'A masterful book … the precious results of decades of work into longevity – read it'
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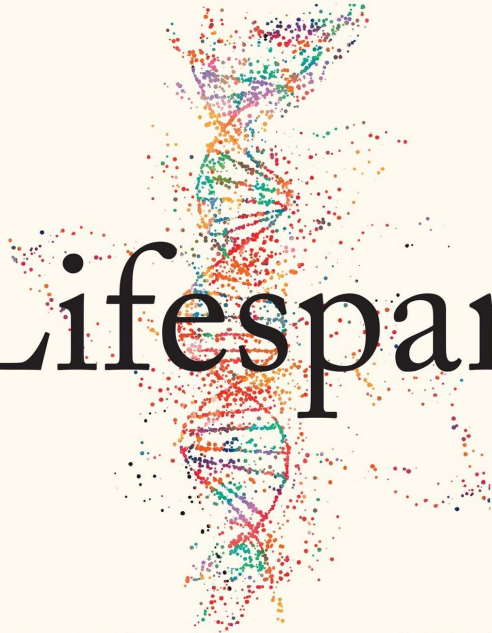

Lifespan

Why We Age – and Why We Don't Have To

David A. Sinclair PhD
with Matthew D. LaPlante

David Sinclair
Lifespan

http://www.litres.ru/pages/biblio_book/?art=44917533
Lifespan:
ISBN 9780008292362

Аннотация

In this paradigm-shifting book from acclaimed Harvard Medical School doctor and one of TIME magazine's 100 most influential people on earth, Dr. David Sinclair reveals that everything we think we know about ageing is wrong, and shares the surprising, scientifically-proven methods that can help readers live younger, longer.For decades, the medical community has looked to a variety of reasons for why we age, and the consensus is that no one dies of old age; they die of age-related diseases. That's because ageing is not a disease – it is inevitable.But what if everything you think you know about ageing is wrong?What if ageing is a disease? And that disease is curable.In THE EVOLUTION OF AGEING, Dr. David Sinclair, one of the world's foremost authorities on genetics and ageing, argues just that. He has dedicated his life's work to chasing more than a longer lifespan – he wants to enable people to live longer, healthier, and disease-free well into our hundreds. In this book, he reveals a bold new theory of ageing, one that pinpoints a root cause of ageing that lies in an ancient genetic survival circuit. This genetic trick – a circuit designed to halt reproduction in order to repair damage to the

genome –has enabled earth's early microcosms to survive and evolve into more advanced organisms. But this same survival circuit is the reason we age: as genetic damage accumulates over our lifespans from UV rays, environmental toxins, and unhealthy diets, our genome is overwhelmed, causing gray hair, wrinkles, achy joints, heart issues, dementia, and, ultimately, death.But genes aren't our destiny; we have more control over them than we've been taught to believe. We can't change our DNA, but we can harness the power of the epigenome to realise the true potential of our genes. Drawing on his cutting-edge findings at the forefront of medical research, Dr. Sinclair will provide a scientifically-proven roadmap to reverse the genetic clock by activating our vitality genes, so we can live younger longer. Readers will discover how a few simple lifestyle changes – like intermittent fasting, avoiding too much animal protein, limiting sugar, avoiding x-rays, exercising with the right intensity, and even trying cold therapy – can activate our vitality genes. Dr. Sinclair ends the book with a look to the near future, exploring what the world might look like – and what will need to change – when we are all living well to 120 or more.Dr. Sinclair takes what we have long accepted as the limits of human potential and mortality and turns them into choices. THE EVOLUTION OF AGEING is destined to be the biggest book on genes, biology, and longevity of this decade.

Содержание

David Sinclair, Matthew D. LaPlante
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The Revolutionary Science of
Why We Age – and
Why We Don't Have To

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An imprint of HarperCollins*Publishers*
1 London Bridge Street
London SE1 9GF

www.harpercollins.co.uk

First published by Atria Books, an imprint of Simon & Schuster, Inc.
This UK edition published by Thorsons 2019

FIRST EDITION

Illustrations and Sinclairfont by Catherine L. Delphia
Illustrations in Cast of Characters by David Sinclair

Thanks to Christine Liu and her team at the Innovative Genomics Institute (IGI) for permission to use the Glossary icons. Thanks to Wikipedia for biographical facts in the cast of

characters.

A catalogue record of this book is available from the British Library

Source ISBN: 9780008353742
Ebook Edition © October 2019 ISBN: 9780008292362
Version 2019-10-29
Information about External Hyperlinks in this ebook

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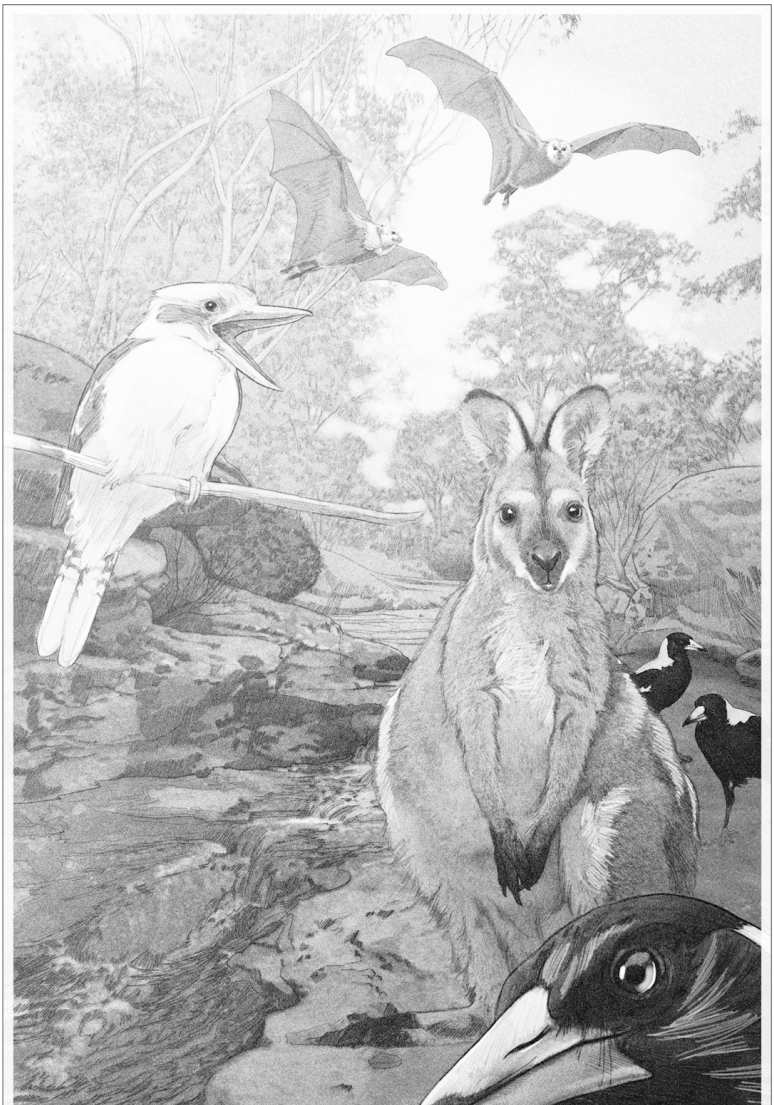
Dedication

To my grandmother Vera, who taught me to see the world the way it could be

To my mother, Diana, who cared more about her children than herself

To my wife, Sandra, my bedrock

And to my great-great-grandchildren; I am looking forward to meeting you



THE BUSH. In the wild and wonderful world of the Garigal clan, waterfalls and saltwater estuaries wind through ancient sandstone escarpments, under shadowy canopies of charred bloodwoods, angophoras, and scribbly gums that kookaburras, currawongs, and wallabies call home.

INTRODUCTION
A GRANDMOTHER'S PRAYER

I GREW UP ON THE EDGE OF THE BUSH. IN FIGURATIVE TERMS, MY BACKYARD was a hundred-acre wood. In literal terms, it was much bigger than that. It went on as far as my young eyes could see, and I never grew tired of exploring it. I would hike and hike, stopping to study the birds, the insects, the reptiles. I pulled things apart. I rubbed the dirt between my fingers. I listened to the sounds of the wild and tried to connect them to their sources.

And I played. I made swords from sticks and forts from rocks. I climbed trees and swung on branches and dangled my legs over steep precipices and jumped off of things that I probably shouldn't have jumped off. I imagined myself as an astronaut on a distant planet. I pretended to be a hunter on safari. I lifted my voice for the animals as though they were an audience at the opera house.

"Coooeey!" I would holler, which means "Come here" in the language of the Garigal people, the original inhabitants.

I wasn't unique in any of this, of course. There were lots of kids in the northern suburbs of Sydney who shared my love of adventure and exploration and imagination. We expect this of children. We *want* them to play this way.

Until, of course, they're "too old" for that sort of thing. Then we want them to go to school. Then we want them to go to work. To find a partner. To save up. To buy a house.

Because, you know, the clock is ticking.

My grandmother was the first person to tell me that it didn't have to be that way. Or, I guess, she didn't tell me so much as show me.

She had grown up in Hungary, where she spent Bohemian summers swimming in the cool waters of Lake Balaton and hiking in the mountains of its northern shore at a holiday resort that catered to actors, painters, and poets. In the winter months, she helped run a hotel in the Buda Hills before the Nazis took it over and converted it to the central command of the Schutzstaffel, or "SS."

A decade after the war, in the early days of the Soviet occupation, the Communists began to shut down the borders. When her mother tried to cross illegally into Austria, she was caught, arrested, and sentenced to two years in jail and died shortly after. During the Hungarian Uprising in 1956, my grandmother wrote and distributed anti-Communist newsletters in the streets of Budapest. After the revolution was crushed, the Soviets began arresting tens of thousands of dissidents, and she fled to Australia with her son, my father, reasoning that it was the furthest they could get from Europe.

She never set foot in Europe again, but she brought every bit of Bohemia with her. She was, I have been told, one of the first

women to sport a bikini in Australia and got chased off Bondi Beach because of it. She spent years living in New Guinea—which even today is one of the most intensely rugged places on our planet—all by herself.

Though her bloodline was Ashkenazi Jew and she had been raised a Lutheran, my grandmother was a very secular person. Our equivalent of the Lord's Prayer was the English author Alan Alexander Milne's poem "Now We Are Six," which ends:

> But now I am six,
> I'm as clever as clever.
> So I think I'll be six now
> for ever and ever.

She read that poem to my brother and me again and again. Six, she told us, was the very best age, and she did her damnedest to live life with the spirit and awe of a child of that age.

Even when we were very young, my grandmother didn't want us to call her "grandmother." Nor did she like the Hungarian term, "nagymama," or any of the other warm terms of endearment such as "bubbie," "grandma," and "nana."

To us boys, and everyone else, she was simply Vera.

Vera taught me to drive, swerving and swaying across all of the lanes, "dancing" to whatever music was on the car's radio. She told me to enjoy my youth, to savor the feeling of being young. Adults, she said, always ruined things. Don't grow up, she said. Never grow up.

Well into her 60s and 70s, she was still what we call "young at heart," drinking wine with friends and family, eating good food, telling great stories, helping the poor, sick, and less fortunate, pretending to conduct symphonies, laughing late into the night. By just about anyone's standard, that's the mark of a "life well lived."

But yes, the clock was ticking.

By her mid-80s, Vera was a shell of her former self, and the final decade of her life was hard to watch. She was frail and sick. She still had enough wisdom left to insist that I marry my fiancée, Sandra, but by then music gave her no joy and she hardly got out of her chair; the vibrancy that had defined her was gone.

Toward the end, she gave up hope. "This is just the way it goes," she told me.

She died at the age of 92. And, in the way we've been taught to think about these things, she'd had a good, long life. But the more I have thought about it, the more I have come to believe that the person she *truly* was had been dead many years at that point.

Growing old may seem a distant event, but every one of us will experience the end of life. After we draw our last breath, our cells will scream for oxygen, toxins will accumulate, chemical energy will be exhausted, and cellular structures will disintegrate. A few minutes later, all of the education, wisdom, and memories that we cherished, and all of our future potential, will be irreversibly erased.

I learned this firsthand when my mother, Diana, passed away.

