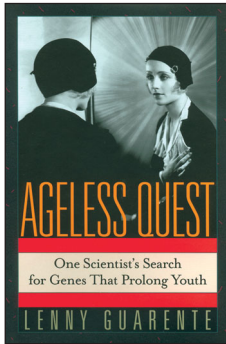


## Surviving aging


**Ageless Quest: One Scientist's Search for Genes that Prolong Youth**

by Lenny Guarente

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Reviewed by Jan Vijg

Almost since the dawn of the human race, mortality must have struck the more imaginative individuals as something that could be overcome. The first documented example of this quest for immortality can be found in the Gilgamesh epos, in which the hero makes every attempt to rescue his lover and companion, Enkidu, from death. After Gilgamesh, many bright and resourceful individuals followed his footsteps trying to beat the odds and find ways to preserve life. With the emergence of modern science in the nineteenth century, a more down-to-earth approach became the norm, and our current focus on human disease in the biomedical sciences descends directly from that nonsense attitude. Quests for immortality moved out of the mainstream and became the territory of quacks and charlatans. It is often forgotten that, as Nietzsche argued in his *Frohliche Wissenschaft (The Gay Science)*, scientists would not have emerged and blossomed were it not for the magicians, witches and alchemists who preceded them and whetted their appetite for hidden and forbidden powers. Indeed, creative scientists do not find their spiritual ancestors primarily among the logical and rational minds but among those individuals who had set their minds on turning lead into gold. In biology and medicine, the science of aging is probably the battlefield *par excellence* for investigators dreaming to be the *ubermensch*, climbing the summit of ultimate human fulfillment—provided, of course, that they can afford the risk of operating outside the main stream.

*Ageless Quest* is the story of a self-reincarnated scientist, Leonard Guarente, a professor at MIT who abandoned his well respected research on gene regulation in favor of pursuing the ancient elixir of immortality. The low level of appreciation for such a scientific mindset is nicely illustrated by his chairman's response to the author's plan to leave his mainstream yeast studies and embark on the study of aging: "you're gonna what?" Understanding this response is the key to appreciating the book, which, as its title implies, is not the story of pursuing a respectable research problem,

free of controversy, such as the development of a vaccine for AIDS or a cure for cancer. Instead, in the eyes of many a serious scientist the science of aging must look like a quest for the Holy Grail—equally confusing and with an often contradictory nest of approaches towards some elusive object.

Today the road to immortality can roughly be divided into three main branches: (i) the biometric branch, which sees aging as infinitely complex and hardly amenable to intervention; (ii) the inductive branch, which attempts to explain aging in terms of few relatively simple, universal mechanisms; and (iii) the regeneration and renewal branch, which has no interest in the analytical approach but prefers to replace and remodel. As a modern Perceval, Dr. Guarente became a pioneer of the simple, inductive branch of aging research, trying to cure aging in humans on the basis of genes and pathways discovered to increase life span in short-lived invertebrate organisms.

In many respects, *Ageless Quest* is the story of *Sir2*, a so-called silencing gene required for suppression of gene expression and genomic instability by promoting a more closed chromatin structure, and its potential role as a lightning rod for interventions in human aging. Dr. Guarente has been criticized for being oversimplistic and underestimating the complexity and multifactorial nature of aging. But he makes a strong case for a core survival mechanism, operating across multiple species, that can teach us how to postpone or ameliorate the unpleasant effects of human aging. His deceptively simple story about aging and survival goes as follows.

Aging is caused by the adverse effects of genes late in life. Such adverse gene actions are not cleansed by natural selection, which gradually diminishes in power after the age of first reproduction. Dr. Guarente adopts this concept, which has now become part of the general consensus. But rather than drawing the conclusion most evolutionary biologists do, namely that there must be an infinite number of genes involved in aging and longevity, he argues for a possible core anti-aging mechanism that becomes most active in times of scarcity. Such a mechanism would postpone reproduction until better times, offering a competitive advantage to individuals inheriting this gene. The book describes the search for genes in yeast that influence the number of times a mother cell gives rise to offspring before it becomes worn out and aged, eventually identifying the gene *Sir2*, which encodes a highly conserved NAD-dependent histone deacetylase. Dr. Guarente's hugely successful experiments, published in the most respected scientific journals, then show that higher levels of this gene in yeast, as well as in the nematode *Caenorhabditis elegans*, extend life span, whereas its inactivation has the opposite effect. He finally shows that *Sir2* and its homolog in *C. elegans* may trigger longevity and postpone reproduction when conditions are poor. In *C. elegans*, *Sir2* seems to act by attenuating the insulin-signaling pathway, a road to longevity that was previously discovered for this organism in several other labs.

Basically a personal account of research into aging, including descriptions of his students and postdocs and their work at the laboratory bench, the book is a pleasure to read. The author writes with the clarity of a first-class journalist, an infectious enthusiasm and an eye for the revealing anecdote. His descriptions of experiments with

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accompanying illustrations are precise and economic, albeit often too brief to my taste.

As expected, in his quest for the Grail, Dr. Guarente has a bias towards the simple. Like Perceval, the author has his moments of doubt. In Chapter 12, he asks himself “what if *SIRT* genes [the human equivalents of *Sir2* in yeast] will turn out not to be at all relevant for human aging?” Fortunately, rather than pondering this question for too long (which may eventually have converted him to the biometric branch of aging research), Dr. Guarente begins to describe approaches to test this question in earnest,

which eventually result in an excursion into the realm of drug discovery and the foundation of a company, aptly named “Elixir”!

Although the relevance of *Sir2* and survival mechanisms discovered in short-lived laboratory organisms to aging in mammals is still questionable, I am convinced that by opening this avenue of research, Guarente and kindred spirits have done much to draw outstanding scientists into aging research, thereby shaking this field out of its stuffy reputation. That alone makes *Ageless Quest* and the story of its simple pursuit a timely contribution to the growing literature on why and how we age. ■