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ALZHEIMER MOVEMENT RE-EXAMINED 25 YEARS LATER: IS IT A "DISEASE" OR A SENILE CONDITION IN MEDICAL NATURE?

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1. ABSTRACT

Dementia in the elderly used to be rare, but why has it become a major social threat today? There can be many potential answers, but an ultimate one is clear: the longer life expectancy today. This knowledge indicates that "advanced aging" is a primary suspect in the origin of senile dementia. If so, then why can many elderly remain healthy at the same old age? We know, for example, that elderly people commonly have a certain degree of atherosclerosis and osteoporosis, but only some of them develop severe clinical symptoms at the same age. These different outcomes generally can be explained by "risk factors" in life (exercise, diet, individual background, etc). It thus appears to be a general pattern that advanced aging (after age 80) will set the stage for various senile disorders, but risk factors largely determine the onset age as well as individual specificity of their clinical manifestations. In this context, senile disorders including senile dementia would differ fundamentally from the pathogen-caused conventional diseases (AIDS, polio, cancer, Down's, etc.) by origin, incidence, and intervention strategy. This view would call into question the current definition of senile dementia as a conventional "disease" (Alzheimer's). The term "Alzheimer's disease" originally referred to "midlife" dementia, but it is defined today to be the same medical entity as senile dementia on the basis that they both display the same hallmarks and symptoms despite their onset age difference. Now, after in-depth scrutiny, we finally come to realize that they are not the same disease, but as different as heart failure at midlife versus the "same" failure at advanced age (i.e., a conventional disease versus a senile condition). Thus, by eliminating the age difference, the new definition has converted a senile condition into a conventional "disease", thereby changing the course of its scientific inquiry to miss the main targets. This may be why after extensive studies for 25 years, the origin of senile dementia has remained an enigma.

2. INTRODUCTION

Alzheimer's disease (AD) is characterized by amyloid plaques and neurofibrillary tangles (1, 2). These histological lesions are widely thought to be caused by pathogenic factors (i.e., gene mutations, metabolic errors in protein trafficking, or post-translational modifications, etc.) and they, in turn, lead to cell death in the AD brain (2-5). However, following this concept and after intensive studies for decades, the common pathological cause of late-onset sporadic AD has remained obscure (6). This contrasts sharply to many other human diseases where it usually takes a few years for the causes to be found (so current studies are mostly on intervention methods)(7).

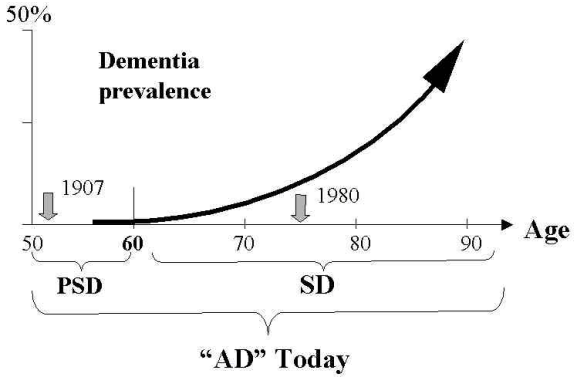

Figure 1. Prevalence of dementia as a function of age. PSD affects only a few patients, but SD is a social threat today (the U.S. government data; ref. 6). Other senile disorders also display similar patterns. Two small arrows denote the average life expectancy at the Dr. Alzheimer's time and now.

This puzzle has prompted us to undertake a comprehensive and step-by-step analysis of research data including our own (8), together with the general features of AD. This theoretical work has led us to conclude that plaques and tangles are the results of metabolic inefficiency, a *natural* and *necessary* event during aging (9-15). This finding implies that AD would need to be explained by factors more profound than plaques and tangles. Accordingly, we have further deduced that *advanced aging* intensified by *risk factors* most likely underlie late-onset sporadic AD (16, 17). The essence of this view coincides with those proposed by other investigators from different research perspectives (18-22). However, as this model confronts current concepts about AD, it has provoked a heated debate about the medical nature of the disease (23-26). Because this debate centers on the definition of AD, we have therefore traced this definition to its inception and now found that it may be an initial problem.

3. AD WAS ORIGINALLY DEFINED BY DISTINGUISHING IT FROM SENILE DEMENTIA

AD was first described by Dr. Alois Alzheimer in 1907 based on his study of a patient who suffered from dementia in her 50s and died at age 56. Her postmortem brain exhibited two prominent histological lesions: amyloid plaques and neurofibrillary tangles, which Dr. Alzheimer took as diagnostic markers for the disease (18, 21).

It was also well-known at the time that people older than age 60 could develop similar dementia with similar histological markers. That condition was known as "senile dementia" (SD). As the name implied, it was considered a senility-related condition at old age, but not a discrete disease in its common sense (i.e., pathogens-caused).

Could the two conditions be the same medical entity? Dr. Alois Alzheimer believed that although the disease he found was similar to senile dementia in pathologies and symptoms, it also differed significantly from the latter by the *unusually younger age* of the patient. So he considered the disorder he had found to be a new disease (18, 21 and references therein).

This view was found convincing after a briefly debate in the medical community. Apparently, senility could not explain dementia at middle age. So this newly identified disease was coined by his name, Alzheimer's disease, and was also called "pre-senile dementia" (PSD), a name that emphasizes its major distinction to SD: *the age difference*. Thus, for most of the century, AD was defined as "a rare disease in which there is mental deterioration similar to senility, but the disease occurs in middle age" (27). The question of whether PSD and SD were the same or different diseases was not important in Dr. Alzheimer's time, because both of them were rare.

