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Review

Parting with the Concept of Alzheimer's Disease in Senium

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Abstract

The understanding of mental deterioration associated with old age has undergone several changes over the past two centuries, and has spurred major scientific debates. In the 19th century, this disorder was still considered an inevitable part of aging. The beginning of the 20th century offered a histological explanation for presenile dementia, and Alois Alzheimer was credited as the discoverer of a new disease that bears his name to date. In the last quarter of the 20th century, findings of Alois Alzheimer were applied massively to late-onset dementia as well, thereby virtually excluding natural intellectual impairment as an explanation to dementia. In contradiction to the original concept provided by Alzheimer, amyloid plaques and neurofibrillary tangles are now being considered as the cause of psychological depreciation at all ages, and the presence of these is interpreted as a disease.

The present review is aimed at disputing these common views and suggests that continuing with this approach may prove to be increasingly counterproductive.

Instead, the present review offers an unbiased view without any preconceived ideas, which considers a long list of natural biological failures that inevitably accompany every human life, such as micro-injuries, microinfarcts, leukoaraiosis, as a consequence of partial failing of the

cerebral blood flow, microbleeds, glycemic fluctuations in diabetics, influences of alcohol and toxins, decreasing anisotropy, increasing mean diffusivity on MRIs, and others.

Keywords
Cognition; Alzheimer´s disease; dementia; senile; aging brain; criticism; amyloid; neurofibrillary tangles; executive functions

1. Introduction

More than a century has gone with a tradition considering two histological issues, namely, extracellular amyloid plaques and the intracellular neurofibrillary tangles, as the causes for the development of dementia. In the present review, we intend to demonstrate that the aforementioned concept, when applied to large numbers of elderly people, not only deviated from the original idea of the eponym but has been surpassed by the latest discoveries, and that the continued reliance on certain particular degenerative diseases (nosological units) for inducing dementia would become increasingly counterproductive. The deposits of amyloid and the degeneration of the intracellular filaments found in the brains of older people are appealing targets to be held responsible for the frequent, or even ubiquitous, age-related decrease in their mental abilities, a decline in agility and wit, or a demolition of psychological life. This concept is, however, being eroded by numerous findings revealing other aging processes, which occur inevitably during the general disintegration of the brain as it ages. Additionally, several semantic inaccuracies complicate the agreement on the processes of senium.

2. Inaccuracies in Terminology

The cases of Alzheimer´s disease (AD) that are not explicable by the familiar genetic provenience are designated as sporadic. Contradictory to the literal meaning of the word “sporadic”, such cases are much more common in comparison to the cases with a genetic link, and despite their “sporadicity”, their increasing numbers are presented as an epidemic that threatens the world. Similar confusion prevails in relation to the word dementia. While the exact definition of the word “dementia” should be restricted to those stages of mental derangement in which the victim is unable to perform his/her day-to-day personal necessities, the majority of the authors use the term to represent the process of degradation from complete psychological integrity to a complete permanent dysfunction. Besides, the word “dementia”, which is basically just a complex of symptoms, is being misused by referring as a “disease”.

In addition, there are numerous discrepant uses of the term “cognition”. The original meaning of “cognition” was derived from the Latin root “scire”, which means “to know”, and from “cognoscere”, which means “to recognize”; therefore, the term should represent a perceptive process. However, many authors use the term “cognition” as a synonym for almost every mental function. Most of the authors include memory, language, as well as executive functions under the list of cognitive functions. However, memory should not be listed as a cognitive function, because it is a unique phenomenon of mental retention of a perception that has already ceased to exist,

and therefore, memory is a prerequisite for cognition allowing the comparison of a new perception with a previously retained perception preserved in the form of memory traces.

Similarly, executive functions do not represent a subcategory of cognition; they should be considered the final element of the intellectual performance [perception → cogitation → execution]. It is also problematic to list language, along with its variety of specific mental operations, under cognitive functions. While understanding language is, without doubt, a cognitive achievement (i.e., comparing a new sound with previously retained sound imprints), talking represents a separate function. The process of formulating an answer, along with its components such as the active recall of words from the memory, the addition of a proper grammatical and meaningful construction to the selected words, and securing a proper motor-proprioceptive execution, belongs to the category of executive functions.

3. Confusion Regarding Disease versus Aging: A Historical Perspective

The semantics of defining the conventional diseases in contradistinction to aging is another area where misunderstandings occur. The primary suspect for the cause of senile dementia (SD) is advanced aging. Senile disorders differ fundamentally from conventional diseases such as AIDS, polio, cancer, Down´s syndrome, etc., in terms of their origin, incidence, and intervention strategy [1]. In the textbooks of physiology, aging is usually described as not being a disease or a disease process.

