5 MIND'S FRAILTY

Elements of a "Geriatric Logic" in the Clinical Discourse about Dementia Prevention

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Introduction

We tend to think about the manifestation of disease as a clear-cut departure from a state of species-specific physiological normality. Dementia, in particular, is generally understood, both in clinical and in common parlance, as a disruption of high-order cognitive functions such as memory, communication, and reasoning, and it is often associated with the appearance of psychiatric symptoms and personality traits that a person has never exhibited before. In a person affected by dementia, departure from normal cognitive functioning is a radical transformation that disrupts the very biographical continuity of that person and that others frequently perceive as a loss of personal identity. Few other diseases lend themselves so easily to be understood as a qualitative shift between a normal and a pathological state. While this dichotomy intuitively make sense, French historian and philosopher of medicine Georges Canguilhem (1904–1995) famously warned against assuming that such qualitative distinctions are uncontroversial (Canguilhem 2012a). According to Canguilhem, the way in which medicine understands and tries to tackle the manifestation of pathological states is inseparable from its assumptions about what it means to be normal, or in good health. In the words of anthropologist Paul Rabinow (1996: 85)—who has been an acute reader of Canguilhem—the French philosopher demonstrated "the constant presence of evaluative notions like 'preservation,' 'regulation,' 'adaptation,' 'normality,' in both every-day and scientific approaches to life." Those assumptions are normative in nature in two ways. On the one hand, they include practical injunctions about how one should be leading one's life in order to preserve a healthy state. On the other hand, life itself is often represented as phenomenon animated by inner tendencies or forces determining an organism to acquire

certain vital states. Such vital forces manifest themselves, for instance, in development, in spontaneous recovery from illness, or in the progressive loss of an organism's capacity to cope with its environment over the course of its biological life.

Until recently, however, the clinical discourse about dementia has not paid much explicit attention to life's normativity. The clinical manifestation of dementia as an obvious and inexorable departure from a previously attained level of cognitive functioning has militated against seeing this disease along a progressive continuum of cognitive decline whose origin can be located back in a person's normal or healthy life course. But the conceptualization of dementia and of Alzheimer's disease (AD) in particular has switched between several different models (Leibing 2014) over the last few decades. In present days, the clinical discourse about dementia is showing signs of yet another epistemological and normative shift toward new ways of representing dementia and new strategies to prevent it. The main thesis of this chapter is that the vision that is taking shape in the new clinical discourse about dementia relocates cognitive decline along a broader trajectory of age-related functional decline, emphasizing dementia as a phenomenon that, while not being fully controllable, can be modulated through the course of a person's life experience. In what follows, I maintain that the new clinical discourse about dementia is trying to reconnect the pathological abnormality of this disease with the forces that shape the vitality of an organism, its capacity to cope with its environment, and to actively produce the conditions to resist degradation. In other words, the new epistemology of dementia is trying to conceptualize the normal and the pathological along the same vital continuum.

The already prominent clinical narratives about preventing dementia, I will show, are branching out in the direction of emerging paradigms in geriatrics—namely, research on frailty and research on geroprotectors, which are drugs designed to prevent or postpone the effects of aging. This encounter between the science of dementia and aging research represents a hybrid space of epistemological experimentation where specific ways of thinking about cognitive decline and intervening in it are tentatively taking shape. Emergent paradigms in geriatrics, as I will show, reinforce the idea of preventing dementia as scientifically and technically plausible. I reconstruct the early steps of such epistemological convergence, which started between 2007 and the early 2010s, based on a careful analysis of relevant scientific literature. Such literature shows the possible emergence of a new clinical discourse about dementia. I do not intend to claim that such novel understandings are bound to become mainstream. Nor, as a matter of fact, do I look at such new epistemological trajectories as more than early signs of a possible new articulation of dementia and dementia prevention. The

status of such novel discourses is still far from established, as they rather represent a still-precarious epistemology of dementia. However, it is precisely such precariousness that makes such discourses a privileged site to observe the potential emergence of new "styles of thought" (Fleck 1981; Löwy 1988) about dementia and cognitive health. From a disciplinary perspective, this paper offers an epistemological analysis of a still ongoing realignment of the normal and the pathological that makes preventing dementia conceptually possible. My focus is partly sociological, in the sense that I do trace back the realignment of the normal and the pathological to actual instances of exchange and contamination between different biomedical fields. However, I also take a more philosophical stance as I attempt to draw essentially conceptual connections between certain emerging models of aging and disease that play a role in recasting the clinical discourse about dementia both epistemologically and practically. To this aim, I take inspiration from Canguilhem's constructivist understanding of medical normality as a concept that "when considered within the human order, always remains a normative concept of properly philosophical scope" (Canguilhem 2008: 133). This stance invites one to pay close attention to the practical or, as it were, ethical demands that derive from specific ways of thinking about life, health, and illness. In particular, in attributing to the individual self the responsibility for the preservation of cognitive functioning, the new clinical discourse about dementia attempts to construct a more hopeful narrative around the disease. But, at the same time, it buys into broader currents of thought that see health as a *product* of individual care and agency.

In the coming sections, I reconstruct what in the title of this chapter I call a new "geriatric logic" about dementia prevention as a series of conceptual shifts in the understanding of cognitive decline and in the notion of prevention as applied to cognition, for which I have coined the expression "ground-state prevention."

Normal Trajectories of Functional Decline

Preventing dementia is not a new idea. Repeated failures in the development of drugs to target AD biomarkers (such as amyloid and tau proteins) have certainly influenced the quest for earlier interventions. But as Annette Leibing (2014, 2018) showed, specific epistemological changes were needed for the consolidation of the preventive narrative. First, the rediscovery in the 1990s and the further development of studies highlighting the link between dementia and atherosclerosis of brain vessels introduced what Leibing and Kampf (2013) call a "cardiovascular logic." According

to this logic, the etiopathology of dementia can be assimilated to the same modifiable risk factors that have been identified for cardiovascular diseases—that is, hypertension, diabetes, obesity, and sedentary habits (see also Leibing 2014). The second epistemological change is the interest in early—even presymptomatic—predictive biomarkers and cognitive signs of an incipient dementia. In particular, the identification of mild cognitive impairment (MCI) as a possible prodromal syndrome affecting individuals who may be on their way to develop clinical dementia has given further impetus to the cardiovascular logic, since people affected by MCI are ideal candidates for lifestyle adaptations that may slow down or delay the onset of dementia. These epistemological elements configure what Leibing (2018) calls a "new dementia."

