoms and pathology only—"AD" would not belong to the NIA, but in actuality it is a centerpiece there – defined by age. This double-dealing game has rendered "AD" a dual-faced sphinx: its SD face for social recognition and funding, and the PSD face for claiming research breakthroughs (e.g., mutant genes and mutant-based animal models). This is why after so many "dramatic research advances" claimed [2], SD can remain a persistent enigma.

What if senile hearing loss is redefined as "a single disease" with *presenile* cases? The public, drug makers, media and researchers would be overly thrilled, since the causes underlying presenile cases (mutations, pathogens, toxin, injury, etc.) would now also explain senile cases, incurable no more! Policymakers would take credit, but senile cases would fall into enigma, perhaps forever.

Ever since SD was defined as a "disease", it must have been justified by a causal factor. Under this pressure, plaques and tangles would have to be studied as such, despite their universal existence in the elderly though with varying quantity and density, not unlike gray hair and wrinkled skin. Thus, this definition has misled research at its starting point by directing most attention to the presumptive causal factors as drug targets for silver bullets. Such well-intentioned studies would generate numerous exciting data, some of which

are of significant scientific values, but off-target to the origins of SD.

It may be argued that, whatever its name or definition is, as long as scientific methods are used and data are collected and interpreted by scientific rules, the scientific truth of SD would be found in the end.

Or will it? What will happen to a driver who, with high skills and experience, uses a quality car and follows the traffic rules faithfully – but is only guided by a wrong roadmap?

TODAY'S "AD" HAS MISPLACED ALOIS ALZHEIMER IN HISTORY

Alois Alzheimer made his discovery by distinguishing a new type of disease from the existing one. Thus, lumping them together in one entity today would not only deny his discovery, but also misplace him in history.

Let's say, you found a new species of Orchids and it was named after you, "XY flower", a great honor. But then some said that this and an existing Orchid were "a single species". Did you still have a discovery? Further, if it was not a new species, then the flower would have simply remained as Orchid and the case would have been closed. But what happened next was really bizarre: while denying your discovery, they miraculously abandoned the long-existing name, Orchid, and replaced it by your name, "XY flower"! Is this still an honor to you?

What will people think in the future when they are puzzled: Orchid has been known for thousands of years, but why is it named after XY, who lived only one hundred years ago and mistook the flower he found as a new species?

Or, did someone use Alois Alzheimer's name for their own purpose? The tricky name change, a seemingly semantic matter, has allowed them to push through a fantastic idea, PSD = SD, meaning that a 51-year-old can suffer from a *senile* condition and defying the essence of Geriatric Medicine and the NIA itself.

Or, perhaps what they really dislike is *senile*, a key word that correctly defines the medical nature of SD. Unfortunately, the word has been mistaken to mean inevitability and hopelessness [2, 13]. But it is well-known today that, although aging is inevitable, the pace of brain aging is fully modifiable by various ways [15–17]. Notably, a 5-year delay in onset age will reduce the number of the SD victims by half, so the significance of delay should not be underestimated.

SHOULD SCIENTIFIC INQUIRY SUCCUMB TO SOCIAL PRESSURE?

It has been feared that if AD is an aging problem, then everyone will eventually get it if they live long enough. How can this grim fate be accepted?

Modern SD research is driven by fear, yet the fear may be exaggerated. Although every radio in the old car will eventually die, there are always some radios that will outlast the lifespan of the car. So SD, or any other senile conditions, will not victimize everyone.

It should be pointed out, however, that a profound problem arises here; that is, the fear has infiltrated into scientific reasoning and subtly altered the study goal. What should the primary study goal be, "find truth first", or "find cure" whatsoever [2, 13]? These are different starting points for reasoning and so will lead to different data interpretations and conclusions.

This is reminiscent of the study field of evolution, where scientific data are interpreted differently under distinct guidelines: Darwinism or Intelligent Design. Neither side can convince the other because one pursues scientific truth, while the other wants to fulfill a predetermined ideological conviction.

Is there, then, an objective means for data interpretation in science? Perhaps, science does not accept any predetermined beliefs that are not testable/falsifiable. But this proves difficult to be accepted by all.

Indeed, how can SD research not have a predetermined belief? If a cure is not found, then it will bankrupt the governments and disable society! How can we stay indifferent to the suffering of millions and settle for delaying just a few years instead of looking for its eradication? After all, "find cure" has long been the predetermined goal in the research of many diseases like AIDS and SARS and has led to glorious victories. What is wrong with it?

Perhaps by such emotions, a result of confusing two disease families, the current definition of AD is so deeply rooted that it inhibits scholarly debates and self-correcting mechanisms of science. But it must be noted that "find truth" and "find cure" are two distinct research areas. The former, science, a free and truth-seeking inquiry with unpredictable outcomes, must be conducted independent of any social influences for its integrity and objectivity. The latter, application, will be governed by the nature of the truth: to cure or to delay.