On the other hand, aging is notoriously accompanied by functional failures, which at a younger age would be referred to as diseases. While osteoarthritis in the young would elicit concerns of a disease, in the old age it is considered just a natural occurrence. While an osteoporotic fracture of a vertebra at a young age is an obvious sign of a disease, its occurrence, and prevalence in the elderly is unremarkable. Claude Bernard once stated, “Life is in the same time death of the organic substance, which means that a cell cannot survive otherwise as to proceed permanently toward death.”

According to Chen, conventional diseases occur only in a small percentage of the population, and are, therefore, considered exceptions to the norm. However, this is not the case with senile dementia. Since its prevalence among people aged 85 or 90 years is greater than 50% of the total population, it should no longer be considered an accident, nor should it be considered a disease; it rather should be an expected event [1]. With the commencement of aging, metabolic prosperity begins to reduce, which becomes apparent in decreased peripheral nerve conduction, diminished renal and pulmonary capacity, reduced muscle strength, presbycusis, presbyopia, and several other such conditions.

In the process of life, all individuals accumulate damages caused by a variety of factors (the wear and tear theory). Alzheimer was aware of this fact and noted that there was no behavioral difference between the early-onset and late-onset Alzheimer´s dementia. His hesitation was apparent in his article of 1912, in which he stated, “The question, therefore, arises as to whether the cases of disease which I considered peculiar, are sufficiently different clinically or histologically for being distinguished from senile dementia or whether they should be included under that rubric” [2]. Moreover, Gaetano Perusini, Alzheimer´s pupil who played a role in popularizing the cases of presenile dementia, was aware of quite similar changes in the senile cases as well, which he stated in the following manner: “Fibrillary changes, which, in regard to morphology and localization, are

identical with those which I have described, are also sporadically found in old men [3].” In his polemic with Alzheimer, Oskar Fischer quoted Alzheimer´s disagreement with the idea, that “Sphaerotrichia (Fischer´s name for plaques) represents the essence of a particular, clinically characterizable image.” He further quoted Alzheimer: “The next question is now whether the druses (geode; drusen-shaped growth; consisting of filamentous material; plaques), or as Fischer referred to them, Sphaerotrichia could be considered the cause of a completely specific, classifiable, and clinically diagnosable psychosis. Some cases of an unequivocal Dementia senilis, in which the druses are not many in number, have been identified. Furthermore, it has been observed that in locations with no presence of druses in the cortex, there is the occurrence of dispersed known senile changes, such as sclerotic-fatty-pigmented distorted ganglionic cells, changes in their fibrils as described by Brodmann & Bielschowski, formation of fibers in the glia, and degenerative changes in the vascular wall, which we cannot interpret to be caused by druses. We have found changes in basal ganglia, cerebellum, and oblongata even in the absence of druses. Therefore, we must come to the conclusion that druses are not a cause of senile dementia, but only an accompanying feature of the senile involution of the central nervous system.”

Fischer, who was one of the pioneers in senile brain histology [4-6], reacted to Alzheimer with an energetic defense, in the following manner: “In the first place, I would like to explain a small misunderstanding which has interloped here. I have never mentioned in my publication that Sphaerotrichia would produce senile dementia. According to the system of senile psychoses, the (simple) senile dementia for me is nothing else, but a decline in all mental functions as a consequence of a simple, beyond the normal limit, proceeding atrophy of brain, since I have not found any Sphaerotrichia in any case of a simple stupefaction/madness (Verblödung in original). For me, presbyophrenic dementia and senile dementia were (and still are) two completely different disorders [7].”

In the period between 1890 and 1920, several neuroscientists considered “the epoch of senility as the physiological loss of mind” [Spratling, 1895], “continuous gradually progressing loss” [Mercier, 1895], “permanent, progressive, and uncontrollable senile changes” [Nascher, 1911], and the “separation line between the physiological changes of normal senility and the milder form of senile dementia being wholly arbitrary” [Diefendorf, 1907], [all quoted in 8]. Psychiatrists began focusing on searching for somatic explanations for presenile dementia, without disrupting the commonly, although not universally, accepted view that senility was a part of the normal aging process [8].

Whether the original Alzheimer´s (presenile) disease and the late-onset senile dementia (SD) are a continuum of the same entity, or do they deserve to be distinguished as a conventional disease for the former and aging for the latter, is a question that remains debatable even after 100 years. Consequently, Alzheimer´s disease (AD), if using the original definition for it, is a rare disease but not a social threat; whereas, senile dementia (SD), due to its high prevalence, is a serious social threat but not a conventional disease in a medical sense. However, when the two medical entities are combined into a single hybrid monster, a socially threatening disease is created [1].

