1 A WINDOW TO ACT?

Revisiting the Conceptual Foundations of Alzheimer's Disease in Dementia Prevention

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Introduction

THROUGHOUT THE TWENTIETH CENTURY AND up till the present, Alzheimer's disease has served as a working title. This chapter offers a historical and epistemological perspective that allows us to locate and evaluate the promises of dementia prevention that allude to Alzheimer's disease as a much feared medical condition and simultaneously capitalize on the idea of a window to act (before it is too late).[1] The current popular scientific understanding of Alzheimer's disease presents the long inconspicuous trajectory of a pathology that ultimately results in devastating symptoms of dementia, such as severe mental decline and the loss of the capacity to lead one's life autonomously.[2] Accordingly, the notion of a window to act refers to a biologically defined time frame—namely, before an irreparable pathological process has caused perceivable cognitive and functional deficits. This chapter argues that this picture is based on shaky grounds, and that it represents a collage of different ways in which the disease has been conceptualized within the last century. Alzheimer's disease has acted as an ambiguous term for the diagnosis of a very severe mental disorder with dramatic effects for affected patients, their families, and care givers, as well as for the underlying, yet-to-be-fully-characterized biological process that presumably starts many years, even decades, before the manifestation of symptoms. This chapter shows that the conceptual foundations of the medical category of Alzheimer's disease rest on a history of shifting question marks concerning the relation between the pathological process, clinical symptoms, and nosological category. The window to act might serve as a sound scientific hypothesis; however, it can transform into a questionable justification for assigning a broad range of people the responsibility to

take action and adopt preventive or early intervention strategies against developing dementia. If the proposed actions come with potential negative side effects (like taking a drug after an early—uncertain—diagnosis), this is even more problematic. To give an example, the mobilization of concerned potential patients was marketed in an online advertisement campaign of the pharmaceutical companies Pfizer (who closed its Alzheimer's disease research and development program in 2018) and Eisai, which presented a middle-aged, healthy, and determined-looking man vis-à-vis a teeth-baring tiger and the slogan "face the fear of Alzheimer's disease," along with these lines: "the earlier you diagnose Alzheimer's disease, the sooner you can do something about it / fighting Alzheimer's disease right from the start / Aricept® donepezil hydrochloride (click here for healthcare professional information on prescribing and adverse event reporting)." This advertisement, which went online in 2009, evokes a picture of a clearly identified enemy. However, medical experts have redrawn the composite sketch of this enemy several times from the first description of Alzheimer's disease to the most recent formulation of a research framework.

This chapter successively presents and discusses three of the most influential sketches of Alzheimer's disease: those found within the proposals of Emil Kraepelin and Alois Alzheimer around 1910; of Bob Katzman around 1976; and of the recently published NIH-AA work group for a new research framework on a biological definition of Alzheimer's disease (Jack et al. 2018). It shows that the key questions framed by the respective research programs differed significantly from each other, yet none of them could so far be answered conclusively: the relationship between Alzheimer's disease and senile dementia, the identification of the pathological process, the biological definition of the disease—all of the enquiries remain open. However, every agenda replaced unresolved questions with working assumptions in order to probe new avenues for solving the ongoing problem of determining a diagnosis of Alzheimer's disease, and finding a way to manage, cure, or prevent it.

I have selected the mentioned positionings of Alzheimer's disease for this analysis because the respective approaches and actors already figure prominently within the existing historiography of Alzheimer's disease and have been assigned argumentative roles especially in the context of discussing the origins of, and possible measures against, the frustrating futility of research on effective treatments against Alzheimer's disease and other dementias.[3] Drawing on my own historical and philosophical research, I suggest a different understanding of the reconceptualizations of Alzheimer's disease that focuses more on the shifting epistemological roles that have been assigned to this purported medical entity. Against this background, I have considered how the acclaimed new paradigm of dementia

prevention differs from past and present conventional dementia research. I will conclude that this question must be answered case by case, but that many dementia prevention strategies draw on the above depicted "window to act"—an epistemology that also motivates the current research framework toward a biological definition of Alzheimer's disease, even if the aims and means to act may differ largely in the case of general recommendations for healthy aging versus biomarker profile–specific interventions.

The main conceptual shifts between the three research frameworks and a fourth framework that some proponents of prevention seem to embrace and that questions the coherence of the past century's approach to classifying diseases altogether will be illustrated in simple figures in the four succeeding sections of this chapter. Like all simplifications, they must be handled with care. The reality is always more complex, and the influence that the discussed proposals and their antecedent or succeeding variants have had can only be explained by looking more closely into the contexts, conditions, and incentives of using and propagating these programs. All of the discussed proposals have been controversially discussed within their times by psychiatrists and medical scientists from various institutions. This chapter restricts itself to providing a comparative representation of the conceptual foundations in which Alzheimer's disease has figured within the selected frameworks. The aim is to visualize what has remained and what has changed between them. The concluding section details why the medical category of Alzheimer's disease can be best conceptualized as a working title, and exemplifies how this perspective helps us to raise meaningful questions for evaluating present promises of dementia prevention.