In this section, I would like to show how the prevention narrative that characterizes the "new dementia" is enabling further epistemological reconfigurations of dementia possibly producing yet a newer interpretation of this disease. To begin with, I will focus on the emerging interest for the identification of frailty as a modifiable risk factor not only in geriatric medicine in general, but specifically in the context of cognitive disorders.

Despite its centrality for current research and clinical practice in geriatrics, there is no unique scientific definition of frailty. Frailty is generally understood as a progressive, age-related decline affecting an organism's intrinsic capacity (defined as the total physical and mental capacity an individual can rely on; WHO 2015), increasing both vulnerability to environmental stressors and the risk of disability and other adverse health outcomes. This multidimensional geriatric condition can be measured through different scales. Two of the most widely used methods are the frailty phenotype (Morley et al. 2013) and the frailty index (Rockwood et al. 2005). The frailty phenotype aims at detecting five symptoms: involuntary weight loss, exhaustion, slow gait speed, poor hand grip strength, and sedentary behavior. The absence of any of such symptoms is typical of robust individuals. The presence of three or more of those features denotes a frail person.

The frailty index is instead composed of seventy criteria describing the health deficits of an individual. This index is based on the deficit accumulation model by Mitnitski and Rockwood (Mitnitski and Rockwood 2007; Rockwood and Mitnitski 2011) and measures the capacity of an organisms to absorb the progressive accumulation of deficits (Cesari et al. 2014).

According to this model, "with aging, damage accumulates in cells and tissues, whether by random or genetic mechanisms, involving sub-cellular and organ-specific pathways" (Mitnitski and Rockwood 2007: 724). This process is controlled by mechanisms such as DNA damage response (Ou and Schumacher 2018), cell senescence (Zhu et al. 2015), protein kinase

pathways (Wei et al. 2017), and oxidative stress (Sohal and Weindruch 1996).

Evidence about an association between frailty and dementia started to emerge in the field of neurology between 2007 and 2008 through the work of Aaron Buchman and colleagues (Buchman et al. 2007, 2008). Such research was based on previous studies highlighting an association between general physical function and cognition (Stewart et al. 2005; Rosano et al. 2005; Wang et al. 2006). The idea that the best screening models for dementia should be based on multiple risk factors can be considered established by 2010 (Stephan et al. 2010). Based on such data and on this newly emerging paradigm, at the beginning of the new decade, the community of geriatrics started to produce retrospective studies further corroborating the association between frailty—a multiparametric measure of physical function—and dementia, showing that the age-related accumulation of deficits, in addition to known risk factors, is indeed a risk factor for dementia and AD (Song, Mitnitski, and Rockwood 2011). Further research is currently underway to better understand the potential role of frailty in dementia. In a 2017 observational study on people diagnosed with MCI, individuals with a higher baseline frailty index score had a significantly higher risk of converting to AD (Trebbastoni et al. 2017). In other words, this study hypothesizes that frailty may contribute to the transition from MCI to clinical AD or to weakening the capacity of people affected by MCI to revert to normality or remain stable over time. A recent meta-analysis has shown that frail older adults are at higher risk of incident cognitive disorder, in particular vascular dementia, as compared to nonfrail elders (Borges et al. 2019). The interest of these studies for the prevention of dementia lies in the fact that frailty is considered to be amenable to interventions and therefore to improvement, both through public health measures and by adopting healthier individual lifestyles in terms of nutrition and physical activity (Landi, Onder, et al. 2007; Kelaiditi, van Kan, and Cesari 2014; Bonnefoy et al. 2015; Landi, Calvani, et al. 2016).

Targeting frailty as a proxy to preventing dementia is reminiscent of the interest in the cardiovascular determinants of dementia. What may be at play here is a geriatric reconceptualization of dementia or, otherwise stated, the emergence of a "geriatric logic" in the quest for preventing dementia. This new logic pushes for the conceptual inclusion of frailty in a broader, multidimensional understanding of dementia. From a conceptual point of view, frailty is one possible way to measure the cumulative effects of an organism's overall biological and environmental determinants. Such complexification of dementia as a disorder owing to a multiplicity of factors (which frailty captures by measuring a variety of functional parameters) represents dementia in the perspective of an organism's whole life—as

opposed to a sudden, almost serendipitous disruption of higher cognitive functions. This view is reminiscent of Canguilhem's invitation to look at health from the perspective of a whole life, lived by a subject as its capacity to "cope with." As Canguilhem (2012b: 72) very clearly argues: "What is proper of an organism is to live as a whole and not to be able to live except as a whole."

The quest for conceptualizing dementia (also) in light of frailty foregrounds a more holistic idea of health that manifests itself through a person's whole experience (Blasimme 2020).[1] The geriatric logic is therefore sustained by an epistemological aspiration to recast dementia under a broader clinical perspective, reconnecting it to the normal trajectory of age-related decline that frailty tries to capture in all its complexity. The aspirational or, as it were, reformistic character of the geriatric logic in dementia comes clearly to the fore in another paper questioning the external validity of AD clinical trials that fail to control for frailty as a modulator of dementia. In this study, upon retrospective assessment, AD patients enrolled in randomized controlled trials appear to be less frail than those who are not included, as indicated by both higher frailty index scores and higher prevalence of frailty in the excluded cohort (Canevelli, Trebbastoni, et al. 2017). This is probably due to an unintended effect of inclusion criteria that privilege patients who are overall in better shape.