But since then the world has changed dramatically. One of most profound changes is that human life expectancy substantially extended. As a result, SD, among many other *senile* conditions, has increased sharply to become a major threat to the modern society. At the same time, however, the disease discovered by Dr. Alois Alzheimer, or PSD as defined, remains rare in the midlife people (Figure 1) and there is no evidence that such cases will increase in the future.

Because SD, but not PSD, has become a major social threat, a world-wide war has been declared to control it. Since Dr. Alzheimer made his discovery mainly by distinguishing PSD from SD, one would expect that this war would be declared upon SD as the main target. But in reality, Dr. Alzheimer's name became the focus. Why?

4. A NEW DEFINITION FOR SENILE DEMENTIA SINCE 1970s

This is because, in the 1970s, several leading investigators suggested a new definition for SD. They believed that because PSD and SD exhibit the same symptoms and same hallmarks, they should be redefined as the same disease regardless of age difference. Therefore, the war against SD should take Dr. Alzheimer's name since he used plaques and tangles as the hallmarks of the disease. This occurred despite the fact that dementia in the elderly had been documented long before Dr. Alzheimer's time (18, 21, 25).

This new definition does have several advantages. The social threat of SD in the 1970s was growing but unfamiliar to the general public, so it was important to arouse the attention of society at large. In this regard, the term "senile dementia", which carries a connotation of irreversibility, was not as appealing as that of "disease". The latter term implies that it belongs in the ranks of many other conventional diseases (AIDS, cancer, polio, tuberculosis, epilepsy, Down's syndrome, etc.). Since these diseases are all caused by pathogenic factors (i.e., infectious agents, genetic defects, metabolic mistakes, environmental toxins, etc.)(7), one would naturally assume AD to be also caused by a similar pathogen(s) and that this pathogen, once found, would be quickly blocked, as have been elegantly proven in many other diseases. Thus, the

Alzheimer movement has very successfully aroused public awareness and attracted an explosion of research attentions.

Scientifically, defining AD as a new "plaque/ tangle-related" medical entity would distinguish it from some other types of dementia. By focusing on the unique markers that characterize the neurodegenerative process, the new definition would exclude other, mostly known, diseases such as cerebrovascular disorders or mechanical injury as primary causes, thus defining AD as a *mysterious* disorder warranting a target-focused study (1, 2). In this regard, the new definition represents an advance in the disease classification.

Perhaps because of these advantages, together with the caution that pathogens cannot be ruled out from AD without thorough studies, the new definition has been quickly accepted almost universally and constitutes the scientific basis for much of the modern research. Indeed, during the 25 years of investigation, several conventional pathogenic factors have been positively implicated of which the most important one is autosomal dominant gene mutations (3-5). However, it is also known that these mutations are confined to early-onset familial AD, thus mostly PSD, but not SD (late-onset and sporadic). Since the socially threatening disease is the latter, not the former, this would bring an old question to the frontline.

5. IS IT ALWAYS CORRECT TO DEFINE DISEASES BY PATHOLOGIES ONLY, NOT PATIENT'S AGE?

Defining diseases based on their pathologies and symptoms but not on the patient's age, is indeed a commonplace because many diseases, for example, AIDS, leukemia, pneumonia and influenza, can strike people at any age. Regardless of the patient's age, these diseases usually originate from the same pathogens and affect the same cells/organs through similar destructive pathways, and their prevention and treatment strategies are also similar. So there is no doubt that they are the same diseases no matter what age of the patients they affect (7).

But, is it also correct to define other diseases in this way? To address this question, we have with great caution undertaken a review of medical literature. This review reveals, unexpectedly, that there is another group of human diseases that may warrant our special attention.

Take for instance, rare gene mutations on LDL receptors can cause *juvenile-onset* atherosclerosis (7). Although its pathologies and symptoms are similar to those of *senile* atherosclerosis, it is now known that the latter cases are mostly not caused by gene mutations, but rather, a result of *aging*.

Another example is cataracts (lens protein deposit), common in the elderly, but which in rare cases can also affect *juveniles*. The latter form has been attributed to congenital/genetic defects, but the former has not (7). Additional examples are also known: vision or hearing loss, arthritics, Parkinson's disease, hypertension and others. These diseases mostly affect the elderly but also have their juvenile/midlife counterparts in rare cases. In general, the latter forms have mostly been linked to inherited factors or other severe insults, whereas the former cases have not (7, 28) and their incidences also increase exponentially as age advances, similar to SD (Figure 1).

These examples indicate that changes originating for different reasons can end up in the *same* pathologies and *same* symptoms in many human diseases. But their etiologies, as well as the biochemical pathways by which the pathologies are developed, are quite different. So generally speaking, if a disorder occurs in juvenile or middle-aged persons, it must be caused by an invading or inherited pathogen(s), because our organs will not fail without such an insult *at this time.* However, if the "same" condition occurs in *very old* persons, the causation may be quite different. As *onset age* is a defining point for distinguishing these conditions, ignoring age difference would conceivably lead to confusions in the search of their respective origins. For example, had senile and juvenile atherosclerosis been defined as the "same disease", it would have confined the study of senile atherosclerosis to perhaps congenital factors only. Thus, correct definition is critical for understanding these diseases.

6. SENILE DEMENTIA DIFFERS FROM PRE-SENILE DEMENTIA BY MEDICAL NATURE

This consideration would call into question the new definition for PSD and SD. If they are the same disease, then why have conventional pathogens been linked mostly to PSD, but not to SD? Through a systematic comparison of various human diseases, we have noticed that they can be considered in two general groups: "conventional diseases" (AIDS, cancer, epilepsy, Down's, etc.) which are caused by conventional pathogenic factors, and "senile disorders" (senile atherosclerosis, senile osteoporosis, cataracts, muscle atrophy, etc.) in which an age-dependent deterioration plays a primary role. Although they both may involve similar social impact (human suffering, care cost, family burden, etc.) and the general public therefore calls them same diseases, it is important for medical researchers to note that they differ by *medical nature* (origin, incidence, intervention strategy, etc.)(16, 17). In this context, we think that PSD should belong in the former group, but SD the latter. Now, further considerations below seem to strengthen this view.