My father, my brother, and I were there. It was a quick death, thankfully, caused by a buildup of liquid in her remaining lung. We had just been laughing together about the eulogy I'd written on the trip from the United States to Australia, and then suddenly she was writhing on the bed, sucking for air that couldn't satisfy her body's demand for oxygen, staring at us with desperation in her eyes.

I leaned in and whispered into her ear that she was the best mom I could have wished for. Within a few minutes, her neurons were dying, erasing not just the memory of my final words to her but all of her memories. I know some people die peacefully. But that's not what happened to my mother. In those moments she was transformed from the person who had raised me into a twitching, choking mass of cells, all fighting over the last residues of energy being created at the atomic level of her being.

All I could think was "No one tells you what it is like to die. Why doesn't anyone tell you?"

There are few people who have studied death as intimately as the Holocaust documentary filmmaker Claude Lanzmann. And his assessment—indeed, his warning—is chilling. "Every death is violent," he said in 2010. "There is no natural death, unlike the picture we like to paint of the father who dies quietly in his sleep, surrounded by his loved ones. I don't believe in that."[1]

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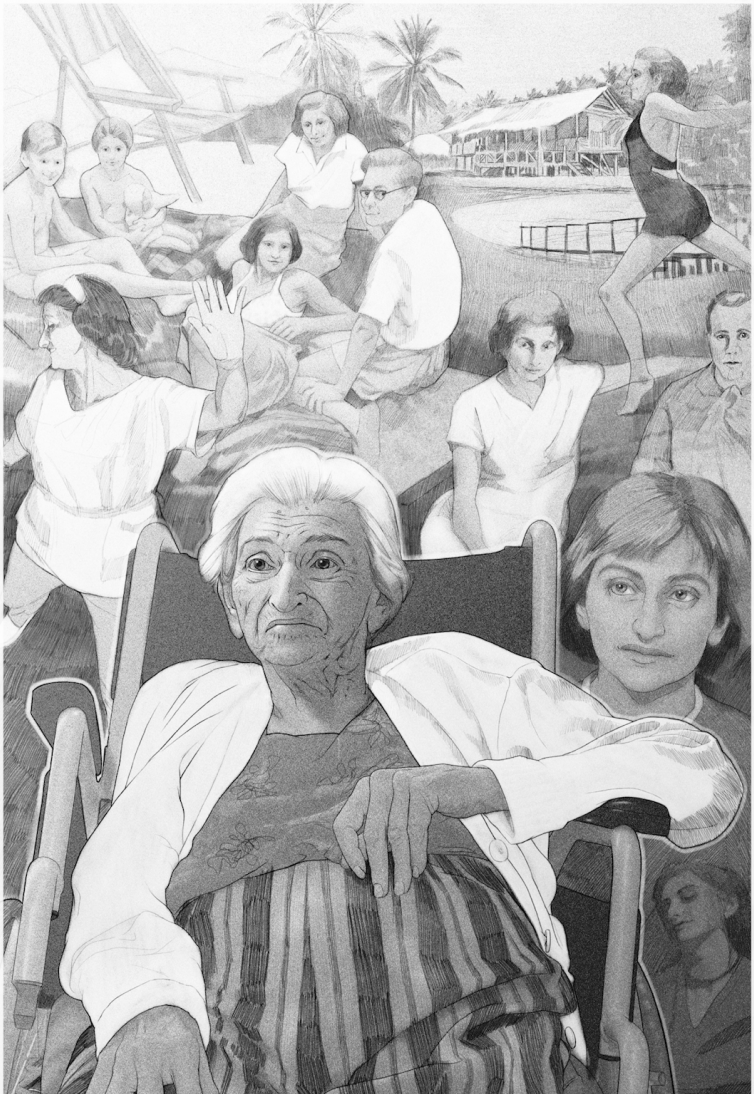
[1] In a wide-ranging interview to promote his memoirs, Lanzmann said of his masterpiece film about the Holocaust, "I wanted to get as close as possible to death. No personal accounts are told in *Shoah*, no anecdotes. It's only about death. The film is not about the survivors." "'Shoah' Director Claude Lanzmann: 'Death Has Always Been a

Even if they don't recognize its violence, children come to understand the tragedy of death surprisingly early in their lives. By the age of four or five, they know that death occurs and is irreversible.[2] It is a shocking thought for them, a nightmare that is real.

Scandal,'" *Spiegel*, September 10, 2010, http://www.spiegel.de/international/zeitgeist/shoah-director-claude-lanzmann-death-has-always-been-a-scandal-a-716722.html.

[2] The study looked at three concepts about death that children come to understand before they are seven years old: irreversibility, nonfunctionality, and universality. M. W. Speece and S. B. Brent, "Children's Understanding of Death: A Review of Three Components of a Death Concept," *Child Development* 55, no. 5 (October 1984): 1671–86, https://www.ncbi.nlm.nih.gov/pubmed/6510050.



A "GOOD, LONG LIFE." My grandmother "Vera" sheltered Jews in World War II, lived in primitive New Guinea, and was removed from Bondi Beach for wearing a bikini. The end of her life was hard to watch. "This is just the way it goes," she said. But the person she truly was had been dead many years at that point.

At first, because it's calming, most children prefer to think that there are certain groups of people who are protected from death: parents, teachers, and themselves. Between 5 and 7, however, all children come to understand the universality of death. Every family member will die. Every pet. Every plant. Everything they love. Themselves, too. I can remember first learning this. I can also very well remember our oldest child, Alex, learning it.

"Dad, you won't *always* be around?"

"Sadly, no," I said.

Alex cried on and off for a few days, then stopped, and never asked me about it again. And I've never again mentioned it, either.

It doesn't take long for the tragic thought to be buried deep in the recesses of our subconscious. When asked if they worry about death, children tend to say that they don't think about it. If asked what they do think about it, they say it is not a concern because it will occur only in the remote future, when they get old.

That's a view most of us maintain until well into our fifties. Death is simply too sad and paralyzing to dwell on each day.

Often, we realize it too late. When it comes knocking, and we are not prepared, it can be devastating.

For Robin Marantz Henig, a columnist at the *New York Times*, the "bitter truth" about mortality came late in life, after she became a grandparent. "Beneath all the wonderful moments you may be lucky enough to share in and enjoy," she wrote, "your grandchild's life will be a long string of birthdays you will not live to see."[3]

It takes courage to consciously think about your loved ones' mortality before it actually happens. It takes even more courage to deeply ponder your own.

It was the comedian and actor Robin Williams who first demanded this courage from me through his portrayal of John Keating, the teacher and hero in the film *Dead Poets Society*, who challenges his teenage students to stare into the faces of the long-dead boys in a fading photo.[4]

"They are not that different from you, are they?" Keating says. "Invincible, just like you feel. … Their eyes are full of hope … But you see, gentlemen, these boys are now fertilizing daffodils."

Keating encourages the boys to lean in closer to listen for a

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[3] The author attended the birth of her daughter's first child along with her son-inlaw. R. M. Henig, "The Ecstasy and the Agony of Being a Grandmother," *New York Times*, December 27, 2018, https://www.nytimes.com/2018/12/27/style/self-care/becoming-a-grandmother.html.

[4] The film's exhortations to make the most of every day took on a darker hue after the suicide of its star, Robin Williams. P. Weir, director, *Dead Poets Society*, United States: Touchstone Pictures, 1999.

message from the grave. Standing behind them, in a quiet, ghostly voice, he whispers, "*Carpe. Carpe diem.* Seize the day, boys. Make your lives extraordinary."

That scene had an enormous impact on me. It is likely that I would not have had the motivation to become a Harvard professor if it hadn't been for that movie. At the age of 20, I had finally heard someone else say what my grandmother had taught me at an early age: Do your part to make humanity be the best it can be. Don't waste a moment. Embrace your youth; hold on to it for as long as you can. Fight for it. Fight for it. Never stop fighting for it.

But instead of fighting for youth, we fight for life. Or, more specifically, we fight against death.

As a species, we are living much longer than ever. But not much better. Not at all. Over the past century we have gained additional years, but not additional life—not life worth living anyway.[5]

And so most of us, when we think about living to 100, still think "God forbid," because we've seen what those final decades look like, and for most people, most of the time, they don't look appealing at all. Ventilators and drug cocktails. Broken hips and diapers. Chemotherapy and radiation. Surgery after surgery after

[5] The author argues that rather than focusing on cancer and cardiovascular issues, medical research should be focusing on "reducing ageing and age-related morbidity, thereby increasing both our health and our wealth." G. C. Brown, "Living Too Long," *EMBO Reports* 16, no. 2 (February 2015): 137–41, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4328740/.

surgery. And hospital bills; my God, the hospital bills.

We're dying slowly and painfully. People in rich countries often spend a decade or more suffering through illness after illness at the ends of their lives. We think this is normal. As lifespans continue to increase in poorer nations, this will become the fate of billions of additional people. Our successes in extending life, the surgeon and doctor Atul Gawande has noted, have had the effect of "making mortality a medical experience."[6]

But what if it didn't have to be that way? What if we could be younger longer? Not years longer but decades longer. What if those final years didn't look so terribly different from the years that came before them? And what if, by saving ourselves, we could also save the world?

Maybe we can never be six again—but how about twenty-six or thirty-six?

What if we could play as children do, deeper into our lives, without worrying about moving on to the things adults *have to do* so soon? What if all of the things we need to compress into our teenage years didn't need to be so compressed after all? What if we weren't so stressed in our 20s? What if we weren't feeling middle-aged in our 30s and 40s? What if, in our 50s, we wanted

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[6] In a survey coconducted by the *Economist*, the majority of respondents from four countries expressed the wish to die at home, although only a small number thought that they would do so. With the exception of Brazilians, most felt that dying without pain was more important than extending life. "A Better Way to Care for the Dying," *Economist*, April 29, 2017, https://www.economist.com/international/2017/04/29/a-better-way-to-care-for-the-dying.

to reinvent ourselves and couldn't think of a single reason why we shouldn't? What if, in our 60s, we weren't fretting about leaving a legacy but *beginning* one?

What if we didn't have to worry that the clock was ticking? And what if I told you that soon—very soon, in fact—we won't?

Well, that's what I'm telling you.

I'm fortunate that after thirty years of searching for truths about human biology, I find myself in a unique position. If you were to visit me in Boston, you'd most likely find me hanging out in my lab at Harvard Medical School, where I'm a professor in the Department of Genetics and codirector of the Paul F. Glenn Center for the Biological Mechanisms of Aging. I also run a sister lab at my alma mater, the University of New South Wales in Sydney. In my labs, teams of brilliant students and PhDs have both accelerated and reversed aging in model organisms and have been responsible for some of the most cited research in the field, published in some of the world's top scientific journals. I am also a cofounder of a journal, *Aging*, that provides space to other scientists to publish their research on one of the most challenging and exciting questions of our time, and a cofounder of the Academy for Health and Lifespan Research, a group of the top twenty researchers in aging worldwide.

In trying to make practical use of my discoveries, I've helped start a number of biotechnology companies and sit as a chair of the scientific boards of advisers of several others. These companies work with hundreds of leading academics

in scientific areas ranging from the origin of life to genomics to pharmaceuticals.[7] I am, of course, aware of my own labs' discoveries years before they are made public, but through these associations, I'm also aware of many other transformational discoveries ahead of time, sometimes a decade ahead. The coming pages will serve as your backstage pass and your front-row seat.

Having received the equivalent of a knighthood in Australia and taken on the role of an ambassador, I've been spending quite a bit of my time briefing political and business leaders around the world about the ways our understanding of aging is changing—and what that means for humanity going forward.[8]

I've applied many of my scientific findings to my own life, as have many of my family members, friends, and colleagues. The results—which, it should be noted, are completely anecdotal—are encouraging. I'm now 50, and I feel like a kid. My wife and kids will tell you I act like one, too.

That includes being a *stickybeak*, the Australian term for someone who is overly inquisitive, perhaps derived from the currawong crows that used to punch through the foil lids of the milk bottles delivered to our homes and drink the milk out of them. My old high school friends still like to tease me about

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[7] See my conflict disclosures at the end of this book and at https://genetics.med.harvard.edu/sinclair-test/people/sinclair-other.php.

[8] My editor made me write self-centered things about myself to give me credibility. I hope she doesn't see this endnote and make me delete it.

how, whenever they came over to my parents' house, they would find me pulling something apart: a pet moth's cocoon, a spider's curled-up leaf shelter, an old computer, my father's tools, a car. I became quite good at it. I just wasn't very good at putting these things back together.