In Search of a Nosological Position: Alzheimer's Disease around 1910

This section reassesses the introduction of Alzheimer's disease more than a century ago to highlight how this category was used as a working title to encourage research in histopathology and clinical psychiatry with the aim of better classifying mental disorders. Against this background, the remaining part of this chapter discusses the continuities and changes in the premises and promises of succeeding programmatic approaches to dementia research.

In 1910, Alzheimer's disease was first presented within the senile dementia section of the eighth edition of one of the most influential textbook classifications of the time, authored by German psychiatrist Emil Kraepelin (1856–1926) (Kraepelin 1910: 624–629).[4] Four years earlier, Alois Alzheimer (1864–1915), who worked in Kraepelin's psychiatric university

clinic in Munich and headed the institution's microscopic laboratory, had discussed the clinically and histopathologically "peculiar case" of a female patient who had died in her fifties of a severe form of dementia. The woman, Auguste D[eter] (1850–1906), later became known as the first case of the disease that Alzheimer "discovered" and that Kraepelin "baptized" (Alzheimer 1907).[5]

Within their time, however, Alzheimer and Kraepelin remained cautious about claiming a new disease entity. For sure, they marked their stakes: their publications feature detailed descriptions of both the clinical picture of an accelerated, progressive, ultimately fatal mental deterioration and the histopathological autopsy of plaques, tangles, and degenerated cortex tissue. Alzheimer's disease was regarded as an organic brain disease that gave rise to severe symptoms of dementia and that left its pathological traces in the anatomical substrate of a patient's brain. Similar to the characterization of infectious diseases such as syphilis and rabies that could give rise to madness, the pathological anatomy of organic brain diseases—for instance, arteriosclerosis in brain vessels—was regarded as proof of principle that psychiatry could become increasingly scientific and thereby legitimate itself as a medical university discipline. While the theoretical potential of the classification of Alzheimer's disease was ambitious, its actual realization remained underdetermined. In none of their publications did Alzheimer and Kraepelin take a definitive stance on whether the small group of "peculiar cases" should be regarded as atypical variants of senile dementia or as a distinct entity. Rather, they presented this question of how to relate Alzheimer's disease to senile dementia and other organic brain diseases within a clinical theory of diseases—the nosology—as a task for further research.

The patient records of the Munich clinic provide further evidence for the use of Alzheimer's disease as a clinical diagnosis, which did not serve to settle a medical issue but to mark interesting cases and recommend, if possible, examination of the patients' brains postmortem: not only was the diagnosis regularly accompanied with question marks and corrections, but also the parameter that most historians of psychiatry considered to be a clear defining feature of Alzheimer's disease—namely, the presenility or comparably young age of the patients (in their forties or fifties) at the onset of dementia—was not a criterion of exclusion for an Alzheimer's diagnosis. In general, the category was rarely applied: the clinic records from 1909 to 1912 list more than eight thousand patients, out of which seven received a clinical diagnosis of Alzheimer's disease. Within this small group were patients that were in their late sixties, and in the case of a 63-year-old female patient, the diagnosis was even named "senile Alzheimersche Krankheit" (see Keuck 2018a).

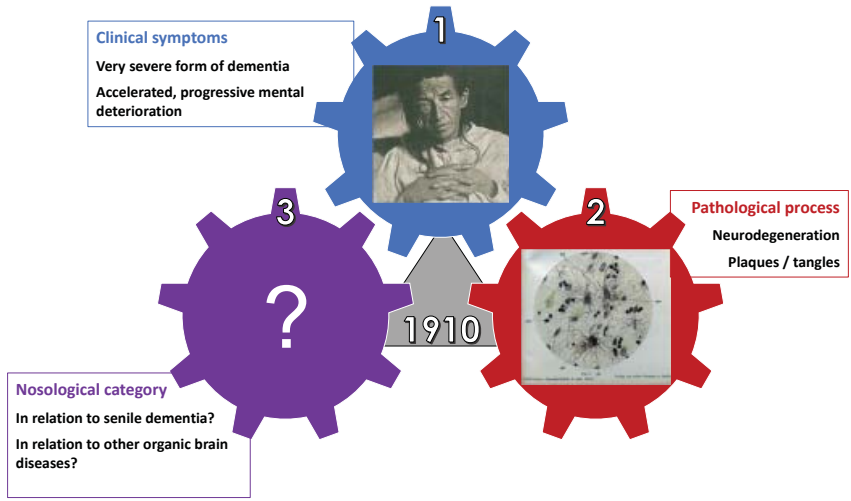

FIGURE 1.1. Schematic representation of the nosological puzzle that Alzheimer's disease presented in 1910. Picture referring to clinical symptoms: "Auguste Deter aus Frankfurt am Main," unknown photographer, 1902 (public domain, Wikimedia Commons, https://commons.wikimedia.org/wiki/File:Auguste_D_aus_Marktbreit.jpg); picture referring to the pathological process: Alois Alzheimer, 1911, "Über eigenartige Krankheitsfälle des späteren Alters," *Zeitschrift für die Gesamte Neurologie und Psychiatrie* 4: 356–385, plate IV, figure 2.

