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The Aging Issue

G. Wick

Introduction

Gerontology deals with an issue that affects every living organism. One may perhaps argue that bacteria and certain other single-cell organisms are not aging since they reproduce by division into equal halves with neither half being parent or descendant. One could also point to the fact that germline cells (i.e., eggs and sperm) that have been passed on from generation to generation for billions of years have been maintained alive without aging [1]. Except for these special cases, the somatic cells of all organisms undergo senescence, a process of age-dependent loss of function. Studying this phenomenon is both of theoretical and practical interest.

My personal interest in gerontological research was spawned when I was engaged in basic research focusing on the age-dependent decline of immune functions reflected by thymic involution. I was fascinated by the phenomenon of autoimmunity, the loss of immunological self-recognition leading to autoimmune diseases that begin early in life and become clinically manifest later [2]; my whole career as a gerontologist was motivated by the question of whether we can learn anything about the aging process by studying age-related diseases in animals and humans.

When we look at age-related diseases, it may be worthwhile to distinguish between those that are a primary manifestation of senescence, such as Werner's disease or Hutchinson-Gilford syndrome, and those which represent secondary phenomena, suffered as a consequence of reaching old age because our cultural evolution by far outpaces biological evolution. However, I think such a distinction between 'pure' senescence and pathological age-associated processes is a rather academic issue, raising unnecessary barriers between basic and applied gerontological research that may impair the crucial and beneficial dialogue between various disciplines. In addition, we should not forget that gerontology in a broader sense encompasses many fields outside of biology, the aging society representing one of the most important socioeconomic problems facing not only the developed world, but increasingly also the less developed countries.

Age-Related Diseases: The Price for the Vigor of Youth

In 1900, the mean life expectancy in Central Europe and the USA was about 49 years. Since that time, life expectancy has increased more than in the 10,000 years before. This has been due to advances in medicine and hygiene, as well as improvements in socioeconomic conditions.

Although the mean life expectancy has increased, this has been associated with a rather constant value for maximally attainable age. When plotted on a graph, this leads to a 'rectangularization' of the human survival curve (Fig. 1, page 2). This observation is one of many indications that the aging process is governed by both genetic and environmental factors. Discussing this issue in depth is beyond the scope of this article. Suffice it to mention that different species exhibit different maximal lifespans that show a significant correlation with their capacity to repair DNA damage.

Increasing age is fraught with increasing morbidity. The list of diseases associated with aging is long and includes diabetes, cancers, cardiovascular diseases, osteoporosis, arthrosis and dementia. It has, however, to be kept in mind that all these diseases start early in life – initially without clinical symptoms – and only become manifest in later years. Thus, diseases in older age are not the consequence of the body's failure, but rather the result of its long survival. However, in this context we should remind ourselves that the design of the human body is both astoundingly precise and surprisingly slipshod. Overall, it has been shaped by evolution to become an optimal compromise for its final destiny: reproduction. Importantly, natural selection is only effective during the reproductive period and individuals living into postreproductive age, as is the case for the majority of people in developed societies, are no longer subjected to selective pressure. The question of whether having grandparents increases the survival chances of an individual has still not been completely settled [3].

From the above-mentioned rectangular pattern of the human survival curve one can deduce that, based on an individual fixed genetic background, modification of environmental factors is presently the only tool to achieve 'healthy aging'.

The concept of pleiotropic antagonism is relevant when considering age-related diseases. It is based on the observation that genes that are beneficial early in life may play a detrimental role later on when they are expressed at sites other than their original position (pleiotropy). For instance, some genes allow for calcification of bones (*osteocalcin* and bone *sialoprotein*), making them stronger and improving fighting and fleeing capacity, but they acquire negative, antagonistic effects later in life if they are expressed elsewhere, leading, for example, to calcified atherosclerotic lesions. Therefore, the diseases of aging may be the price we pay for the vigor of youth.

It should also be reiterated that the natural rules underlying the development of age-related diseases are today skewed by the pace of change in human lifestyle (cultural evolution), which is far too fast for genetic adaptation to keep up with. Thus, we live under 21st century conditions with a pre-stone age genome. In the words of the evolutionary biologists Nesse and Williams, 'The price of not being eaten by a lion at the age of 30 may be a heart attack at 80' [4].

Anti-Aging and Science Kitsch

Often, gerontologists working in basic research at the single cell level, such as yeast, or with lower multicellular organisms, such as the worm *C. elegans* or the fruit fly *Drosophila*, are confronted with the risk of having their data overinterpreted, raising false hopes in lay people. Drum-beating by the scientists themselves in the media has

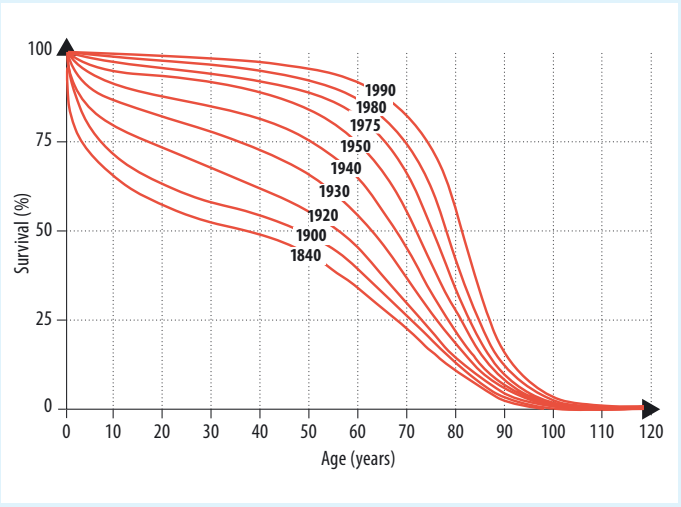

Fig. 1. Over the last 170 years, improvements in hygiene, medicine and socioeconomic conditions have resulted in more humans living longer, but the maximum attainable age has not increased.

an even more pronounced unwarranted effect. Thus, although there is a surprising homology between the genomes of *C. elegans* and men, humans are, of course, much more complex organisms. It is therefore unrealistic to translate the prolongation of the life of *C. elegans* by genetic manipution into the human situation.

Unfortunately, the distinction between serious science and fiction occasionally also led to the formulation of whole theories of aging and its prevention that are examples of agism with no empirical evidence. Although thought-provoking, I am inclined to classify this type of research as 'science kitsch', denoting kitsch as 'works executed to pander to popular demand and purely for commercial purposes' (here, selling science to the public), rather than works created as self-expression by an artist (here, scientist).

However, throughout the world, but especially in Europe, East and Southeast Asia and the USA, the propagation of 'anti-aging' medicine mainly targeting middle-aged and elderly people has become a multi-billion dollar enterprise. Most disturbingly, 'anti-aging' measures including the use of 'anti-aging' drugs or supplements of various kinds follow a clear-cut commercial trend. In a report by the US General Accounting Office to the US Senate, various 'anti-aging' health products have been scrutinized. This report provides unequivocal proof that nearly all such products not only have no beneficial effect but may even pose physical and economical harm to the customers. For these and other reasons, I am always reluctant when encountering an 'anti-aging' advertisement at a doctor's office, a wellness center, or even on the menu in a restaurant.

Healthy Aging

There is no doubt that modern geriatric medicine is able to foster maximization of a normal individual's lifespan due to advances in diagnosis, prevention and therapy, but the aging process itself is not affected. As a matter of fact, primary or intrinsic aging should be considered apart from secondary or pathological aging, which is manifested in age-related diseases.

But what is healthy aging? The World Health Organization has identified three parameters to define healthy or 'active' aging: participation and inclusion in society, physical and mental health, and security. With regard to participation and inclusion as well as the provision of security, interesting data have been gathered by a group of experts under the auspices of the German Academy of Sciences, Leopoldina [5]. This document addresses topics such as

- images of aging: notions of old age and age stereotypes
- individual development across the lifespan: development, learning, and work
- aging, work, and the company setting
- productivity and living standards in aging societies
- aging in local communities and regions
- aging and technology
- healthy aging and its limits
- aging, the family, and civil society
- aging and politics

In its report on improving the living conditions of the elderly, the Academy calls for broad reorganization of people's lives. The Academy suggests that instead of seeing ourselves as progressing from education in childhood to employment in adulthood to leisure in retirement, all three activities should be present at all three stages (Fig. 2). The report also discusses so-called 'myths' on aging, such as that the elderly are less productive, that they steal jobs from the young or that increased life expectancy creates a burden on care systems. Each are refuted. Thus, the myth that higher average life expectancy means more sickness and greater need for care is certainly unwarranted and medical progress has, for example, made strokes and heart attacks more survivable. The myth that a clash of generations is imminent is also wrong since empirical research shows that coherence within families, civil society or even politics surpasses differences between generations in these entities.

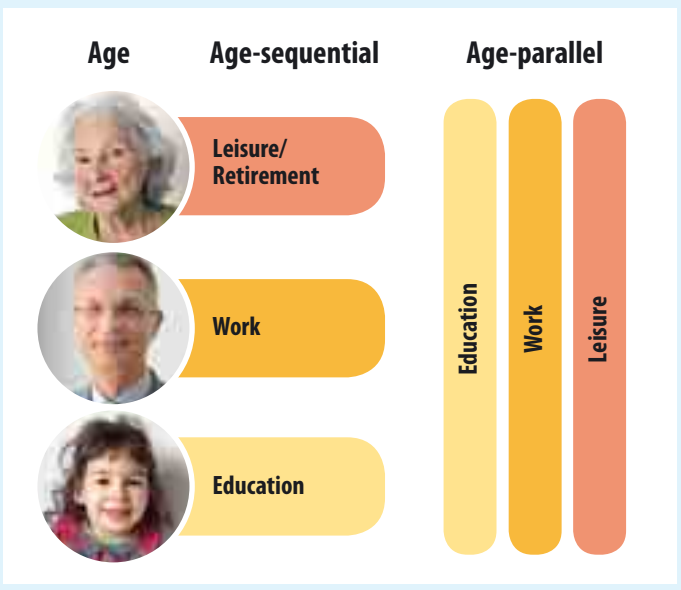

Fig. 2. According to a report by the German Academy of Sciences, successful aging in the future will depend on society's ability to reorganize itself so education, work and leisure are no longer confined to specific life stages.

