LIFESPAN

WHY WE AGE—

AND

WHY WE DON'T HAVE TO

David A. Sinclair, PhD, AO,
with Matthew D. LaPlante
Illustrations by Catherine L. Delphia

ATRIA
BOOKS

An Imprint of Simon & Schuster, Inc.
1230 Avenue of the Americas
New York, NY 10020

First Atria Books hardcover edition September 2019

ATRIA BOOKS and colophon are trademarks of Simon & Schuster, Inc.

For information about special discounts for bulk purchases, please contact Simon & Schuster Special Sales at 1-866-506-1949 or business@simonandschuster.com.

The Simon & Schuster Speakers Bureau can bring authors to your live event. For more information, or to book an event, contact the Simon & Schuster Speakers Bureau at 1-866-248-3049 or visit our website at www.simonspeakers.com.

Illustrations and Sinclairfont by Catherine L. Delphia.
Illustrations in Cast of Characters by David A. Sinclair, PhD.
For reproductions, contact David A. Sinclair, PhD.

Interior design by Ruth Lee-Mui

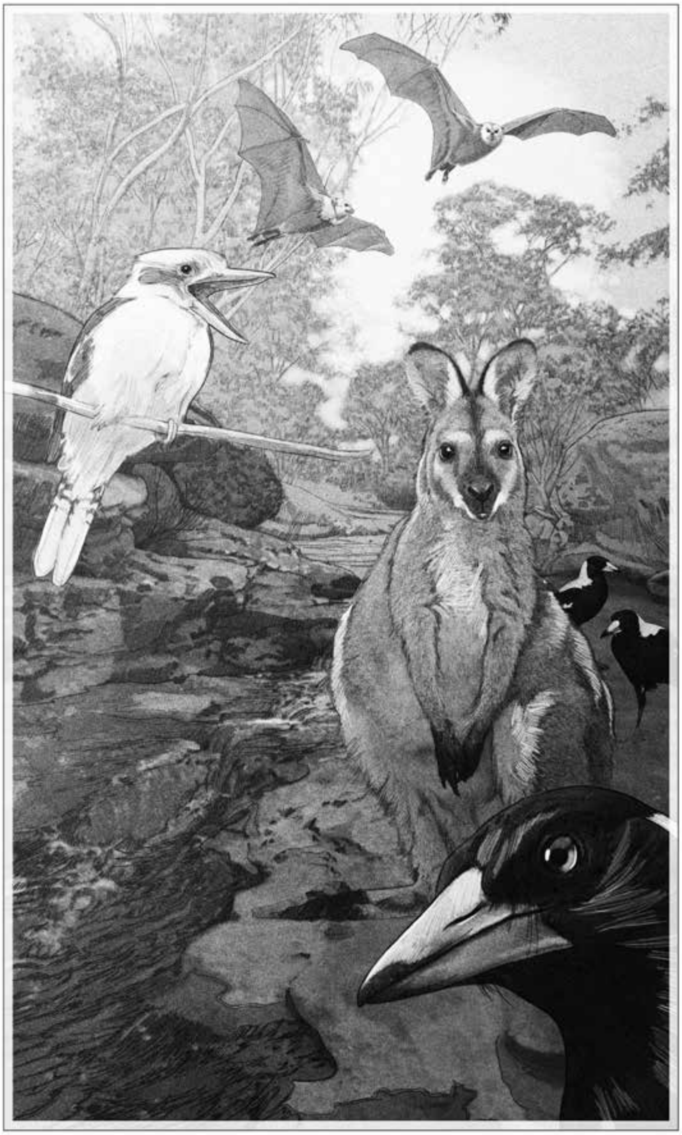
Manufactured in the United States of America