Figure 1.1 schematically represents my reconstruction of the conceptualization of Alzheimer's disease at the time of its incorporation in Kraepelin's textbook. Two aspects are salient: first, the triadic structure constituting this psychiatric category, which connects clinical symptoms with a pathological process and a nosological category; and, second, the unsettledness of the very place of this category vis-à-vis the umbrella classes of senile dementia and organic brain disorders. As mentioned above, Kraepelin (and Alzheimer, who provided all the microphotographs for Kraepelin's book) discussed the "peculiar cases" alongside a handful of other organic brain diseases as exemplars for the general potential of using pathological anatomy (alongside other service sciences that had already been incorporated into Kraepelin's vision of clinical psychiatry) to scientifically found psychiatric nosology and guide clinical differential diagnosis: when postmortem examinations showed distinctions within a clinically lumped group of patients, these should guide the clinician to search for matching differences in the symptomatology of living patients.

From the point of view of Kraepelin's clinical psychiatry and Alzheimer's cortex pathology, most of the mental disease categories were considered provisional.[6] The use of these categories served nonetheless important purposes for compiling statistics to call for more funding, for managing and overseeing the flow of in-patients from the clinics to cheaper asylums for long-term stays, and for establishing psychiatry as a sound medical discipline that strives for systematic knowledge. The latter was based on an equally systematic recording and archiving of diagnostic procedures and evaluations during the initial anamnesis at admission, the psychiatrists' visitations during the clinic stay, the epicrisis (i.e., the final medical judgment of the case after the patient was released or had died), and the review and reassessment of this empirical material in light of new theories within the qualification works (habilitation theses) of aspiring professors of psychiatry.[7]

Alzheimer's disease was presented as a nosological puzzle and used as an exploratory category in a specific way: it was left open whether the closer examination of related "peculiar cases" would give more insights into the pathological process responsible for the development of dementia symptoms in general, or whether these cases only superficially resembled forms of senile dementia and rather constituted a pathologically distinct entity. In other words, the solution to this nosological puzzle would either contribute to a refined histopathological description of senile dementia or to the characterization of Alzheimer's disease as an etiopathologically and prognostically differentiable classification. Kraepelin and Alzheimer did not take preconfigured sides on this issue; rather, they discussed potential in-between nosological positions that Alzheimer's cases could represent—for instance, as atypical forms of senile dementia. Operating with provisional categories opened up room for speculation while remaining circumspect about present conclusions: Kraepelin mused that the occasional early onset could either indicate that the symptoms associated with senile dementia were actually independent from senility or that these patients aged too early. Evidence of a "senium praecox" would strengthen the conceptual connection between the pathological process of dementia and its association with aging.

The psychiatrists could operate the triadic structure between clinical symptoms, pathological process, and nosological category as an epistemic machine: if we imagine the three aspects as cogs, in which the teeth of each cog—the specific symptoms, pathological aberrations, categorical descriptions—are worked on, are filed and oiled, we can look at how the movement of each cog changes when one of them is altered. Awkward clinical symptoms (cog 1) directed the clinician-histopathologist to look

into deceased patients' brains, where plaques and tangles were identified (cog 2). If such alterations appeared exclusively in a subgroup of patients, clinicians should look for matching differential diagnostic symptoms in living patients (moving cog 1) and revise their provisional taxonomy accordingly (moving cog 3). New categories—like that of Alzheimer's disease—were then used to label patients in the clinics, which again provided the empirical basis for testing and refining the specificity and questioned relations between a putative pathological process and the presentation of significant symptoms (so that ideally cog 1, 2, and 3 would ceaselessly bite into each other).

Throughout the twentieth century, this epistemic machine was used to set up speculative questions and research hypotheses for characterizing the nature of Alzheimer's disease. In Kraepelin and Alzheimer's texts, the main aim was to probe a new nosology. They raised questions about the specificity of the clinical symptoms and the pathological process, but these were always connected to the nosological puzzle. In the following, I analyze two further programmatic approaches to conceptualizing Alzheimer's disease that were issued to propagate research and direct it in certain directions. I argue that while these successive frameworks kept the triadic structure of Kraepelin's nosological research program, they moved the main question mark from the nosological category onto a different cog (first the pathological process, and then the clinical symptoms). This was not because the previous questions had been answered successfully; quite the contrary. The argumentative point of departure for both of the succeeding research frameworks was that the relation between clinical symptoms, pathological process, and the specificity of Alzheimer's disease as a distinct entity had remained an unresolved biomedical issue, not least because earlier attempts had put the big question mark on the wrong cog. Such negative views were not only motivated by the failure to resolve the muddle of defining Alzheimer's disease and dementia, but also mirrored a reconfiguration of the object of concern in light of the status and tasks of patients, physicians, and researchers within different sociopolitical landscapes.

In Search of a Common Pathological Process: Alzheimer's Disease around 1976

The sociopolitical landscape of postwar capitalist America, in which dementia, in particular of the Alzheimer's type, amounted to a major public health problem of the aging society, as well as a promising target for the booming pharmaceutical companies and public research funding scheme,

has been described in detail by historian Jesse Ballenger (2006a, b, for example). In this section, I zoom in on one formulation of a research program that encapsulates the main reconfigurations of conceptualizing Alzheimer's disease and that has guided much of dementia research in the last quarter of the twentieth century—not least because it was intentionally coupled to large-scale research funding.