I couldn't bear *not* knowing how something worked or where it came from. I still can't—but at least now I get paid for it.

My childhood home is perched on a rocky mountainside. Below is a river that runs into Sydney Harbor. Arthur Phillip, the first governor of New South Wales, explored these valleys in April 1788, only a few months after he and his First Fleet of marines, prisoners, and their families established a colony on the shores of what he called the "finest and most extensive harbor in the universe." The person most responsible for him being there was the botanist Sir Joseph Banks, who eighteen years earlier had sailed up the Australian coastline with Captain James Cook on his "voyage round the world."[9]

[9] In 2018, my family and I made a pilgrimage to London to see the original account of Captain James Cook's "voyage round the world" and the original Australian botanical specimens collected by Sir Joseph Banks. There were stop-offs to see Watson and Crick's original model of DNA, fossils of early life, a Moai statue from Rapa Nui, a cross-sectional cut through a 1,500-year-old sequoia tree trunk, a statue of Charles Darwin, the Broad Street pump, Winston Churchill's War Rooms, and the Royal Society, of course. Tracing the path of Cook along the lower east coast of Australia, or "New Holland," as it was called then, it is obvious that Banks already had a colony in mind, one that would never forget him. Not only was the original site named Botany Bay, the coast was named "Cape Banks." After exploring Botany Bay, the explorers' tall ship, the HMS *Endeavor*, sailed north, past the heads of a harbor they called Port Jackson, which, thanks to its much deeper waters and the presence of a stream to

After returning to London with hundreds of plant specimens to impress his colleagues, Banks lobbied King George III to start a British penal colony on the continent, the best site for which, he argued, not coincidentally, would be a bay called "Botany" on "Cape Banks."[10] The First Fleet settlers soon discovered that Botany Bay, despite its most excellent name, had no source of water, so they sailed up to Sydney Harbor and found one of the world's largest "rias," a highly branched, deep waterway that formed when the Hawkesbury River system had been flooded by rising sea levels after the last ice age.

At the age of 10, I had already discovered through exploration that the river in my backyard flowed down into Middle Harbor, a branch of Sydney Harbor. But I could no longer stand not knowing where the river originated. I needed to know what the *beginning* of a river looked like.

I followed it upstream, left the first time it forked and right the time after that, wending into and out of several suburbs. By nightfall I was miles from home, beyond the last mountain on the horizon. I had to ask a stranger to let me call my mother to beg her to come pick me up. A few times after that I tried searching upstream, but never did get anywhere close to the fount. Like Juan Ponce de León, the Spanish explorer of Florida known for

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supply fresh water, ended up being a far superior site for Governor Phillip to start a penal colony eight years later.

[10] "Phillip's Exploration of Middle Harbour Creek," Fellowship of the First Fleeters, Arthur Phillip Chapter, http://arthurphillipchapter.weebly.com/exploration-of-middle-harbour-creek.html.

his apocryphal quest to find the Fountain of Youth, I failed.[11]

Ever since I can remember, I have wanted to understand why we grow old. But finding the source of a complex biological process is like searching for the spring at the source of a river: it's not easy.

On my quest, I've wound my way left and right and had days when I wanted to give up. But I've persevered. Along the way, I have seen a lot of tributaries, but I've also found what may be the spring. In the coming pages, I will present a new idea about why aging evolved and how it fits into what I call the Information Theory of Aging. I will also tell you why I have come to see aging as a disease—the most common disease—one that not only can but *should* be aggressively treated. That's part I.

In part II, I will introduce you to the steps that can be taken right now—and new therapies in development—that may slow, stop, or reverse aging, bringing an end to aging as we know it.

And yes, I fully recognize the implications of the words "bringing an end to aging as we know it," so, in part III, I will acknowledge the many possible futures these actions could create and propose a path to a future that we can look forward to, a world in which the way we can get to an increased lifespan is through an ever-rising *healthspan*, the portion of our lives spent

[11] The Spanish explorer and conquistador's search for the mystical spring known as the Fountain of Youth is apocryphal, but it makes for a good story. J. Greenspan, "The Myth of Ponce de León and the Fountain of Youth," "History Stories," April 2, 2013, A&E Television Networks, https://www.history.com/news/the-myth-of-ponce-de-leon-and-the-fountain-of-youth.

without disease or disability.

There are plenty of people who will tell you that's a fairy tale—closer to the works of H. G. Wells than those of C. R. Darwin. Some of them are very smart. A few are even people who understand human biology quite well and whom I respect.

Those people will tell you that our modern lifestyles have cursed us with shortening lifespans. They'll say you're unlikely to see 100 years of age and that your children aren't likely to get to the century mark, either. They'll say they've looked at the science of it all and done the projections, and it sure doesn't seem likely that your grandchildren will get to their 100th birthdays, either. And they'll say that if you *do* get to 100, you probably won't get there healthy and you definitely won't be there for long. And if they grant you that people will live longer, they'll tell you that it's the worst thing for this planet. Humans are the enemy!

They've got good evidence for all of this—the entire history of humanity, in fact.

Sure, little by little, millennia by millennia, we've been adding years to the *average* human life, they will say. Most of us didn't get to 40, and then we did. Most of us didn't get to 50, and then we did. Most of us didn't get to 60, and then we did.[12] By

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[12] According to the Creation Wiki: the Encyclopedia of Creation Science (a website of the Northwest Creation Network, http://creationwiki.org/Human_longevity), in Genesis, most of us once got to 900 years, then we didn't. Then most of us got to 400, then we didn't. Then most of us got to 120, then we didn't. In more recent times, as Oeppen and Vaupel have written, "Mortality experts have repeatedly asserted that life expectancy is close to an ultimate ceiling; these experts have repeatedly been proven

and large, these increases in life expectancy came as more of us gained access to stable food sources and clean water. And largely the average was pushed upward from the bottom; deaths during infancy and childhood fell, and life expectancy rose. This is the simple math of human mortality.

But although the *average* kept moving up, the *limit* did not. As long as we've been recording history, we have known of people who have reached their 100th year and who might have lived a few years beyond that mark. But very few reach 110. Almost no one reaches 115.

Our planet has been home to more than 100 billion humans so far. We know of just one, Jeanne Calment of France, who ostensibly lived past the age of 120. Most scientists believe she died in 1997 at the age of 122, although it's also possible that her daughter replaced her to avoid paying taxes.[13] Whether or

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wrong. The apparent leveling off of life expectancy in various countries is an artifact of laggards catching up and leaders falling behind." J. Oeppen and J. W. Vaupel, "Broken Limits to Life Expectancy," *Science* 296, no. 5570 (May 10, 2002): 1029–31.

[13] There is some debate as to what constitutes verifiable age. There are humans who have claimed, and provided considerable evidence, of being of great age, but who don't have formal Western-style records of their year of birth. In any case, these people are one in a billion, if that. In November 2018, the Russian gerontologist Valery Novoselov and the mathematician Nikolay Zak claimed that after much research, they believe that Jeanne Calment's daughter, Yvonne, usurped Jeanne's identity in 1934, claiming that the daughter had died instead of the mother to avoid paying estate taxes. The debate continues. "French Scientists Dismiss Russian Claims over Age of World's Oldest Person," Reuters, January 3, 2019, https://www.reuters.com/article/us-france-oldest-woman-controversy/french-scientists-dismiss-russian-claims-over-age-of-worlds-oldest-person-

not she actually made it to that age really doesn't matter; others have come within a few years of that age but most of us, 99.98 percent to be precise, are dead before 100.

So it certainly makes sense when people say that we might continue to chip away at the average, but we're not likely to move the limit. They say it's easy to extend the maximum lifespan of mice or of dogs, but we humans are different. We simply live too long already.

They are wrong.

There's also a difference between extending life and prolonging vitality. We're capable of both, but simply keeping people alive—decades after their lives have become defined by pain, disease, frailty, and immobility—is no virtue.

Prolonged vitality—meaning not just more years of life but more active, healthy, and happy ones—is coming. It is coming sooner than most people expect. By the time the children who are born today have reached middle age, Jeanne Calment may not even be on the list of the top 100 oldest people of all time. And by the turn of the next century, a person who is 122 on the day of his or her death may be said to have lived a full, though not particularly long, life. One hundred and twenty years might be not an outlier but an expectation, so much so that we won't even call it longevity; we will simply call it "life," and we will look back with sadness on the time in our history in which it was not so.

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idUSKCN1OX145.

What's the upward limit? I don't think there is one. Many of my colleagues agree.[14] There is no biological law that says we must age.[15] Those who say there is don't know what they're talking about. We're probably still a long way off from a world in which death is a rarity, but we're not far from pushing it ever farther into the future.

All of this, in fact, is inevitable. Prolonged healthy lifespans are in sight. Yes, the entire history of humanity suggests otherwise. But the science of lifespan extension in this particular century says that the previous dead ends are poor guides.

It takes radical thinking to even begin to approach what this will mean for our species. Nothing in our billions of years of evolution has prepared us for this, which is why it's so easy, and even alluring, to believe that it simply cannot be done.

But that's what people thought about human flight, too—up until the moment someone did it.

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[14] Italian researchers found after studying 4,000 elderly people that if you make it to age 105, the risk of death effectively plateaus from one birthday to the next, the odds of dying in the next year becoming approximately fifty-fifty. E. Barbi, F. Lagona, M. Marsili, et al., "The Plateau of Human Mortality: Demography of Longevity Pioneers," *Science* 360, no. 396 (June 29, 2018): 1459–61, http://science.sciencemag.org/content/360/6396/1459.

[15] "If people live on average to 80 or 90, like they do now, then the very long lived make it to 110 or 120," says Siegfried Hekimi, professor of genetics at McGill University in Canada. "So if the average lifespan keeps expanding, that would mean the long-lived would live even longer, beyond 115 years"; A. Park, "There's No Known Limit to How Long Humans Can Live, Scientists Say," *Time*, June 28, 2017, http://time.com/4835763/how-long-can-humans-live/.

Today the Wright brothers are back in their workshop, having successfully flown their gliders down the sand dunes of Kitty Hawk. The world is about to change.

And just as was the case in the days leading up to December 17, 1903, the majority of humanity is oblivious. There was simply no context with which to construct the idea of controlled, powered flight back then, so the idea was fanciful, magical, the stuff of speculative fiction.[16]

Then: liftoff. And nothing was ever the same again.

We are at another point of historical inflection. What hitherto seemed magical will become real. It is a time in which humanity will redefine what is possible; a time of ending the inevitable.

Indeed, it is a time in which we will redefine what it means to be human, for this is not just the start of a revolution, it is the start of an evolution.

[16] "Any sufficiently advanced technology is indistinguishable from magic." "Arthur C. Clarke," Wikiquote, https://en.wikiquote.org/wiki/Arthur_C._Clarke.

PART I
WHAT WE KNOW
(THE PAST)

ONE
VIVA PRIMORDIUM

IMAGINE A PLANET ABOUT THE SIZE OF OUR OWN, ABOUT AS FAR FROM ITS STAR, rotating around its axis a bit faster, such that a day lasts about twenty hours. It is covered with a shallow ocean of salty water and has no continents to speak of—just some sporadic chains of basaltic black islands peeking up above the waterline. Its atmosphere does not have the same mix of gases as ours. It is a humid, toxic blanket of nitrogen, methane, and carbon dioxide.

There is no oxygen. There is no life.

Because this planet, our planet as it was 4 billion years ago, is a ruthlessly unforgiving place. Hot and volcanic. Electric. Tumultuous.

But that is about to change. Water is pooling next to warm thermal vents that litter one of the larger islands. Organic molecules cover all surfaces, having ridden in on the backs

of meteorites and comets. Sitting on dry, volcanic rock, these molecules will remain just molecules, but when dissolved in pools of warm water, through cycles of wetting and drying at the pools' edges, a special chemistry takes place.[17] As the nucleic acids concentrate, they grow into polymers, the way salt crystals form when a seaside puddle evaporates. These are the world's first RNA molecules, the predecessors to DNA. When the pond refills, the primitive genetic material becomes encapsulated by fatty acids to form microscopic soap bubbles—the first cell membranes.[18]

It doesn't take long, a week perhaps, before the shallow ponds are covered with a yellow froth of trillions of tiny precursor cells filled with short strands of nucleic acids, which today we call genes.