Future Aims of Gerontological Research

In basic research, emphasis should be put on the distinction of genetic versus environmental factors that influence the aging process on a cellular and organismal level. With respect to genetic factors, genome-wide association studies will certainly reveal genetic facets of the aging process that have so far gone unnoticed in purely hypothesis-driven investigations. Perhaps even more important, studies of epigenetic influence will bridge the gap between genetics and environment. In a reverse approach, the molecular basis of known environmental factors that modulate the maximum lifetime should be further elucidated, e.g., the molecular pathways mediating the effect of calorie restriction, physical exercise and hormone replacement therapy.

Models for aging research range from yeast and lower animals, such as *C. elegans* and *Drosophila*, to higher species like primates. However, there is still ample room for improvement and extension, for example, to very long-lived deep-sea organisms [6]. Also, understanding the aging process of plants is not only of theoretical but of practical relevance. Progress in regenerative biology (e.g., stem cell therapy) should be quickly translated into geriatric application.

Coping with the aging of mankind will require scientific efforts in many different disciplines above and beyond biology and medicine. Here, developing ways to tap the physical and intellectual potential of the elderly, especially their professional experience, will be of utmost importance.

The use of modern tools of information technology for the improvement of ambient assisted living will have a particular impact on the elderly (see also the article on p. 11). We must not overlook the political aspects, either. Persuading our leaders to make decisions in areas such as pension reform that are based on sound scientific facts is a task which will call for all the missionary efforts gerontologists can summon up, but it is nonetheless crucial.

Final Thoughts on Healthy Aging

From a pragmatic viewpoint, 'successful healthy aging' can be achieved by following the rules of common sense. I have coined a phrase (the three L's in German) that encompasses this fact in a nutshell: Lieben, Laufen, Lernen [7].

Lieben (to love) not only stands for love towards a partner, if still present, but in general for friendship and social contacts. Laufen (to run) does not really stand for jogging – that may even be detrimental for the elderly – but for looking after one's body in general, and physical exercise, healthy diet and avoiding addictive toxins in particular. Lernen (to learn) stands for life-long learning and constant, intellectual stimulation. As a matter of fact, these recommendations, almost trivial at first sight, can all be underpinned by biochemical data. Lack of positive social contacts leads to an increase of stress hormones entailing immunosuppression that causes higher susceptibility to infection and a lower immune response to vaccinations. Physical exercise brings about an improved ratio of high-density lipoproteins to low-density lipoproteins, i.e., an increase of 'good cholesterol' over 'bad cholesterol'. Constant intellectual activities postpone the possible emergence of Alzheimer's disease by stimulating neuronal interconnections in the brain, taking advantage of the plasticity of the central nervous system.

The goal of gerontological research should, of course, not be to add more years to our life, but rather to add life to our years. Thus, in my opinion, significant prolongation of the human lifespan is not a primary issue, but extension of life in good health should be the scientific focus in the near future, with emphasis on fast translation of basic scientific knowledge from all disciplines into practical use.

Interestingly, being preoccupied scientifically with the problem of aging seems to help me cope with my own aging process.

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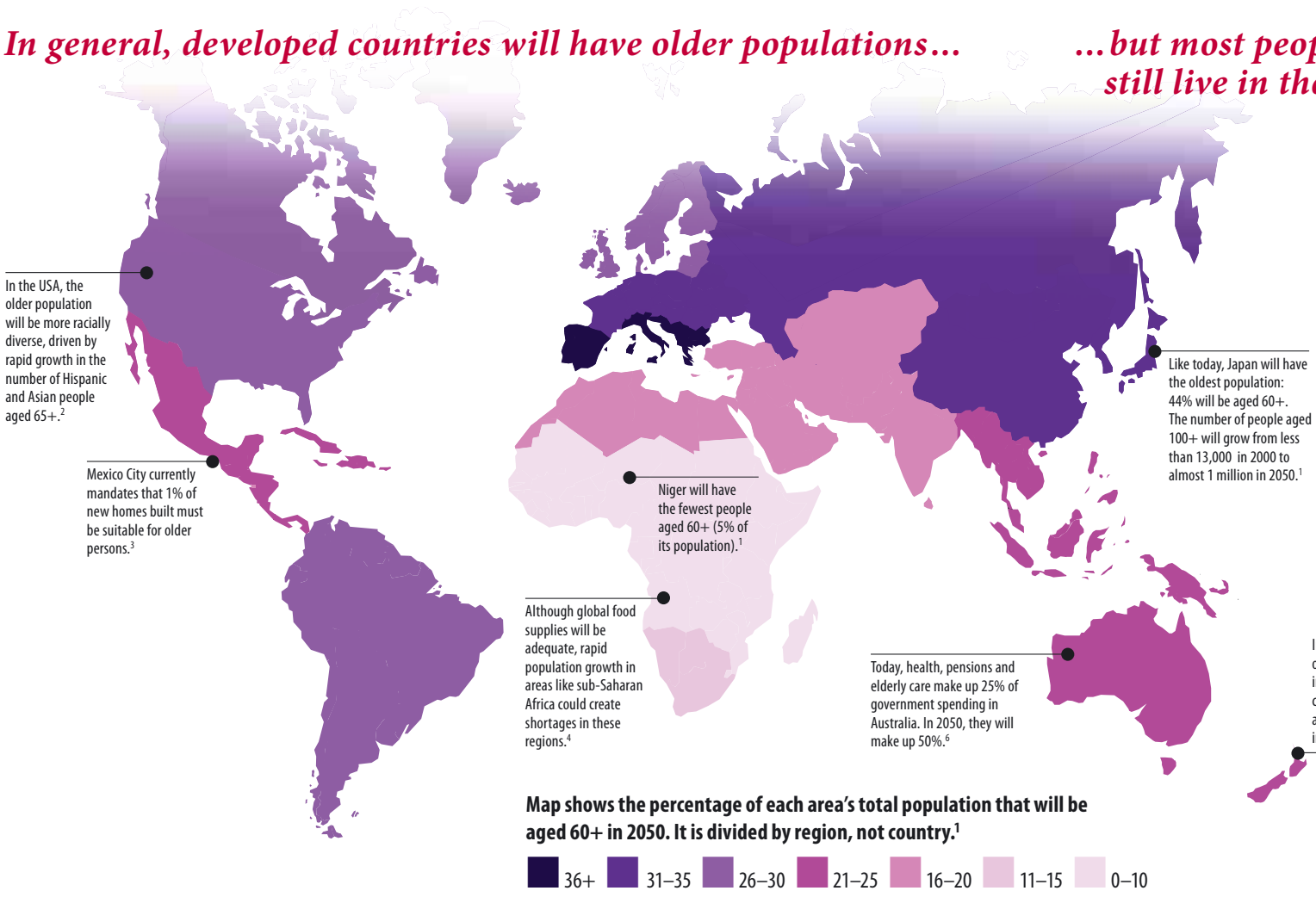
The World in 2050

The next four decades will see dramatic changes in the age structure of the global population. How big those changes will be, when they will happen and where they will be most felt are subjects of much concern. We take a look at some of the projections.

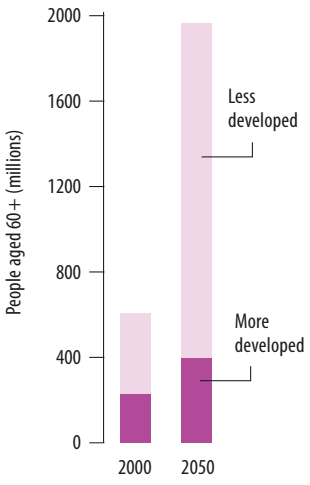
In general, developed countries will have older populations…

…but most people aged 60+ will still live in the developing world[7]



Map shows the percentage of each area's total population that will be aged 60+ in 2050. It is divided by region, not country.[1]

36+ | 31–35 | 26–30 | 21–25 | 16–20 | 11–15 | 0–10



76 YEARS
Global life expectancy in 2050, up from 68 years today.[7]

ONE IN FIVE
By 2050, one in five people will be aged 60+; they will outnumber people under 14.[1]

4.1 MILLION
Number of people aged 100+ globally in 2050, up from 454,000 in 2009.[1]

Ratio of Workers to Seniors

The chart shows the number of people of working age (15–64) per person aged 65+ globally. In developed countries today, only 24% of men and 14% of women aged 60+ are economically active. The dramatic fall in the ratio of workers to seniors will have major impacts on the solvency of social security and healthcare systems.[1]

The Built Environment

Driven by growth in African and Asian cities, urbanization will be a major trend of the 21st century. By 2050, up to 70% of the world's population will live in cities. WHO sees making urban environments more friendly to seniors crucial to healthy, active aging.

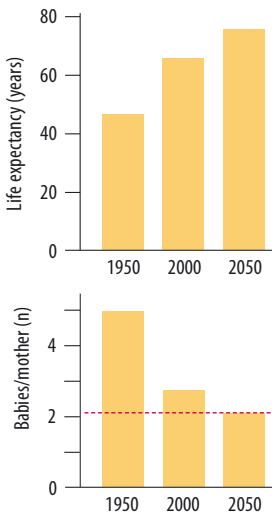
Among its aims: appropriate housing; barrier-free buildings; seating areas; accessible public transit, and enabling participation in community life.[3]

'In general, training for health professionals includes little if any instruction about specific care for older people.'
World Health Organization

Longer Life, Fewer Babies: The Causes of Demographic Shift

The aging of the global population is driven by two trends: declining fertility and increasing life expectancy. By 2050, life expectancy (top graph) will have risen by a decade, to hit 76 years. The most dramatic rises will be in the less developed regions. The gap in life expectancy between the developed and developing worlds will narrow to seven years (from 12 years in 2000).