The convergence of dementia and frailty research is promising, but it is still in its infancy (Lim, Canevelli, and Cesari 2018). Available studies are limited in number, and evidence for establishing and explaining an association is still preliminary. What is more, a recent review has shown evidence from published observational studies that both frailty and MCI can spontaneously revert to, respectively, robustness and normal cognition (Canevelli et al. 2017). These findings and the current paucity of dedicated observational or interventional studies on the topic invite caution in embracing the geriatric logic about dementia. Still, this body of work is starting to attract attention in the scientific community as a way to systematically screen for who should be a candidate for preventive interventions. What I want to highlight here is that the geriatric logic rests on an epistemological move that aligns the pathology of dementia with the normality of age-related decline. Since frailty does not refer to a disease but to a spectrum of parameters describing a trajectory of decline, looking at frailty and dementia along the same life-course continuum operates a sort of geriatric normalization of cognitive disruption. Conceptually speaking, this normalization of dementia is a result of a pre-existing emphasis on dementia prevention, but it relies on distinctively novel epistemological elements with respect to the antecedent cardiovascular framing. What the geriatric logic shares with the cardiovascular framing is that both cast aging individuals as be-

ing "at risk" for dementia. As a consequence, normalization opens the door to a countertrajectory of pathologization of normal age-related decline. Considering dementia as the result of life-long exposure to multiple risk factors that progressively debilitate a person's resilience to age-related decline makes room for a novel interpretation of what preventing dementia ultimately means.

Preventing Cognitive Decline

The idea that health depends on an intrinsic kernel of properties that an individual employs to counteract the inner tendency toward age-related decline is also visible in the current clinical discourse about preventing cognitive decline. In particular, lifestyle-based preventive measures have focused on three domains: cognitive training, physical activity, and nutrition.

Cognitive Training

The notion of cognitive reserve (Stern 2002; Stern et al. 2018; Pettigrew and Soldan 2019; Giovacchini et al. 2019) suggests that innate cognitive abilities, education, and occupational attainments offer "a set of skills or repertoires that allow some people to cope with progressing AD pathology better than others" (Scarmeas and Stern 2003). According to this model, an intellectually and socially engaged lifestyle can delay the onset of dementia (Scarmeas and Stern 2003). While the idea of cognitive reserve, its relation to AD, and its characteristic emphasis on "cumulative life experiences" have been attracting considerable attention since the late 1980s (Cosentino and Stern 2019), evidence in support of cognitive training to prevent dementia is encouraging but still inconclusive. According to the 2017 report on preventing cognitive decline and dementia by the US National Academies of Sciences, some randomized controlled trials like the ACTIVE trial (Advanced Cognitive Training for Independent and Vital Elderly) show that cognitive training can delay or slow age-related cognitive decline, but no evidence from interventional studies supports the notion that cognitive training can prevent, delay, or slow down MCI or AD (National Academies of Sciences 2017). In particular, the ACTIVE trial showed that training can improve cognitive function in the specific domain being trained (moderate-strength evidence at two years; low-strength evidence at five and ten years), but transfer to other domains was infrequent (National Academies of Sciences 2017). Interestingly, the ACTIVE trial also showed greater maintenance of independence in instrumental activities of daily living for individuals who received cognitive training—although

with a five- to ten-year lag since the intervention. Based on these findings, it can be argued that more prospective randomized controlled trials with long follow-up are needed to produce conclusive evidence about the potential benefit of cognitive training as a way to boost cognitive reserve and possibly prevent, delay, or slow down cognitive decline and dementia (Cosentino and Stern 2019).

Physical Activity

Physical activity has been proposed and widely investigated as another strategy to improve an organism's inner capacity to cope with age-related decline. In geriatrics, numerous studies have addressed the role of physical activity on frailty components, including functional impairment and cognitive performance. One review dating back to 2010 reports that physical inactivity is an established very strong predictor of disability in elders (Landi, Abbatecola, et al. 2010). The same review suggests that while physical activity decreases the risk of early cognitive decline and poor cognition in late life, some studies undermine the association between physical activity and dementia (Landi, Abbatecola, et al. 2010). In this respect, the authors observe that in most studies, the effect of physical activity is assessed in older adult life, whereas regular levels of physical activity throughout life may be required to exert a protective function against cognitive impairment. A retrospective analysis of ilSIRENTE trial (Aging and Longevity in the Sirente geographic area, Italy) data shows that a history of high physical activity is associated with better cognitive performance in very old community dwellers (Landi, Russo, et al. 2007). Many other studies have addressed physical activity in relation to maintenance of cognitive performance throughout life (Laurin et al. 2001; Rovio et al. 2005; Ravaglia et al. 2008; Forbes et al. 2008). A 2014 systematic review and meta-analysis concludes that longitudinal observational study lend support to the notion that higher levels of physical activity reduce the risk of cognitive decline and dementia (Blondell, Hammersley-Mather, and Veerman 2014).

Nutrition

Emerging notions like "nutritional frailty" and "diet resilience" conceptualize poor nutrition as a determinant of age-related vulnerability and, by the same token, identify diet as a key area of intervention to conserve an organism's functional capacity and to protect it against age-related decline (Shlisky et al. 2017). Systematic reviews and meta-analyses of randomized controlled trials established lower risk of dementia and a positive impact on cognitive trajectories of specific nutritional patterns (Cao et al. 2016;

Canevelli et al. 2016). In particular, the so-called Mediterranean diet (rich in starchy foods, vegetables, fruits, and fish, and low in saturated fatty acids) has received specific attention. Reviews based on epidemiological evidence and data from interventional studies established that the Mediterranean diet might benefit cognition in healthy adults (Loughrey et al. 2017) and have a potential protective role against the risk of dementia (Lourida et al. 2013; Petersson and Philippou 2016; Canevelli et al. 2018). Most of the above-mentioned studies, however, highlight that available evidence is still not sufficient to support specific recommendations in the absence of long follow-up randomized controlled trials.

Geroprotectors

Geriatrics also studies the effect of fasting and reduced calorie intake on the longevity and health span in animal models. Recent studies have demonstrated that the mechanism is effective even in primates, in which it leads to longer life span and delayed onset of age-dependent diseases, including cancer, diabetes, cardiovascular diseases, and brain atrophy (Colman et al. 2009). Evidence that caloric restriction delays aging and leads to longer lives in mammalians has been available since the 1930s (Heilbronn and Ravussin 2003), and, as a matter of fact, the existence of a possible correlation between eating less and living longer has been known since antiquity (Schäfer 2005). Nevertheless, the long-term effects of calorie restriction on longevity in humans are still poorly known due to the lack of studies with sufficiently long follow-up. However, it is established that calorie restriction in humans causes the same metabolic adaptations as in rodents and primates, therefore decreasing risk for diabetes, cardiovascular disease, and cancer (Fontana and Klein 2007). Recent studies in humans have also shown that a fasting-mimicking diet for five days a month has a favorable impact on aging markers and risk factors such as weight, body fat, blood pressure, glucose levels, triglycerides, cholesterol, IGF-1 hormone, and an inflammation marker called C-reactive protein (Wei et al. 2017). But caloric restriction and fasting, like healthy, varied and balanced nutrition, may be difficult regimens to adhere to—especially for those who belong to lower socioeconomic strata (Payette and Shatenstein 2005; Darmon and Drewnowski 2008).