Most of the protocells are recycled, but some survive and begin to evolve primitive metabolic pathways, until finally the RNA begins to copy itself. That point marks the origin of life. Now that life has formed—as fatty-acid soap bubbles filled with

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[17] D. Damer and D. Deamer, "Coupled Phases and Combinatorial Selection in Fluctuating Hydrothermal Pools: A Scenario to Guide Experimental Approaches to the Origin of Cellular Life," *Life* 5, no. 1 (2015): 872–87, https://www.mdpi.com/2075-1729/5/1/872.

[18] According to precise radiological and geological readings and recent discoveries about the early chemistry of life, this is an accurate picture of how the inanimate was animated and life took hold. M. J. Van Kranendonk, D. W. Deamer, and T. Djokic, "Life on Earth Came from a Hot Volcanic Pool, Not the Sea, New Evidence Suggests," *Scientific American*, August 2017, https://www.scientificamerican.com/article/life-on-earth-came-from-a-hot-volcanic-pool-not-the-sea-new-evidence-suggests/.

genetic material—they begin to compete for dominance. There simply aren't enough resources to go around. May the best scum win.

Day in and day out, the microscopic, fragile life-forms begin to evolve into more advanced forms, spreading into rivers and lakes.

Along comes a new threat: a prolonged dry season. The level of the scum-covered lakes has dropped by a few feet during the dry season, but the lakes have always filled up again as the rains returned. But this year, thanks to unusually intense volcanic activity on the other side of the planet, the annual rains don't fall as they usually do and the clouds pass on by. The lakes dry up completely.

What remains is a thick, yellow crust covering the lake beds. It is an ecosystem defined not by the annual waxing and waning of the waters but by a brutal struggle for survival. And more than that: it is a fight for the future—because the organisms that survive will be the progenitors of every living thing to come: archaea, bacteria, fungi, plants, and animals.

Within this dying mass of cells, each scrapping for and scraping by on the merest minimums of nutrients and moisture, each one doing whatever it can to answer the primal call to reproduce, there is a unique species. Let's call it *Magna superstes*. That's Latin for "great survivor."

It does not look very different from the other organisms of the day, but *M. superstes* has a distinct advantage: it has evolved a

genetic survival mechanism.

There will be far more complicated evolutionary steps in the eons to come, changes so extreme that entire branches of life will emerge. These changes—the products of mutations, insertions, gene rearrangements, and the horizontal transfer of genes from one species to another—will create organisms with bilateral symmetry, stereoscopic vision, and even consciousness.

By comparison, this early evolutionary step looks, at first, to be rather simple. It is a circuit. A gene circuit.

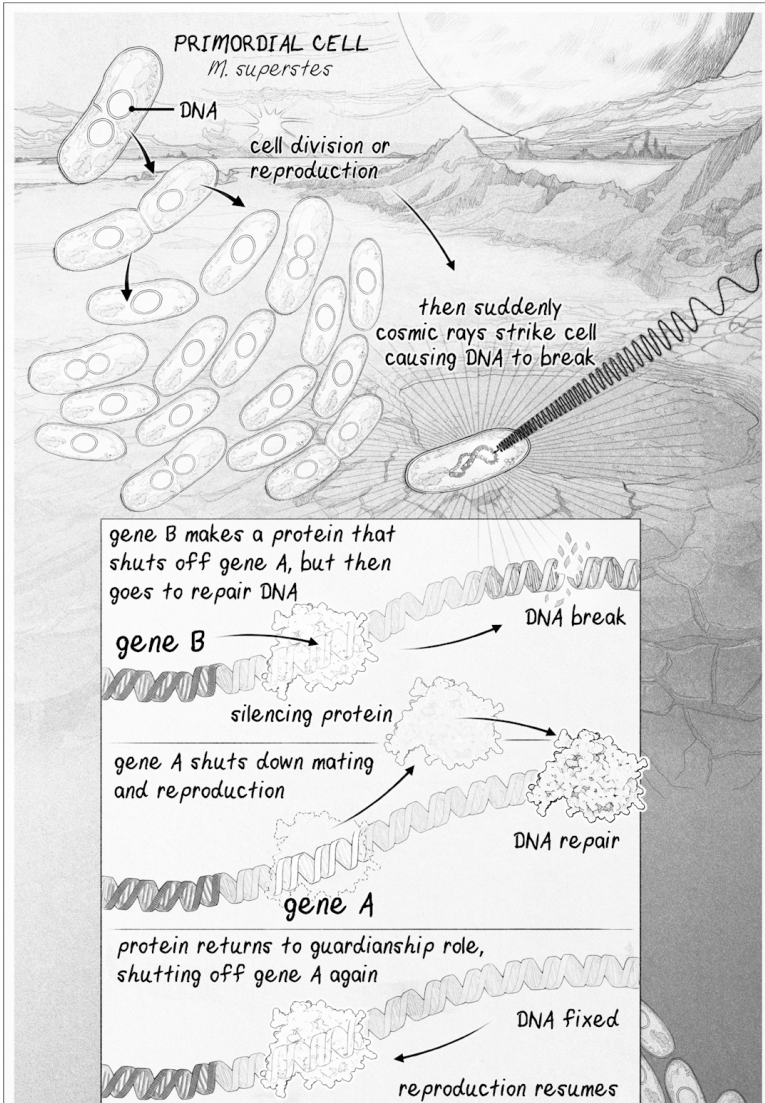
The circuit begins with gene A, a caretaker that stops cells from reproducing when times are tough. This is key, because on early planet Earth, *most* times are tough. The circuit also has a gene B, which encodes for a "silencing" protein. This silencing protein shuts gene A off when times are good, so the cell can make copies of itself when, and only when, it and its offspring will likely survive.

The genes themselves aren't novel. All life in the lake has these two genes. But what makes *M. superstes* unique is that the gene B silencer has mutated to give it a second function: it helps repair DNA. When the cell's DNA breaks, the silencing protein encoded by gene B moves from gene A to help with DNA repair, which turns on gene A. This temporarily stops all sex and reproduction until the DNA repair is complete.

This makes sense, because while DNA is broken, sex and reproduction are the last things an organism should be doing. In future multicellular organisms, for instance, cells that fail

to pause while fixing a DNA break will almost certainly lose genetic material. This is because DNA is pulled apart prior to cell division from only one attachment site on the DNA, dragging the rest of the DNA with it. If DNA is broken, part of a chromosome will be lost or duplicated. The cells will likely die or multiply uncontrollably into a tumor.

With a new type of gene silencer that repairs DNA, too, *M. superstes* has an edge. It hunkers down when its DNA is damaged, then revives. It is superprimed for survival.


PRIMORDIAL CELL
M. superstes
DNA
cell division or reproduction
then suddenly cosmic rays strike cell causing DNA to break
gene B makes a protein that shuts off gene A, but then goes to repair DNA
gene B
DNA break
silencing protein
gene A shuts down mating and reproduction
DNA repair
gene A
protein returns to guardianship role, shutting off gene A again
DNA fixed
reproduction resumes

THE EVOLUTION OF AGING. A 4-billion-year-old gene circuit in the first life-forms would have turned off reproduction while DNA was being repaired, providing a survival advantage. Gene A turns off reproduction, and gene B makes a protein that turns off gene A when it is safe to reproduce. When DNA breaks, however, the protein made by gene B leaves to go repair DNA. As a result, gene A is turned on to halt reproduction until repair is complete. We have inherited an advanced version of this survival circuit.

And that's good, because now comes yet another assault on life. Powerful cosmic rays from a distant solar eruption are bathing the Earth, shredding the DNA of all the microbes in the dying lakes. The vast majority of them carry on dividing as if nothing has happened, unaware that their genomes have been broken and that reproducing will kill them. Unequal amounts of DNA are shared between mother and daughter cells, causing both to malfunction. Ultimately, the endeavor is hopeless. The cells all die, and nothing is left.

Nothing, that is, but *M. superstes*. For as the rays wreak their havoc, *M. superstes* does something unusual: thanks to the movement of protein B away from gene A to help repair the DNA breaks, gene A switches on and the cells stop almost everything else they are doing, turning their limited energy toward fixing the DNA that has been broken. By virtue of its defiance of the ancient imperative to reproduce, *M. superstes* has survived.

When the latest dry period ends and the lakes refill, *M. superstes* wakes up. *Now* it can reproduce. Again and again it does so. Multiplying. Moving into new biomes. Evolving. Creating generations upon generations of new descendants.

They are our Adam and Eve.

Like Adam and Eve, we don't know if *M. superstes* ever existed. But my research over the past twenty-five years suggests that every living thing we see around us today is a product of this great survivor, or at least a primitive organism very much like it. The fossil record in our genes goes a long way to proving that every living thing that shares this planet with us still carries this ancient genetic survival circuit, in more or less the same basic form. It is there in every plant. It is there in every fungus. It is there in every animal.

It is there in us.

I propose the reason this gene circuit is conserved is that it is a rather simple and elegant solution to the challenges of a sometimes brutish and sometimes bounteous world that better ensures the survival of the organisms that carry it. It is, in essence, a primordial survival kit that diverts energy to the area of greatest need, fixing what exists in times when the stresses of the world are conspiring to wreak havoc on the genome, while permitting reproduction only when more favorable times prevail.

And it is so simple and so robust that not only did it ensure life's continued existence on the planet, it ensured that Earth's chemical survival circuit was passed on from parent to

offspring, mutating and steadily improving, helping life continue for billions of years, no matter what the cosmos brought, and in many cases allowing individuals' lives to continue for far longer than they actually needed to.

The human body, though far from perfect and still evolving, carries an advanced version of the survival circuit that allows it to last for decades past the age of reproduction. While it is interesting to speculate why our long lifespans first evolved—the need for grandparents to educate the tribe is one appealing theory—given the chaos that exists at the molecular scale, it's a wonder we survive thirty seconds, let alone make it to our reproductive years, let alone reach 80 more often than not.

But we do. Marvelously we do. Miraculously we do. For we are the progeny of a very long lineage of great survivors. Ergo, we are great survivors.

But there is a trade-off. For this circuit within us, the descendant of a series of mutations in our most distant ancestors, is also the reason we age.

And yes, that definite singular article is correct: it is *the* reason.

TO EVERYTHING THERE IS A REASON

If you are taken aback by the notion that there is a singular cause of aging, you are not alone. If you haven't given any thought at all as to why we age, that's perfectly normal, too. A lot of biologists haven't given it much thought, either. Even gerontologists, doctors who specialize in aging, often don't ask

why we age—they simply seek to treat the consequences.

This isn't a myopia specific to aging. As recently as the late 1960s, for example, the fight against cancer was a fight against its symptoms. There was no unified explanation for why cancer happens, so doctors removed tumors as best they could and spent a lot of time telling patients to get their affairs in order. Cancer was "just the way it goes," because that's what we say when we can't explain something.

Then, in the 1970s, genes that cause cancer when mutated were discovered by the molecular biologists Peter Vogt and Peter Duesberg. These so-called oncogenes shifted the entire paradigm of cancer research. Pharmaceutical developers now had targets to go after: the tumor-inducing proteins encoded by genes, such as *BRAF*, *HER2*, and *BCR-ABL*. By inventing chemicals that specifically block the tumor-promoting proteins, we could finally begin to move away from using radiation and toxic chemotherapeutic agents to attack cancers at their genetic source, while leaving normal cells untouched. We certainly haven't cured all types of cancer in the decades since then, but we no longer believe it's impossible to do so.

Indeed, among an increasing number of cancer researchers, optimism abounds. And that hopefulness was at the heart of what was arguably the most memorable part of President Barack Obama's final State of the Union address in 2016.

"For the loved ones we've all lost, for the family we can still save, let's make America the country that cures cancer once and

for all," Obama said as he stood in the House of Representatives chamber and called for a "cancer moon shot." When he placed then Vice President Joe Biden—whose son Beau had died of brain cancer a year earlier—in charge of the effort, even some of the Democrats' staunch political enemies had trouble holding back the tears.

In the days and weeks that followed, many cancer experts noted that it would take far more than the year remaining to the Obama-Biden administration to end cancer. Very few of those experts, however, said it absolutely couldn't be done. And that's because, in the span of just a few decades, we had completely changed the way we think about cancer. We no longer submit ourselves to its inevitability as part of the human condition.