I refer here to the canonical editorial to a 1976 special section on Alzheimer's disease in the *Archives of Neurology* by US neurologist Robert Katzman (1925–2008), who later became known as a dedicated lobbyist of research on Alzheimer's in American funding bodies and cofounder of the Alzheimer's Disease and Related Disorders Association (ADRDA; today, Alzheimer's Association).[8] The editorial gave weight to a standpoint that had been discussed since about 1960, namely that Alzheimer's disease might refer to a common pathological process responsible for most cases of "senile dementia." Katzman stressed the importance of this reconfiguration: "senility" or "senile dementia" were at the time of his writing not causes of death, but considered as effects of aging, and therefore a very common medical issue lacked recognition as a disease that in principle could be prevented and treated. He estimated that this disease would be the fourth or fifth most common cause of death. President Nixon's "war on cancer" and the $100 million founding of the National Institute of Cancer, which framed the funding of cancer research as a political act, had been issued and signed in the form of the National Cancer Act just five years earlier in 1971.[9] Katzman's hint at cancer ("malignant neoplasms") reveals a call for similar medical and political awareness for dementia research:

> The death certificates of patients with senile dementia bear witness to the bronchopneumonia, myocardial infarct, pulmonary embolus, cerebrovascular accident, or other acute event occurring at death. But such events also may mercifully end the life of patients with malignant neoplasms. Yet, the latter diagnosis enters the death certificate as the first cause of death while we officially ignore the existence of senile dementia. (Katzman 2008 [1976]: 379)

Katzman is but one contributor to the "politicization of Alzheimer Disease" in the last third of the twentieth century (Lock 2013: 38). While the consequences of this politicization, especially the dramatic extension of the patient group who would receive a diagnosis of Alzheimer's disease, received a lot of attention, the conceptual differences of Katzman's conception to earlier accounts of Alzheimer's disease have often been reduced to the broadening of the category from a diagnosis restricted to presenile dementia to including many of the much more common cases of senile dementia.

I briefly wish to point to one analysis that shows some similarities to, but also important differences from, mine. In his insightful essay "Alzheimer Disease: Epistemological Lessons from History?," clinician and philosopher Rob Dillmann describes Katzman's conceptualization of senile dementia as being potentially retractable to the disease entity of Alzheimer's disease as a neo-Kraepelinian move (Dillmann 2000). I have argued that Kraepelin's ideals of nosology should not be conflated with the actual use of diagnostic categories, which demonstrate in the case of Alzheimer's disease the provisional character of an exploratory category to guide further research and potentially settle the nosological puzzle that the "peculiar cases" presented. Some have stressed that the claiming of a new disease and the naming of it served strategic uses, such as the consolidation of Alois Alzheimer's career as clinical psychiatrist (e.g., Weber 1997; Berrios n.d.). Without doubt, the presentation of medical categories has always had a political dimension. It is, however, also without doubt that the reconfiguration of Alzheimer's disease illustrated in Katzman's 1976 editorial brought about a hitherto unknown dynamic into dementia-related research. This was a key aim, as Katzman and Katherine Bick (2000: xi) recount in their retrospective account on the founding of the ADRDA:

> We had two goals [in 1979]. The first was to reach consensus that Alzheimer disease (AD) was not just a relatively rare neurodegenerative disorder of the presenium, but was the major cause of dementia in the elderly in developed countries. The second quite different goal was to bring together investigators who had already made important contributions to the field and others whom we sought to recruit to the field in order to help "jump-start" research in AD.

The identification of the pathological process of the proposed new disease entity was framed as a political agenda—that is, a socially relevant medical problem that required substantial funding—and marked important differences from the 1910 presentation of Alzheimer's disease (see figure 1.2): while the setup remained "Kraepelinian" in its triadic structure of connecting nosology, clinical diagnosis, and pathological examination with each other, both the starting assumptions and the positioning of the main question mark moved.

Instead of presenting Alzheimer's disease as a nosological puzzle, they "reached consensus" that it should include most cases of "dementia in the elderly" (Katzman and Bick 2000: xi). The elucidation of the pathological process, on the other side, was not restricted any longer to histopathology, but should include genetics, epidemiology, and many more biomedical subdisciplines. The characterization of a pathological process specific to Alzheimer's disease was no longer primarily a means for bringing order