As a consequence, in recent years researchers have been devoting increasing attention to pharmacological compounds that could attain the same health-related outcomes of healthy nutritional regimens. Research in model organisms has led to the identification of a class of drugs, now commonly called geroprotectors (Bellantuono 2018), that can slow down aging, extend life span, and increase health span acting on the same bi-

ological mechanisms—namely, metabolic and inflammatory pathways (Mercken et al. 2013)—that are activated by caloric restriction. The list of geroprotectors is a long one and includes, among others, already approved compounds like metformin (Martin-Montalvo et al. 2013)—already in use for type II diabetes and metabolic syndrome—and rapamycin—already employed to prevent transplanted liver rejection and occlusion of cardiac stents (Ehninger, Neff, and Xie 2014). Another class of age-delaying drugs is senolytics (Xu et al. 2018), which are small molecules that cause apoptosis in senescent cells. A senescent cell is a cell that, as a defensive response to the accumulation of DNA damage (due, for instance, to UV light, ionizing radiation, smoking, or oxygen radicals), enters a state of proliferative arrest. In a senescent state, they produce pro-inflammatory factors that eventually lead to organ failure or malfunctioning (Baumann 2018). Along the course of an organism's life, the number of senescent cells increases. Senolytic drugs can reduce their number by pushing them toward apoptosis—that is, cellular death.

The current interest for the use of geroprotectors to prevent dementia is a further instantiation of the emergence of the geriatric logic I introduced above. In a commentary published in *Nature*, prominent scientists in this field argue for a reconsideration of the way we study age-related conditions such as AD (Fontana et al. 2014). Instead of addressing one disease at a time, the authors maintain, we should try to "stall incremental cellular damage and changes that eventually yield several infirmities" (Fontana et al. 2014: 405). This quotation confirms that dementia—at least as a translational research entity—may be undergoing a conceptual reconfiguration. More specifically, from an epistemic point of view, this disease is being normalized as one of the many chronic age-related conditions that can be addressed by trying to improve individual health span.

Since in animal models geroprotectors have the capacity to delay age-related conditions, including declining cognitive performance, and to boost resilience, they have recently been hypothesized to have a potential role in the delay or even reversal of frailty and thus to improve the capacity of an organism to resist or recover from adverse events (Trendelenburg et al. 2019). According to the geriatric logic, age and age-related conditions, including those affecting cognition, shall be seen along the same continuum and treated accordingly from a clinical point of view. In keeping with this vision, and drawing on initial evidence of an association between metformin use and reduced risk of cognitive impairment (Ng et al. 2014), a recent review has analyzed the evidence in favor of metformin (an inhibitor of gluconeogenesis acting through the AMP kinase pathway) as a geroprotector (Piskovatska et al. 2019). This study concludes that there are positive effects of metformin use in metabolic disorders, cardiovascu-

lar disease, inflammation, cancer, and frailty, but evidence is conflicting as to whether metformin can address age-related cognitive decline. Yet it is known that activation of certain kinase pathways, such as AMP, may have a role against aging-related conditions including AD (Salminen et al. 2011).

Research is currently underway to isolate a subclass of geroprotectors that could pass the blood-brain barrier and specifically target cognitive conditions such as AD. A paper by Schubert and colleagues labels this subclass "gero*neuro*protectors" (GNPs) and suggests a drug screening pipeline to identify suitable candidates (Schubert et al. 2018). GNPs are not expected to prevent dementia per se, but to "promote healthier brain aging and long-term neural function" (Schubert et al. 2018: 1004). Geroneuroprotectors, like geroprotectors, should thus not be understood as disease or risk-specific, but rather as targeting multiple neurodegenerative and age-related processes. Interestingly, the authors say that bona fide GNPs should intervene through the same molecular pathways that are implicated by caloric restriction, metformin, and rapamycin (Schubert et al. 2018: 1006). This condition further demonstrates the extent to which the geriatric normalization of dementia creates an epistemological line of continuity between aging itself and cognitive decline.

Ground-State Prevention

The logic that operates here is that of boosting an organism's intrinsic capacity to cope with age-related decline. I have illustrated how this logic operates in the geriatrization of cognitive health in the current clinical discourse around dementia prevention. I would like to propose that the idea of prevention at play here be called "ground-state prevention" of the degradation that occurs due to accumulated deficits along an organism's life and of the consequent deterioration of that organism's intrinsic capacity to cope with age-related decline. Ground-state prevention, as opposed to primary, secondary, and tertiary prevention, is not risk-specific (i.e., it does not target a specific risk factor), nor even disease-specific (i.e., it does not address a specific disorder). Moreover, it does not aim to provide or restore any measure of species-typical functioning or normality. Rather, ground-state prevention is a sort of biological enhancement aimed at boosting the intrinsic capacity of an organism to face its progressive functional decline and the appearance of age-related pathologies. As far as dementia is concerned, ground-state prevention is an attempt to operationalize the geriatric normalization of dementia in a more holistic perspective—that is, along the continuum of aging and age-related diseases. It will not escape the at-

tention of the reader, however, that, by the same token, ground-state prevention does not privilege one specific type of practical approach, as it can be achieved through either lifestyle-based or drug-based interventions. The aim of ground-state prevention is to boost resilience, and it does so by extending the preventive medical gaze not only to presymptomatic but also to not-yet-senior individuals. While it is too early to assess how ground-state prevention will play out in practice, in terms of public health and health promotion strategies, it has to be noticed that this approach might actually reinforce the long-debated risk of biomedicalization of old age—a problem that emerges precisely from seeing aging as a process of decline (Estes and Binney 1989).