Globally, fertility will decline from five babies per mother in 1950 to the replacement level of 2.1 in 2050 (bottom graph). In developed countries, fertility hit a record low in 2000–2005 of 1.5 children per woman.[7]

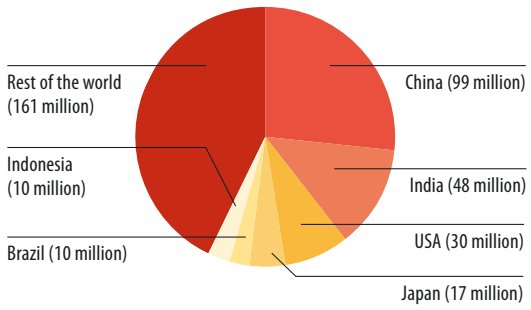


Number of Hip Fractures Worldwide (in millions)

Fractures associated with osteoporosis are a major cause of disability among the elderly. As the world ages, bone fractures are likely to become a greater health burden, especially among the female population, which is at greater risk of osteoporosis. In 2001–2002, the Australian government estimated the average cost of a fall among people aged 65+ to be USD 3,611.[8]

The Oldest Old

In 2050, six countries will have populations of more than 10 million people aged 80+, accounting for 57% of the world's 'oldest old'.[7]



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Will We Ever Know What Causes Aging?

Aging is a process that affects every person on the planet, yet we still struggle to explain how and why it occurs. Now, after decades of research, we may finally be in sight of a unified theory to explain how we get old.

T. Fulop

Photo: U. Willin

Since mankind developed philosophical thinking, two important existential questions have loomed large in our minds: why we age and why we die. This, of course, led to the next question: how can we stay young forever, free of disease and suffering? We still do not know this as, despite all our modern advances in molecular biology and genetics, the real causes of aging are still to be unraveled.

Aging can be defined as a decline in performance and fitness with advancing age, creating difficulty in adapting to new situations. It is an almost universal feature of living organisms.

What do we know presently on the possible causes of aging? More than 300 theories exist but each of them is only a snapshot on aging, even if they pretend to integrate a broad range of the existing theories. The most important ideas – those that have really helped to progress research and further our understanding – are the evolutionary theories, the oxidative/mitochondrial theories and ideas on genetic regulation. The best way to classify these theories is to distinguish between those that are evolutionary and those that are mechanistic.

Evolution's Trade-Off

Among the evolutionary theories, two have found favor in explaining how aging emerged: antagonistic pleiotropy and disposable soma theory.

Antagonistic Pleiotropy. This theory suggests that pleiotropic genes reduce vigor and limit longevity in adults, but since they also promote fitness and reproduction in young individuals they are selected and retained in the gene pool.

Disposable Soma. Whereas persistent somatic change is necessary for normal development, it also inherently leads to the erosion of homeostasis in adults after maturation has been completed. The disposable soma theory views aging as the result of accumulating damage, caused by the body's inability to sustain proper maintenance of its entire system.

From an evolutionary perspective, aging can, then, be explained by asserting that this deficient maintenance exists because the required resources have been better invested in reproduction. Thus, a decline in homeostasis and a loss of integration among the body's interdependent systems seem to be the general mechanisms by which aging progresses over time. Consequently, this global internal dysregulation creates an environment in which the age-associated physiologic and metabolic alterations can arise as the consequences, rather than causes, of aging. When we consider the putative underlying mechanisms through which deficiencies in the maintenance requirement may act to create aging, they include differences in metabolic rate and the associated production of reactive oxygen species (ROS), as well as differences in insulin/IGF-1 signaling. Insulin/IGF-1 signaling, a prime regulator of growth, is invariably associated with lifespan regulation in mammals. In animals, the role of these changes has been well demonstrated; however, in humans this remains to be established. Though these evolutionary theories are very appealing, they cover only a few aspects of the aging process and cannot really explain individual aging.

> Despite all our modern advances in molecular biology and genetics, the real causes of aging are still to be unraveled.

A System under Strain

There are a number of theories that explain aging in terms of progressive failures in cellular mechanisms, which lead to accumulating damage and systemic dysregulation.

Free Radicals. This is the most popular theory to explain aging, and it is based on a number of observations. There are several sources of ROS within a cell: they are generated as by-products of aerobic respiration and various other catabolic and anabolic processes. Mitochondria are the major producers of ROS, the bulk of which are generated in the electron transport chain. ROS can also be produced in response to various environmental stimuli, such as growth factors, inflammatory cytokines, ionizing radiation, UV, chemical oxidants, chemotherapeutics, hyperoxia, toxins and transition metals. Concomitantly, the damaging effects of ROS can be neutralized via elevated antioxidant defenses, which scavenge ROS to nontoxic forms. Such defensive entities include superoxide dismutase, catalase and glutathione peroxidase, as well as nutrition-derived antioxidant agents, such as vitamins C and E.

Mitochondrial Damage. Because mitochondria are the major producers of ROS in mammalian cells, mitochondrial DNA (mtDNA) is especially vulnerable to oxidative damage. Thus, as both the major producer and primary target of ROS, mitochondria might play an important role in aging. The mitochondrial theory of aging, which complements the free radical theory, proposes that oxidative damage to various macromolecules (e.g. DNA/mtDNA, proteins, lipids) leads to cellular dysfunction and is responsible for aging. Moreover, as mtDNA encodes essential components of the machinery for oxidative phosphorylation and protein synthesis, oxidative damage to mtDNA may induce mutations that impair the assembly or function of the respiratory chain, which will in turn trigger further accumulation of ROS. Thus, a vicious cycle is created that leads to energy depletion in the cell and ultimately its death. The consequences would be particularly deleterious for nonproliferative cells in organs such as the heart and brain that have only minimal capacity to regenerate. Mitochondria, then, are thought to play an important role in the pathogenesis of age-associated neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington's disease.

These theories are appealing, and they have been corroborated to some extent by experimental results, but they cannot be taken without caution. Much research will be necessary, mainly in humans, before we can confidently accept this theory as an explanation for aging.

Telomere Theory. With age, chromosomes become increasingly damaged. Telomeres, which are cap-like nucleopro-

teins at the tips of chromosomes, prevent such damage. When the protective function of telomeres fails – due to excessive telomere shortening resulting from multiple cellular divisions or sustained oxidative stress – a standard response is triggered that activates the cell's DNA repair machinery. This response, which involves the protein p53, halts DNA replication and other processes involved in cellular proliferation. This process results in cellular replicative senescence, where normal somatic cells enter an irreversible growth arrest after a finite number of cell divisions. Consequently, this has been proposed to contribute to organismal aging (Hayflick's theory). Senescent cells have high levels of intracellular ROS and accumulated oxidative damage to their DNA and protein. Thus, the telomere theory of aging holds that, over the course of multiple cell divisions, telomere function is degraded, which brings cellular proliferation to an end and, ultimately, leads to cell death. Cells that have rapid turnover rates, such as blood and endothelial cells, would be particularly affected. Although this theory helps us understand replicative senescence, there is still a debate over how great is its contribution to organismal aging and how it can be related to the evolutionary theories. And while current thinking rejects previously held ideas that these cells are biologically inert, we do not know exactly how they are active or what their biological and pathological consequences are, especially in relation to aging.

> A decline in homeostasis and a loss of integration among the body's interdependent systems seem to be the general mechanisms by which aging progresses over time.

A Unified Theory of Aging

One other important question is whether specific age-associated biomarkers can be determined. Among the aims of most ongoing longitudinal studies (e.g. the Women's Health and Aging Study, the Baltimore Longitudinal Study of Aging, the InCHIANTI, and Nutrition and Age [NUAGE] studies) is the discovery of age-associated biomarkers. There are numerous candidates (e.g. inflammatory, nutritional and metabolic markers), but to date none of them have been experimentally shown to be exclusively age-related and not impacted by other factors, such as diseases. Until this search is complete, it will be very difficult to find a unified theory of aging. However, it is still possible to integrate most of the above theories into a single mechanistic framework for understanding the aging process. This framework proposes that much of the aging process is attributable to a progressive breakdown in the regulatory relationships that maintain homeostasis. Because homeostasis is a property of the regulatory system as a whole, rather than its component parts, it is likely that a breakdown in one area of the system will influence the others. For example, both oxidative stress and inflammation likely contribute to system dysregulation, but they themselves are also likely influenced by dysregulation in the system more generally. This framework is thus a powerful tool for integrating much of our current knowledge, and for beginning to understand the links between different types of dysregulation.

It is not yet clear whether there is a single, unified process of dysregulation, or whether there are multiple, semi-independent processes. Indeed, one of the key benefits of a biomarker approach to aging biology is the potential to quantify, identify and characterize whatever dysregulatory processes may be operating. Dysregulation itself may be a fundamental aging mechanism that is based on systemic structural weakness, or it may be a consequence of other factors, such as genetics, epigenetics, psychology and/or the environment. In either case, currently available data strongly suggest that dysregulation does occur, does underlie and precede multiple disease processes, and is affected by social and environmental factors.

In this context, biomarkers can be considered measurable physiological parameters that indicate underlying processes of dysregulation. Most putative aging biomarkers studied to date are blood metabolites, but it is likely that there are other types of important biomarkers as well. In particular, the neuroendocrine system plays a critical regulatory role at the organism level, and it is likely that neuroendocrine dysregulation leads to specific types of aging-related dysregulation throughout the body. Molecular imaging technologies and bioinformatics approaches to gene expression and proteomics have great potential in the study of dysregulation and biomarkers. Finding ways to integrate the measurement of several biomarkers will be important if there are several semi-independent dysregulatory processes at work.

Today, however, we can say that there is a consensus emerging that aging is a multifactorial process that is genetically determined and heavily influenced by the environment. Most aging theories postulate a single physiological cause of aging; probably they are correct to a certain degree for certain aspects of aging, but none of them appears to be fully satisfactory. It is likely that the factors at play in many of the proposed theories actually interact with each other in a complex way.

I believe that we are very close to unraveling the mystery that is the aging process. However, in order to solve this puzzle, we should not be thinking of individual theories but rather in terms of a complex system of dysregulation that, when taken together, creates the process we call aging.

Photo: U. Willin

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Why Does Aging Stop?

Aging is characterized by declines in the capacity to survive and reproduce but, counter-intuitively, these declines cease in later adult life. To find out why this happens, researchers have turned to experiments with *Drosophila*. The results suggest natural selection can easily influence the rate and duration of aging, raising the tantalizing question: Could we choose when human aging stops?

M.R. Rose
L.D. Mueller

Jeanne Calment (1875–1997), at the age of 120 years

When Jeanne Calment died on August 4, 1997, she had attained a greater lifespan than any other human, at least among those with verified vital records. She is the only person whom we are sure survived more than 120 years, dying at the age of 122. Born on February 21, 1875, in Arles, France, she survived two world wars and the economic crises of the interwar years. Her lucidity remained intact up until her last months and she liked to tell visiting journalists how she used to sell art supplies to Vincent Van Gogh, whose time in Arles was of great significance for his development as an artist. We can be sure that her memory of him was not a false one gilded by his reputation, because she described him as a rather disagreeable and dirty customer.