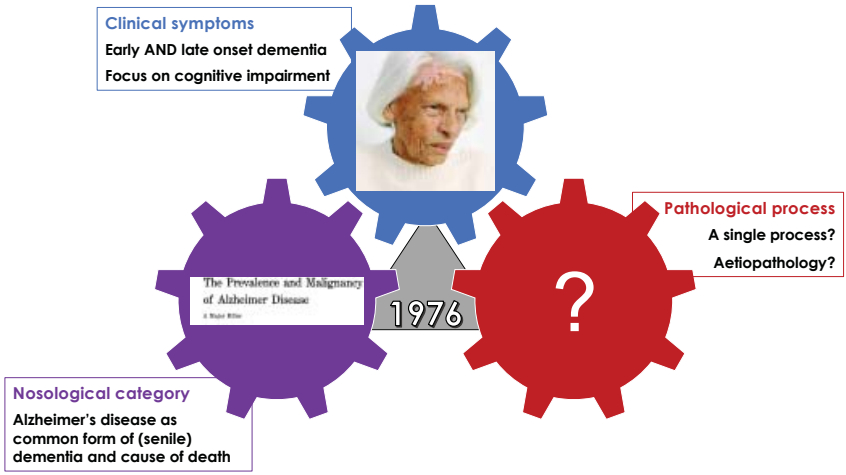

FIGURE 1.2. Schematic representation of the reconfiguration of the assumptions and the research agenda concerning Alzheimer's disease in 1976. Picture referring to the nosological category: Robert Katzman, "The Prevalence and Malignancy of Alzheimer Disease: A Major Killer," *Archives of Neurology* 33, no. 4 (1976): 217–218; picture referring to clinical symptoms: photographed by Peter Granser, reprinted from his book *Alzheimer* (Kehrer Verlag, 2005) with permission from Peter Granser/laif.

into psychiatric classification; it became an aim and object of inquiry in itself. Katzman reflected in his editorial not least on the provisional nature of the scientific evidence on which he suggested the nosological "consensus." This might again remind us of Kraepelin. However, contrary to Dillmann, I think his characterization as "neo-Kraepelinian" overshadows the re-addressing of an unresolved nosological query as a grand biomedical research program.

If we follow the Alzheimer's research field to the turn of the millennium, we can see again how the cogs were rotating—that is, how researchers refined questions and assumptions, as evidenced, for instance, through the introduction of staging and subtyping of dementia and possible precursors such as mild cognitive impairment. While the starting hypothesis and the positioning of the main question mark undoubtedly served to organize and fund research and collect a lot of data, they also increasingly gave rise to fundamental doubts, especially in the light of the failure to develop new therapeutics or vaccines despite massive private and public research efforts in the past fifteen years.

In Search of Clinical Consequences: Alzheimer's Disease around 2018

This and the following concluding section discuss two alternative frameworks that have been presented as responses to the futility of past research, in particular with respect to the development of effective drugs. They can be seen as existing in opposition to each other; however, dementia prevention strategies might be associated with both suggested reconceptualizations of Alzheimer's disease: the first, visualized in figure 1.3, is the continuation of the above-described rotating cogs with respect to early detection, subtyping and staging until the point where the main question mark shifts from the question of identifying an etiology to defining the disease via biomarker profiles and turning the successive occurrence of clinical symptoms into an empirical question. Already in the context of the revision process of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, the *DSM*-5, and in the updating of the diagnostic criteria issued by the National Institute of Aging (NIA) and the Alzheimer's Association in 2012, the controversy regarding the status of mild cognitive impairment as a diagnosis with unclear clinical relevance has received a lot of attention—not only within Alzheimer's research but also within the social sciences of medicine (see Moreira, this volume; Katz, Peters, and Ballantyne, this volume; as well as, e.g., Hughes 2006; Moreira et al. 2009): the inclusion of potential early mild forms of Alzheimer's disease has crystallized the current state of clinical research that aims for ever earlier diagnosis, thereby contributing itself to the creation of both uncertainty and new medical demands. In 2018, an expert group at the forefront of early diagnosis approaches to dementia research commissioned by the NIA went a step further when they finally published a new framework for research purposes. I will compare their conceptualization of Alzheimer's disease to the above-discussed earlier frameworks, as well as to the other currently discussed approach, visualized in figure 1.4, which follows from the futility of past research that the whole biomedical disease entity–based approach should be reconsidered in favor of public health and community-based approaches that increase the quality of life and decrease the social segregation of aging people, be they demented or not.

The comparison between the 1976 and 2018 schemes is somewhat different from their comparison to Kraepelin and Alzheimer's presentation in 1910 because there are many more direct personal, organizational, and political connections and continuities between the two more recent research programs. Indeed, as mentioned above, the definition of stages and "placeholder" categories (this is how the new *DSM*-5 category of "Minor Neuro-

cognitive Disorder" was introduced by the revision work group) could be described in terms of wheeling cogs and as a refinement of Katzman's program, in which the hypothesis of one disease entity is successively replaced with more sophisticated (potential) subtypes. However, I want to argue that the consortium surrounding Clifford Jack that proposed a new "biological definition of Alzheimer's disease," which shall not least be applied within grant proposals to the National Institute of Aging, signifies a larger conceptual reconfiguration because it alters the role of the assumed pathological features from being objects of query to acting as defining features in a nosological setup that moves the main question mark to the onset of clinical symptoms. I share both of my evaluations with critical observers from epidemiology and social work: the first being that this new framework involves experts, epistemic and economic interests, technologies (mainly neuroimaging devices) and hypotheses from the mild cognitive impairment research community; and the second being that the way in which this position is presented and powered by the National Institute of Aging provides a rather dramatic shift compared with the research criteria of the 1980s, in which the clinical diagnosis was a primary activity for selecting patient groups and not a secondary outcome of research.[10]