Discussion

What I have described as the emergence of a geriatric logic in dementia prevention presents family resemblances with broader currents of thought about aging. Current medical thinking about aging is devoting considerable attention to the so-called healthy aging model, spearheaded by the World Health Organization (WHO). Healthy aging is defined as the capacity to develop and preserve levels of functionality that are conducive to wellbeing in older age (Ou and Schumacher 2018). The healthy aging model insists on the combination of intrinsic capacity and environmental factors. In this model, intrinsic capacity is the sum of three elements: a person's genetic endowment, health-related features, and socioeconomic characteristics. The environment—natural, physical, and social—interacts with a person's intrinsic capacities to determine the quality of that person's aging.

In the healthy aging model, aging is represented in terms of one's life trajectory. Throughout the aging process, a person's capacity to function in his or her own environment degrades with time. However, different people decline in different ways, as some remain sufficiently functional for longer, while others experience earlier or more rapid age-related degradation depending on their intrinsic capacities and dwelling conditions. While progressive decline in intrinsic capacity is assumed as a biological fact in the healthy aging model, intrinsic capacity is clearly represented as modifiable, that is, amenable to capacity-enhancing behaviors such as physical activity and good nutrition.

By now, the resemblance between the geriatric narrative about dementia prevention and the healthy aging model should not strike the reader as surprising. In both ambits, a realignment of the normal and pathological is at play. The metaphor that depicts life as a trajectory of age-related de-

cline operates a normalization of old age, while at the same time orienting ground-state prevention as early as possible in the course of an organism's life. It is premature to say whether and how the epistemic shifts I have illustrated in this chapter will yield clinical fruits. However, one cannot fail to notice that the inner tendency of the geriatric style of thought about dementia prevention is, so to say, the "agification" of life itself. Boosting resilience operates by projecting the management of the age-related health risks into earlier (younger) phases of life. The effects of these epistemological reconfigurations of dementia and prevention are even harder to anticipate. For this reason, future work on the broader anthropological, social, and ethical consequences of the geriatric framing shall be giving careful consideration not only to the epistemic merits of this framing, but also to its undesirable consequences. As pointed out by Stephen Katz (2020: 54) in a chapter on precarious forms of life, the very idea of resilience, while "promot[ing] a positive and democratic approach to coping with old age," still reinforces a socially exclusive model of successful aging. This bifurcation, according to Katz (2020: 54), "creates a division between being resilient and failing to cope." Resilience, Katz (2020: 54) reminds us, is and "remains . . . an individual trait." The intrinsically individualistic character of resilience, as a consequence, demands a broader imagination about how individual decline can be integrated into community care in the pursuit of collective security from the vagaries of old age.

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Note

1. Here I use the word *experience* in a philosophical way, drawing on Gadamer's (2004) elucidation of the notion of *Erlebnis*. In its philosophical meaning, *Erlebnis* indicates the immediate lived experience of a subject in its present manifestation, but also, at the same time, the sediment of a person's life, the cumulated effect of his or her immediate experiences, the memory of what occurred to a person throughout life (Gadamer 2004).

References

Baumann, Kim. 2018. "Rejuvenating Senolytics." *Nature Reviews Molecular Cell Biology* 19 (9): 543–543.

Bellantuono, Ilaria. 2018. "Find Drugs That Delay Many Diseases of Old Age." *Nature* 554: 293–295.

Blasimme, Alessandro. 2020. "Producing Health: Canguilhem and the Contemporary Clinical Discourse about Aging." In *Vital Norms: Canguilhem's* The Normal and the Pathological *in the Twenty-First Century*, edited by Pierre-Olivier Methot. Paris: Hermann Éditeurs, Collection Med.

Blondell, Sarah J., Rachel Hammersley-Mather, and J. Lennert Veerman. 2014. "Does Physical Activity Prevent Cognitive Decline and Dementia?: A Systematic Review and Meta-Analysis of Longitudinal Studies." *BMC Public Health* 14 (1): 510.

Bonnefoy, Marc, Gilles Berrut, Bruno Lesourd, Monique Ferry, Thomas Gilbert, Olivier Guerin, Olivier Hanon, Claude Jeandel, Elena Paillaud, Agathe Raynaud-Simon, Geneviève Ruault, and Yves Rolland. 2015. "Frailty and Nutrition: Searching for Evidence." *Journal of Nutrition, Health & Aging* 19 (3): 250–257.

Borges, Marcus Kiiti, Marco Canevelli, Matteo Cesari, and Ivan Aprahamian. 2019. "Frailty as a Predictor of Cognitive Disorders: A Systematic Review and Meta-Analysis." *Frontiers in Medicine* 6: 26.

Buchman, Aron S., Patricia A. Boyle, Robert S. Wilson, Yuxiao Tang, and David A. Bennett. 2007. "Frailty Is Associated with Incident Alzheimer's Disease and Cognitive Decline in the Elderly." *Psychosomatic Medicine* 69 (5): 483–489.

Buchman, Aron S., Julie A. Schneider, Sue Leurgans, and David A. Bennett. 2008. "Physical Frailty in Older Persons Is Associated with Alzheimer Disease Pathology." *Neurology* 71 (7): 499–504.

Canevelli, Marco, Giuseppe Bruno, Francesca Remiddi, Carlo Vico, Eleonora Lacorte, Nicola Vanacore, and Matteo Cesari. 2017. "Spontaneous Reversion of Clinical Conditions Measuring the Risk Profile of the Individual: From Frailty to Mild Cognitive Impairment." *Frontiers in Medicine* 4: 184. https://doi.org/10.3389/fmed.2017.00184.

Canevelli, Marco, Giuseppe Bruno, Nicola Vanacore, and Matteo Cesari. 2018. "Mediterranean Diet and Dementia: Can This Be a Preventive Approach?" In *Role of the Mediterranean Diet in the Brain and Neurodegenerative Diseases*, edited by Tahira Farooqui and Akhlaq Farooqui, 103–115. Cambridge, MA: Elsevier Academic Press.