In the last decades of the twentieth century, psychiatrists and neurologists respected the prevailing belief that AD was a unity of three phenomena: dementia was a consequence of amyloid plaques and neurofibrillary tangles. Since dementia could be caused by a variety of pathogens, circumstances, metabolic diseases, trauma, etc., a histological postmortem

confirmation was required for reaching a definitive diagnosis. Nevertheless, most of the publications have been based on studies conducted with groups of demented persons, without obtaining this essential confirmation. Often, the people who are simply demented are labeled as patients of AD, and the term AD is broadly used as a synonym for mental deterioration during old age.

4. Amyloid as a Natural Component of Brain Aging?

Numerous studies have demonstrated that people with AD (read presbyophrenia, dementia, or cognitive impairment), as well as the people with mild cognitive impairment (MCI), exhibit the presence of increased levels of β-amyloid in their brains compared to healthy controls. In a meta-analysis of 24 PET studies, it was revealed that β-amyloid was present mainly in the precuneus, cingulate gyrus, temporal gyri, and the supramarginal gyrus. These same structures were observed to exhibit decreased FDG metabolism. The precuneus and frontal cingulate gyrus are affected by both of these abnormalities in MCI [9]. However, in the same meta-analysis, it was identified that several regions of the brain did not exhibit higher β-amyloid content in parallel with lower glucose metabolism. In the posterior cingulate, right insula, lentiform nucleus, and putamen, only amyloid content was observed to have increased, while in the frontal gyrus and angular gyrus only glucose hypometabolism was detected. This implied that in the damaged gray matter, amyloid content does not necessarily overlap with decreased metabolism (= decreased synaptic activity). Moreover, it has become apparent that amyloid is not a prerequisite for dementia. There are not only cases of dementia unrelated to the retention of amyloid (traumatic dementia, postinfectious dementia, post-stroke dementia, diabetic encephalopathy, alcohol encephalopathy, etc.), but also, there are people who exhibit the presence of cerebral amyloid in significant levels and do not have dementia.

The causal role of amyloid in the development of dementia has often been questioned [10]. Nevertheless, until recently, amyloid has maintained its reputation as the initial elicitor for both presenile and senile mental deterioration. Moreover, the three preclinical stages of AD were defined as: (a) abnormal levels of β-amyloid, (b) amyloid combined with decreased FDG metabolism and hippocampal atrophy, and (c) stage two symptoms and additional subtle cognitive changes [11]. Two types of amyloid plaques have been identified: diffuse plaques and neuritic plaques. Diffuse plaques are considered relatively innocent and accompany the pre-symptomatic stage of the disease. On the other hand, the neuritic plaques, which stain with thioflavin S, are believed to be involved in tau histopathology and are, therefore, associated with symptoms.

The progressive growth of amyloid, first in the neocortical and subsequently in the allocortical regions of the brain, appears to stabilize when a certain degree of the amyloid load has been reached. In a large population-based autopsy study, while a strong relationship between dementia and neuritic plaques was observed in people up to the age of 75 years, it became increasingly impossible to identify a correlation between dementia and the amyloid load in persons over the age of 75 years [12]. The study was conducted with 456 subjects, aged between 69 and 103 years, among whom 243 were demented. While neuritic plaques and neurofibrillary tangles were observed to be strongly associated with dementia at the age of 75 years, this association was less conspicuous at the age of 95 years. The authors also confirmed that in subjects without dementia, the burden of Alzheimer´s type histological disease in the population increases with the age at

death. In the advanced ages, however, the ability to predict dementia on the basis of the burden of neuritic plaques in the hippocampus and neocortex and the burden of neurofibrillary tangles in the hippocampus decreases.

The last 15 years of development of radioligands has rendered it possible to study the brain amyloid content while the patients are alive; this has allowed the visualizing of the relationship between the increasing amyloid levels and the deteriorating mental capacity. Comparative studies have revealed a strong correlation between the amyloid ligand retention and the true density of the amyloid plaques observed in necropsy. Both diffuse plaques and neuritic plaques bind the ligands, although the neuritic plaques exhibit a higher affinity toward the ligands [13].

The regional developments of the three main pathological markers of AD often do not overlap. Amyloid depositions, hypometabolism in PET, and regional atrophy are often observed to be dissociated. For instance, volume loss in the hippocampus was observed to be dissociated from the negligible load of amyloid and relatively well-preserved levels of metabolism. On the other hand, it was observed that a high load of amyloid in the dorsolateral prefrontal cortex was not accompanied by a local loss of volume [13]. Unlike the relatively close relationship between temporal lobe atrophy detected in the structural studies and FDG hypometabolism detected in PET, which correlated with the psychometric results, the correlation between the PET measures of Aβ depositions and the cognitive scores was weak or even absent [13].