One of the most promising breakthroughs in the past decade has been immune checkpoint therapy, or simply "immunotherapy." Immune T-cells continually patrol our body, looking for rogue cells to identify and kill before they can multiply into a tumor. If it weren't for T-cells, we'd all develop cancer in our twenties. But rogue cancer cells evolve ways to fool cancer-detecting T-cells so they can go on happily multiplying. The latest and most effective immunotherapies bind to proteins on the cancer cells' surface. It is the equivalent of taking the invisible cloak off cancer cells so T-cells can recognize and kill them. Although fewer than 10 percent of all cancer patients currently benefit from immunotherapy, that number should increase thanks to the hundreds of trials currently in progress.

We continue to rail against a disease we once accepted as fate, pouring billions of dollars into research each year, and the effort is paying off. Survival rates for once lethal cancers are increasing dramatically. Thanks to a combination of a BRAF inhibitor and immunotherapy, survival of melanoma brain metastases, one of the deadliest types of cancer, has increased by 91 percent since 2011. Between 1991 and 2016, overall deaths from cancer in the United States declined by 27 percent and continue to fall.[19] That's a victory measured in millions of lives.

Aging research today is at a similar stage as cancer research was in the 1960s. We have a robust understanding of what aging looks like and what it does to us and an emerging agreement about what causes it and what keeps it at bay. From the looks of it, aging is not going to be that hard to treat, far easier than curing cancer.

Up until the second half of the twentieth century, it was generally accepted that organisms grow old and die "for the good of the species"—an idea that dates back to Aristotle, if not further. This idea feels quite intuitive. It is the explanation

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[19] J. B. Iorgulescu, M. Harary, C. K. Zogg, et al., "Improved Risk-Adjusted Survival for Melanoma Brain Metastases in the Era of Checkpoint Blockade Immunotherapies: Results from a National Cohort," *Cancer Immunology Research*, 6, no. 9 (September 2018): 1039–45, http://cancerimmunolres.aacrjournals.org/content/6/9/1039.long; R. L. Siegel, K. D. Miller, and A. Jemal, "Cancer Statistics, 2019," *CA: A Cancer Journal for Clinicians* 69, no. 1 (January–February 2019): 7–34, https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21551.

proffered by most people at parties.[20] But it is dead wrong. We do not die to make way for the next generation.

In the 1950s, the concept of "group selection" in evolution was going out of style, prompting three evolutionary biologists, J. B. S. Haldane, Peter B. Medawar, and George C. Williams, to propose some important ideas about why we age. When it comes to longevity, they agreed, individuals look out for themselves. Driven by their selfish genes, they press on and try to breed for as long and as fast as they can, so long as it doesn't kill them. (In some cases, however, they press on too much, as my great-grandfather Miklós Vitéz, a Hungarian screenwriter, proved to his bride forty-five years his junior on their wedding night.)

If our genes don't ever want to die, why don't we live forever? The trio of biologists argued that we experience aging because the forces of natural selection required to build a robust body may be strong when we are 18 but decline rapidly once we hit 40 because by then we've likely replicated our selfish genes in sufficient measure to ensure their survival. Eventually, the forces of natural selection hit zero. The genes get to move on. We don't.

Medawar, who had a penchant for verbiage, expounded on a nuanced theory called "antagonistic pleiotropy." Put simply, it says genes that help us reproduce when we are young don't just become less helpful as we age, they can actually come back to

[20] As far back as Aristotle, scientists and philosophers have struggled to resolve the enigma of aging, the authors wrote. D. Fabian and T. Flatt, "The Evolution of Aging," *Nature Education Knowledge* 3, no. 10 (2011): 9, https://www.nature.com/scitable/knowledge/library/the-evolution-of-aging-23651151.

bite us when we are old.

Twenty years later, Thomas Kirkwood at Newcastle University framed the question of why we age in terms of an organism's available resources. Known as the "Disposable Soma Hypothesis," it is based on the fact that there are always limited resources available to species—energy, nutrients, water. They therefore evolve to a point that lies somewhere between two very different lifestyles: breed fast and die young, or breed slowly and maintain your *soma*, or body. Kirkwood reasoned that organisms can't breed fast *and* maintain a robust, healthy body—there simply isn't enough energy to do both. Stated another way, in the history of life, any line of creature with a mutation that caused it to live fast and attempt to die old soon ran out of resources and was thus deleted from the gene pool.

Kirkwood's theory is best illustrated by fictitious but potentially real-life examples. Imagine you are a small rodent that is likely to be picked off by a bird of prey. Because of this, you'll need to pass down your genetic material quickly, as did your parents and their parents before them. Gene combinations that would have provided a longer-lasting body were not enriched in your species because your ancestors likely didn't escape predation for long (and you won't, either).

Now consider instead that you are a bird of prey at the top of the food chain. Because of this, your genes—well, actually, your ancestors' genes—benefited from building a robust, longer-lasting body that could breed for decades. But in return, they

could afford to raise only a couple of fledglings a year.

Kirkwood's hypothesis explains why a mouse lives 3 years while some birds can live to 100.[21] It also quite elegantly explains why the American chameleon lizard, *Anolis carolinensis*, is evolving a longer lifespan as we speak, having found itself a few decades ago on remote Japanese islands without predators.[22]

These theories fit with observations and are generally accepted. Individuals don't live forever because natural selection doesn't select for immortality in a world where an existing body plan works perfectly well to pass along a body's selfish genes. And because all species are resource limited, they have evolved to allocate the available energy either to reproduction or to longevity, but not to both. That was as true for *M. superstes* as it was and still is for all species that have ever lived on this planet.

All, that is, except one: *Homo sapiens*.

Having capitalized on its relatively large brain and a thriving civilization to overcome the unfortunate hand that evolution dealt it—weak limbs, sensitivity to cold, poor sense of smell, and

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[21] A bat from Siberia set a world record when it reached 41 years of age. R. Locke, "The Oldest Bat: Longest-Lived Mammals Offer Clues to Better Aging in Humans," *BATS Magazine* 24, no. 2 (Summer 2006): 13–14, http://www.batcon.org/resources/media-education/bats-magazine/bat_article/152.

[22] Small colonies of lizards on a series of Caribbean islands were likely to explore islands where there weren't predators, while less adventurous animals survived better when predators were present. O. Lapiedra, T. W. Schoener, M. Leal, et al., "Predator-Driven Natural Selection on Risk-Taking Behavior in Anole Lizards," *Science* 360, no. 3692 (June 1, 2018): 1017–20, http://science.sciencemag.org/content/360/6392/1017.

eyes that see well only in daylight and in the visible spectrum—this highly unusual species continues to innovate. It has already provided itself with an abundance of food, nutrients, and water while reducing deaths from predation, exposure, infectious diseases, and warfare. These were all once limits to its evolving a longer lifespan. With them removed, a few million years of evolution might double its lifespan, bringing it closer to the lifespans of some other species at the top of their game. But it won't have to wait that long, nowhere near that. Because this species is diligently working to invent medicines and technologies to give it the robustness of a much longer lived one, literally overcoming what evolution failed to provide.

CRISIS MODE

Wilbur and Orville Wright could never have built a flying machine without a knowledge of airflow and negative pressure and a wind tunnel. Nor could the United States have put men on the moon without an understanding of metallurgy, liquid combustion, computers, and some measure of confidence that the moon is not made of green cheese.[23]

In the same way, if we are to make real progress in the effort to alleviate the suffering that comes with aging, what is needed is a unified explanation for why we age, not just at the evolutionary

[23] Richard Dawkins eloquently made this point in *River Out of Eden*, arguing that primitive societies don't have a place in science, using as an example their belief the moon is an old calabash tossed into the sky. R. Dawkins, *River Out of Eden* (New York: Basic Books, 1995).

level but at the fundamental level.

But explaining aging at a fundamental level is no easy task. It will have to satisfy all known laws of physics and all rules of chemistry and be consistent with centuries of biological observations. It will need to span the least understood world between the size of a molecule and the size of a grain of sand,[24] and it should explain simultaneously the simplest and the most complex living machines that have ever existed.

It should, therefore, come as no surprise that there has never been a unified theory of aging, at least not one that has held up —though not for lack of trying.

One hypothesis, proposed independently by Peter Medawar and Leo Szilard, was that aging is caused by DNA damage and a resulting loss of genetic information. Unlike Medawar, who was always a biologist, who built a Nobel Prize–winning career in immunology, Szilard had come to study biology in a roundabout way. The Budapest-born polymath and inventor lived a nomadic life with no permanent job or address, preferring to spend his time staying with colleagues who satisfied his mental curiosities about the big questions facing humanity. Early in his career, he was a pioneering nuclear physicist and a founding collaborator on the Manhattan Project, which ushered in the age of atomic warfare. Horrified by the countless lives his work had helped end, he turned his tortured mind toward making life maximally long.[25]

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[24] See "The Scale of Things" at the end of this book.

[25] Szilard spent his last years as a fellow of the Salk Institute for Biological Studies

The idea that mutation accumulation causes aging was embraced by scientists and the public alike in the 1950s and 1960s, at a time when the effects of radiation on human DNA were on a lot of people's minds. But although we know with great certainty that radiation can cause all sorts of problems in our cells, it causes only a subset of the signs and symptoms we observe during aging,[26] so it cannot serve as a universal theory.

In 1963, the British biologist Leslie Orgel threw his hat into the ring with his "Error Catastrophe Hypothesis," which postulated that mistakes made during the DNA-copying process lead to mutations in genes, including those needed to make the protein machinery that copies DNA. The process increasingly disrupts those same processes, multiplying upon themselves until a person's genome has been incorrectly copied into oblivion.[27]

Around the same time that Szilard was focusing on radiation, Denham Harman, a chemist at Shell Oil, was also thinking atomically, albeit in a different way. After taking time off to finish medical school at Stanford University, he came up with the "Free Radical Theory of Aging," which blames aging on

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in La Jolla, California, as a resident fellow. He lived in a bungalow on the property of the Hotel del Charro and died on May 30, 1964.

[26] R. Anderson, "Ionizing Radiation and Aging: Rejuvenating an Old Idea," *Aging* 1, no. 11 (November 17, 2009): 887–902, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2815743/.

[27] L. E. Orgel, "The Maintenance of the Accuracy of Protein Synthesis and Its Relevance to Ageing," *Proceedings of the National Academy of Sciences of the United States of America* 49, no. 4 (April 1963): 517–21, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC299893/.

unpaired electrons that whiz around within cells, damaging DNA through oxidation, especially in mitochondria, because that is where most free radicals are generated.[28] Harman spent the better part of his life testing the theory.

I had the pleasure of meeting the Harman family in 2013. His wife told me that Professor Harman had been taking high doses of alphalipoic acid for most of his life to quench free radicals. Considering that he worked tirelessly on his research well into his 90s, I suppose, at the very least, it didn't hurt.

Through the 1970s and 1980s, Harman and hundreds of other researchers tested whether antioxidants would extend the lifespan of animals. The results overall were disappointing. Although Harman had some success increasing the average lifespan of rodents, such as with the food additive butylated hydroxytoluene, none showed an increase in *maximum* lifespan. In other words, a cohort of study animals might live a few weeks longer, on average, but none of the animals was setting records for individual longevity. Science has since demonstrated that the positive health effects attainable from an antioxidant-rich diet are more likely caused by stimulating the body's natural

[28] Harman concluded that the diseases related to aging, as well as aging itself, stem fundamentally from "the deleterious side attacks of free-radicals on cell constituents and on the connective tissues." The source of the free radicals, he continued, was "molecular oxygen catalyzed in the cell by the oxidative enzymes" and metal traces. D. Harman, "Aging: A Theory Based on Free Radical and Radiation Chemistry," *Journal of Gerontology* 11, no. 3 (July 1, 1956): 298–300, https://academic.oup.com/geronj/article-abstract/11/3/298/616585?redirectedFrom=fulltext.

defenses against aging, including boosting the production of the body's enzymes that eliminate free radicals, not as a result of the antioxidant activity itself.