Conceptually, if dementia occurs before age 60 (PSD), we can infer that it should involve a severe pathogen/mistake, because the brain, like other organs, cannot fail without such an insult at a time when most people are normal. The prevalence of PSD is very low (<1%; Figure 1), suggesting that it is an "accident" in nature (like car accident), as is the case of most conventional diseases such as heart failure at midlife. Their low prevalence is not a coincidence, but because the probability that our body and its defense systems are overtaken by a pathogen/mistake should be low. Therefore, conventional diseases usually occur in a small percentage of population. Notably, this is the main reason we call them "diseases"; i.e., exceptions from majority/normality.

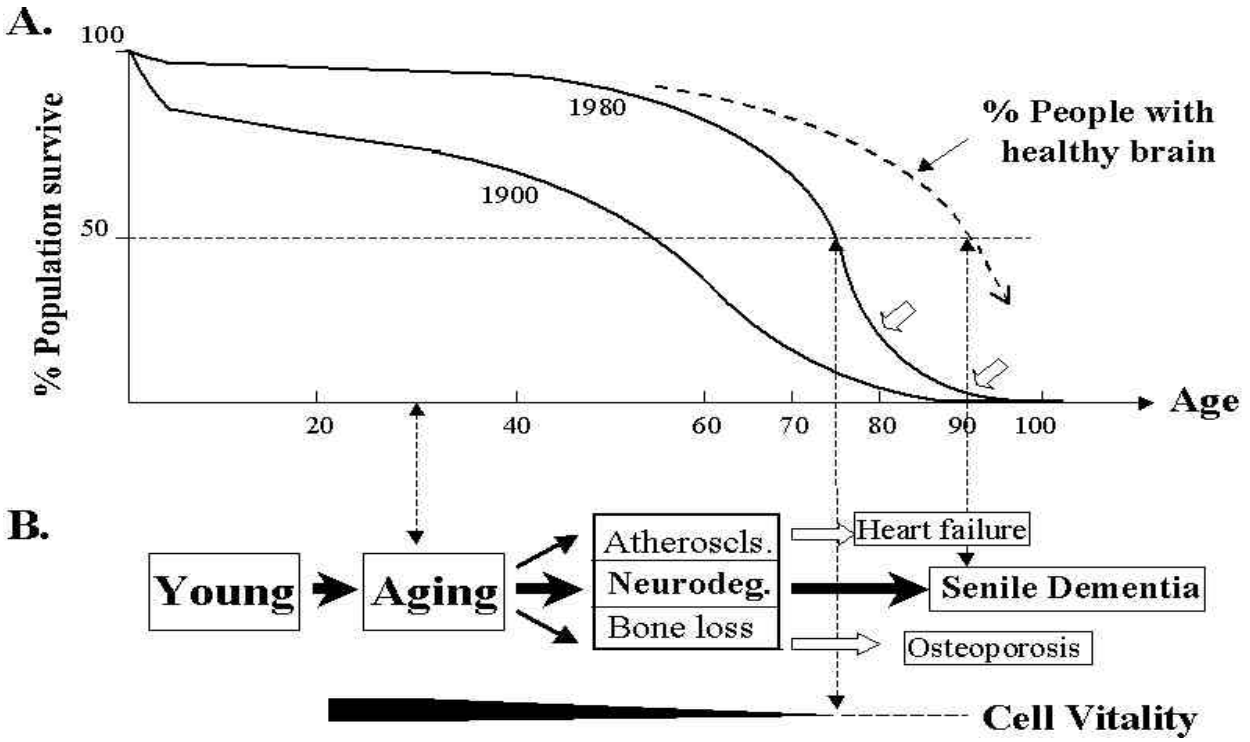

Figure 2. Life expectancy changes today in comparison with the states of the brain. **A.** A dramatic increase in the aging population particularly in the >70 age group in the U.S. today (data from ref. 30). Note the average life expectancy today is 75 years but the average brain lifespan is about 90 years (the brain curve is deduced from the data in Fig. 1). **B**. We propose that aging progressively diminishes the vitality of all organs, leading to their eventual failures at advanced stages, but the brain lasts longer.

But SD is quite different. The most striking feature is that its prevalence has reached 30-40% by age 80 and surpassed 50% by age 85 (29) or 90 (6). When tragedy affects the *majority* of people at a certain age, as is the case of other senile illnesses, it may not be an "accident" anymore, nor a "disease" in its common sense. Rather, it may be taken as an "expected" or "normal" event (in terms of its medical nature, not social impact; like heart failure at advanced age, or eventual death of the car). Evidently, a "normal" event may not be attributed to an "accident" (pathogen) as its *common* cause (Table 1). We hope that this point could draw the attention of the investigators.

But, it has been a law of medicine that pathogens cause diseases and, thus, a disease must have a pathogen(s). Following this concept, numerous human diseases have been understood. But now, how can the devastating SD, in some cases, not be caused by pathogens? To address this difficult question, we first consider the life expectancy changes over time.

In the long human history, people were mostly dead before age 60 (Figure 2A, curve 1900) due in large part to widespread pathogens/diseases. But now, many deadly diseases are under control so the average life expectancy is much longer, and most human deaths today occur within a narrow range of ages 70 to 80 (curve 1980).