Canevelli, Marco, Flaminia Lucchini, Federica Quarata, Giuseppe Bruno, and Matteo Cesari. 2016. "Nutrition and Dementia: Evidence for Preventive Approaches?" *Nutrients* 8 (3): 144.

Canevelli, Marco, Alessandro Trebbastoni, Federica Quarata, Fabrizia D'Antonio, Matteo Cesari, Carlo de Lena, and Giuseppe Bruno. 2017. "External Validity of Randomized Controlled Trials on Alzheimer's Disease: The Biases of Frailty and Biological Aging." *Frontiers in Neurology* 8: 628. https://doi.org/10.3389/fneur.2017.00628.

Canguilhem, Georges. 2008. *Knowledge of Life*. New York: Fordham University Press.

———. 2012a. *On the Normal and the Pathological*. Vol. 3. Dordrecht: Springer.

———. 2012b. *Writings on Medicine*. New York: Fordham University Press.

Cao, Lei, Lan Tan, Hui-Fu Wang, Teng Jiang, Xi-Chen Zhu, Huan Lu, Meng-Shan Tan, and Jin-Tai Yu. 2016. "Dietary Patterns and Risk of Dementia: A Systematic Review and Meta-Analysis of Cohort Studies." *Molecular Neurobiology* 53 (9): 6144–6154.

Cesari, Matteo, Giovanni Gambassi, Gabor Abellan van Kan, and Bruno Vellas. 2014. "The Frailty Phenotype and the Frailty Index: Different Instruments for Different Purposes." *Age and Ageing* 43 (1): 10–12. https://doi.org/10.1093/ageing/aft160.

Colman, Ricki J., Rozalyn M. Anderson, Sterling C. Johnson, Erik K. Kastman, Kristopher J. Kosmatka, T. Mark Beasley, David B. Allison, et al. 2009. "Caloric Restriction Delays Disease Onset and Mortality in Rhesus Monkeys." *Science* (New York) 325 (5937): 201–204. https://doi.org/10.1126/science.1173635.

Cosentino, Stephanie, and Yaakov Stern. 2019. "Consideration of Cognitive Reserve." In *Handbook on the Neuropsychology of Aging and Dementia*, edited by Lisa D. Ravdin and Heather L. Katzen, 11–23. Cham, Switzerland: Springer.

Darmon, Nicole, and Adam Drewnowski. 2008. "Does Social Class Predict Diet Quality?" *American Journal of Clinical Nutrition* 87 (5): 1107–1117.

Ehninger, Dan, Frauke Neff, and Kan Xie. 2014. "Longevity, Aging and Rapamycin." *Cellular and Molecular Life Sciences* 71 (22): 4325–4346.

Estes, Carroll L., and Elizabeth A. Binney. 1989. "The Biomedicalization of Aging: Dangers and Dilemmas." *Gerontologist* 29 (5): 587–596. https://doi.org/10.1093/geront/29.5.587.

Fleck, Ludwik. 1981. *Genesis and Development of a Scientific Fact*. Edited by Thaddeus J. Trenn and Robert K. Merton. Translated by Frederick Bradley. Chicago: University of Chicago Press.

Fontana, Luigi, Brian K. Kennedy, Valter D. Longo, Douglas Seals, and Simon Melov. 2014. "Medical Research: Treat Ageing." *Nature News* 511 (7510): 405.

Fontana, Luigi, and Samuel Klein. 2007. "Aging, Adiposity, and Calorie Restriction." *JAMA* 297 (9): 986–994.

Forbes, Dorothy, Sean Forbes, Debra G. Morgan, Maureen Markle-Reid, Jennifer Wood, and Ivan Culum. 2008. "Physical Activity Programs for Persons with Dementia." *Cochrane Database of Systematic Reviews*, no. 3. https://doi.org/10.1002/14651858.CD006489.pub2.

Gadamer, Hans-Georg. 2004. *Truth and Method*. New York: Continuum International Publishing Group.

Giovacchini, Giampiero, Elisabetta Giovannini, Elisa Borsò, Patrizia Lazzeri, Mattia Riondato, Rossella Leoncini, Valerio Duce, Luigi Mansi, and Andrea Ciarmiello. 2019. "The Brain Cognitive Reserve Hypothesis: A Review with Emphasis on the Contribution of Nuclear Medicine Neuroimaging Techniques." *Journal of Cellular Physiology* 234: 14865–14872.

Heilbronn, Leonie K., and Eric Ravussin. 2003. "Calorie Restriction and Aging: Review of the Literature and Implications for Studies in Humans." *American Journal of Clinical Nutrition* 78 (3): 361–369. https://doi.org/10.1093/ajcn/78.3.361.

Katz, S. 2020. "Precarious Life, Human Development and the Life Course: Critical Intersections." In *Precarity and Ageing: Understanding Insecurity and Risk in Later Life*, edited by Amanda Grenier, Chris Phillipson, and Richard A. Settersten Jr., 41–65. Bristol: Policy Press.

Kelaiditi, Eirini, Gabor Abellan van Kan, and Matteo Cesari. 2014. "Frailty: Role of Nutrition and Exercise." *Current Opinion in Clinical Nutrition & Metabolic Care* 17 (1): 32–39. https://doi.org/10.1097/mco.0000000000000008.

Landi, Francesco, Angela M. Abbatecola, Mauro Provinciali, Andrea Corsonello, Silvia Bustacchini, Luca Manigrasso, Antonio Cherubini, Roberto Bernabei, and Fabrizia Lattanzio. 2010. "Moving against Frailty: Does Physical Activity Matter?" *Biogerontology* 11 (5): 537–545.

Landi, Francesco, Riccardo Calvani, Matteo Tosato, Anna Maria Martone, Roberto Bernabei, Graziano Onder, and Emanuele Marzetti. 2016. "Impact of Physical Function Impairment and Multimorbidity on Mortality among Community-Living Older Persons with Sarcopaenia: Results from the ilSIRENTE Prospective Cohort Study." *BMJ Open* 6 (7): e008281. https://doi.org/10.1136/bmjopen-2015-008281.

Landi, Francesco, Graziano Onder, Iain Carpenter, Matteo Cesari, Manuel Soldato, and Roberto Bernabei. 2007. "Physical Activity Prevented Functional Decline among Frail Community-Living Elderly Subjects in an International Observational Study." *Journal of Clinical Epidemiology* 60 (5): 518–524. https://doi.org/10.1016/j.jclinepi.2006.09.010.