If old habits die hard, the free-radical idea is heroin. The theory was overturned by scientists within the cloisters of my field more than a decade ago, yet it is still widely perpetuated by purveyors of pills and drinks, who fuel a $3 billion global industry.[29] With all that advertising, it is not surprising that more than 60 percent of US consumers still look for foods and beverages that are good sources of antioxidants.[30]

Free radicals do cause mutations. Of course they do. You can find mutations in abundance, particularly in cells that are exposed to the outside world[31] and in the mitochondrial genomes of old individuals. Mitochondrial decline is certainly a hallmark of aging and can lead to organ dysfunction. But mutations alone,

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[29] Nutraceuticals World predicts that a rising appetite for synthetic antioxidants at the same time as a fall in costs, combined with increasing demand for them by food and beverage companies, will power market growth for the next few years. "Global Antioxidants Market Expected to Reach $4.5 Billion by 2022," *Nutraceuticals World*, January 26, 2017, https://www.nutraceuticalsworld.com/contents/view_breaking-news/2017-01-26/global-antioxidants-market-expected-to-reach-45-billion-by-2022

[30] The sharp growth in demand for drinks with a health benefit, a beverage industry website finds, goes hand in hand with consumers wanting ingredients they value. A. Del Buono, "Consumers' Understanding of Antioxidants Grows," *Beverage Industry*, January 16, 2018, https://www.bevindustry.com/articles/90832-consumers-understanding-of-antioxidants-grows?v=preview.

[31] I. Martincorena, J. C. Fowler, A. Wabik, et al., "Somatic Mutant Clones Colonize the Human Esophagus with Age," *Science* 362, no. 6417 (November 23, 2018): 911–17, https://www.ncbi.nlm.nih.gov/pubmed/30337457.

especially mutations in the nuclear genome, conflict with an ever-increasing amount of evidence to the contrary.

Arlan Richardson and Holly Van Remmen spent about a decade at the University of Texas at San Antonio testing if increasing free-radical damage or mutations in mice led to aging; it didn't.[32] In my lab and others, it has proven surprisingly simple to restore the function of mitochondria in old mice, indicating that a large part of aging is not due to mutations in mitochondrial DNA, either, at least not until late in life.[33]

Although the discussion about the role of nuclear DNA mutations in aging continues, there is one fact that contradicts all these theories, one that is difficult to refute.

Ironically, it was Szilard, in 1960, who initiated the demise of his own theory by figuring out how to clone a human cell.[34] Cloning gives us the answer as to whether or not mutations cause aging. If old cells had indeed lost crucial genetic information and this was the cause of aging, we shouldn't be able to clone new

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[32] The authors concluded that their data "calls into serious question the hypothesis that alterations in oxidative damage/stress play a role in the longevity of mice." V. I. Pérez, A. Bokov, H. Van Remmen, et al., "Is the Oxidative Stress Theory of Aging Dead?," *Biochimica et Biophysica Acta* 1790, no. 10 (October 2009): 1005–14, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2789432/.

[33] A. P. Gomes, N. L. Price, A. J. Ling, et al., "Declining NAD(+) Induces a Pseudohypoxic State Disrupting Nuclear-Mitochondrial Communication During Aging," *Cell* 155, no. 7 (December 19, 2013): 1624–38, https://www.ncbi.nlm.nih.gov/pubmed/24360282.

[34] W. Lanouette and B. Silard, *Genius in the Shadows: A Biography of Leo Szilard: The Man Behind the Bomb* (New York: Skyhorse Publishing, 1992).

animals from older individuals. Clones would be born old.

It's a misconception that cloned animals age prematurely. It has been widely perpetuated in the media and even the National Institutes of Health website says so.[35] Yes, it's true that Dolly, the first cloned sheep, created by Keith Campbell and Ian Wilmut at the Roslin Institute at the University of Edinburgh, lived only half a normal lifespan and died of a progressive lung disease. But extensive analysis of her remains showed no sign of premature aging.[36] Meanwhile, the list of animal species that have been cloned and proven to live a normal, healthy lifespan now includes goats, sheep, mice, and cows.[37]

Because of the fact that nuclear transfer works in cloning, we

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[35] According to the NIH fact sheet, "clones created from a cell taken from an adult might have chromosomes that are already shorter than normal, which may condemn the clones' cells to a shorter life span." "Cloning," National Human Genome Research Institute, March 21, 2017, https://www.genome.gov/25020028/cloning-fact-sheet/.

[36] In the debates over Dolly the cloned sheep, the question that has proved to be challenging to answer is how old an animal is at birth when cloned from an adult's cell. The answer an author on the site The Conversation found was that other clones born from the same cell as Dolly lived normal lifespans. "The new Dollies are now telling us that if we take a cell from an animal of any age, and we introduce its nucleus into a nonfertilized mature egg, we can have an individual born with its lifespan fully restored." J. Cibell, "More Lessons from Dolly the Sheep: Is a Clone Really Born at Age Zero?," The Conversation, February 17, 2017, https://theconversation.com/more-lessons-from-dolly-the-sheep-is-a-clone-really-born-at-age-zero-73031.

[37] Though some cloned animals match their species' rates of normal aging, it's a field that still needs further analysis to get beyond the largely anecdotal evidence so far collected. J. P. Burgstaller and G. Brem, "Aging of Cloned Animals: A Mini-Review," *Gerontology* 63, no. 5 (August 2017): 417–25, https://www.karger.com/Article/FullText/452444.

can say with a high degree of confidence that aging isn't caused by mutations in nuclear DNA. Sure, it's possible that some cells in the body don't mutate and those are the ones that end up making successful clones, but that seems highly unlikely. The simplest explanation is that old animals retain all the requisite genetic information to generate an entirely new, healthy animal and that mutations are not the primary cause of aging.[38]

It's certainly no dishonor to those brilliant researchers that their theories haven't withstood the test of time. That's what happens to most science, and perhaps all of it eventually. In *The Structure of Scientific Revolutions*, Thomas Kuhn noted that scientific discovery is never complete; it goes through predictable stages of evolution. When a theory succeeds at explaining previously unexplainable observations about the world, it becomes a tool that scientists can use to discover even more.

Inevitably, however, new discoveries lead to new questions that are not entirely answerable by the theory, and those questions beget more questions. Soon the model enters crisis mode and

[38] University of Bath researchers found in cloned mice that the telomeres protecting the ends of chromosomes were, surprisingly, slightly longer in successive generations and demonstrated no evidence of premature aging. T. Wakayama, Y. Shinkai, K. L. K. Tamashiro, et al., "Ageing: Cloning of Mice to Six Generations," *Nature* 407 (September 21, 2000): 318–19. "Despite the length of telomeres reported in different studies, most clones appear to be aging normally. In fact, the first cattle clones ever produced are alive, healthy, and are 10 years old as of January 2008"; "Myths About Cloning," U.S. Food & Drug Administration, August 29, 2018, https://www.fda.gov/animalveterinary/safetyhealth/animalcloning/ucm055512.htm.

begins to drift as scientists seek to adjust it, as little as possible, to account for that which it cannot explain.

Crisis mode is always a fascinating time in science but one that is not for the faint of heart, as doubts about the views of previous generations continue to grow against the old guard's protestations. But the chaos is ultimately replaced by a paradigm shift, one in which a new consensus model emerges that can explain more than the previous model.

That's what happened about a decade ago, as the ideas of leading scientists in the aging field began to coalesce around a new model—one that suggested that the reason so many brilliant people had struggled to identify a single cause of aging was that there wasn't one.

In this more nuanced view, aging and the diseases that come with it are the result of multiple "hallmarks" of aging:

- Genomic instability caused by DNA damage
- Attrition of the protective chromosomal endcaps, the telomeres
- Alterations to the epigenome that controls which genes are turned on and off
- Loss of healthy protein maintenance, known as proteostasis
- Deregulated nutrient sensing caused by metabolic changes
- Mitochondrial dysfunction
- Accumulation of senescent zombielike cells that inflame healthy cells

- Exhaustion of stem cells
- Altered intercellular communication and the production of inflammatory molecules

Researchers began to cautiously agree: address these hallmarks, and you can slow down aging. Slow down aging, and you can forestall disease. Forestall disease, and you can push back death.

Take stem cells, which have the potential to develop into many other kinds of cells: if we can keep these undifferentiated cells from tiring out, they can continue to generate all the differentiated cells necessary to heal damaged tissues and battle all kinds of diseases.

Meanwhile, we're improving the rates of acceptance of bone marrow transplants, which are the most common form of stem cell therapy, and using stem cells for the treatment of arthritic joints, type 1 diabetes, loss of vision, and neurodegenerative diseases such as Alzheimer's and Parkinson's. These stem cell–based interventions are adding years to people's lives.

Or take senescent cells, which have reached the end of their ability to divide but refuse to die, continuing to spit out panic signals that inflame surrounding cells: if we can kill off senescent cells or keep them from accumulating in the first place, we can keep our tissues much healthier for longer.

The same can be said for combating telomere loss, the decline in proteostasis, and all of the other hallmarks. Each can be addressed one by one, a little at a time, in ways that can help us

extend human healthspans.

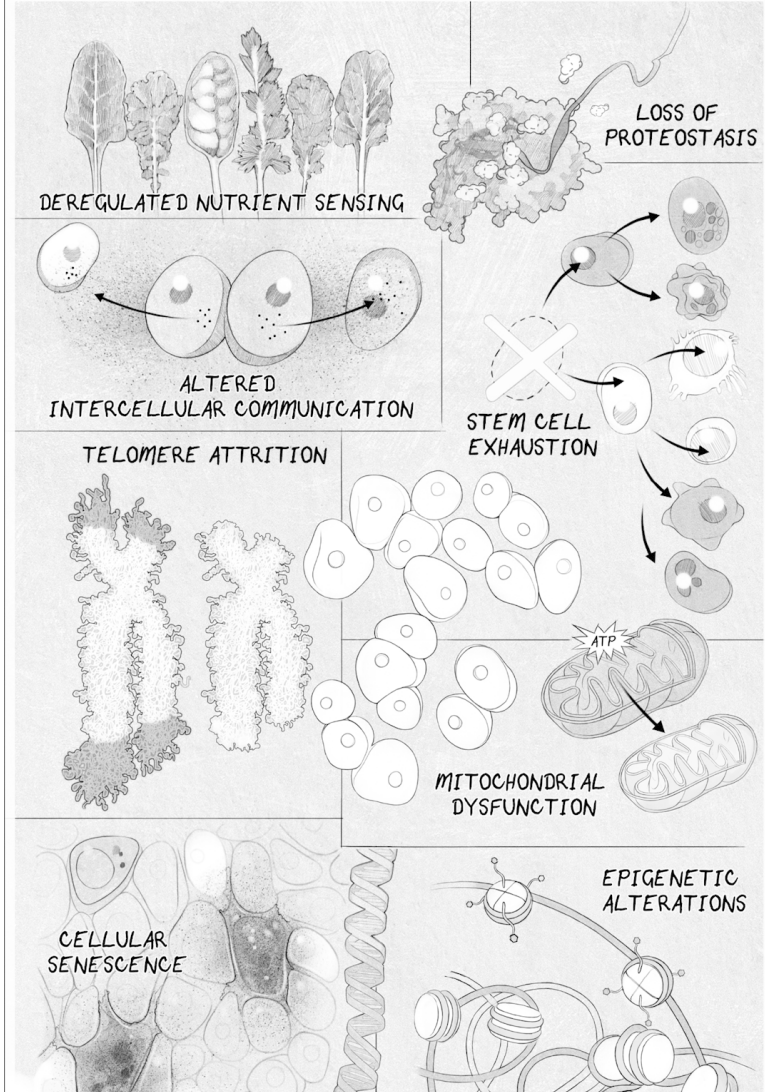
Over the past quarter century, researchers have increasingly honed their efforts in on addressing each of these hallmarks. A broad consensus formed that this would be the best way to alleviate the pain and suffering of those who are aging.

There is little doubt that the list of hallmarks, though incomplete, comprises the beginnings of a rather strong tactical manual for living longer and healthier lives. Interventions aimed at slowing any one of these hallmarks may add a few years of wellness to our lives. If we can address all of them, the reward could be vastly increased *average* lifespans.

As for pushing way past the *maximum* limit? Addressing these hallmarks might not be enough.