It has also become apparent that a number of cognitively normal people contain β-amyloid depositions in their brains. In a study conducted with 177 subjects, Rowe et al. demonstrated, by using PIB compound in PET scans, that 33% of the cognitively normal adults were amyloid positive [14]; Jagust reported 47% of the cognitively normal adults as amyloid positive. Substantial agreement was obtained between PIB-PET and the levels of Aβ1–42 in the CSF, which were, however, not related to cognitive impairment [15]. In other studies [16-18], the reported amyloid positivity among the mentally intact people ranged between 15% and 30%. Similarly, studies using Florbetapir also detected positive β-amyloid depositions in 21%–28% [19], 20% [20], or 14%–23% [21] of the cognitively healthy people.

On the other hand, several studies have reported that the individuals diagnosed with AD were negative for cerebral β-amyloid; for example, in a study, β-amyloid was reported to be absent in 32% of the total of 31 AD subjects studied [22]. Consequently, the positive outcomes for β-amyloid in cognitively healthy people and negative outcomes for β-amyloid in the AD-diagnosed individuals raise doubts against the role of amyloid in causing the pathogenesis of dementia. These findings of the PET studies conducted with living individuals confirmed and further expanded the knowledge obtained from the autopsy studies conducted in the nineties, that the people who were documented to be in normal mental health condition were repeatedly identified to contain considerable levels of β amyloid histological depositions [23, 24].

The biomarkers of the aging process [progressing from normal to abnormal], namely, amyloid in PET, hippocampal atrophy, gray matter volume, FDG hypometabolism, and CSF findings, along with the deterioration of episodic memory and non-memory cognitive domains, could be properly demonstrated in the data-driven models of the neurodegenerative disease [25].

A huge study reported by the Mayo Clinic investigated a total of 430 cognitively normal subjects (median age = 78 years), using PET with the amyloid ligand Pittsburgh compound B as well as with 18Fluoro-Deoxy-Glucose and 3T MRI. These extraordinarily valuable data allowed a comparison of the β-amyloid load with the measurements of metabolism, hippocampal volume,

and the burden of white matter hyperintensities in FLAIR. Extremely accurate counting using statistical parametric mapping secured a quantitative unification of the different sizes and shapes of heads and brains. It was observed that one-third of these probands (32%) exhibited elevated PiB cortical amyloid, according to a standardized uptake value (SUV) > 1.5 (for combined regions of prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus). In addition, half of these probands appeared to exhibit abnormal hippocampal atrophy or abnormal FDG PET hypometabolism. The group of people with β-amyloid < 1.5 SUV were observed to contain 35% individuals with hippocampal atrophy or FDG hypometabolism, and the authors designated this subgroup (102 subjects) with normal or low amyloid content plus hippocampal atrophy or FDG hypometabolism as the group with suspected "non-Alzheimer pathway (sNAP) of aging" [26].

The load of β-amyloid, which increases over time, has been observed to be higher in the at-risk populations, and the individuals with higher loads have a worse prognosis. However, the attempts to divide the aging people in a dichotomous way, into those who accumulate β-amyloid and those who do not, have failed. The intermediate cases represent a non-negligible proportion of cognitively normal elderly [27]. All these observations have led to the conclusion that the groups of cognitively normal people either with or without β-amyloid depositions are indistinguishable when examined through a variety of other imaging markers, clinical features, and risk factors. Therefore, the initial appearance of the brain injury biomarkers (hypometabolism and hippocampal atrophy) in cognitively normal elderly may not be dependent on β-amyloidosis [28].

When debating this issue, one should attribute the deleterious effects of amyloid to other neuronal functions as well. Although the highest load of amyloid usually affects the posterior and anterior cingulate cortex, amyloid has been detected in all the cortical regions. Therefore, if it is assumed that amyloid exerts harmful effects on the tissue it is present in, then it should be suspected as the culprit leading to deterioration in motor, extrapyramidal, sensitive, and sensorial functions as well, in addition to causing deteriorations in mental functions.

Is the idea of neurotoxicity of amyloid reliable? Are β-amyloid oligomers, the early stage of protein aggregates, toxic elements that damage cells? The aforementioned are rarely true. In the results of the experiments conducted on mice, the relationship between the amount of β-amyloid plaques and cognitive decline was rather vague [29]. The same was true for humans. In community-based neuropathological investigations, a considerable overlap of AD-type and vascular-type histological changes has been repeatedly observed. A study conducted with 209 individuals (aged 70–103 years at the time of death; median age = 86 years) in the UK identified cerebrovascular (78%) and Alzheimer-type (70%) changes in the subjects, while only 100 members of the total study population were demented. The proportion of individuals with AD-type histology in demented and non-demented subjects was observed to be 64% and 33%, respectively. Vascular lesions were equally common in the demented and non-demented groups, while the proportion of individuals with multiple vascular pathologies was higher in the demented group compared to the non-demented group (46% vs. 33%) [30].