Landi, Francesco, Andrea Russo, Christian Barillaro, Matteo Cesari, Marco Pahor, Paola Danese, Roberto Bernabei, and Graziano Onder. 2007. "Physical Activity and Risk of Cognitive Impairment among Older Persons Living in the Community." *Aging Clinical and Experimental Research* 19 (5): 410–416.

Laurin, Danielle, René Verreault, Joan Lindsay, Kathleen MacPherson, and Kenneth Rockwood. 2001. "Physical Activity and Risk of Cognitive Impairment and Dementia in Elderly Persons." *Archives of Neurology* 58 (3): 498–504.

Leibing, Annette. 2014. "The Earlier the Better: Alzheimer's Prevention, Early Detection, and the Quest for Pharmacological Interventions." *Culture, Medicine, and Psychiatry* 38 (2): 217–236.

———. 2018. "Situated Prevention: Framing the 'New Dementia.'" *Journal of Law, Medicine & Ethics* 46 (3): 704–716.

Leibing, Annette, and Antje Kampf. 2013. "Neither Body nor Brain: Comparing Preventive Attitudes to Prostate Cancer and Alzheimer's Disease." *Body & Society* 19 (4): 61–91.

Lim, Wee-Shiong, Marco Canevelli, and Matteo Cesari. 2018. "Editorial: Dementia, Frailty and Aging." *Frontiers in Medicine* 5: 168. https://doi.org/10.3389/fmed.2018.00168.

Loughrey, David G., Sara Lavecchia, Sabina Brennan, Brian A. Lawlor, and Michelle E. Kelly. 2017. "The Impact of the Mediterranean Diet on the Cognitive Functioning of Healthy Older Adults: A Systematic Review and Meta-Analysis." *Advances in Nutrition* 8 (4): 571–586.

Lourida, Ilianna, Maya Soni, Joanna Thompson-Coon, Nitin Purandare, Iain A. Lang, Obioha C. Ukoumunne, and David J. Llewellyn. 2013. "Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review." *Epidemiology* 24 (4): 479–489.

Löwy, Ilana. 1988. "Ludwik Fleck on the Social Construction of Medical Knowledge." *Sociology of Health & Illness* 10 (2): 133–155.

Martin-Montalvo, Alejandro, Evi M. Mercken, Sarah J. Mitchell, Hector H. Palacios, Patricia L. Mote, Morten Scheibye-Knudsen, Ana P. Gomes, et al. 2013. "Metformin Improves Healthspan and Lifespan in Mice." *Nature Communications* 4: 2192. https://doi.org/10.1038/ncomms3192, https://www.nature.com/articles/ncomms3192#supplementary-information.

Mercken, Evi M., Seth D. Crosby, Dudley W. Lamming, Lellean JeBailey, Susan Krzysik-Walker, Dennis T. Villareal, Miriam Capri, Claudio Franceschi, Yongqing Zhang,

and Kevin Becker. 2013. "Calorie Restriction in Humans Inhibits the PI 3 K/AKT Pathway and Induces a Younger Transcription Profile." *Aging Cell* 12 (4): 645–651.
Mitnitski, Arnold, and Kenneth Rockwood. 2007. "Frailty in Relation to the Accumulation of Deficits." *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 62 (7): 722–727. https://doi.org/10.1093/gerona/62.7.722.
Morley, John E., Bruno Vellas, G. Abellan van Kan, Stefan D. Anker, Juergen M. Bauer, Roberto Bernabei, Matteo Cesari, et al. 2013. "Frailty Consensus: A Call to Action." *Journal of the American Medical Directors Association* 14 (6): 392–397. https://doi.org/10.1016/j.jamda.2013.03.022.
National Academies of Sciences, Engineering, and Medicine. 2017. *Preventing Cognitive Decline and Dementia: A Way Forward*. Washington, DC: National Academies Press.
Ng, Tze Pin, Liang Feng, Keng Bee Yap, Tih Shih Lee, Chay Hoon Tan, and Bengt Winblad. 2014. "Long-Term Metformin Usage and Cognitive Function among Older Adults with Diabetes." *Journal of Alzheimer's Disease* 41 (1): 61–68.
Ou, Hui-Ling, and Björn Schumacher. 2018. "DNA Damage Responses and P53 in the Aging Process." *Blood* 131 (5): 488–495.
Payette, Hélène, and Bryna Shatenstein. 2005. "Determinants of Healthy Eating in Community-Dwelling Elderly People." *Canadian Journal of Public Health/Revue Canadienne de Sante'e Publique* 96: S27–31.
Petersson, Sara Danuta, and Elena Philippou. 2016. "Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review of the Evidence." *Advances in Nutrition* 7 (5): 889–904.
Pettigrew, Corinne, and Anja Soldan. 2019. "Defining Cognitive Reserve and Implications for Cognitive Aging." *Current Neurology and Neuroscience Reports* 19 (1): 1.
Piskovatska, Veronika, Nadiya Stefanyshyn, Kenneth B. Storey, Alexander M. Vaiserman, and Oleh Lushchak. 2019. "Metformin as Geroprotector: Experimental and Clinical Evidence." *Biogerontology* 20 (suppl. 1): 1–16.
Rabinow, Paul. 1996. *Essays on the Anthropology of Reason*. Princeton: Princeton University Press.
Ravaglia, Ginafranco, Paola Forti, Anna Lucicesare, Nicoletta Pisacane, Elisa Rietti, Matteo Bianchin, and Edoardo Dalmonte. 2008. "Physical Activity and Dementia Risk in the Elderly: Findings from a Prospective Italian Study." *Neurology* 70 (19, part 2): 1786–1794.
Rockwood, Kenneth, and Arnold Mitnitski. 2011. "Frailty Defined by Deficit Accumulation and Geriatric Medicine Defined by Frailty." *Clinics in Geriatric Medicine* 27 (1): 17–26.
Rockwood, Kenneth, Xiaowei Song, Chris MacKnight, Howard Bergman, David B. Hogan, Ian McDowell, and Arnold Mitnitski. 2005. "A Global Clinical Measure of Fitness and Frailty in Elderly People." *Canadian Medical Association Journal* 173 (5): 489–495. https://doi.org/10.1503/cmaj.050051.
Rosano, Caterina, Eleanor M. Simonsick, Tamara B. Harris, Steven B. Kritchevsky, Jennifer Brach, Marjolein Visser, Kristine Yaffe, and Anne B. Newman. 2005. "Association between Physical and Cognitive Function in Healthy Elderly: The Health, Aging and Body Composition Study." *Neuroepidemiology* 24 (1–2): 8–14.
Rovio, Suvi, Ingemar Kåreholt, Eeva-Liisa Helkala, Matti Viitanen, Bengt Winblad, Jaakko Tuomilehto, Hilkka Soininen, Aulikki Nissinen, and Miia Kivipelto. 2005. "Leisure-Time Physical Activity at Midlife and the Risk of Dementia and Alzheimer's Disease." *Lancet Neurology* 4 (11): 705–711.