But the science is moving fast, faster now than ever before, thanks to the accumulation of many centuries of knowledge, robots that analyze tens of thousands of potential drugs each day, sequencing machines that read millions of genes a day, and computing power that processes trillions of bytes of data at speeds that were unimaginable just a decade ago. Theories on aging, which were slowly chipped away for decades, are now more easily testable and refutable.

Although it is in its early days, a new shift in thinking is again under way. Once again we find ourselves in a period of chaos —still quite confident that the hallmarks are accurate indicators of aging and its myriad symptoms but unable to explain why the hallmarks occur in the first place.


DEREGULATED NUTRIENT SENSING
LOSS OF PROTEOSTASIS
ALTERED INTERCELLULAR COMMUNICATION
STEM CELL EXHAUSTION
TELOMERE ATTRITION
ATP
MITOCHONDRIAL DYSFUNCTION
CELLULAR SENESCENCE
EPIGENETIC ALTERATIONS

THE HALLMARKS OF AGING. Scientists have settled on eight or nine hallmarks of aging. Address one of these, and you can slow down aging. Address all of them, and you might not age.

It is time for an answer to this very old question.

Now, finding a universal explanation for anything—let alone something as complicated as aging—doesn't happen overnight. Any theory that seeks to explain aging must not just stand up to scientific scrutiny but provide a rational explanation for every one of the pillars of aging. A universal hypothesis that seems to provide a reason for cellular senescence but not stem cell exhaustion would, for example, explain neither.

Yet I believe that such an answer exists—a cause of aging that exists upstream of all the hallmarks. Yes, a *singular* reason why we age.

Aging, quite simply, is a loss of information.

You might recognize that loss of information was a big part of the ideas that Szilard and Medawar independently espoused, but it was wrong because it focused on a loss of *genetic* information.

But there are two types of information in biology, and they are encoded entirely differently. The first type of information —the type my esteemed predecessors understood—is *digital*. Digital information, as you likely know, is based on a finite set of possible values—in this instance, not in base 2 or binary, coded as 0s and 1s, but the sort that is quaternary or base 4, coded as

adenine, thymine, cytosine, and guanine, the nucleotides A, T, C, G of DNA.

Because DNA is digital, it is a reliable way to store and copy information. Indeed, it can be copied again and again with tremendous accuracy, no different in principle from digital information stored in computer memory or on a DVD.

DNA is also robust. When I first worked in a lab, I was shocked by how this "molecule of life" could survive for hours in boiling water and thrilled that it was recoverable from Neanderthal remains at least 40,000 years old.[39] The advantages of digital storage explain why chains of nucleic acids have remained the go-to biological storage molecule for the past 4 billion years.

The other type of information in the body is *analog*.

We don't hear as much about analog information in the body. That's in part because it's newer to science, and in part because it's rarely described in terms of information, even though that's how it was first described when geneticists noticed strange nongenetic effects in plants they were breeding.

Today, analog information is more commonly referred to as the *epigenome*, meaning traits that are heritable that aren't

[39] The authors discovered mitochondrial DNA in a Neanderthal bone in Croatia that revealed older dates of survival than previously thought. T. Devièse, I. Karavanić, D. Comeskey, et al., "Direct Dating of Neanderthal Remains from the Site of Vindija Cave and Implications for the Middle to Upper Paleolithic Transition," *Proceedings of the National Academy of Sciences of the United States of America* 114, no. 40 (October 3, 2017): 10606–11, https://www.ncbi.nlm.nih.gov/pubmed/28874524.

transmitted by genetic means.

The term *epigenetics* was first coined in 1942 by Conrad H. Waddington, a British developmental biologist, while working at Cambridge University. In the past decade, the meaning of the word epigenetics has expanded into other areas of biology that have less to do with heredity—including embryonic development, gene switch networks, and chemical modifications of DNA-packaging proteins—much to the chagrin of orthodox geneticists in my department at Harvard Medical School.

In the same way that genetic information is stored as DNA, epigenetic information is stored in a structure called chromatin. DNA in the cell isn't flailing around disorganized, it is wrapped around tiny balls of protein called histones. These beads on a string self-assemble to form loops, as when you tidy your garden hose on your driveway by looping it into a pile. If you were to play tug-of-war using both ends of a chromosome, you'd end up with a six foot-long string of DNA punctuated by thousands of histone proteins. If you could somehow plug one end of the DNA into a power socket and make the histones flash on and off, a few cells could do you for holiday lights.

In simple species, like ancient *M. superstes* and fungi today, epigenetic information storage and transfer is important for survival. For complex life, it is essential. By complex life, I mean anything made up of more than a couple of cells: slime molds, jellyfish, worms, fruit flies, and of course mammals like us. Epigenetic information is what orchestrates the assembly of

a human newborn made up of 26 billion cells from a single fertilized egg and what allows the genetically identical cells in our bodies to assume thousands of different modalities.[40]

If the genome were a computer, the epigenome would be the software. It instructs the newly divided cells on what type of cells they should be and what they should remain, sometimes for decades, as in the case of individual brain neurons and certain immune cells.

That's why a neuron doesn't one day behave like a skin cell and a dividing kidney cell doesn't give rise to two liver cells. Without epigenetic information, cells would quickly lose their identity and new cells would lose their identity, too. If they did, tissues and organs would eventually become less and less functional until they failed.

In the warm ponds of the primordial Earth, a digital chemical system was the best way to store long-term genetic data. But information storage was also needed to record and respond to environmental conditions, and this was best stored in analog format. Analog data are superior for this job because they can be changed back and forth with relative ease whenever the environment within or outside the cell demands it, and they can store an almost unlimited number of possible values, even in

[40] A. S. Adikesevan, "A Newborn Baby Has About 26,000,000,000 Cells. An Adult Has About 1.9×10^3 Times as Many Cells as a Baby. About How Many Cells Does an Adult Have?," Socratic, January 26, 2017, https://socratic.org/questions/a-newborn-baby-has-about-26-000-000-000-cells-an-adult-has-about-1-9-10-3-times-.

response to conditions that have never been encountered before.[41]

The unlimited number of possible values is why many audiophiles still prefer the rich sounds of analog storage systems. But even though analog devices have their advantages, they have a major disadvantage. In fact, it's the reason we've moved from analog to digital. Unlike digital, analog information degrades over time—falling victim to the conspiring forces of magnetic fields, gravity, cosmic rays, and oxygen. Worse still, information is lost as it's copied.

No one was more acutely disturbed by the problem of information loss than Claude Shannon, an electrical engineer from the Massachusetts Institute of Technology (MIT) in Boston. Having lived through World War II, Shannon knew firsthand how the introduction of "noise" into analog radio transmissions could cost lives. After the war, he wrote a short but profound scientific paper called "The Mathematical Theory of Communication" on how to preserve information, which many consider the foundation of Information Theory. If there is one paper that propelled us into the digital, wireless world in which we now live,

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[41] C. B. Brachmann, J. M. Sherman, S. E. Devine, et al., "The *SIR2* Gene Family, Conserved from Bacteria to Humans, Functions in Silencing, Cell Cycle Progression, and Chromosome Stability," *Genes & Development* 9, no. 23 (December 1, 1995): 2888–902, http://genesdev.cshlp.org/content/9/23/2888.long; X. Bi, Q. Yu, J. J. Sandmeier, and S. Elizondo, "Regulation of Transcriptional Silencing in Yeast by Growth Temperature," *Journal of Molecular Biology* 34, no. 4 (December 3, 2004): 893–905, https://www.ncbi.nlm.nih.gov/pubmed/15544800.

that would be it.[42]

Shannon's primary intention, of course, was to improve the robustness of electronic and radio communications between two points. His work may ultimately prove to be even more important than that, for what he discovered about preserving and restoring information, I believe, can be applied to aging.

Don't be disheartened by my claim that we are the biological equivalent of an old DVD player. This is actually good news. If Szilard had turned out to be right about mutations causing aging, we would not be able to easily address it, because when information is lost without a backup, it is lost for good. Ask anyone who's tried to play or restore content from a DVD that's had an edge broken off: what is gone is gone.

But we can usually recover information from a *scratched* DVD. And if I am right, the same kind of process is what it will take to reverse aging.

As cloning beautifully proves, our cells retain their youthful digital information even when we are old. To become young again, we just need to find some polish to remove the scratches.

This, I believe, is possible.

A TIME TO EVERY PURPOSE

The Information Theory of Aging starts with the primordial

[42] It is one of the most interesting and important papers I've ever read. C. E. Shannon, "A Mathematical Theory of Communication," *Bell System Technical Journal* 27, no. 3 (July 1948): 379–423, and 27, no. 4 (October 1948): 623–66, http://math.harvard.edu/~ctm/home/text/others/shannon/entropy/entropy.pdf.

survival circuit we inherited from our distant ancestors.

Over time, as you might expect, the circuit has evolved. Mammals, for instance, don't have just a couple of genes that create a survival circuit, such as those that first appeared in *M. superstes*. Scientists have found more than two dozen of them within our genome. Most of my colleagues call these "longevity genes" because they have demonstrated the ability to extend both average and maximum lifespans in many organisms. But these genes don't just make life longer, they make it healthier, which is why they can also be thought of as "vitality genes."

Together, these genes form a surveillance network within our bodies, communicating with one another between cells and between organs by releasing proteins and chemicals into the bloodstream, monitoring and responding to what we eat, how much we exercise, and what time of day it is. They tell us to hunker down when the going gets tough, and they tell us to grow fast and reproduce fast when the going gets easier.

And now that we know these genes are there and what many of them do, scientific discovery has given us an opportunity to explore and exploit them; to imagine their potential; to push them to work for us in different ways. Using molecules both natural and novel, using technology both simple and complex, using wisdom both new and old, we can read them, turn them up and down, and even change them altogether.

The longevity genes I work on are called "sirtuins," named after the yeast *SIR2* gene, the first one to be discovered. There

are seven sirtuins in mammals, *SIRT1* to *SIRT7*, and they are made by almost every cell in the body. When I started my research, sirtuins were barely on the scientific radar. Now this family of genes is at the forefront of medical research and drug development.

Descended from gene B in *M. superstes*, sirtuins are enzymes that remove acetyl tags from histones and other proteins and, by doing so, change the packaging of the DNA, turning genes off and on when needed. These critical epigenetic regulators sit at the very top of cellular control systems, controlling our reproduction and our DNA repair. After a few billion years of advancement since the days of yeast, they have evolved to control our health, our fitness, and our very survival. They have also evolved to require a molecule called nicotinamide adenine dinucleotide, or NAD. As we will see later, the loss of NAD as we age, and the resulting decline in sirtuin activity, is thought to be a primary reason our bodies develop diseases when we are old but not when we are young.

Trading reproduction for repair, the sirtuins order our bodies to "buckle down" in times of stress and protect us against the major diseases of aging: diabetes and heart disease, Alzheimer's disease and osteoporosis, even cancer. They mute the chronic, overactive inflammation that drives diseases such as atherosclerosis, metabolic disorders, ulcerative colitis, arthritis, and asthma. They prevent cell death and boost mitochondria, the power packs of the cell. They go to battle with muscle

wasting, osteoporosis, and macular degeneration. In studies on mice, activating the sirtuins can improve DNA repair, boost memory, increase exercise endurance, and help the mice stay thin, regardless of what they eat. These are not wild guesses as to their power; scientists have established all of this in peer-reviewed studies published in journals such as *Nature*, *Cell*, and *Science*.

And in no small measure, because sirtuins do all of this based on a rather simple program—the wondrous gene B in the survival circuit—they're turning out to be more amenable to manipulation than many other longevity genes. They are, it would appear, one of the first dominos in the magnificent Rube Goldberg machine of life, the key to understanding how our genetic material protects itself during times of adversity, allowing life to persist and thrive for billions of years.

Sirtuins aren't the only longevity genes. Two other very well studied sets of genes perform similar roles, which also have been proven to be manipulable in ways that can offer longer and healthier lives.

One of these is called target of rapamycin, or TOR, a complex of proteins that regulates growth and metabolism. Like sirtuins, scientists have found TOR—called mTOR in mammals—in every organism in which they've looked for it. Like that of sirtuins, mTOR activity is exquisitely regulated by nutrients. And like the sirtuins, mTOR can signal cells in stress to hunker down and improve survival by boosting such activities as DNA repair,

reducing inflammation caused by senescent cells, and, perhaps its most important function, digesting old proteins.[43]

When all is well and fine, TOR is a master driver of cell growth. It senses the amount of amino acids that is available and dictates how much protein is created in response. When it is inhibited, though, it forces cells to hunker down, dividing less and reusing old cellular components to maintain energy and extend survival—sort of like going to the junkyard to find parts with which to fix up an old car rather than buying a new one, a process called autophagy. When our ancestors were unsuccessful in bringing down a woolly mammoth and had to survive on meager rations of protein, it was the shutting down of mTOR that permitted them to survive.