Are these deaths also caused by pathogens/ diseases? While some of them certainly are, many others may not. These other deaths are usually triggered by such minor factors as a cold, a fall, or even emotional fluctuations. If these factors are considered "pathological causes" for the deaths, then why do they not cause the death of *young* people? This suggests that many human deaths today may not be fully explained without taking into consideration a new factor; that is, their *advanced age*.

We, therefore, would favor a traditional explanation. During the long aging process, the rate of basic metabolisms will slowly reduce ("wear and tear" theory)(29) and this will diminish the livability of vital organs (heart, lung, liver, etc.). This may not be a problem in its early stages, but if it progresses into an "advanced" stage, then these organs would become so weak that the boundary between life and death can blur (Figure 2B). Under this circumstance, minor factors which may not be important at other life stages can push them over the brink, in much the same as the last straw is to an overburdened camel. In other words, advanced aging has quietly become a *primary* culprit in many vital organ failures today.

If advanced aging can overtake the lives of vital organs, then it should do the same to non-vital ones because these organs function by the same basic mechanisms of life (Kreb cycle, ATP genesis, signal transduction, etc.)(Figure 2B). Human life expectancy is determined by the states of the vital organs, but hearing, vision, higher cognitive function of the brain are not vital for life (they determine the quality of life). Now, if the lifespan of the former organs has been extended but that of the latter has not in the same period, then what will

Table 1. Basic differences between PSD and SD

Feature	Pre-Senile Dementia (< age 60) (early-onset AD)	Senile Dementia (> age 70-80) (late-onset sporadic AD)
Documentation	First by Dr. Alois Alzheimer	Known since ancient time
Victim/symptm.	Middle aged; abrupt	In longevity; continuous and progressive
Prevalence	Rare	From common to majority as age advances
Social impact	Minor; stable	Enormous; rapidly increasing
Future trend	Decrease by medical progress	Increase due to longer life expectancy
Origin	Inherent or invading pathogens	Age-related metabolic decline to extreme
Association	Minor with other factors	Strongly influenced by many risk factors
Classification	Conventional disease, like heart failure at midlife	Senile condition, like heart failure at advanced age
Intervention strategy	Inhibiting or correcting the erroneous factors	Re-activating the inefficient basic metabolisms and avoiding risk factors
Research goal	Cure or eliminate	Postpone to a certain extent

happen? Expectedly, there will be an exponential increase in the rates of dementia (Figure 2A), osteoporosis, hearing and vision loss, Parkinson's disease, and many other senile disorders in the oldest-old people today (28).

7. "ADVANCED AGING PLUS RISK FACTORS" CAN EXPLAIN MOST SENILE DEMENTIA

This reasoning would point to *advanced aging* as a primary culprit in the origin of SD. This outcome came as a surprise to ourselves at first, but it may be a logical conclusion if we ask: SD used to be rare, but why has it become a major social threat today? There can be many potential answers, but an ultimate one is clear: the elderly used to live to ages 60s or 70s, but today, many of them live to their 80s or 90s. If this knowledge is used as a starting point for reasoning, then advanced aging would be an indisputable primary culprit in SD.

However, this common view was abandoned long ago, mainly because it did not explain why many elderly can remain perfectly healthy at the same old age. If this puzzle is not solved, then it would seem necessary to assume a pathogenic factor(s) in additional to aging to explain the individual specificity of SD (24, 25, 31).

But, comparison of SD with other senile conditions may suggest an alternative explanation. For instance, our heart will eventually fail as a consequence of aging, but why can some people live to age 100 whereas others die in the 80s? Also, the elderly commonly have a certain degree of bone loss, but why do only some of them develop severe osteoporosis?

While some of these cases do involve pathogens, we also know that, in most elderly patients, these are primarily due to the influences of the "risk factors" in life (exercise, diet preference, alcoholism, individual background, etc.)(28). Hence, although it is correct to assume a factor additional to aging to explain the different outcomes in the elderly individuals, this factor may not always be a *pathogen*. Instead, it seems to be a general pattern that advanced aging will predispose the elderly to various senile disorders, but risk factors largely determine the *onset age* as well as *individual specificity* of their clinical manifestations.

On the basis of this and other analyses (10-17), we conclude that *advanced aging* plus *risk factors* — but not conventional pathogens — may underlie most SD cases. This SD (also known as "senile dementia of Alzheimer type" or late-onset sporadic AD) typically starts at about age 80 in high prevalence as its primary feature. It progresses very slowly but generally through three stages: normal → mild cognitive impairment (MCI) → dementia. It is clinically diagnosed mainly by excluding apparent causes and it is the only type of dementia that threats the society today and will in the future, but its origins remain a mystery (Table 1)(1, 28, 32).

This model for SD may also be compared to the mechanisms of some other peculiar disorders. For example, modern lifestyle is known to be generally responsible for the widespread presence of obesity, diabetes, midlife atherosclerosis and other so-called "luxury" diseases — despite the fact that not everyone is affected under the same living conditions (this may also be explained by risk factors and their non-"cause-effect", but *probabilistic*, nature)(7, 16). Together, these modern disorders may impact our traditional perception of human diseases.

As this model is a departure from current concepts in the SD study field, it will naturally be met with skepticism and alternative views. Here we examine some of the challenging views to it. For example, it is a popular belief today that even if our brain can die by natural course, this should occur only after age 120, because healthy individuals of that age do exist. If our brain can last that long, then most SD cases today (around age 80) would be considered a typical disease (24, 25, 31).

It should be emphasized that healthy centenarians are an exception rather than representative of the general population. The SD rate has surpassed the 50% landmark by age 90 in the population (6, 29). This means that our brain, like other organs, will not last forever, but the current lifespan of the brain in the general population is about 90 years on average. This lifespan is about 15 years longer than that of vital organs (average life expectancy is about 75 years in the U.S. today). These numbers dictate that most people will not develop SD in real life, but those who live beyond age 80 will be exponentially affected (compare this to the exponential increase of vital organ failures after age 65; Figure 2A).