The NIA consortium proposed to harmonize terminology by introducing a new category, "Alzheimer continuum," which incorporated four subsets of "biomarker profiles." These profiles are determined by the abundance or lack of deposits of beta-amyloid, pathologic tau, and neurodegeneration (abbreviated as A, T, and N in the framework) as evidenced through neuroimaging in living persons. This serves to fulfill the seemingly paradoxical double task of offering a coherent biological definition of the disease to enlarge the comparability of research designs, and of presenting a conceptual and practical toolkit to put the question of what pathogenesis actually characterizes this disease itself under scrutiny. The price for this biomarker approach to defining Alzheimer's disease (AD) is the bracketing of the clinical syndrome as the primary reference point: "a syndrome is not an etiology but rather a clinical consequence of one or more diseases. A biological rather than a syndromal definition of AD is a logical step toward greater understanding of the mechanisms underlying its clinical expression," the framework's authors state (Jack et al. 2018).[11] This research framework is so much based on the epistemology of the window to act—that is, the possibility to detect and possibly intervene into biological alterations before clinical symptoms occur—that it systematically excludes approaches to identifying dementia via symptoms if they are not accompanied by an assessment of the proposed biomarkers. As a consequence, the "biological construct" is no longer the searched-for explanation of the clinical syn-

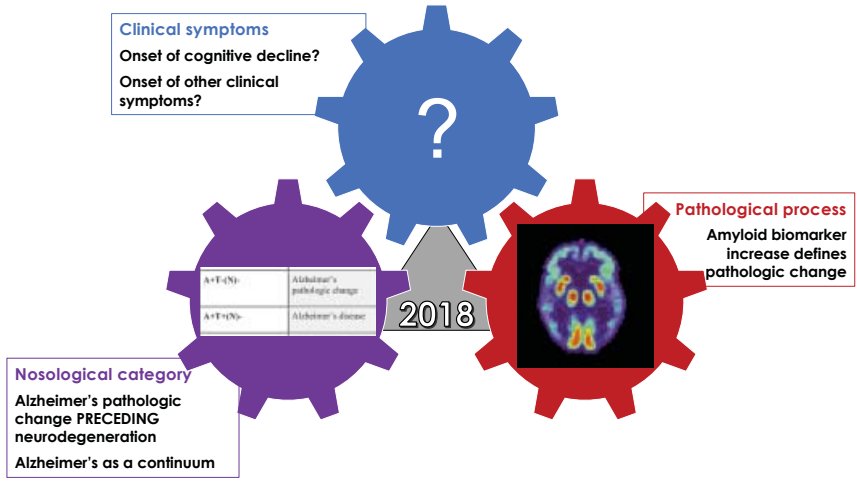

FIGURE 1.3. Schematic representation of the reconfiguration of the assumptions and the research agenda concerning Alzheimer's disease in 2018. Picture referring to the nosological category is a cutout from table 2 in Jack et al. 2018; picture referring to the pathological process: US National Institute on Aging, "PET Scan of a Human Brain with Alzheimer's Disease" (Wikimedia Commons, public domain, https://upload.wikimedia.org/wikipedia/commons/4/49/PET_Alzheimer.jpg).

drome, but becomes itself something that requires an explanation irrespective of its connection to the occurrence of clinical symptoms:

> We emphasize though that **A and T proteinopathies define AD as a unique disease** among the many that can lead to dementia. As a consequence, **disease models where A and T are not in the primary causal pathway must provide a mechanistic explanation for the development of both of these diagnostic proteinopathies**, as well as neurodegeneration and clinical symptoms. (Jack et al. 2018, their highlights)

Jack et al.'s (2018) framing of Alzheimer's disease does not undermine the triadic structure that they inherited from the early days of psychiatric nosology. However, it is utilized in a very different way, as illustrated in figure 1.3.

Time will tell how the cogs will turn this time, but two points shall be noted, which I will summarize in the conclusion with respect to the topic of dementia prevention: first, none of the three presented frameworks has so far resulted in the conclusive answering of the problems that they charted. Neither the clinical symptoms nor the pathological process have been suf-

ficiently characterized to serve as specific differential diagnostic features. The unresolved questions are carried on: Jack and colleagues motivate their new framework with both the lack of a clear taxonomic positioning of Alzheimer's disease and the past failure to identify the etiology of the disease. However, and this is the second point, given the significant conceptual reconfigurations, it is not clear how the results of the research that adheres to the new framework will relate to the questions set by earlier accounts. This does not mean that it cannot be relevant, but that extra work needs to be done to show this relevance.

The conceptualization of a window to act is a contemporary and consumerist interpretation of capitalizing on the time between the potential identification of suspicious biomarkers and the manifest experience of illness. This is the common point of conjuncture of early diagnosis and primary prevention, in which the latter shifts the timing (and often the means) of intervening even more outside of the traditional confines of medicine: early diagnosis precedes the experience of illness; prevention precedes (and ideally hinders) the onset of pathology. While some proponents of dementia prevention regard a biomarker-based early diagnosis as important to develop effective interventions, others take a seemingly contradictory step and advertise general preventive strategies, which leave open which pathological process these strategies are actually intervening in. Irrespective of the concrete operationalization of dementia, with each step ahead of time, the group of people that ought to do something—take a drug, undergo a test, eat healthy—gets bigger: from people with severe symptoms to people with mild problems or "at-risk" to everyone. What is more, both approaches legitimate themselves by alluding to the public image of devastating symptoms of dementia and the fear associated with the label of Alzheimer's disease. These legitimations build on an understanding of prevention that keeps the object of concern—what shall be prevented—relatively stable.