In living so long, Mme Calment annihilated one of the greatest quantitative rules in biology, Gompertz's Law. Benjamin Gompertz was an actuary and self-educated mathematician who in 1825 first drew attention to the exponential rise in death rates among adults. This was regarded as a firm illustration of the inescapable deterioration that has been assumed among virtually all Western biologists and physicians who have studied aging since the time of Aristotle. Evidently, this formidable French woman did not take actuaries too seriously.

Cracks in the Wall of Death

Mme Calment stands out as a singular individual in the annals of human aging. But she is by no means alone. The Supercentenarian Research Foundation has documented more than 1,000 individuals who have lived past the age of 110. And at such late ages, there is no Gompertzian acceleration in death rates (Fig. 1a). While there is a great deal of fluctuation from year to year, the annual death rate among supercentenarians averages around 50%.

Demographers have long studied the demographic anomaly that allows supercentenarians to survive so long. In 1939, Greenwood and Irwin published a statistical analysis of death rates among English women who died in the first decades of the 20th century. To their evident surprise, they found a well-defined pattern of slowing increases in mortality after the age of 90 (Fig. 1b). They even raised the possibility that annual death rates might approach a plateau of no more than 50% per year. With Gompertzian acceleration in mortality, by contrast, extrapolating from the acceleration that takes place from 25 to 85 years of age should lead to virtually no one surviving past 105 years of age. That is, if Gompertz were always right, supercentenarians should not exist. But they do. The question is why?

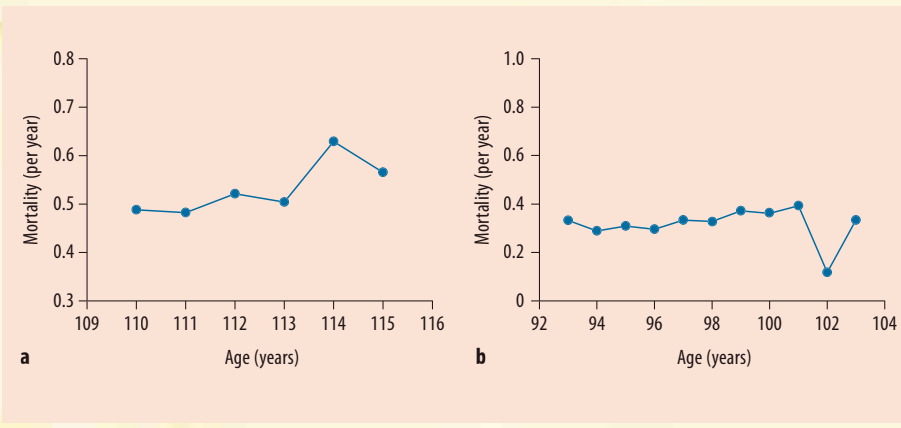

Fig. 1. In later life, mortality rates plateau. **a** Mortality rates in men and women aged over 110. **b** Mortality rates from age 93 for English women between 1900 and 1920. Figures amended from [7].

Better Evidence from Laboratory Species

There is an excellent case to be made against taking these human data seriously. Many societies revere the elderly, and the oldest old are often maintained in supervised facilities devoted to their care. Human data are never going to provide scientifically reliable evidence for a slowing or cessation of aging. That left most gerontologists unconvinced that it does eventually stop.

But things changed for gerontology in 1992, when the laboratories of James Carey and James Curtsinger published cohort mortality data from very large populations of medflies and fruit flies, respectively. Carey's data were unprecedented, involving the careful monitoring of two million medflies in a large rearing facility, and they suggested that aging in the medfly stops by 18 days of adult life. And that stop is remarkably abrupt.

In our laboratories, we study the evolution of life-history, particularly aging, and we too have collected data of this kind using fruit flies. We have seen that aging slows or stops reproducibly in fruit flies as early as 30 days of adult life. At the very latest ages, the fly mortality rates fluctuate – as seen among supercentenarians – but the consistent upward trend in mortality seen at earlier ages has stopped.

Multiple laboratories have now shown that aging stops at late ages in the 'model organisms', such as fruit flies and nematodes, that scientists like to work with. Showing that aging stops in the lab requires mortality rate data from very large experimental cohorts. And lab conditions have to be stable and free of contagious disease. But otherwise the cessation of aging is not tricky to observe.

Is It an Effect of Heterogeneity?

These findings have challenged the assumption that aging is a process of deterioration that continues without stopping. But they do not explain *why* aging stops. There have been two main proposals to solve this scientific puzzle. We will explain the more popular idea first: heterogeneity.

Starting with Greenwood and Irwin in 1939, and continuing ever since, it has been proposed that aging only seems to stop. The hypothesis is that aging at the level of the individual continues, but total mortality rates stabilize because populations contain *extreme* and *lifelong* heterogeneity for robustness. That is, some individuals are imagined to be highly vulnerable, and thus die off early in the large cohorts needed to estimate mortality rates. This hypothetical dying off of the vulnerable leaves only the more robust individuals, who continue to age, but do so at a slower rate than the population did when it still contained the less robust individuals mixed in. For this theory to work, it requires differences in robustness that are very large in magnitude, differences that have never been directly observed in any experimental cohort of animals maintained in good conditions.

An intense effort has been made to find evidence in support of this hypothesis – we have attempted ourselves – but so far it has not been found.

Thus, we face the possibility that aging does in fact stop among individuals, not just heterogeneous cohorts. But why, and how? That is where the second theory comes in, the one that we have developed and tested.

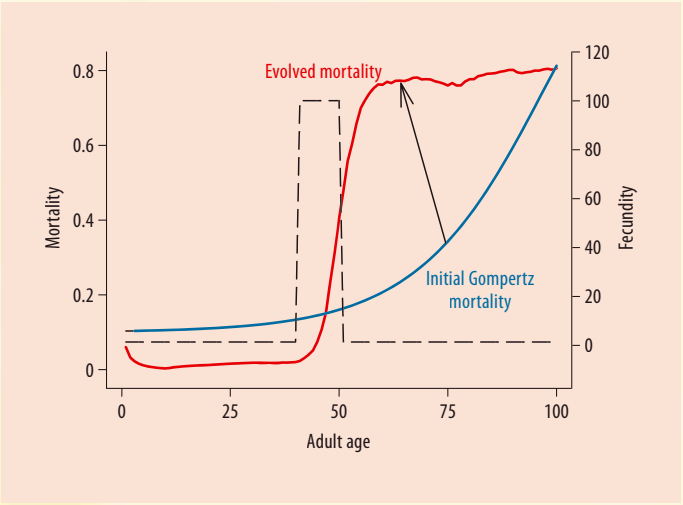

Fig. 2. The theoretical evolution of late-life mortality. The simulation started with a Gompertz pattern of mortality. After simulated evolution, mortality in late life plateaus following the peak of reproduction [2, 8]. Dashed line = Period of peak reproduction.

Evolution of When Aging Stops: Theory

In 1992, when the first insect studies found that aging stops, we were horrified. As evolutionary biologists, we thought that aging must continue without stopping. We derived this expectation from William Hamilton's 1966 theory for aging, based on declining forces of natural selection with adult age [1]. Hamilton's theory implied that, after the last age of reproduction in a population's evolutionary history, natural selection is no longer sensitive to whether individuals live or die. Intuitively, we and everyone else who had studied the evolution of aging thought that this result meant that the process of aging must result in a death sentence after reproduction stops. Indeed, a death sentence to be carried out very soon.

> The aging phase of life is unusual in its consistency – virtually all functional characters undergo a steady decline. But before and after aging, physiology is much more complex.

But we went back to basic evolutionary equations for how populations evolve and, as we showed in a 1996 article, our first intuition about the impossibility of aging ceasing was wrong [2]. Evolutionary genetics allows aging to stop. Aging is not a cumulative collapse that is the result of low to negligible forces of natural selection. Instead, aging reflects the steady fall in the forces of natural selection during the first part of adulthood. At some point after that fall stops, aging stops too. An example of one of our theoretical calculations is shown in Fig. 2. The figure shows that, even if we suppose that a population starts with a Gompertzian pattern of steadily accelerating death rates, after some generations of selection evolution instead produces a pattern in which aging stops after the end of the window during which reproduction occurs.

Thus the interpretation that we, like other evolutionary biologists, had inferred from Hamilton's mathematics before 1992 was wrong: aging occurs while and for a short time after the forces of natural selection decline. But after those forces have plateaued at zero, aging can come to a full stop, at least in theory.

Evolution of When Aging Stops: Experiments with Mortality

From modeling theoretical populations, we had come up with a number of predictions. One general observation was that, when we modeled populations reproducing during a single early window of opportunity, they evolved faster aging, but it stopped sooner; when we made the theoretical populations reproduce later, they evolved slower rates of aging, but aging stopped later.

To test this theoretical result, we collected data from 25 different fly populations that had been maintained with different patterns of reproduction. The results that we published in 2002 showed that aging stops in flies as predicted by our theoretical calculations [3]. No one had ever looked for evolutionary patterns like this, but they were quite clear in our data.

Results like ours for when death rates stop increasing might still be explained by some kind of heterogeneity theory in which the less robust die early, specially adjusted after the fact to fit the data. (Demographic heterogeneity theories have the strategic advantage of allowing purely speculative types of heterogeneity to explain virtually any result, much like the many astronomical objects invoked by astrology.) However, the theoretical and experimental results that we have mentioned to this point concerned only one of Hamilton's two forces of natural selection, the force of natural selection that shapes mortality.

Evolution of When Aging Stops: Experiments with Fertility

There is a second set of forces of natural selection that Hamilton identified, those which tune fecundity and virility. Those forces too eventually plateau. And the same type of theory implies, therefore, that there should be plateaus for these life history characters too. Even the common declines in the rate of reproduction should stop in experimental animals maintained under stable conditions. Virility, for example, should stabilize in older males.