If our organs will eventually fail, then why is it the brain that fails first in SD patients? If old people are considered as a group, it would be obvious that any organ

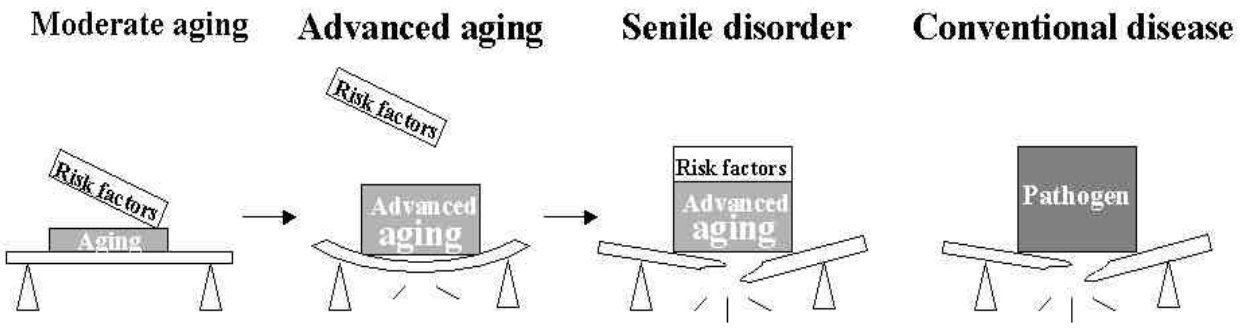

Figure 3. Advanced aging plus risk factors can explain senile disorders. At early or moderate stages, aging acts just like other risk factors. But at advanced stages, its burdens will increase dramatically (plaques, tangles, free radicals, cholesterol, DNA transcription errors all accumulated to critical levels). Under this circumstance, various risk factors which may not be harmful in young people can push cells over the brink. Thus, advanced aging plus risk factors can play a causal role, similar to conventional pathogens.

can be the first to fail (widespread senile diseases in various organs; in most people, it is vital organs that fail first). But it is we, SD researchers, who have selected a particular group of patients to focus on. Why do only certain regions of the brain fail in SD (25)? Again, many regions of the oldest-old brain (sensory, movement, cognition, etc.) are failing (hearing and vision loss, Parkinson's, SD, etc.), but certain areas will fail faster in a particular disease, like different parts of an old car which will not fail at same time. Obviously, if its *senile* feature is emphasized, then SD would be quite different from conventional diseases in the origins.

Indeed, conventional diseases will not only occur in low incidence, but also involve a *new* biochemical pathway that is independent of normal metabolisms (e.g., HIV proliferation or cancer growth). Thus, AIDS and cancer are "all-or-none" in an individual. But senile atherosclerosis, osteoporosis, and memory decline are *progressive* or *continuous* processes. Although some people develop into clinical stages but others do not, this classification is based mainly on the *quantitative* parameters (e.g., 30% vs. 70% bone loss, or minor vs. severe vessel blockage in the two cases), but not on the existence of a *new* pathway. As such, although dementia differs dramatically from forgetfulness in terms of *social impact*, such a difference may be only quantitative in *medical nature* (19).

8. ADVANCED AGING IS QUITE DIFFERENT FROM MODERATE AGING

Aging has long been recognized as a "risk factor" in SD, but this view may not accurately describe its role today. The term "risk factor" in its general sense means that it enhances the potency of pathogens to cause clinical diseases, such as smoking and alcoholism in cancers. In this case, they play only an *enhancing* or *supplementary* role, but as long as pathogens are absent, risk factors themselves will not cause clinical diseases.

But the role of aging in senile disorders may be quite different. Aging will eventually overtake the lives of all human and all living organisms. Such a decisive role is perhaps more than "risk-enhancing". Although SD affects only some elderly, its incidence *doubles* every 5 years (24, 25) from age 60 to 90 by at least 50-fold (from <1% to >50%)(Figure 1). Such a rate explosion is not seen with any other risk factors (e.g., a cancer is only a small percentage at any age). Thus, unlike other risk factors which increase the disease incidence to a *limited* extent, aging will allow SD and other senile disorders to eventually *overwhelm* the surviving population.

It thus seems useful to re-define the role of aging in SD today. Accordingly, we propose that advanced brain aging is a *necessary* but *not sufficient* condition for SD. This means that typical SD will not occur before aging has reached *advanced* stages. On the other hand, because not all elderly develop SD, advanced aging alone is not sufficient, that is, it requires a critical cooperation of additional factors to cross the clinical threshold (Figure 3). These are the *bona fide* risk factors (sedentary lifestyle, certain diets, low brain reserve, apolipoprotein genotype, depression, etc)(16).

By this view, there will be three groups of factors that can act as initial causes for human diseases and their rank order potency in general is: pathogens > advanced aging > risk factors. But the latter two, if combined, can be causal (Figure 3).

Why is it so difficult to define the role of aging in SD? Perhaps because the term "aging" generally refers to a wide range of life stages from age 30 up to over 100, but its role at each stage is different. In the early stages (e.g., ages 50-60), aging may act just like other risk factors to enhance the potency of pathogens (e.g., in PSD and other midlife disorders). But as aging advances to the 8^{th} or 9^{th} decade, its burden will dramatically increase to become a *primary contributor* to senile disorders. In this regard, it must be noted that the meaning of "aging" and "elderly" has substantially changed today from that of only a few decades ago. Thus, while SD before 1950s may be due mainly to pathogens (most patients were in ages 60s or 70s), this may not be the case anymore for the "same" SD today since many more patients are in their 80s or 90s (Figure 1). Therefore, brain conditions developed during these *extra* years of longevity are perhaps a *new* study area we face. We hope that this point could also draw the attention of the investigators.