5. Neurofibrillary Degeneration: Correlated to Other Biomarkers of Dementia?

In the autopsies of elderly individuals, varying degrees of neurofibrillary degeneration were commonly observed in demented as well as non-demented individuals. The percentage of individuals exhibiting the presence of pathological proteins among a total of 233 subjects (77–87 years at the time of death) was observed to be 68.7% for β-amyloid, 24.9% for α-synuclein, 23.2% for non-AD tau, and 13.3% for TDP–43. None of these pathologies exhibited an increased probability of co-occurrence with any of the others. Therefore, the authors concluded that neurodegenerative pathologies and their combinations are common, and have been underestimated [31].

Other authors have reported that the overlapping presence of various histological abnormalities, observed in the autopsy results of community-based cohorts, is common. Particularly interesting was a review of 12 large studies conducted in the USA, the UK, Finland, Japan, and Austria, which summarized the neuropathological findings of community-based studies. Irrespective of the clinical symptoms, AD-related pathology was reported in 19%–67% of the cases, Lewy body pathology was reported in 6%–39%, vascular pathology in 28%–70%, TDP–43 proteinopathy in 13%–46%, hippocampal sclerosis in 3%–13%, and mixed pathologies were reported in 10%– 74% of the cases. White matter pathologies, not defined in any of the reviewed studies, were estimated by the authors to be present in greater than 80% of all the aging brains [32]. Interestingly, vascular pathology (28%–70%) included only infarctions. Given the synergistic interaction between the small vessel disease and AD pathology [33], one should consider the huge proportion (greater than 80%) of leuko-araiotic lesions which are the major contributors to vascular encephalopathy. In a study conducted with 39 non-demented, 15 mildly-demented, and three demented individuals aged 51–88 years, the formation of neurofibrillary tangles (NFT) and the formation of plaques, during normal aging, were observed to be mutually independent events. The average tangle concentration was observed to increase exponentially with age [34]. In this excellent histological study, the formation of tangles was observed to be separate from that of plaques, spatially as well as temporally. While the tangles were formed preferentially in the limbic structures, plaques were initially formed in the neocortex. Therefore, the authors concluded that the initial formation of tangles and the earliest amyloid depositions in the form of plaques were two independent events.

A study conducted by Braak et al. provided a substantial contribution to the knowledge regarding the natural life-long histological changes. The study was based on 2332 non-selected brains of individuals aged 1–100 years. It appeared that the pre-tangle changes gradually turned into argyrophilic neurofibrillary tangles, progressing in parallel with NFT stages I–VI. Immunohistochemistry for the abnormally phosphorylated tau protein, AT8, was observed to be positive in a few individuals during the first two decades of life, with the frequency of positive outcomes increasing with time. The β-amyloid pathology also correlated with age, beginning with the fourth decade of life. The abnormal tau deposits began appearing mainly in the nor-adrenergic projection neurons of the locus coeruleus [35]. The issue of NFT brain pathology in the absence of amyloid has also been studied. Designated as tangle-only dementia or tangle-predominant senile dementia, these were observed to be indistinguishable from the cases of Alzheimer´s disease. A study recommended referring to these cases as primary age-related tauopathy (PART) [36].

6. Other Ubiquitous Candidates for the Cause of Deterioration of Aging Brain

6.1 Microinfarcts

Microinfarcts are the minute tissue defects up to 500 µm in diameter, with up to 50 μm^3 of CSF-like content. Microinfarcts are colliquative, and consequently, cystic. Other similar ischaemic lesions are, however, only the foci of neuronal loss and gliosis, which appear pale upon hematoxylin-eosin staining. Microinfarcts, similar to macroinfarcts, were never considered a component of classical AD. However, several authors viewed them as contributors to AD-associated senescent decline, probably because they equated AD with dementia. Microinfarcts are often described as belonging to vascular cognitive impairment. A review of 32 original patient neuropathological studies involving 10,515 people reported that microinfarcts appeared to be common, particularly in the populations labeled with vascular dementia, in which the weighted average of the microinfarcts was 62%. Microinfarcts were also detected in 43% of the individuals labeled with Alzheimer´s disease. In demented individuals with combined AD and cerebrovascular pathology, microinfarcts occurred in 33% of the total cases, and this percentage was 24% in the non-demented elderly (Figure 1). The examined articles included 14 to 6,189 individuals, with their mean age at the time of death varying between 69 and 95 years [37].