In our experiments, we looked to see if reproduction plateaus too. That is, we looked for reproduction to stop aging at later adult ages, with a stabilization in age-specific fecundity and virility. The results from our fruit flies are shown in Fig. 3. As with death rates, reproductive characters achieve a steady plateau at later ages [4, 5]. Demographic aging stops in all respects, at least in fruit flies that live long enough.

As in the case of mortality, theoretical calculations of ours showed that the timing of when reproductive aging stops should *also* be manipulable by experimental evolution in the laboratory. All that was required was to compare populations that had long had different last ages of survival in our laboratory cultures of fruit flies. Our doctoral student Casandra Rauser showed that the timing of when reproductive aging stops also evolves according to Hamilton's forces of natural selection acting on reproduction, as predicted [6]. Populations that were kept as adults longer also stopped their reproductive aging at later ages.

Thus, in four different respects, in our studies we tested our Hamiltonian theory for why aging stops: (1) experimental evolution of a cessation of aging for mortality; (2) demonstrating a plateau in female fecundity at late ages; (3) demonstrating a plateau in male virility at late ages, and (4) experimental evolution of a cessation of aging for fecundity. And every time, our Hamiltonian theory for why aging stops passed our tests.

> The functional changes among the post-aging population may reveal features of human physiology that have remained unknown to this point.

What this means scientifically is that there is a viable theory for why aging stops. *Aging stops after the forces of natural selection stop falling.* There is usually a time lag between when Hamilton's forces stop falling and when aging stops. This is because genetic benefits of selection at earlier ages sometimes have long-lasting benefits. But when we manipulated the evolutionary forces in our laboratory, we manipulated the age at which aging stops in parallel. Please note that there is nothing special about the fruit flies or the mathematics that we have used, so as biologists, we feel that our results are potentially true in general, among all animals.

What this means medically is that long-lived humans may eventually reach a point where they are no longer deteriorating overall. As individuals, we propose that they have stopped aging. That is why Mme Calment reached 122 years of age. Her chance of dying had stabilized at around 50% per year after the age of 100, and she was one of the lucky centenarians who kept getting the better outcome of each year's coin toss deciding her survival. At least until she turned 122.

What Happens When Aging Stops?

As of 2006, we had published 10 years of theory and experiments based on our hypothesis that aging does indeed stop, but no one had shown that *physiological* aging stops when demographic aging stops. So we were curious to know what happens to functional physiological characters when demographic aging stops – when mortality rates plateau, for example. One intuitive expectation might be that functional aging should stop too, across all aspects of an animal's physiology.

So our doctoral student Parvin Shahrestani looked at four physiological characters in fruit flies (activity, climbing, and resistance to desiccation or starvation) and found that there was no common trend in their rate of decline after demographic aging stopped [5].

Our conclusion is that, after aging stops, physiology can continue to change. But we suggest the changes among the many different physiological characters average out to give stability of life history characters. We think of post-aging life as a period like that of biological development. During development, some functional characters improve, while other functional characters decline. There are capacities for healing and language learning in which young children are superior to older children. But older children are athletically and mathematically more adept than younger children. Perhaps people in post-aging will systematically lose short-term memory, but get better at long-term recollection. But this is a mere speculation. Clearly, research with this group is urgently needed.

In a sense, the aging phase of life is unusual in its consistency – virtually all functional characters, along with survival and reproduction, undergo a steady decline. In that respect, it is the simplest phase of life. But before and after aging, physiology is much more complex, with unpredictable shifts among characters.

A New Phase of Life

From its inception, the study of aging has assumed that the process continues without pause until everyone dies. Now we know that this assumption is not true.

More and more people are achieving extremely great ages. This will lead to a burgeoning group that no longer age. They will be frail. And their functional physiology will continue to change, perhaps in some respects deteriorating rapidly. But because their death rates will have stopped increasing rapidly, they will live much longer than we might expect.

As a patient population, this group may need different patterns of care than those who are still aging. As a population of great scientific interest, their functional changes may reveal features of human physiology that have remained unknown to this point. In particular, they raise the fascinating possibility that we might find a way to stop our aging long before our nineties or our centenarian years. This is a possibility that we have discussed in some detail in our 2011 book with Dr. Rauser *Does Aging Stop?* [7] and at the website 55theses.org.

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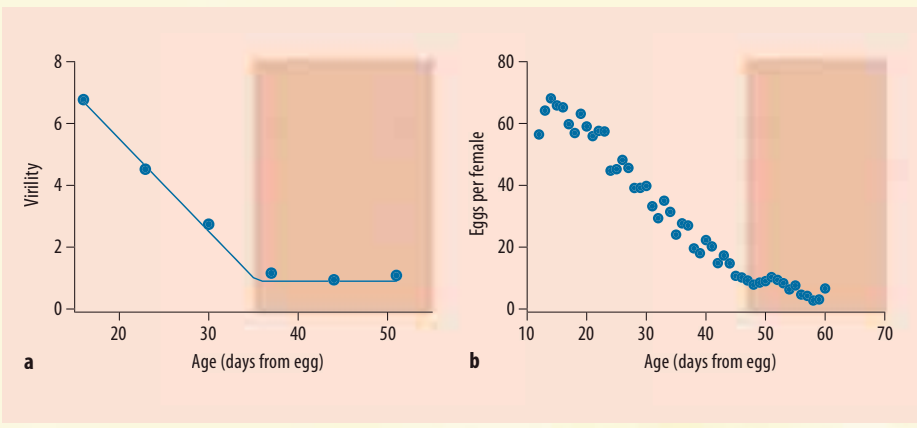

Fig. 3. Male and female reproductive aging in fruit flies *(Drosophila melanogaster).* **a** Virility of males, in virgins fertilized [4]. **b** Female fecundity. These data are taken from individuals that are at least five days from their age at death. Both plots show a cessation of reproductive aging later in life (dark area).

If we could stop human aging at 50 years, for example, the societal effects could be enormously beneficial. The vast majority of fifty-somethings can be treated effectively by modern medicine, which can often rebuild their hearts and excise their cancers. This is very different from the situation among those over 75 years of age. People that are elderly are at significant risk of not surviving medical procedures like open-heart surgery or the removal of a kidney. If we can stop aging at 50 or 55 instead, retirement would no longer be a necessity, but a luxury. Many people could continue to be productive, most importantly those who have received long years of training, like specialist physicians.

But we would emphasize that we have much still to learn about how aging stops. Like genetics early in the 20th century, we have some promising results with fruit flies, and just a few other species. Now we need to see how well these findings generalize. And their application to medicine should be hesitant at first.

Still, the question remains. Would you be interested in having your aging stop when you are still fairly healthy? Something to think about.

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Silent

The Quiet

After age 65, a person's chances of developing Alzheimer's disease roughly double every five years. As the world population ages and more people live into and beyond their seventh decade, the number of cases of Alzheimer's will explode. Our best hope for slowing disease progression in patients lies in early intervention, but it is no simple task to spot a disease years before symptoms occur.

H. Hampel
S. Lista

As the world population ages, the number of people affected by Alzheimer's disease (AD) is likely to increase rapidly. While in 2010 there were 35.6 million people living with AD or other dementia worldwide, by 2030 that number is projected to be 65.7 million. By 2050 it could top 115 million [1]. Those numbers reflect the harsh arithmetic of AD: after age 65, a person's chance of developing an AD-related dementia roughly doubles every five years. Regardless of variations in regional prevalence, the world as a whole is facing an epidemic of AD. When you consider that in 2009 the global cost of AD and other dementias was already estimated at USD 422 billion [1], it is easy to see how the consequences of that epidemic will be devastating – economically, politically and socially.

> No currently available treatment has been demonstrated to prevent the onset of AD, a prerequisite for reducing the number of incident cases.

Tackling it will be hugely challenging, not least because the underlying AD processes in the brain begin much earlier in life than is commonly expected, long before the first subtle alterations can be diagnosed by specialist physicians through clinical symptoms such as short-term or episodic memory decline.

A Gathering Storm: The Stealthy Development of AD

AD begins silently in a pre-symptomatic stage in which a subject has AD pathology but is cognitively normal. The disease then progresses to a phase of mild cognitive impairment, before entering the third and final phase in which patients' mental abilities decline to such an extent they have difficulties with the activities of daily living.

Our present conception of AD is based on neuropathological autopsy findings in AD patients. They have shown widespread extra-cellular amyloid plaques caused by abnormal enzymatic processing and aggregation of toxic amyloid beta (Aβ) peptides (which are in turn produced from the physiologically normal β-amyloid precursor protein [APP]) and intraneuronal neurofibrillary tangles, whose major protein subunit is the abnormally hyperphosphorylated tau protein (p-tau). As the biochemical substrates of brain lesions, Aβ peptides and p-tau are believed to play a crucial role in AD development, but several additional mechanisms have been suggested, including pro-inflammatory responses, oxidative stress, mitochondrial dysfunction, programmed cell death and various genetic, epigenetic and environmental risk factors. These alterations form the basis of AD etiopathogenesis. Over time, these changes affect synaptic integrity and cause regional loss of neuronal cells, which ultimately leads to late-stage severe cognitive impairment.