No matter how much technology has advanced nor which specific issues one chooses as study foci, investigation of a disease usually starts by asking the first question: to which known category does the disease in question belong, or is it an infectious, inherited, or senile disease? If a disorder can be grouped into the *senile* class, its study will take as a role model the many other senile conditions. This classification is usually made on the basis of the common knowledge of medicine, but if it is influenced by other factors (such as social impact), the consequences can be far-reaching.

For all these reasons, we think that the traditional term of *senile dementia* is, in its essence, scientifically sound. Thus defined, its primary study areas would be *aging* itself (18-22, 33-35) especially at its *advanced* stages and age-dependent *natural* changes in a particular metabolic pathway (cognition) as well as the cumulative effects of risk factors on it. Interestingly, after intensive studies for decades, it has been "rediscovered" that "AD" does exist in two distinctive forms: early-onset and late-onset, corresponding to PSD and SD (Table 1), known essentially at Dr. Alois Alzheimer's time.

9. CONFUSIONS CAUSED BY THE NEW DEFINITION

This consideration implies that redefining SD as a "disease" but ignoring its uniqueness to conventional diseases and sometimes even calling it "independent of aging" (24, 25) may be an initial mistake. By eliminating the age difference, the new definition would artificially "convert" a senile condition into a conventional disease. This definition was initially proposed as one of scientific opinions, but once it became an authoritative government guideline for research funding (18, 21), most scientists would have no choice but to use it as the starting point for reasoning. As a result, studies on the aging process *per se* would give way to "pathogen-hunting", and this has profoundly changed the course of scientific inquiry to miss the main targets.

In other words, "AD" by original definition is a rare disease but not a social threat, whereas SD, due to its high prevalence, is a severe social threat but not a conventional disease in medical nature. However, when the two medical entities are mixed in one, a hybrid monster, "a socially threatening *disease*", is created. Consequently, many experimental studies would tackle its "AD"-related mutant genes or other prominent insults, but these studies would be expected to relieve the social impact that is actually associated to sporadic SD. As discussed below, such studies may lead to questionable outcomes.

9.1. Studying mutant genes will not resolve the SD puzzle

Today, most early-onset familial AD cases (PSD) have been successfully linked to autosomal dominant gene mutations (in presenilins or β-amyloid precursor protein genes). Perhaps because of this success and the new definition of "SD = PSD", enormous research efforts have been devoted to these rare cases (3-5). Will such studies lead to the discovery of the cause for *sporadic* SD?

As mentioned, rare gene mutations on LDL receptors, glucokinase, or hemoglobin can also cause early-onset familial atherosclerosis, diabetes and sickle-cell anemia, respectively (7, 36). But why can these gene mutations give rise to the same pathologies and symptoms of their *sporadic* counterparts?

This is because LDL receptor gene mutations reduce the LDL-binding ability of the receptors and cause insufficient degradation of cholesterol leading to its deposition, an end result that will also occur in normal aging. Glucokinase gene mutations reduce the phosphorylation ability of the kinase, thereby reducing the normal catabolism of glucose, a result that sporadic diabetes/aging will also give rise to. Likewise, sickle-cell mutations disrupt the hemoglobin's normal structures, whereas sporadic anemia is due to iron deficiency, but they both reduce the normal function of hemoglobin (because hemoglobin carries O_2 through iron)(7, 36).

These best known examples clearly indicate that gene mutations cause familial diseases through *different* pathways from those in their senile/sporadic counterparts, but they can end up with the *same hallmarks* (15). Thus, although studying LDL mutations has found an important pathway leading to cholesterol deposits in familial/juvenile atherosclerosis, such studies will not unravel the reason why and how *senile cholesterol plaques* are formed. The latter reason should exist only in *the aged*, thus will not be found by studying *young* people. In reality, it was the studies of the sporadic diseases that have led to the understanding of the roles of mutant genes in their familial counterparts, not *vice versa* (7, 36).

It is thus clear that although studying mutant presenilins and mutant β-amyloid precursor protein will reveal important pathways leading to amyloid plaques in familial AD, such studies will not uncover why and how *senile plaques* are formed in most SD patients. Although gene mutations, head injury, and trisomy in Down's can lead to similar amyloid plaques, we know that there is only one reason for *senile plaque* formation in most elderly, and that is *normal aging* (15). We hope that this point could also draw the attention of the investigators (it will also raise questions about the use of mutant gene-based animal models for treating SD; will sick-cell mutant gene-based animal models represent sporadic anemia?).

9.2. Plaques and tangles are harmful, but not pathogens

Plaques and tangles are initially used as *diagnostic* markers (1, 2), but today they are widely considered the *cause* for cell death, plaques in particular (3-5, 37). This has been the subject of lengthy controversy (38-40). Here we consider it from a purely theoretical viewpoint.

Amyloid protein starts to accumulate at around age 50, but SD typically strikes after ages 70-80. So, if it is amyloid that kills cells, then it is taking 20-30 years for it to do so. And even by age 80, most people are healthy. This indicates that the effect of amyloid is so mild that it can only increase the *probability* of cell death to a certain degree even after three decades of action. Clearly, this knowledge should have served as the basis for interpretation and extrapolation

of the *in vitro* data, but *not vice versa*. However, many studies have reported that amyloid directly cause rapid cell death (within days, even hours). If these data are interpreted as the effects in the brain (3, 5, 37 and references therein), then amyloid would be as "toxic" as *bona fide* pathogens such as HIV, arsenic, or mercury. But if this is the case, then we would face a difficult dilemma: How can most elderly remain healthy after having carried this "pathogen" for decades?