Our view for SD, a curiosity-driven one, is open-ended and falsifiable – if only a causative factor is found. But the current definition for AD may not be – there seems no way to falsify it. Even if no causative factor is found in next 100 years, the belief of a cure

can still guide research thanks to its popularity and political correctness.

WHY CONTROVERSIES ON "AMYLOID-β TOXICITY" MAY NEVER BE SETTLED

Under the current guideline, simple issues can become overly complicated, e.g., "is amyoid-β toxic?" As a scientific issue it should have been resolved long ago, yet in reality it has lingered on for over 20 years after enormous amount of resources consumed. Why? Because the two camps disagree. To the "non-toxic" camp, the answer is obvious and conclusive because many healthy elderly also display plenty of amyloid-β plaques [23, 24]. However, the "toxic" camp relies mainly on a different set of data showing that amyloid-β causes cell death in culture [1].

Such a discrepancy is common in science and perhaps resolvable by asking, for example: which set of data is more relevant, the *in vivo* or *in vitro* one, when they are contradictory? The answer should be clear as we know that any substance, even water or salt, can be made "toxic" in the cell culture if it is not in the stringent physiological range. For this reason, any *in vitro* data must be interpreted with caution and be validated by *in vivo* observations. Thus, the *in vitro* assays do not carry the same weight as, let alone replace, the *in vivo* observations if they contradict each other.

However, this view may be too naïve as it has only considered science but overlooked the tremendous social implications behind the issue. A "non-toxic" answer would mean no quick cure, that is, the hopelessness of modern science to a human disease. This would be viewed as an irresponsible and unacceptable attitude of a scientist since so many once-incurable diseases have been cured.

In sharp contrast, a "toxic" answer would immediately imply that a silver bullet is around the corner, a huge and desperately-needed relief for the public. After all, it seems to be a reasonable and expected answer by modern science that is armed with state-of-the-art technologies and unprecedented public support. It also seems to be the responsibility of the scientists who always try to find a cure regardless what disease.

Such emotions, arisen mainly by confusing science and application, have been subtly modifying the definition of "toxin", thereby rendering it a never-ending controversy. Of intrigue is the attitude of policymakers in the debates. As the "toxic amyloid-β" provides the strongest support to the current definition of AD, they have ignored the essence of the debates and kept a delicate "neutral" position in the process. This has allowed the "toxic" camp to expand exponentially (amyloid-β is a short peptide and readily available, everyone can test it and claim an "Alzheimer study").

Thus, under the current consensus-based science evaluation system, the claims of "toxic amyloid-β", either in the form of plaques or soluble amyloid-β (which exists in all brains) would be "established" with subsequent publications exploding in number and appearing in prestigious journals and mass media.

But, will they convince the medical community as a whole? Perhaps not, because the few *in vivo* observations have yet to be explained. Why? Because science is *reason*, not just data collection or majority referendum.

Recall that the Ptolemy's dogma (the earth as the center of the universe) used to be supported by a million pieces of evidence (all stars appeared to rotate around us). But why was it overturned? Because Copernicus noted that it did not explain a few additional observations (some planets can stop, reverse or make a circle in their orbits).

So, in science, *a few* sometimes can outweigh *millions*. More interestingly, what happened to those million pieces of evidence today? They are still there, valid – but support another theory. Yes, the same set of data can support different theories – by different interpretations and extrapolations under different ideologies.

FINAL REMARKS

Ever since it was redefined as AD, the study of SD has no longer been a pure scientific project, but a government/policymaker-initiated and overly optimistic social agenda that must be accomplished by science. As such scientific reasoning would have to twist itself between the mandatory agenda and uncompromising scientific laws. The result is a persistent enigma – one in which "dramatic research advances" are made, exciting policymakers, the public, drug makers, and scientists alike, but of little relevance to the medical nature of SD. Examples are mutant genes and "toxic amyloid-β", two areas that have attracted at least 90% of research funding. Despite our warning, such studies are likely to continue into the future for increased social burdens of SD and for status quo. So the enigma will deepen.

SD is an unprecedented socio-economic and scientific subject for mankind. It forces us to reconsider several fundamental questions, e.g., what is the medical nature of senile conditions, why they can affect

the majority of elderly, what is the real meaning of "normal" and "abnormal" events in aging, and also, should science keep its objectivity under the pressing social demands for its translation? These questions should warrant serious attention by the medical community, especially by the policymakers and leading AD researchers, who have been avoiding such issues we raised 10 years ago [3, 25–28].

Finally, how can the two opposing concepts be both widely accepted (Fig. 1)? The secret is: they are both correct, albeit one scientifically, the other politically. Several long-lasting controversies in SD are also more a reflection of ideology and culture than of science [6, 7], and thus may not be resolved by science alone. Perhaps a more profound ideological complex lies in the ever-lasting fantasies of mankind: "the fountain of youth" and "eternal lifespan". They will stay with us forever, continue to influence scientific reasoning and, finally, test the self-correcting mechanisms of science.

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Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=681).

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