Conclusion: Alzheimer's Disease as a Working Title

I have argued in this chapter that the rather rigid understanding of medical entities as representing distinct pathological processes that result in specific clinical symptoms has throughout the history of the category of Alzheimer's disease served as a guiding ideal but was never accomplished. While directed toward this ideal—or, to use George Engel's polemical dictum, dogma—of a biomedical model of mental illness, the existing categories have served as working titles, thereby structuring the ways in which dementia was performed as a medical problem (see Engel 1977).[12] It follows that the question of what would be prevented when a given strategy

of "dementia prevention" is successful is not at all self-evident. If we want a sound assessment of the potential of preventive and other interventionist strategies to change disease trajectories, we need to pay attention to how the target "dementia" will be reshaped through the means that (are at) work.

The notion of a working title picks up the idea of a placeholder label that we briefly encountered in the previous section. These terms unveil an aspect of uncertainty, or undecidedness, and stress that the reference to Alzheimer's disease does not tell us much. This does not mean that possible pathological alterations or suffering from clinical symptoms associated with Alzheimer's disease are not real. It just means to acknowledge the heterogeneity of signs and symptoms and the preliminary nature of their associations to each other, and to evaluate every preventive promise against this background. Serious prevention programs that aim at Alzheimer's disease should be able to give an answer on how they handle the definitory muddle: how exactly could the success of prevention, the nonappearance of Alzheimer's, or, in the case of tertiary prevention, the deceleration of its aggravation be assessed?

Besides the preliminary nature of conceptualizing Alzheimer's disease, there is a second aspect to the notion of the working title, and this is the performative one: the work that labels do. Although, as we have seen, the big questions of defining Alzheimer's disease have not been settled, the introduction of this category, and its incorporation into research programs and the public debate, have undoubtedly had considerable effects—ranging from the structuring of self-help groups and nonprofit organizations around this diagnosis to the possibility of making an academic career as an Alzheimer's expert. Taking this performative force to the forefront—as representatives of critical gerontology have done—we can ask: how could the advertisement and pursuit of a given prevention program change the social representation of Alzheimer's disease? Does it have the potential to alter—for better or for worse—how people conceive of and treat patients with a diagnosis of Alzheimer's disease? Or, does it perhaps even contribute to an understanding of mental health and disease that transcends categorical thinking? This latter option has been propagated within the social sciences of medicine, for instance by Margaret Lock (2013). In light of the lack of success of biomedical research into Alzheimer's disease, she has suggested focusing more on public health measures to enhance the physical and social environment for old people with and without dementia-related symptoms. The prominent scientist-turned-critic Peter Whitehouse suggested even replacing "Alzheimer's disease" with "brain aging": this would enable patients and their relatives to employ less stigmatizing narratives and motivate more community-oriented interventions such as the development of

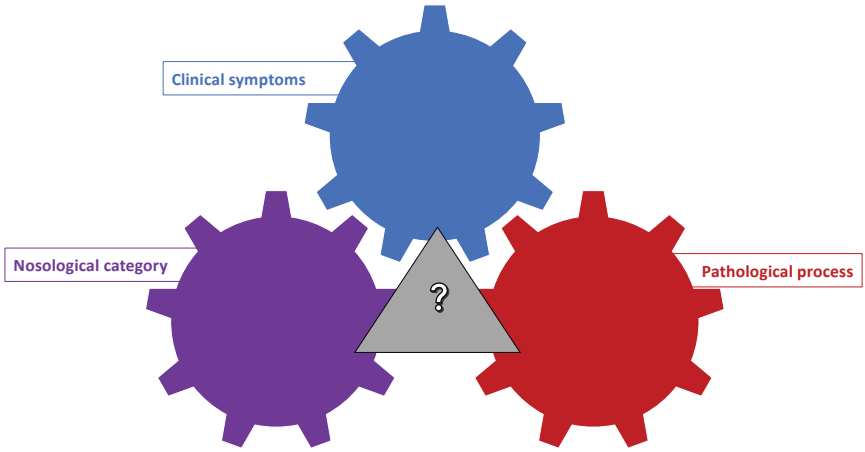

FIGURE 1.4. Schematic representation of the questioning of the medical categorical imperative.

intergenerational living environments, in which, for instance, the burden of losing capacities to live autonomously wouldn't weigh so heavy (Whitehouse and George 2008). Within the scheme of shifting question marks that I presented in this chapter, the move of questioning the integrity and utility of a specific disease entity altogether is visualized in figure 1.4:

The complete deconstruction of the disease entity–based approach and its replacement with a focus on general enhancement of the quality of life does, however, also come at a cost: it is even more difficult to evaluate the success and performative effects of prevention programs that are targeted at brain aging. Furthermore, Whitehouse and Lock might have good intentions, but the danger is that the old normative distinction between health and disease is replaced by new ones—for instance, regarding whether you properly cope with your aging body and brain.