Scarmeas, Nikolaos, and Yaakov Stern. 2003. "Cognitive Reserve and Lifestyle." *Journal of Clinical and Experimental Neuropsychology* 25 (5): 625–633.

Schäfer, Daniel. 2005. "Aging, Longevity, and Diet: Historical Remarks on Calorie Intake Reduction." *Gerontology* 51 (2): 126–130.

Schubert, David, Antonio Currais, Joshua Goldberg, Kim Finley, Michael Petrascheck, and Pamela Maher. 2018. "Geroneuroprotectors: Effective Geroprotectors for the Brain." *Trends in Pharmacological Sciences* 39 (12): 1004–1007.

Shlisky, Julie, David E. Bloom, Amy R. Beaudreault, Katherine L. Tucker, Heather H. Keller, Yvonne Freund-Levi, Roger A. Fielding, Feon W. Cheng, Gordon L. Jensen, and Dayong Wu. 2017. "Nutritional Considerations for Healthy Aging and Reduction in Age-Related Chronic Disease." *Advances in Nutrition* (Bethesda, MD) 8 (1): 17–26.

Sohal, Rajindar S., and Richard Weindruch. 1996. "Oxidative Stress, Caloric Restriction, and Aging." *Science* 273 (5271): 59–63. https://doi.org/10.1126/science.273.5271.59.

Song, Xiaowei, Arnold Mitnitski, and Kenneth Rockwood. 2011. "Nontraditional Risk Factors Combine to Predict Alzheimer Disease and Dementia." *Neurology* 77 (3): 227–234.

Stephan, Blossom C. M., Tobias Kurth, Fiona E. Matthews, Carol Brayne, and Carole Dufouil. 2010. "Dementia Risk Prediction in the Population: Are Screening Models Accurate?" *Nature Reviews Neurology* 6 (6): 318.

Stern, Yaakov. 2002. "What Is Cognitive Reserve? Theory and Research Application of the Reserve Concept." *Journal of the International Neuropsychological Society* 8 (3): 448–460.

Stern, Yaakov, Eider M. Arenaza-Urquijo, David Bartrés-Faz, Sylvie Belleville, Marc Cantilon, Gael Chetelat, Michael Ewers, Nicolai Franzmeier, Gerd Kempermann, and William S. Kremen. 2018. "Whitepaper: Defining and Investigating Cognitive Reserve, Brain Reserve, and Brain Maintenance." *Alzheimer's & Dementia*, 14 September. https://doi.org/10.1016/j.jalz.2018.07.219.

Stewart, Robert, Kamal Masaki, Qian-Li Xue, Rita Peila, Helen Petrovitch, Lon R. White, and Lenore J. Launer. 2005. "A 32-Year Prospective Study of Change in Body Weight and Incident Dementia: The Honolulu-Asia Aging Study." *Archives of Neurology* 62 (1): 55–60.

Trebbastoni, Alessandro, Marco Canevelli, Fabrizia D'Antonio, Letizia Imbriano, Livia Podda, Lidia Rendace, Alessandra Campanelli, Valentina Celano, Giuseppe Bruno, and Carlo de Lena. 2017. "The Impact of Frailty on the Risk of Conversion from Mild Cognitive Impairment to Alzheimer's Disease: Evidences from a 5-Year Observational Study." *Frontiers in Medicine* 4: 178. https://doi.org/10.3389/fmed.2017.00178.

Trendelenburg, Anne-Ulrike, Ariane C. Scheuren, P. Potter, Ralph Müller, and Ilaria Bellantuono. 2019. "Geroprotectors: A Role in the Treatment of Frailty." *Mechanisms of Ageing and Development*.

Wang, Li, Eric B. Larson, James D. Bowen, and Gerald van Belle. 2006. "Performance-Based Physical Function and Future Dementia in Older People." *Archives of Internal Medicine* 166 (10): 1115–1120.

Wei, Min, Sebastian Brandhorst, Mahshid Shelehchi, Hamed Mirzaei, Chia Wei Cheng, Julia Budniak, Susan Groshen, Wendy J. Mack, Esra Guen, and Stefano Di Biase. 2017. "Fasting-Mimicking Diet and Markers/Risk Factors for Aging, Diabe-

tes, Cancer, and Cardiovascular Disease." *Science Translational Medicine* 9 (377): eaai8700.

WHO (World Health Organization). 2015. *World Report on Ageing and Health.* Geneva: WHO.

Xu, Ming, Tamar Pirtskhalava, Joshua N. Farr, Bettina M. Weigand, Allyson K. Palmer, Megan M. Weivoda, Christina L. Inman, Mikolaj B. Ogrodnik, Christine M. Hachfeld, and Daniel G. Fraser. 2018. "Senolytics Improve Physical Function and Increase Lifespan in Old Age." *Nature Medicine* 24 (8): 1246.

Zhu, Yi, Tamara Tchkonia, Tamar Pirtskhalava, Adam C. Gower, Husheng Ding, Nino Giorgadze, Allyson K. Palmer, et al. 2015. "The Achilles' Heel of Senescent Cells: From Transcriptome to Senolytic Drugs." *Aging Cell* 14 (4): 644–658. https://doi.org/doi:10.1111/acel.12344.