The other pathway is a metabolic control enzyme known as AMPK, which evolved to respond to low energy levels. It has also been highly conserved among species and, as with sirtuins and TOR, we have learned a lot about how to control it.

These defense systems are all activated in response to biological stress. Clearly, some stresses are simply too great to

[43] Research by the authors showed that mTORC1 signaling in cancer cells increases survival by "suppressing endogenous DNA damage, and may control cell fate through the regulation of CHK1." X. Zhou, W. Liu, X. Hu, et al., "Regulation of CHK1 by mTOR Contributes to the Evasion of DNA Damage Barrier of Cancer Cells," *Nature Scientific Reports*, May 8, 2017, https://www.nature.com/articles/s41598-017-01729-w; D. M. Sabatini, "Twenty-five Years of mTOR: Uncovering the Link from Nutrients to Growth," *Proceedings of the National Academy of Sciences of the United States of America* 114, no. 45 (November 7, 2017): 11818–25, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5692607/.

overcome—step on a snail, and its days are over. Acute trauma and uncontrollable infections will kill an organism without *aging* that organism. Sometimes the stress inside a cell, such as a multitude of DNA breaks, is too much to handle. Even if the cell is able to repair the breaks in the short term without leaving mutations, there is information loss at the epigenetic level.

Here's the important point: there are plenty of stressors that will activate longevity genes without damaging the cell, including certain types of exercise, intermittent fasting, low-protein diets, and exposure to hot and cold temperatures (I discuss this in chapter 4). That's called hormesis.[44] Hormesis is generally good for organisms, especially when it can be induced without causing any lasting damage. When hormesis happens, all is well. And, in fact, all is *better* than well, because the little bit of stress that occurs when the genes are activated prompts the rest of the system to hunker down, to conserve, to survive a little longer. That's the start of longevity.

Complementing these approaches are hormesis-mimicking molecules. Drugs in development and at least two drugs on the market can turn on the body's defenses without creating *any* damage. It's like making a prank call to the Pentagon. The troops and the Army Corps of Engineers are sent out, but there's no war. In this way, we can mimic the benefits of exercise and

[44] E. J. Calabrese, "Hormesis: A Fundamental Concept in Biology," *Microbial Cell* 1, no. 5 (May 5, 2014): 145–49, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5354598/.

intermittent fasting with a single pill (I discuss this in chapter 5).

Our ability to control all of these genetic pathways will fundamentally transform medicine and the shape of our everyday lives. Indeed, it will change the way we define our species.

And yes, I realize how that sounds. So let me explain why.

TWO
THE DEMENTED PIANIST

ON APRIL 15, 2003, NEWSPAPERS, TELEVISION PROGRAMS, AND WEBSITES around the world carried the story: the mapping of the human genome was complete.

There was just one pesky problem: it really wasn't. There were, in fact, huge gaps in the sequence.

This wasn't a case of the mainstream news media blowing things out of proportion. Highly respected scientific journals such as *Science* and *Nature* told pretty much the same story. It also wasn't a case of scientists overstating their work. The truth is simply that, at the time, most researchers involved in the thirteen-year, $1 billion project agreed that we'd come as close as we possibly could—given the technology of the time—to identifying each of the 3 billion base pairs in our DNA.

The parts of the genome that were missing, generally overlapping sections of repetitive nucleotides, were just not considered important. These were areas of the code of life that were once derided as "junk DNA" and that are now a little better respected but still generally disregarded as "noncoding." From the perspective of many of the best minds in science at the time, those regions were little more than the ghosts of genomes past, mostly remnants of dead hitchhiking viruses that had integrated into the genome hundreds of thousands of years ago. The stuff

that makes us who we are, it was thought, had largely been identified, and we had what we needed to propel forward our understanding of what makes us human.

Yet by some estimates, that genetic dark matter accounts for as much as 69 percent of the total genome,[45] and even within the regions generally regarded as "coding," some scientists believe, up to 10 percent has yet to be decoded, including regions that impact aging.[46]

In the relatively short time that has come and gone since 2003, we have come to find out that within the famous double helix, there were sequences that were not just unmapped but essential to our lives. Indeed, many thousands of sequences had gone undetected because the original algorithms to detect genes were written to disregard any gene less than 300 base pairs long. In fact, genes can be as short as 21 base pairs, and today we're discovering hundreds of them all over the genome.

These genes tell our cells to create specific proteins, and these

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[45] Up to 69 percent of the human genome may be repetitive or derived from endogenous viral DNA repeats, compared to previous estimates of around half. A. P. de Konig, W. Gu, T. A. Castoe, et al., "Repetitive Elements May Comprise over Two-thirds of the Human Genome," *PLOS Genetics* 7, no. 12 (December 7, 2011), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3228813/.

[46] Just what do we mean by the word *finished* when it comes to the sequencing of the human genome? Turns out, more than we thought back in the early 2000s. Regions of the genome previously thought of as nonfunctional are now emerging as playing potential roles in cancer, autism, and aging. S. Begley, "Psst, the Human Genome Was Never Completely Sequenced. Some Scientists Say It Should Be," *STAT*, June 20, 2017, https://www.statnews.com/2017/06/20/human-genome-not-fully-sequenced/.

proteins are the building blocks of the processes and traits that constitute human biology and lived experiences. And as we get closer to identifying a complete sequence of our DNA, we've come closer to having a "map" of the genes that control so much of our existence.

Even once we have a complete code, though, there's something we still won't be able to find.

We won't be able to find an aging gene.

We have found genes that impact the *symptoms* of aging. We've found longevity genes that control the body's defenses against aging and thus offer a path to slowing aging through natural, pharmaceutical, and technological interventions. But unlike the oncogenes that were discovered in the 1970s and that have given us a good target for going to battle against cancer, we haven't identified a singular gene that causes aging. And we won't.

Because our genes did not evolve to *cause* aging.

YEAST OF EDEN

My journey toward formulating the Information Theory of Aging was a long one. And in no small part, it can be traced to the work of a scientist who toiled without fame but whose work helped set the stage for a lot of the longevity research being done around the world today.

His name was Robert Mortimer, and if there was one adjective that seemed to come up more than any other about him after he

passed away, it was "kind."

"Visionary" was another. "Brilliant," "inquisitive," and "hardworking," too. But I've long been inspired by the example Mortimer set for his fellow scientists. Mortimer, who died in 2007, had played a tremendously important role in elevating *Saccharomyces cerevisiae* from a seemingly lowly, single-celled yeast with a sweet tooth (its name means "sugar-loving") to its rightful place as one of the world's most important research organisms.

Mortimer collected thousands of mutant yeast strains in his lab, many of which had been developed right there at the University of California, Berkeley. He could have paid for his research, and then some, by charging the thousands of scientists he supplied through the university's Yeast Genetic Stock Center. But anyone, from impecunious undergraduates to tenured professors at the world's best-funded research institutions, could browse the center's catalog, request any strain, and have it promptly delivered for the cost of postage.[47]

And because he made it so easy and so inexpensive, yeast research bloomed.

When Mortimer began working on *S. cerevisiae* alongside fellow biologist John Johnston[48] in the 1950s, hardly anyone was

[47] Dating back to the 1960s, every three or four years the center has published a catalog of its strains of *Saccharomyces cerevisiae*. R. K. Mortimer, "Yeast Genetic Stock Center," Grantome, 1998, http://grantome.com/grant/NIH/P40-RR004231-10S1.

[48] Yeast researchers have interesting names. John Johnston and my adviser Dick

interested in yeast. To most, it didn't seem we could learn much about our complex selves by studying a tiny fungus. It was a struggle to convince the scientific community that yeast could be useful for something more than baking bread, brewing beer, and vinting wine.

What Mortimer and Johnston recognized, and what many others began to realize in the years to come, was that those tiny yeast cells are not so different from ourselves. For their size, their genetic and biochemical makeup is extraordinarily complex, making them an exceptionally good model for understanding the biological processes that sustain life and control lifespans in large complex organisms such as ourselves. If you are skeptical that a yeast cell can tell us anything about cancer, Alzheimer's disease, rare diseases, or aging, consider that there have been five Nobel Prizes in Physiology or Medicine awarded for genetic studies in yeast, including the 2009 prize for discovering how cells counteract telomere shortening, one of the hallmarks of aging.[49]

The work Mortimer and Johnston did—and, in particular, a seminal paper in 1959 that demonstrated that mother and daughter yeast cells can have vastly different lifespans—would

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Dickinson are just two of them.

[49] In 2016, Dr. Yoshinori Ohsumi won the Nobel Prize in Physiology or Medicine for his work on autophagy in yeast. That's when cells stave off extinction during hard times by digesting nonkey parts of themselves. B. Starr, "A Nobel Prize for Work in Yeast. Again!," Stanford University, October 3, 2016, https://www.yeastgenome.org/blog/a-nobel-prize-for-work-in-yeast-again.

set the stage for a world-shattering change in the way we view the limits of life. And by the time of Mortimer's death in 2007, there were some 10,000 researchers studying yeast around the globe.

Yes, humans are separated from yeast by a billion years of evolution, but we still have a lot in common. *S. cerevisiae* shares some 70 percent of our genes. And what it does with those genes isn't so different from what we do with them. Like a whole lot of humans, yeast cells are almost always trying to do one of two things: either they're trying to eat, or they're trying to reproduce. They're hungry or they're horny. As they age, much like humans, they slow down and grow larger, rounder, and less fertile. But whereas humans go through this process over the course of many decades, yeast cells experience it in a week. That makes them a pretty good place to start in the quest to understand aging.

Indeed, the potential for a humble yeast to tell us so much about ourselves—and do so quite quickly relative to other research organisms—was a big part of the reason I decided to begin my career by studying *S. cerevisiae*. They also smell like fresh bread.

I met Mortimer in Vienna in 1992, when I was in my early 20s and attending the International Yeast Conference—yes, there is such a thing—with my two PhD supervisors, Professor Ian Dawes, a rule-avoiding Australian from the University of New South Wales,[50] and Professor Richard Dickinson, a rule-abiding

[50] Dawes's delightful tour of his experiences in the world of academe and cell biology research is a refreshingly direct and personal account of a remarkable journey

Briton from the University of Cardiff, Wales.

Mortimer was in Vienna to discuss a momentous scientific endeavor: the sequencing of the yeast genome. I was there to be inspired. And I was.[51] If I'd harbored any doubts about my decision to dedicate the opening years of my scientific career to a single-celled fungus, they all went away when I came face to face with people who were building great knowledge in a field that had hardly existed a few decades before.

It was shortly after that conference that one of the world's top scientists in the yeast field, Leonard Guarente of the Massachusetts Institute of Technology, came to Sydney on holiday to visit Ian Dawes. Guarente and I ended up at a dinner together, and I made sure I was sitting opposite him.

I was then a graduate student using yeast to understand an inherited condition called maple syrup urine disease. As you might imagine from its name, the disease is not something most polite people discuss over dinner. Guarente, though, engaged me in a scientific discussion with a curiosity and enthusiasm that was nothing short of enchanting. The conversation soon turned to his latest project—he had begun studying aging in yeast the past few months—work that had its roots in the workable genetic map that Mortimer had completed in the mid-1970s.

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into yeast research over four decades. I. Dawes, "Ian Dawes—the Third Pope—Lucky to Be a Researcher," *Fems Yeast Research* 6, no. 4 (June 2016), https://academic.oup.com/femsyr/article/16/4/fow040/2680350.

[51] I also learned, the hard way, that I should not drink copious quantities of yeasty beer.

That was it. I had a passion for understanding aging, and I knew something about wrangling a yeast cell with a microscope and micromanipulator. Those were essential skills needed to figure out why yeast age. That night, Guarente and I agreed on one thing: if we couldn't solve the problem of aging in yeast, we had no chance in humans.

I didn't just *want*

Конец ознакомительного фрагмента.