Although the pathological interactions between Aβ peptides and tau proteins and their relative impact on the ultimate neurodegenerative process have been scrutinized in depth, they still remain to be fully elucidated. The current predominant hypothesis, the 'amyloid cascade model' (also called the 'amyloid deposition cycle') postulates that the decisive opening events in all AD pathogeneses are the pathological cleavage of APP, the excessive formation and aggregation of toxic soluble Aβ oligomers [2, 3] and deposition of insoluble fibrillar Aβ, with subsequent accumulation in diffuse to senile plaques (Fig. 1). This first biological 'insult' triggers, successively, a converging and self-propagating

Alarm

Epidemic of Alzheimer's Disease

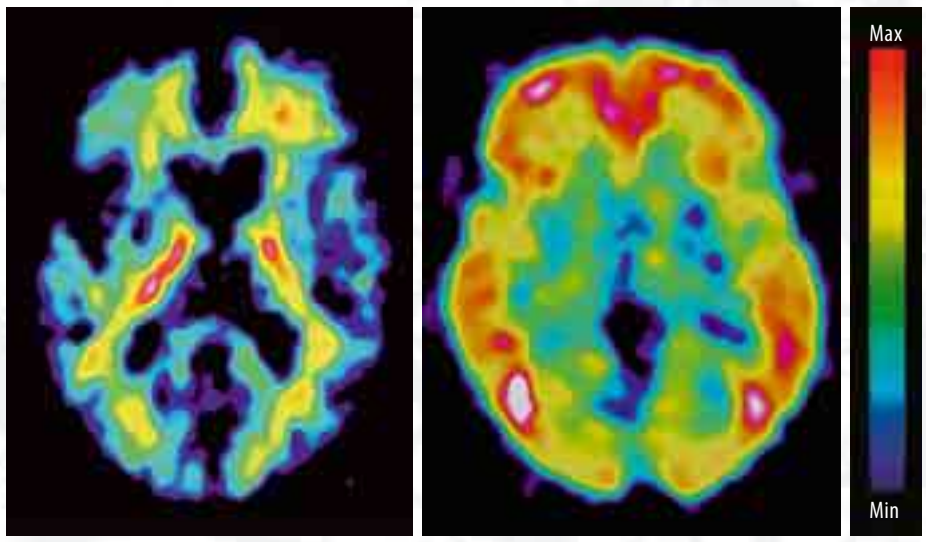

Fig. 1. Over the last 15 years, a number of amyloid-binding compounds have been developed that allow clinicians to visualize amyloid deposition in the brain. One of these is ^{11}C-PIB, which is used in this PET image and shows an amyloid load in large cortical brain regions of an AD patient (right), compared with an age-matched healthy control [7]. (Image from Uppsala PET Centre/Imanet and Karolinska University Hospital Huddinge with permission.)

neurotoxic cascade, which includes the formation of neurofibrillary tangles, a process that ultimately results in synaptic and neuronal loss in critical areas. Certain brain areas and cell types are more susceptible than others, and disease processes typically occur in the areas responsible for higher brain functions, such as memory and attention, confined within the areas of the limbic and association cortices [2].

The Potential of Biomarkers

Advances in basic and clinical research have only recently been translated into new candidate drugs with disease-modifying potential, many of which are now being evaluated in late-stage clinical trials. Studies in transgenic mouse models of AD suggest that the majority of these prospective disease-modifying compounds might be most effective early during the process of Aβ aggregation and have less impact in later stages when there is severe plaque pathology and neurodegeneration. We urgently need to identify and characterize the early stages of AD if we are to begin treatments before the potentially irreversible cascade of neurodegeneration has caused regional atrophy to reach such a stage that the brain is structurally and functionally compromised. There is, therefore, a need for a biological marker or combination of biomarkers that would make it possible to detect the AD mechanisms at work in the brain before they become symptomatic and to rapidly distinguish AD from other causes of dementia in the advent of early, subtle symptoms [3].

An ideal biomarker is one that is easy to measure by reliable and validated non-invasive methods, adequate for large-scale screenings, sensitive to the effects of pharmaceutical interventions and predictive of clinical outcomes. In recent years, there has been much effort to evaluate candidate biomarkers using techniques such as structural, functional and metabolic neuro-imaging; neuro-chemistry on cerebrospinal fluid, plasma/serum and blood; genetics and epigenetics as well as cognitive-behavioral analyses [4]. Figure 2 shows how some of these markers fit into the disease course of AD.

In addition to their use as diagnostic tools, appropriate biomarkers are essential prerequisites to accelerate and improve drug development for AD. Biomarkers that allow researchers to identify the biochemical effects of a drug in short-term pilot studies in humans would help us to recognize promising drug candidates developed by in vitro experiments and animal models. For instance, in clinical academic research, once a biomarker has been qualified for use in a specific patient population it could be of help in population selection and assessment of drug effects on disease progression. In industry-led drug discovery and development, biomarkers could simplify the selection of drug candidates, verify the mechanism of action, define dose effects and allow clinical trials to be shortened and run with reduced sample sizes [3].

Recently, there have been considerable improvements in the accuracy of clinical diagnosis, which have resulted in the first major revision of worldwide diagnostic guidelines for AD in almost 30 years. We are now seeing significant moves towards robust and well-validated clinical procedures for differentiating AD from other dementias and characterizing clinical phenotypes at baseline assessment that are supported by valid biological information derived from living patients through matured biomarker technology.

Identifying Those at Risk

Available treatments for AD either improve patients' symptoms or, more frequently, stabilize cognitive decline for periods ranging from months to a few years. No currently available treatment has been demonstrated to prevent the onset of AD, a prerequisite for reducing the number of incident cases. Primary prevention remains the ultimate goal for researchers, and much attention has focused on determining risk factors for AD. A large number of risk factors have been identified, several of which are outlined in Table 1 (over page). They broadly fall into two categories: those we cannot do much about (family history, age – notwithstanding the research outlined elsewhere in this issue on slowing the aging process) and those we can modify.

Nutrition has been investigated as a potential modifiable risk factor for dementia, and a possible relationship between it and AD has been found. Although no conclusive recommendations have been made, numerous longitudinal studies have linked

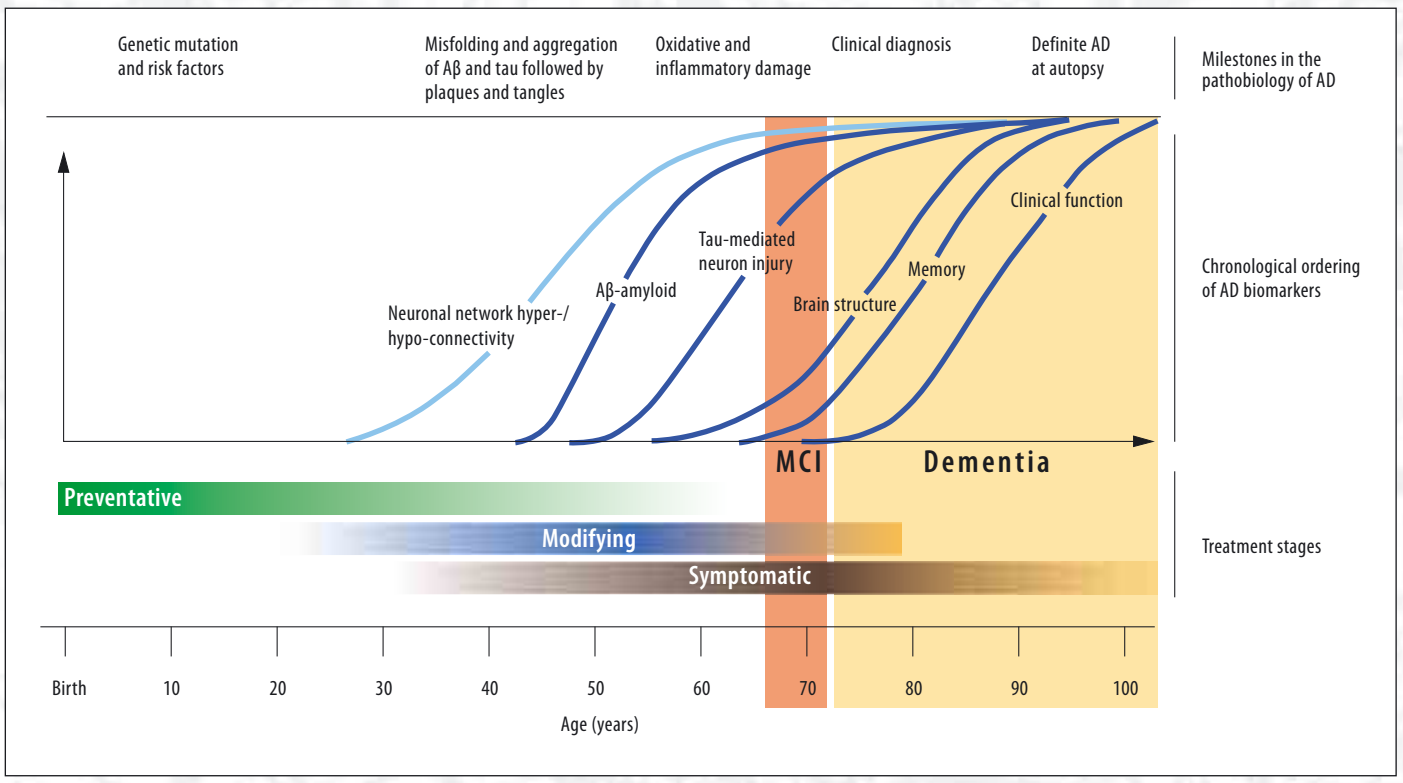

Fig. 2. A hypothetical timeline for the onset and progression of AD neurodegeneration and cognitive impairments. The colored bars indicate the periods during which preventative, disease-modifying and symptomatic interventions are likely to be most effective. The only highly predictive biomarkers for AD years before disease onset are genetic mutations that are pathogenic for familial AD. However, AD biomarkers are needed to accelerate efforts to test the efficacy of preventative and disease-modifying therapies for AD. To do this, it is important to determine the temporal ordering of AD biomarkers. A proposed model illustrating the ordering of biomarkers is shown in the upper half of this figure. The vertical axis indicates the range from normal to abnormal for each of the biomarkers as well as for measures of memory and functional impairments. Amyloid imaging and CSF Aβ are biomarkers of brain Aβ amyloidosis. CSF tau and FDG PET are biomarkers of neuron injury and degeneration while structural MRI is a biomarker of abnormal brain morphology. Functional MRI is used to detect aberrant neuronal activation and network interconnectivity patterns, and although data on the timing of the abnormalities in neuronal network activation are still emerging, this change is a possible very early biomarker, but more studies are needed to define the timing of these changes. (Adapted from [8], with permission from Elsevier.)