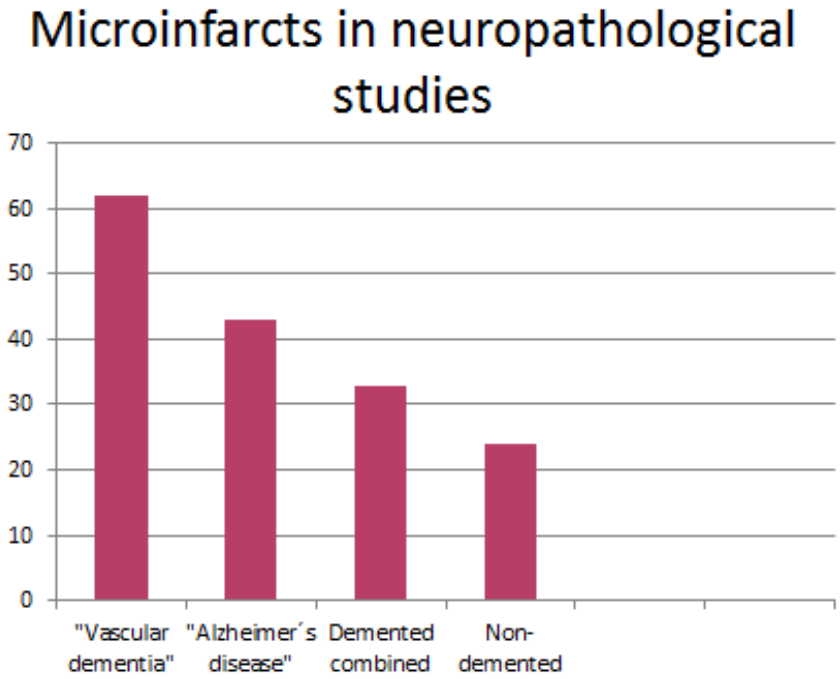

Figure 1 Presence of microinfarcts in 32 neuropathological studies. Diagram based on results from Brundel et al. [37].

Rooden et al. conducted a study to assess the association between cortical microinfarcts and cognitive dysfunction. Using 7-T MRI for FLAIR and T2* images from 14 AD patients and 18 controls, the authors observed higher numbers of cortical microinfarcts [average 7.2 (0–21)] in the AD patients [mean age: 66.2; Mini-Mental State Examination (MMSE) ≥ 19] in comparison to those in the controls [mean age: 69.7; MMSE ≥ 25; microinfarcts: 1.8 (0–7)]. In addition, a negative correlation between the cognitive function and the number of microinfarcts was observed [38].

Microinfarcts were defined with diameters up to 5 mm. The number of microinfarcts detected in the MRI-based studies was higher than that detected in the autopsy-based studies. In the autopsy-based studies, microinfarcts were observed to occur in 33% of the cognitively normal elderly [39]; larger numbers were observed in the cohorts of AD and VaD patients.

The role of cerebral amyloid angiopathy (CAA) has been unclear; nevertheless, hypoperfusion could be attributed to CAA, while hypoperfusion may elicit the deposition of amyloid in vascular walls as well.

6.2 Microbleeds

Cerebral amyloid angiopathy has been reported to be very common in the AD individuals, occurring in approximately 90% of the cases, while in the general population, it has been reported to be prevalent in 50%–60% of the demented individuals and in 20%–40% of the non-demented ones [40, 41]. With its consequence in both tiny infarcts and tiny bleeds, it may serve as a predictor of cognitive dysfunction [42].

Although it is considered that microbleeds are clinically silent, there has been accumulating evidence regarding their effects on cognitive dysfunction. Patients with microbleeds, when compared to age-matched controls, exhibit a striking difference in the prevalence of executive dysfunction, and this difference is apparent even after the logistic regression of white matter lesions; thereby it demonstrates that the harm caused by microbleeds is independent of the extent of white matter changes (presumably of ischemic origin) [43]. The Rotterdam study analyzed 3,979 individuals without dementia and identified that microbleeds correlated negatively with the MMSE score, information processing, and motor speed. This dependence remained valid even after performing adjustments for imaging markers of the small vessel disease [44]. Another large cohort of 2,602 participants aged 66–93 years, and not having dementia, was analyzed in Reykjavik. In this study, cerebral microbleeds appeared to be the strongest correlate for the decline in memory and three cognitive domains; microbleeds were also observed to influence the progressing mental decline within the interval of 5.2 years [45].

7. Leukoaraiosis

The term vascular dementia was conceived at a time when only macro-infarcts and micro-infarcts were registered in association with the cerebrovascular incidents. Multi-infarct dementia became the most common type of this typically stepwise deterioration of the mental faculties. The use of MRI, mainly its FLAIR sequence, later provided insight into the smaller changes occurring in the brain parenchyma, referred to as small vessel/capillary disturbances, which resulted in diffuse, limited damage to the brain tissue. Since the term leukoaraiosis was coined in 1987 [46], the impact of this reduction in the white matter (WM) density on the cognitive functions has been sufficiently documented.

