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?

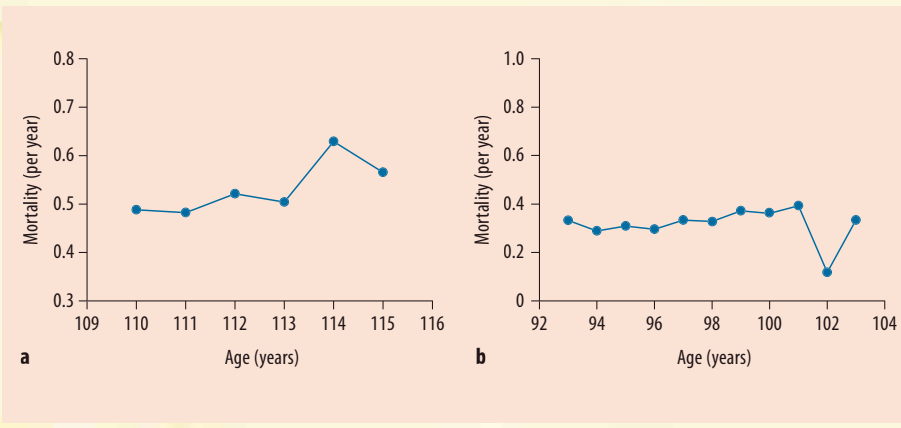

Fig. 1. In later life, mortality rates plateau. **a** Mortality rates in men and women aged over 110. **b** Mortality rates from age 93 for English women between 1900 and 1920. Figures amended from [7].

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.

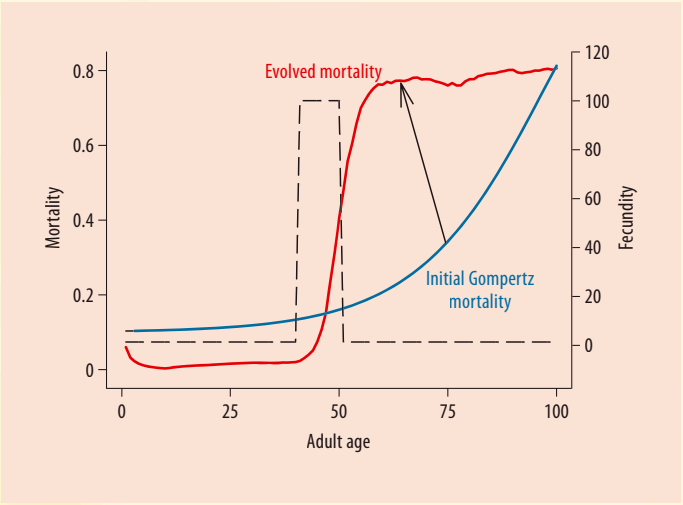

Fig. 2. The theoretical evolution of late-life mortality. The simulation started with a Gompertz pattern of mortality. After simulated evolution, mortality in late life plateaus following the peak of reproduction [2, 8]. Dashed line = Period of peak reproduction.

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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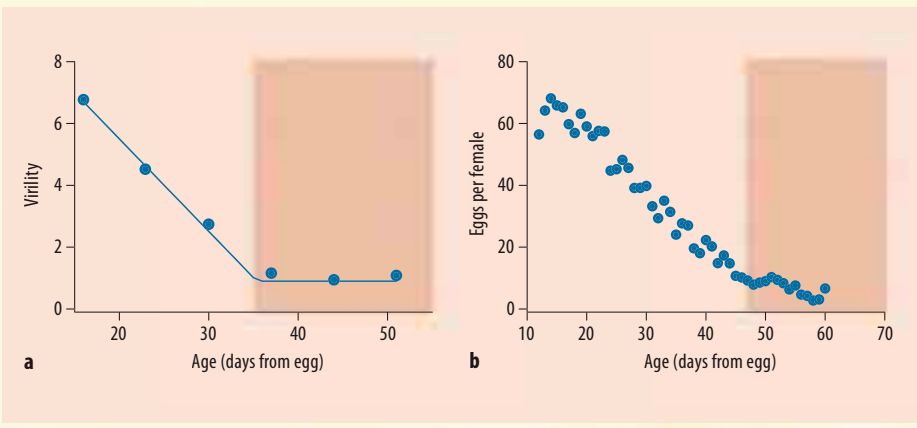

Fig. 3. Male and female reproductive aging in fruit flies *(Drosophila melanogaster).* **a** Virility of males, in virgins fertilized [4]. **b** Female fecundity. These data are taken from individuals that are at least five days from their age at death. Both plots show a cessation of reproductive aging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