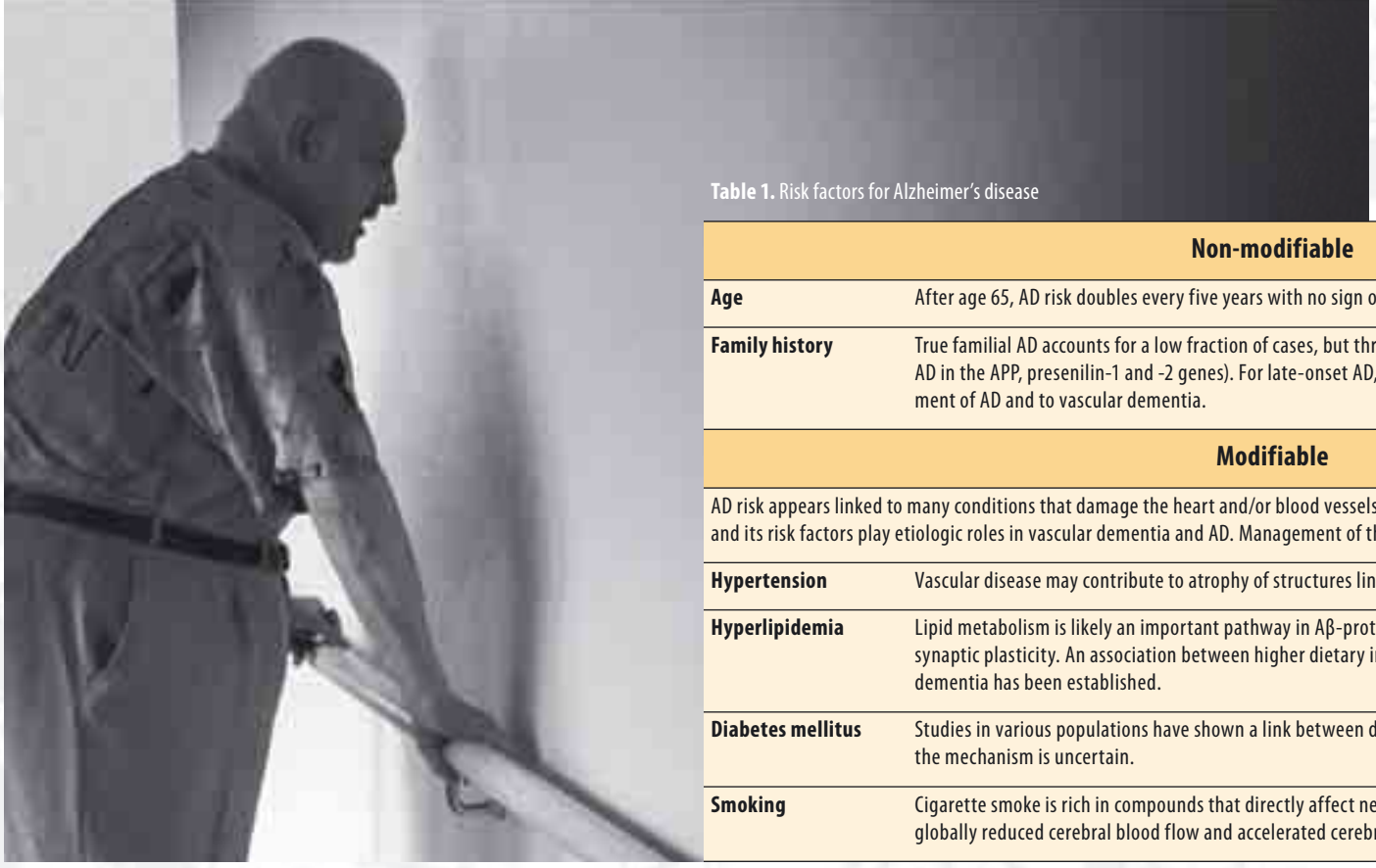

Photo: G. Schmid

Table 1. Risk factors for Alzheimer's disease

Non-modifiable	
Age	After age 65, AD risk doubles every five years with no sign of levelling off. Age is the strongest risk factor for AD.
Family history	True familial AD accounts for a low fraction of cases, but three genetic mutations have been linked with early-onset AD in the APP, presenilin-1 and -2 genes). For late-onset AD, the ApoE ε4 genotype has been linked to the development of AD and to vascular dementia.
Modifiable	
AD risk appears linked to many conditions that damage the heart and/or blood vessels, and there is increasing evidence that vascular disease and its risk factors play etiologic roles in vascular dementia and AD. Management of the following factors may diminish risk of dementia:	
Hypertension	Vascular disease may contribute to atrophy of structures linked with AD pathology.
Hyperlipidemia	Lipid metabolism is likely an important pathway in Aβ-protein deposition, tau phosphorylation and disruption of synaptic plasticity. An association between higher dietary intake of saturated fats or cholesterol and vascular dementia has been established.
Diabetes mellitus	Studies in various populations have shown a link between diabetes and AD, although this is still controversial and the mechanism is uncertain.
Smoking	Cigarette smoke is rich in compounds that directly affect neuronal integrity and function. Chronic smoking is linked to globally reduced cerebral blood flow and accelerated cerebral atrophy. Smoking-induced stroke can lead to dementia.

a Mediterranean diet with a significantly reduced risk for incident AD. The much-praised Mediterranean eating habits are characterized by a high consumption of vegetables, fruits, unrefined cereals and legumes, as well as moderate to high intake of fish and less emphasis on dairy and meat products. Olive oil predominates in the diet and, as it contains large amounts of mono-unsaturated fats and antioxidants, it has been linked to a reduced risk for coronary heart disease, better cholesterol regulation and is thought to have anti-hypertensive and anti-inflammatory properties. Following, the Mediterranean diet may affect not only the risk for AD but also the subsequent disease course resulting in a lower mortality. Physicians should, therefore, advocate action to reduce the effect of possible AD risk factors such as decreasing cholesterol, lowering high blood pressure, controlling diabetes, increasing consumption of fish, reducing consumption of dietary fat, and recommending a moderate consumption of wine.

However, the impact of risk factor modification on any particular patient is likely to be dependent on the genetic makeup, environment and lifestyle of that person. As far as lifestyle is concerned, there is increasing evidence that three components – mental, social and physical activity – are inversely associated with the risk of dementia and AD.

Exercise is believed to have a number of effects that could reduce the risk of AD. It is believed to enhance brain neurotrophic factors and modify apoptosis; it can preserve optimal cardiovascular function, prevent stroke and microvascular disease and improve regional cerebral blood flow; and, as it preserves muscle mass, exercise also reduces the risk of head trauma from falls, which has been linked to an increased risk of AD.

Education level also has a bearing on AD. There is evidence that the risk of AD is increased among people who have received shorter periods of education. Advanced education is assumed to represent a higher cognitive reserve that decreases the impact of AD on cognitive function, rather than providing a protective effect against the accumulation of AD pathology. Daily mental activities of various types have been linked to a reduced risk of dementia, as has a high level of leisure activity. There is emerging evidence that cognitive training, especially when involving novel or unfamiliar tasks, may delay cognitive decline. Therefore, to preserve cognitive function during aging, it seems reasonable that patients should be encouraged to make lifestyle modifications such as exercising regularly and engaging in social and intellectually stimulating activities.

Holding Back the Tide: Therapies for AD

At present, there is still no approved and available disease-modifying drug therapy for AD. In most clinical practices, pharmacological treatment usually begins in the late dementia stages, when the degeneration has advanced to the threshold of diagnostic certainty. Consequently, by the time treatment is initiated, the neurodegenerative damage may be so extensive that the most biologically potent anti-dementia drugs currently available, such as acetylcholinesterase inhibitors (AChEIs) and memantine, a N-methyl-D-aspartate (NMDA) receptor antagonist, are only able to moderately improve clinical symptoms and delay cognitive decline by an average of 6 to 12 months. Thus, novel therapeutic strategies are urgently needed that prevent, inhibit and delay the clinical symptoms of AD and slow biological disease progression [5]. A large number of compounds are being tested in clinical trials for therapeutic use in AD. The success of these molecules may rely on correct stratification of patient groups and accurately recognizing individuals with preclinical AD. Therefore, advances in biomarker discovery may be key to the successful application of disease-modifying compounds [2].

Cognitive intervention is an emerging therapeutic approach that could support prevention and treatment of AD. Recent research suggests that systematic activation of various brain networks by cognitive and/or physical stimulation could significantly contribute to brain health and cognitive status. Furthermore, approaches combining pharmacological and non-pharmacological interventions might effectively enhance cognitive, affective and functional skills in patients with preclinical or clinical AD. Compared with pharmacological management of AD, cognitive treatments are supposed to be less expensive and more cost-effective. Plus, they should not generate adverse events [5].

Currently, there is general support for the idea that delaying or inhibiting cognitive impairments has a bigger impact for public health and economics than providing a short period of symptomatic relief in the later stages of AD. Thus, one of the major challenges for academic research and the pharmaceutical industry is to focus on early detection and prevention. This novel perspective for drug discovery requires the development of technologies to identify the disease earlier and delay the loss of memory for as long as possible [4]. A concerted translational research effort among academic, industry and regulatory stakeholders and worldwide centers of excellence in neurodegeneration has to be advocated if we are to face the enormous challenges of the road ahead. There is no time to lose and it is necessary to forge an international alliance to prevent an AD epidemic or reduce its impact on societies before it becomes the most socially, economically and medically transformative natural disaster humanity has ever encountered [4, 6].

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The Digital World's Silver Lining

Shrinking social circles and a sense of isolation are major concerns among seniors and increase the risk of depression. The internet is celebrated for its ability to connect people, so could getting more seniors online be key to happier, healthier aging?

D. Paterson

In June of this year the USA passed a major technological milestone. It was not the launch of a new smartphone or tablet computer; in fact, it came from an unlikely place – seniors.

According to the Pew Centre's Internet and American Life Project, for the first time ever more than half of seniors reported that they used the internet or e-mail. The Pew study found that the proportion of Americans aged 65 and over who were online had grown to 53%, a result that came after several years in which the number had stagnated.

The news has been welcomed by some gerontologists, who point to a growing body of evidence that the internet can play a key role in promoting healthy aging and a sense of well-being among seniors, particularly those with mobility issues.

'We should be putting a lot of emphasis on getting older adults online,' says Shelia Cotten, a professor at the University of Alabama at Birmingham who studies technology and older people. 'Having access to information, support resources and connections with others through the internet can help older adults take better care of themselves, live independently longer and be more critical of information [they receive].'

Gerontologists have long known that increasing age is frequently accompanied by an increasing sense of isolation. Older adults often see their social networks collapse as partners and friends die, children move away and mobility issues preclude them from social activities they might have once enjoyed. A recently published study in the UK found that between 20 and 25% of seniors were persistently lonely [1], a worrying finding when you consider that social isolation has been linked with an increased risk of depression.