Most authors used to interpret the high signal periventricular and deep white matter lesions (WML) in the brains of the elderly as evidence of a special type of dementia, namely, vascular dementia. Unlike in multi-infarct dementia, these diffuse changes due to their miniature foci do not produce any step-wise clinical deterioration. These changes are so common among the older people that the clinical category to which they are assigned to plays only a minor role. In several studies, these lesions were detected in 50%–98% of the general elderly population, in 67%–98% of

stroke patients, in 28.9%–100% of patients with Alzheimer´s dementia, and in 30%–55% of Parkinson´s patients [47]. Such large numbers confirm that the presence of leukoaraiosis is non-specific and accompanies aging in all the categories of neurodegeneration. The Rotterdam study, conducted with 1,077 individuals of the general population (aged 60–90 years), identified that only 8% of the individuals exhibited the complete absence of subcortical WML; the proportion of positive cases was increased, of course, with age [48]. These hyperintensities on T2WI, even better visualized in FLAIR sequences, could also be observed in the individuals as young as those in their forties [49]. The main predictors of WM hyperintensities were age and hypertension.

The presence of WML, according to 46 longitudinal studies, was significantly associated with the risk of stroke [hazard ratio (H): 3.1], and even more so with high-risk populations (H: 7.4). The progression of WML has also been associated with the increased risk of stroke; moreover, it paralleled with cognitive decline. The baseline volume of WM hyperintensities was associated with even a more noticeable decline in the cognitive functions [50]. Three population-based studies identified a significant association between the WM hyperintensities and the occurrence of all types of dementia (H: 2.9; confidence interval: 1.3–6.3). In the psychological examination, this was the most apparent in the decline observed in the processing speed and executive functions. The disruption of the cortico-subcortical circuits is usually considered the cause of this decline. Surprisingly, six studies conducted with high-risk populations did not confirm such interdependence, perhaps because these studies included only the patients with mild cognitive impairment [50].

Progression of WML and their growth per year may be estimated on the basis of the Austrian Stroke Prevention Study. A tiny increment of 2.7 cm^3 per year occurs in the case of early confluent lesions, and more robust progress of 9.3 cm^3 occurs in the individuals with confluent lesions already at the baseline [51]. The interaction between cognitive decline and leukoaraiosis with brain atrophy is complex [52]. In individuals with progressive leukoaraiosis, cognitive functioning is observed to deteriorate more speedily in comparison to the individuals without progression [53]. Leukoaraiosis is a factor that impedes mental processes not only in the experimental conditions that repeatedly test memory and cognition but also in the activities of daily life. Among a total of 3,930 healthy automobile drivers aged 21–87 years, subcortical leukoaraiosis was diagnosed in 28.52%. Adjusted odds ratios for involvement in traffic accidents were 1.09 for the individuals with single subcortical foci, 3.35 for the subjects with multiple lesions, and 2.45 for the subjects with multiple large MRI-hyperintense T2 lesions. This association was observed to be independent of sex, age, and driving experience [54].

It is completely natural that the changes in the WM density, caused by partial demyelination and increased tissue hydration, result in disturbed connectivity, which has also been demonstrated by elevated mean diffusivity and reduced fractional anisotropy in MRI [55]. White matter hyperintense lesions have also been reported to be permeated by an increased number of cells with fragmented DNA and exhibit a positive outcome for TUNEL reaction, both of which are indicative of apoptotic processes [56]. Additionally, a correlation has been observed between the extent of white matter hyperintensities in T2W imaging and the frontal lobe hypometabolism. In the individuals who transitioned (74 among 203 persons) from mild cognitive impairment to AD over an observation period of three years, a decrease in frontal fluoro-deoxy-glucose (FDG) metabolism was detected predominantly in the individuals with greater WM hyperintensities [57].

8. Further Factors Potentially Harmful for Brain Histological Decomposition

It is possible to list several other ubiquitous old-age-related histological changes supporting the assertion that the senile loss of mental acuity is a complex, unequivocal, multicausal process, which is different from its generally accepted interpretation as the AD disease. An extended list would certainly include clear observations of increasing water diffusibility and decreasing anisotropy [58-61], evidence of neuronal degeneration associated with post-ischemic apoptosis [62-65], and the overexpression of tau protein following brain ischemia in the hippocampus as well as in other cortical regions [66-68]. These experimental outcomes supported the clinical interpretation of the ischemic damage being a substantial component of mental degradation in the individuals labeled with AD [69-72]. Furthermore, disturbances in the chemical composition of cerebral parenchyma, such as the changes in aspartate, phosphoethanolamine, phosphocholine, etc. [73], contribute to the natural aging processes [74]. Novel discoveries in nutritional genomics [75] have attracted attention toward the anti-aging genes. Viewing the senescent brain deterioration as a complex consequence of "wear and tear" due to a multitude of endo-genic and exo-genic factors might also explain the frequent overlap of particular nosological units [76]. In complete agreement with the view of the variability of dementia in aging, Lam et al. stated that, "AD is clinically heterogenous in presentation and progression, demonstrating the variable topographic distribution of atrophy and hypometabolism/hypoperfusion" [77].