The normative dimensions of disease descriptions do not disappear with the classification; they move to other items. As indicated in the above reference to critical gerontology, they can be derived from different disciplinary angles. I have taken here a historical perspective to highlight the shifting of priorities, assumptions, and question marks in the conceptualization of Alzheimer's disease. How the clinical diagnosis of Alzheimer's was used a century ago might not be directly relevant to recent developments in dementia prevention, but the awareness of the ways in which this category has been positioned and reconfigured helps us scrutinize—case by case—two promises of the preventive turn: the newness of its approach, and the relevance of its target of concern. With respect to the latter, I think this per-

spective can help us to think comparatively, to think through alternatives and to question what the most adequate characterization of the target of prevention—in a particular case and context—should be. My conclusion regarding the purported new paradigm of dementia prevention is equally relativist: instead of arguing for or against newness, I hope to have shown that it might be more fruitful to look for the development of overarching assumptions—such as that of a window to act—and study how they are put to work within concrete early intervention versus prevention programs. No doubt the outcome of present research enterprises will shape whether—and, if so, how—the conceptual foundations of understanding and dealing with dementia will move in the future.

Acknowledgments

Research for this chapter was funded through the Branco Weiss Fellowship—Society in Science of the Swiss Federal Institute of Technology (ETH Zürich).

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Notes

1. The British social psychologist and gerontologist Tom Kitwood (1997) coined the polemical slogan of the "Alzheimerization of dementia" to point at the dominant role that biomedical models of Alzheimer's disease (rather than person-centered care) played within the understanding of dementia in the last decades of the twentieth century. In this chapter, I do not intend to argue about whether this dominance is still pertinent. I use Alzheimer's disease as a case study and look into the

history of this medical category. My conclusions will be most informative for approaches to dementia prevention that allude to Alzheimer's disease, but I will use them to present more general questions regarding the legitimacy of the respective scope of dementia prevention.

2. "Alzheimer's worsens over time. Alzheimer's is a progressive disease, where dementia symptoms gradually worsen over a number of years. In its early stages, memory loss is mild, but with late-stage Alzheimer's, individuals lose the ability to carry on a conversation and respond to their environment. Alzheimer's is the sixth leading cause of death in the United States. On average, a person with Alzheimer's lives four to eight years after diagnosis, but can live as long as twenty years, depending on other factors. . . . Alzheimer's has no current cure, but treatments for symptoms are available and research continues. Although current Alzheimer's treatments cannot stop Alzheimer's from progressing, they can temporarily slow the worsening of dementia symptoms and improve quality of life for those with Alzheimer's and their caregivers. Today, there is a worldwide effort under way to find better ways to treat the disease, delay its onset, and prevent it from developing." (Alzheimer's Association, n.d.).
3. For examples on how the establishment of Alzheimer's disease around 1910 and the popularization of the disease in the 1970s figure within analyses of the crisis of Alzheimer's research in the 2000s, see Dillmann 2000; Ballenger 2006a; Whitehouse and George 2008; and Lock 2013. For a critical discussion of the new NIA-AA research framework of a biological definition of Alzheimer's disease with respect to the shifting and closing of unresolved research questions from the point of view of epidemiology, see Glymour et al. 2018.
4. The section about Alzheimer's disease around 1910 is based on my reconstruction of Alois Alzheimer's epistemology of cortex pathology within Kraepelin's clinical psychiatry and my analysis of patient records of the Munich clinic archive; see Keuck 2017, 2018a. The latter also discusses the existing historiography of the "discovery" of Alzheimer's disease (e.g., Berrios 1990; Weber 1997; Ballenger 2006b; Maurer 2006; Gzil 2007; Borri 2012).
5. For a critical discussion on the making of the historical fact of the first case of Alzheimer's disease, and its employment within the recent biomedical discourse on the nature of this disease, see Keuck 2018b.
6. See, for instance, the introduction of Kraepelin's textbook and the programmatic opening paper of a journal that Alzheimer cofounded (Kraepelin 1910; Alzheimer 1910).
7. For a discussion of the uses of Kraepelin's categories for different purposes, see Engstrom 2005. To my knowledge, the first habilitation thesis on Alzheimer's disease was conducted by Ernst Grünthal, who handed in this work in 1925 and published it in 1926 (Grünthal 1926). He argues that Alzheimer's disease should be used as a category distinct from senile dementia, and also introduces an early age of onset as a diagnostic criterion.
8. Alzheimer's disease became such a big research issue that several new journals dedicated to this and related disorders were founded in the past two decades. One of them, *Alzheimer's and Dementia*, reprinted in 2008, the year of Katzman's death, his "landmark 1976 editorial" (Katzman 2008 [1976], quote from the editor's note, footnoted on 378).

9. For historical accounts of the development and impacts of Richard Nixon's National Cancer Act, see, e.g., Rettig 1977; Proctor 1995.
10. See Glymour et al. 2018; and, very polemical and critical, Garrett 2018. The following two paragraphs are slightly amended versions from my analysis of different positions within the biomarker debate and the roles attributed to theories of the normal and the pathological (Keuck and Freeborn, forthcoming).
11. The quoted emphasis style and page number refer to the authors' open access PMC document, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5958625/pdf/nihms960157.pdf, accessed 15 March 2019.
12. For the performative role of medical classification in general, see, e.g., Bowker and Star 2000; Hacking 2007; Conrad 2007.

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