'The main way that internet use benefits older adults is by allowing them to connect and reconnect with members of their social networks,' says Cotten who was lead author on a 2011 study published in *Computers in Human Behavior* that showed a 'large and positive' effect of internet use on reducing depression among older people [2]. Using a database of almost 8,000 observations drawn from the 2006 Health and Retirement study, Cotten and colleagues found that use of the internet reduced the probability of depression among older adults by 20–28%. In a study conducted by an online survey in Australia, researchers found a positive correlation between belonging to an online group and sense of community and well-being [3].

Too Much Information

Although many seniors are interested in learning more about the digital world, they face considerable obstacles getting there. Writing in a recent issue of the journal *Gerontology*, Hartmut Wandke and co-workers cited six common misconceptions about older people and technology, including that they aren't interested in computers. 'Such myths are problematic,' they wrote. 'Designers and engineers often accept them as truths and neglect older users and/or apply information and communication technologies in an age-discriminating manner' [4].

This is a particular problem when it comes to social networking sites, which are of ever-growing importance on the internet. While sites have been launched to cater specifically to the boomer generation and older (e.g. Eons), mainstream sites like Facebook are a daunting prospect. 'Social networking sites, in general, present too much information on the screens,' says Cotten. 'For example, look at the new Timeline layout with Facebook. It can be daunting even to those who are not older adults. Can you imagine how it would appear to someone in their 80s or 90s? Facebook and other social networks need to think about ways to make their sites more relevant to older adults in our society.'

There are, however, a number of companies that have started developing computer interfaces with older people in mind. In the UK, a firm called Wessex Computers has started marketing its *Simplicity* device, which promises to give seniors easy access to the online world. The device is a USB stick that can plug into any computer and transform the standard interface into a simple display of five large buttons leading directly to tools such as e-mail, pictures and tutorials.

In the USA, Venture 3 Systems, which is based just outside Philadelphia, produces an entire computer, the Telikin, that is designed to be senior-friendly. It has a touchscreen interface, large print and big menu buttons and, since its development in 2010, has gathered around 13,000 users.

Fred Allegrezza, CEO of Venture 3, says that most seniors have fairly simple computing needs, desiring mainly to keep in touch with family and friends. 'Many seniors are restricted in travel by their health,' he says. 'Some have lost their driver's license due to vision or mobility, but they still have very active minds. The computer lets them interact and stay connected. Often they have retired to Florida, Arizona or other warm states, while their family is back home. Telikin allows them to have a video chat with their grandchildren, see photos of the soccer game or just e-mail the kids.'

Another benefit of entering the digital world is one that is known to bored office workers everywhere: the internet can take you places you cannot physically get to. Seniors with mobility issues can use the internet to view websites of places they used to enjoy visiting or groups they used to belong to. Cultural institutions such as Paris' Louvre art gallery and the Smithsonian National Museum of Natural History in Washington, D.C., already offer virtual tours of major works and exhibitions online, allowing people like seniors who might struggle physically or financially to visit the actual gallery to enjoy their collections on screen. 'By visiting these sites, they are able to escape the boundaries imposed by the type of communities they reside in and their health limitations,' says Cotten.

Photo: G. Schmid

The Doctor Will E-mail You Now

The internet also offers the possibility of putting seniors in greater control of their healthcare, through better provision of information about conditions and medications. Cotten points out that health literacy among older adults is generally extremely poor, yet the average doctor in the USA will spend less than 15 minutes with a patient. 'This is not much time to explain in detail procedures, treatments, etc.' she says. Online, there is no shortage of health information, like the CDC's Health Information for Older Adults web pages, which seniors can access and use to guide their behaviors.

Considering the rising costs of healthcare in developed countries, development of online ill-health prevention tools could also be financially beneficial. One Australian study noted that 60% of people aged over 50 already used the internet to seek health-related information, although it also found that there was a lack of enthusiasm for receiving unsolicited information such as cancer screening advice online.

The New Digital Age

The advent of usable voice-recognition software, such as Apple's Siri, is seen by some researchers as the first step in the development of a potentially game-changing technology for seniors. There is anecdotal evidence that seniors already find touchscreens more intuitive than keyboard and mouse-based devices, raising the possibility that voice recognition will make online access simpler for people with dexterity issues.

But while technology may be making it easier to open the door to the online world, seniors will still need a lot of support and encouragement to step through it. A report on online access among people aged over 50 in the UK from the Nominee Trust, which aims to broaden access to the internet, highlighted seniors' fear of the unknown and perceptions that technology is 'dangerous' among challenges to improving internet use among the older generations. The authors concluded that 'we need to develop and support practices that adopt practical ways of motivating and helping older people to access and use computers and the internet.' They cited a need for training and ongoing support, as well as financial subsidies, to increase the number of seniors surfing the web.

It may yet be a while before seniors are poking each other on Facebook but it seems that, as in real life, the population of the digital world is about to get a whole lot older. What that will mean for the way we age remains to be seen.

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In conversation with

Brian Kennedy

CEO, Buck Institute for Research on Aging

Anyone who doubts that the universe has a sense of irony should meet Brian Kennedy, the CEO of the Buck Institute near San Francisco. Kennedy leads the first independent institute in the USA that is dedicated to researching aging and its link to chronic diseases. Each day, he steers an organization that aims to promote 'healthspan' (essentially increasing the number of healthy years of life). But while he spends his days studying aging, Kennedy will likely have little need for his own research: his grandmother is a centenarian, meaning he is likely to be long lived, too. Kennedy's family is among the winners in life's genetic lottery.

'The best thing you can do to live longer is win that lottery,' says Kennedy, speaking on the phone from his office at the Buck's modern campus in Novato, Calif., about 25 minutes' drive north of the Golden Gate Bridge. To Kennedy and other aging researchers, people who live to 100 are a fascinating group because they exhibit 'compressed morbidity'. People who receive birthday cakes with three digits on them are more likely to have lived healthier lives than the rest of us: they do not fall sick as often, they get less aggressive forms of cancer and they are likely to live independently longer than non-centenarians (sometimes living alone until their mid-90s). But at the end of their lives, their decline in health is often precipitous. Essentially, centenarians are remarkably healthy people until shortly before they die.

Researchers like Kennedy and his colleagues at the Buck do not necessarily aim for a world where everyone lives to 100, but they are interested in trying to make those of us with average lifespans age in the healthy way centenarians do. To do this the Buck takes a two-pronged approach. About half its 19 labs look at specific age-related diseases, such as Alzheimer's or types of cancer, while the remainder conduct more basic research into the aging process in general. Recent publications include a paper in *Cell Cycle* on reversing the aging of human adult stem cells, a paper on the importance of mRNA translation in *C. elegans* aging, and one on the ability of lithium to prevent brain damage in Parkinson's disease. It is hoped that having this diverse group of researchers together under one roof will help integrate ideas from the various lines of enquiry.

Though the utility of disease-focused research is obvious, basic research into aging is, says Kennedy, a harder sell to funding bodies. In an era of tight budgets, it is easy to see why work with less direct clinical utility might slip down priority lists. In a 2011 article he wrote for the *Sacramento Bee* newspaper, Kennedy called for bodies like the NIH to move away from primarily seeking to treat disease and towards preventing it, a point he reiterates on the phone: 'At the moment, most of the funding goes towards specific diseases like Alzheimer's or cancers, but aging is a major risk factor for all of these.' Understanding the links between aging and disease could, he believes, allow us to significantly increase the number of healthy years of life through preventing these diseases.

'Nature doesn't care about aging, it cares about fitness,' says Kennedy, who sees aging as a malleable process. He points to how the naked mole rat, for instance, lives about 30 years, while its relative the mouse lives just three. 'The more we know about aging, the more we may be able to adjust it, but we might not find out unless the resources are available for important experiments,' he adds.

Kennedy identifies the institute's work on the study of rapamycin as being among its most important projects. Rapamycin is a clinically approved drug that has been found to slow aging in mice, and Buck researchers are now trying to determine how it affects aging and whether it prevents a range of age-related diseases.

Kennedy also highlights a recent finding at the institute that senescent cells secrete inflammatory proteins that may accelerate aging. 'These cells accumulate as we get old, and if we can get rid of them, it may be possible to stay healthy longer,' he says.

And that, really, is the institute's goal. Simply elongating life is of little value unless ways can be found to maintain health into old age. 'If you ask people 'Do you want to live longer?' most people will say no,' says Kennedy. 'They have seen their grandmother in a home or suffering from dementia. But when you say, 'We can let you stay more active for longer so you can play with your grandkids or play a round of golf,' they all say that is what they want. We don't want to increase unhealthy lifespan, we want to increase healthy lifespan.' (dp)

Silver

A State of Mind

Five years ago, artist Vicki Topaz turned 60 and became curious about how other women were experiencing aging. The result is *Silver: A State of Mind*, a collection of 52 startling black-and-white portraits and interviews with women who have let their hair go gray. The works are currently on display at the Buck Institute. We caught up with Topaz to talk about what it means to be an older person today.

Why did you choose only women to be in your photographs?

In American society, women have different kinds of experiences from men in dealing with gray hair, aging, the workplace and sexuality. I wanted *Silver* to help me, and others, understand if times were changing from the 1950s and 1960s when aging women were considered to be all washed up by the time they were 50 or 60-something, when gray hair represented a loss of beauty and sexual appeal and the grandmother syndrome set in.

What do you hope viewers will take from the exhibit?

Perhaps as viewers see these images and read the women's words, they will see that the aging process offers new beginnings, not endings. At this age with all of the experience and wisdom that comes with it, there is so much to offer to family, younger generations looking for role models, the workplace and the community in general. If a viewer can take from these images anything that helps crack the stigmas so long held by our society, and find a rejuvenation – well, that's what it's all about.

How have the works been received?

Silver has been very well received. There has been a fair amount of media coverage which has resulted in many women (and men) writing in to tell their own stories about embracing their gray hair, their looks, their enthusiasm for their lives as they are growing older and how they have become role models for younger women. And, in the cases of those who have survived grave illnesses, how they wear their white hair as a badge of courage and rebirth.

What color is your hair?

While my actual hair color is mostly gray, I still dye my hair – as I have for years – to a reddish auburn (my original color). It's ironic, of course, and I took a lot of ribbing from the women I was photographing but in the end, they all agreed it is about choice. No judgment.

You can check out more images from ***Silver: A State of Mind*** *at www.womenonaging.com*