Amyloid plaques, due to their proximity to neurons, are expected to have negative effects to cells similar to many other aging markers (tangles, lipofuscins, enlarged vacuoles, cataracts, cholesterol, etc.). Although they are negative and eventually *harmful*, such an action is quite different from *toxic*, a term that describes the *acute* and *outright* killing ability of classic pathogens. Thus, ignoring the "semantic" difference between the two actions would mix SD with conventional diseases.

Plaques and tangles are the prominent lesions in SD patients, but also exist in essentially all elderly, even in some old animals. So we think that they are the results of insufficient degradation of proteins, a natural event during aging, similar to the cholesterol or gallstone depositions (15). As such, they would be neither the cause nor the result of cell death, but are intimately *accompanying* the neurodegenerative process, in much the same way as cholesterol plaques accompanying, but not triggering vascular degeneration. Although plaques and tangles are deposited at a faster rate and thus are more abundant in SD patients than in the age-matched controls, this can be generally explained by *risk factors* in life, again similar to the faster cholesterol and gallstone depositions in some people.

It may be argued that although cholesterol and gallstones are not directly toxic, they can still cause severe diseases when overly deposited, so amyloid may do the same in the brain when it is overly deposited (37). While such roles of cholesterol and gallstones are clearly seen in the *abrupt onset* of the diseases they underlie (7), no similar acute symptom, however, is seen in the progressive and insidious SD. (This may be because cholesterol and gallstones can obstruct circulation systems, but neuritic plaques and tangles may not)

Even if overly deposited plaques eventually kill cells, it will take several *extra* years/decades for them to reach this stage. Thus, this concept is, in essence, the same as saying that *advanced aging* is a primary culprit. Evidently, during this long period, not only amyloid but also other age-dependent lesions (metabolic decline, ion imbalance, free radicals, etc.) will all reach critical levels thus contribute to cell death (especially the invisible effects of risk factors). Hence, unlike AIDS study which can be largely reduced to "HIV study", the SD study may not be reduced solely to "amyloid study", although we all eagerly hope that a conventional pathogen can be found.

9.3. "Why do cells die?" versus "why do the oldest-old cells die?"

Examination of the dementia brains also reveals the presence of cell structural changes, severe oxidative stress, ion imbalance, DNA fragmentation, cell cycle error, and other severe damages that are absent in normally aged brains. Can these cellular damages, therefore, be taken as the culprits for cell death in SD?

In the SD brain, cells are already injured or dead, so the observed cellular damages are *expected* to present. This is because we are looking at the end result of a long process, not the initial cause. In conventional diseases, we identify the pathogenic causes by simply comparing patients with normal subjects (e.g., AIDS, pneumonia, or cancer). But in chronic senile disorders such as osteoporosis, the same comparison would reveal numerous "pathogenic errors" associated with the dying bone cells (ion imbalance, oxidative stress, etc.). But evidently, these are not the initial cause, because this cause should have occurred decades earlier, that is, at a time when the patients were *normal*. Apparently, subjects at that stage do not display any clear-cut difference compared to truly normal persons. Therefore, we need to search for *invisible* elements that can lead to severe consequences only after *decades* of action. Logically, such elements would be the risk factors.

If the invisible but critical roles of risk factors are not emphasized, then a difficult question would always persist: where do those cellular damages come from? Today, they have been almost all attributed to amyloid deposition. But as discussed above, such a traditional "cause-effect" model may not explain the *individual specificity* of SD in the elderly. Studies by Snowdon (41) and others have found that some very old people whose brains contain abundant plaques and tangles, but are perfectly healthy in cognition. Moreover, because many senile disorders in other organs also involve those cellular damages but do not have amyloid plaques, it is difficult to attribute the damages in the brain to amyloid only.

It should be pointed out that once SD is officially defined as a "disease", it would desperately need a toxin/pathogen to justify it. Under this pressure, the cellular damages, mutant genes, plaques, tangles, or other prominent lesions would have to be taken as common "pathological causes" because they fit in with the definition. Following this definition, a central question has been: "Why do cells die" (25, 31)? When the question is posed this way, the expected answer would be pathogens only. This has justified an exhaustive search of numerous pathogenic factors known to cause other diseases.

However, if it is defined as a *senile* condition, then the central question would become: "why do the *oldest-old* cells die"? Or more precisely, "why do the oldest-old cells die *slightly faster than average*"? Had it been asked this way, the answers may have been quite different.

10. SENIL DEMENTIA IS NOT HOPELESS, BUT NEEDS A NEW INTERVENTION STRATEGY

SD is a devastating social threat, and as such, one would naturally expect that finding a cure would be our only hope. However, defining SD as a senile condition does not mean that it is hopeless, but only points to a "new" intervention strategy, that is, to extend the lifespan of the brain instead of inhibiting pathogens in conventional

Table 2. Which reasoning is more reasonable?