The number of neuroscientists having doubts regarding the inclusivity of the AD diagnosis is increasing. These neuroscientists state that the amyloid hypothesis is, at best, incomplete, and quite possibly largely incorrect, and that the amyloid deposition is predominantly associated with normal aging and not a disease per se [78]. Others have realized that the distinction between neuropathological changes (which represent a change from the normal state) and the clinical symptoms has become vague, i.e., the syndrome is no more defined by its etiology and is rather considered a clinical consequence of one or more "diseases". Therefore, a shift in research has been recommended, where AD would be identified by the presence of biomarkers in the prodromal stadia prior to the appearance of symptoms [79]. This novel approach to the definition of AD appears to be a rescue maneuver for the preservation of AD unit at any cost. Logically, it raises certain objections, which may be directed against "the use of biology as the only indicator of the disease, while ignoring the clinical aspects." Additionally, "the Frameworks proposition ensures that all the older adults be diagnosed with AD. There are no older adults who do not exhibit the presence of plaques and tangles in their brains" [80]. The fact that even the combined association of amyloid and tau pathology does not necessarily lead to dementia, in addition to the fact that other factors might be playing a leading or accelerating role in the age-associated cognitive decline, brings a few researchers to the conviction that research should be aimed at understanding the interactions among these factors during the progress of brain aging, and that the biological, genetic, and cognitive profiles of individuals must be analyzed on an individual basis [81].

9. Conclusions

In the last 40 years, the histological observations in presenile dementia by Alois Alzheimer have been extrapolated massively in order to explain the mental deterioration in old age in general. The

focus has been placed on the two supposed major culprits of the deteriorating psychic acuity, memory, and processing speed: the amyloid depositions and the neurofibrillary tangles. The designation of this process as a disease represents a threat to people feeling that they have been affected, and at the same time, a social threat to the administrative institutions. Novel discoveries have demonstrated that amyloid and NFT are only two among a multitude of degenerative changes that occur in the aging brain. These ubiquitous and complex changes are finding increasing acceptance as a part of the natural aging processes occurring in the cerebral parenchyma in the community of neuroscientists. This, however, creates a semantic problem: Is the decrease in the intellectual capacity that occurs in advanced ages a result of people getting ill or people getting old? Here, both situations are possible. It has to be emphasized here that the conventional diseases affect people as an extraordinary event in the midst of a healthy life, while aging affects all the people as an inherent phenomenon caused by an infinite number of degradation processes. With this belief, we join the other researchers who question the usefulness of designating the old-age-related mental decline as Alzheimer´s disease and instead recommend using the findings of the latest research as descriptions of aging. This approach may reveal novel categories of brain degradation in the elderly, which would better specify these inescapable phenomena.

Although the discoveries by Alois Alzheimer's must be appreciated always, nonetheless the elderly must be liberated from the "threat of Alzheimer's disease", and efforts should be made to understand the various phenomena of the old-age progressive degradation individually with their multiple specific causes. The research conducted on these phenomena in the categories of atrophy, leukoaraiosis, hypometabolism, disappearing anisotropy, apoptosis, amyloidosis, increasing diffusivity, and innumerable others should be supported, since any of these research perspectives may result in the discovery of novel efficient therapeutic measures. It is desirable to define the age limit of 60 years for presenile dementia, further to abandon the term sporadic for AD and to accept dementia as a combined consequence of all the harmful events of life. The findings of the histological and imaging investigations should always be interpreted in relation to age; for example, 1.5 SUV for amyloid or 1.5 points for leukoaraiosis on the Fazekas scale should be considered pathological only when the age is, say, less than 65 years. While conducting research, greater attention should be paid to the fornix, which is a key structure involved in the process of recall from the memory as well as for the storage of new cognitive items.

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Author Contributions

P. Kalvach has elaborated the idea of novel approaches to the senile dementia to replace the old concept of a disease (Alzheimer´s). M. Vogner collected papers elucidating observations on aging. Both authors elaborated the final sounding of the review.

Competing Interests

The authors have declared that no competing interests exist.

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