Common Rationale	Alternative Rationale
AD is a devastating disease, a disease must have a pathogen or metabolic error	Senile diseases differ from conventional diseases by origin; distinguishing them is important
Dementia can strike at any age, so AD is "independent of aging"	This "AD" has mixed three distinct diseases: Down's, PSD and SD; distinguishing them is a key
Down's, PSD and SD all have the same amyloid plaques, so they are the same disease	But these "same" plaques have different causes: trisomy (Down's), gene mutations or other insults (PSD), and aging (SD), respectively
Vascular diseases, family inheritance, head trauma and infectious agents all can cause dementia, so AD is a "complex" of many diseases	Sporadic SD is defined and diagnosed by excluding those diseases. Its ultimate reason is known: longer life expectancy, thus its origin may not be overly complicated in concept
Only some people get it, so AD is all-or-none like AIDS; only pathogens can explain it	Memory decline is common in the elderly, but why does it progress faster in SD? Risk factors may explain most
A murder must have a killer	Are all human (or organ) deaths due to murder?
It is a fact that amyloid deposits when AD develops (so amyloid can be a killer like HIV)	It is true but not fully, also true is that amyloid deposits but most elderly are healthy (so amyloid is bad but not HIV)
If amyloid is bad, then it is toxic; if toxic, it is no different from classic pathogens	"Bad" or "toxic" can distinguish senile and conventional diseases and point to different intervention strategies
If no poison, then why do cells die?	Why will cells eventually die in a well-maintained culture?
Cells will not die without severe damages such as Ca2+ rises or apoptosis. So targeting them will prevent AD regardless of the initial causes	If so, then why can osteoporosis, muscle atrophy and heart failure be significantly postponed by taking actions and avoiding risk factors decades earlier when those damages were absent?
Aging is only a risk factor, it cannot kill cells without a pathogen	This was correct, but today's aging is different because it is much more advanced
Even if brain cells can die by natural course, that can only happen after age 120, because such healthy people do exist	Such cases are rare rather than rule. SD rate reaches ≥50% in the population by age 90, so aging may explain most SD in age 90s, many in the 80s, though only some in the 60-70s
If it is due to senility plus risk factors, then AD would be hopeless	The lifespan of many organs has been prolonged, so why not the brain?
Neuroprotective drugs and exercises have only limited effects, so they cannot be our hope	Should our goal be set by hope or by reality? Effects of current drugs can be improved by modern technology and social supports
Although SD is senility-related, one cannot rule out pathogens without thorough studies	This caution was correct. But now, 25 years later, should we also consider other possibilities?

diseases. This goal can be achieved by targeting advanced aging and risk factors.

The metabolic rate of the old brain cells will diminish partly because the life-supporting factors such as growth factors and hormones are progressively reducing as aging advances. This is also the ultimate reason for the accumulation of aging markers and damages (15). Thus, at the present time, replenishing these vital factors is perhaps the most important approach to slowing down neurodegeneration, similar to the strategies for extending the lifespan of old bones and muscles.

But growth factors and hormones have only limited protective effects today. This is mainly because when administrated through ordinary routes, they may not reach the brain (blood brain barrier) and also because of their short-term actions and side-effects (e.g., estrogen will increase the risk of breast cancer in old women). Such shortcomings would call for a revolutionary drug-delivery method to ensure brain-specific and extra long-lasting effects of the drugs. In this regard, recent studies have reported that, for example, transplanting cells carrying genes for nerve growth factor into animal brain has slowed down age-related neurodegeneration (42, 43).

Based on current knowledge, it appears that if practical obstacles can be overcome, studies along this line"cocktail" of several neurotrophic factors, rather than a single one as currently used, may be more effective. Such study areas have remained largely unexplored today and thus warrant vigorous and systematic studies. may offer a new promise for the development of more effective and safe therapies. It is also possible that a "cocktail" of several neurotrophic factors, rather than a single one as currently used, may be more effective. Such study areas have remained largely unexplored today and thus warrant vigorous and systematic studies

Furthermore, genetic engineering methods aiming at enhancing neuronal functions may also be a useful approach (44, 45). Additionally, because SD is characterized by diminished synaptic activities, there is a possibility that a group of psychostimulants which selectively stimulate synaptic transmissions in CNS (such as nicotine, caffeine, marijuana, amphetamine, etc.) may ameliorate SD symptoms to a certain extent (46). Although these drugs have adverse effects in healthy people, they are known to play positive roles in many neurological disorders when delivered through appropriate routes and at suitable doses (46-49).

A more general and important target is risk factors. Among them, perhaps the most common and important one is lifestyle, because the functional lifespan of the old brain, like that of old muscles or bones, critically depends on their usage. But unlike muscles, brain usage in

the elderly further depend on a supportive social network (50). Our aging population today has unprecedented longevity, thus equally *unprecedented* social supports are urgently needed.

Current social security systems and supportive practices (such as visiting the elderly once a year) may have taken care of them in their 60s or 70s, but these may not be enough today. Visiting our elderly (i.e., allow them to exercise the brain) as frequently as once a week or more, for instance, may be necessary for those in their 80s or 90s where social isolation is common. Special opportunities should also be provided for the elderly to exercise their oldest-old synapses through, for example, story-telling with young children, because "Snow White-type" or early-life memories are formed and lost in people together with their own names and basic living abilities. So, exercising one may also activate others. Such social supports (to list but a few) should be part of a national awareness program, because medical treatments will not be fully successful without them (41, 50-52), just as drugs alone will not prevent osteoporosis without proper exercises.

If many people's brains can remain healthy up to nearly age 90, then it is reasonable to anticipate that, with modern research and the participation of society as a whole, the average onset age of SD may be postponed to age 90 (from about 80 today). This will significantly reduce the number of the victims (compare population survival rates at age 80 vs. 90; two unfilled arrows, Figure 2A). Thus we are optimistic that such a postponement may give rise to a social relief comparable to a cure in conventional diseases.

11. CONCLUSIONS

A profound demographic change underlies the SD epidemic today. This common knowledge, however, was ignored when the disorder was defined perhaps under the pressure of arousing the public and Congress to support research. Once this definition became an official guideline for research funding,, it has changed the direction of scientific investigations. As such, several problematic rationales have dominated the research field (summarized in Table 2). Consequently, they have given rise to numerous controversies today but the mystery of SD remains unsolved. It is now very difficult to question this guideline 25 years later, but if the goal of research is to find the truth, then eventually we may have to revisit it.

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