1 3 5 7 9 10 8 6 4 2

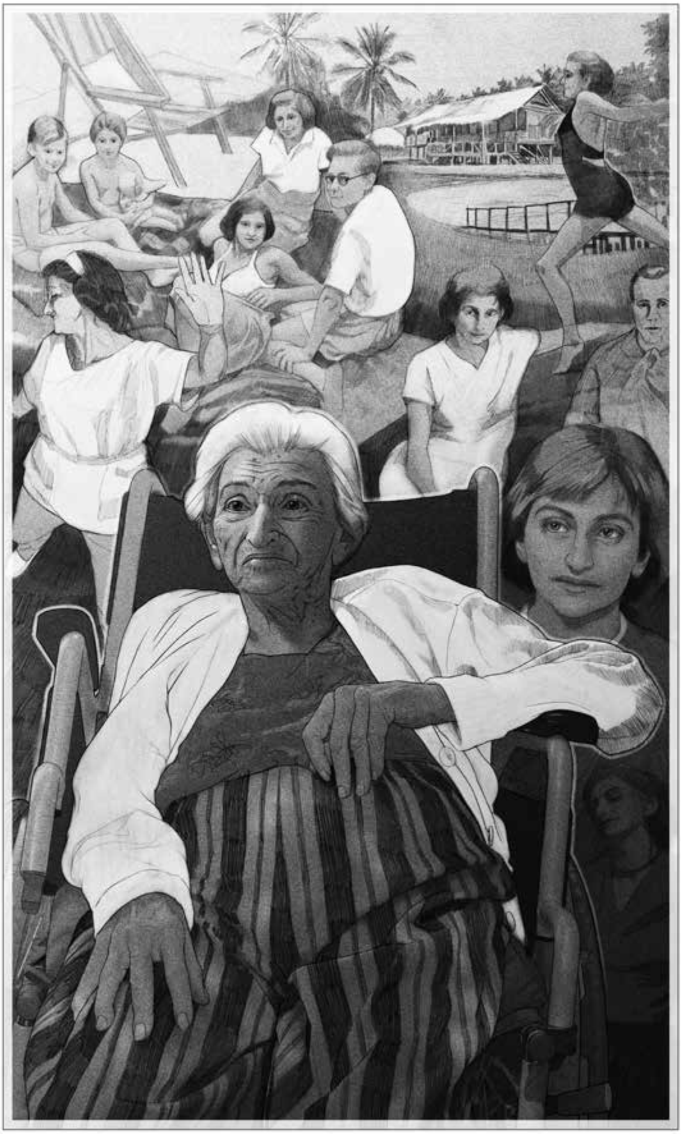
Library of Congress Cataloging-in-Publication Data
Names: Sinclair, David A., 1969– author. | LaPlante, Matthew D., author.
Title: Lifespan : why we age—and why we don't have to / David A. Sinclair, Ph.D., A.O. with Matthew D. LaPlante ; illustrations and Sinclairfont by Catherine L. Delphia.
Description: First Atria Books hardcover edition. | New York : Atria Books, 2019. | Includes bibliographical references and index.
Identifiers: LCCN 2019007196 (print) | LCCN 2019009229 (ebook) | ISBN 9781501191992 (eBook) | ISBN 9781501191978 (hardback)
Subjects: LCSH: Life spans (Biology) | Longevity. | BISAC: SCIENCE / Life Sciences / Genetics & Genomics. | HEALTH & FITNESS / Diseases / Genetic.
Classification: LCC QH528.5 (ebook) | LCC QH528.5 .S56 2019 (print) | DDC 570—dc23
LC record available at https://lccn.loc.gov/2019007196

ISBN 978-1-5011-9197-8
ISBN 978-1-5011-9199-2 (ebook)

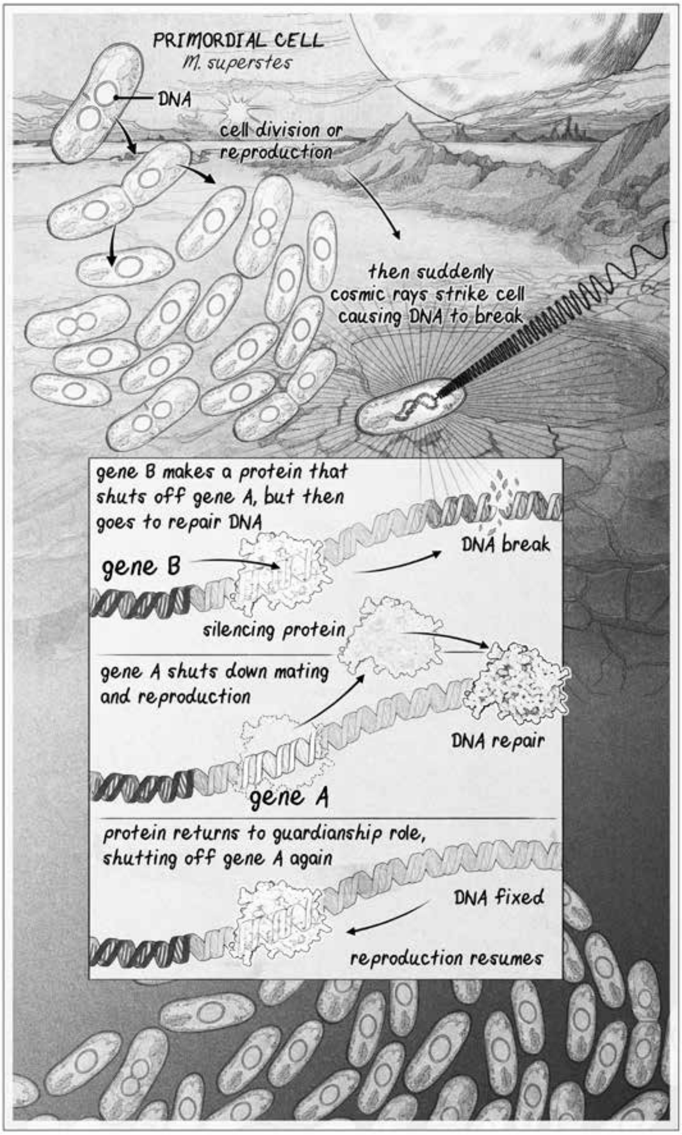
Thanks to Christine Liu and her team at the Innovative Genomics Institute (IGI) for permission to use the Glossary icons. Thanks to Wikipedia for biographical facts in the cast of characters.



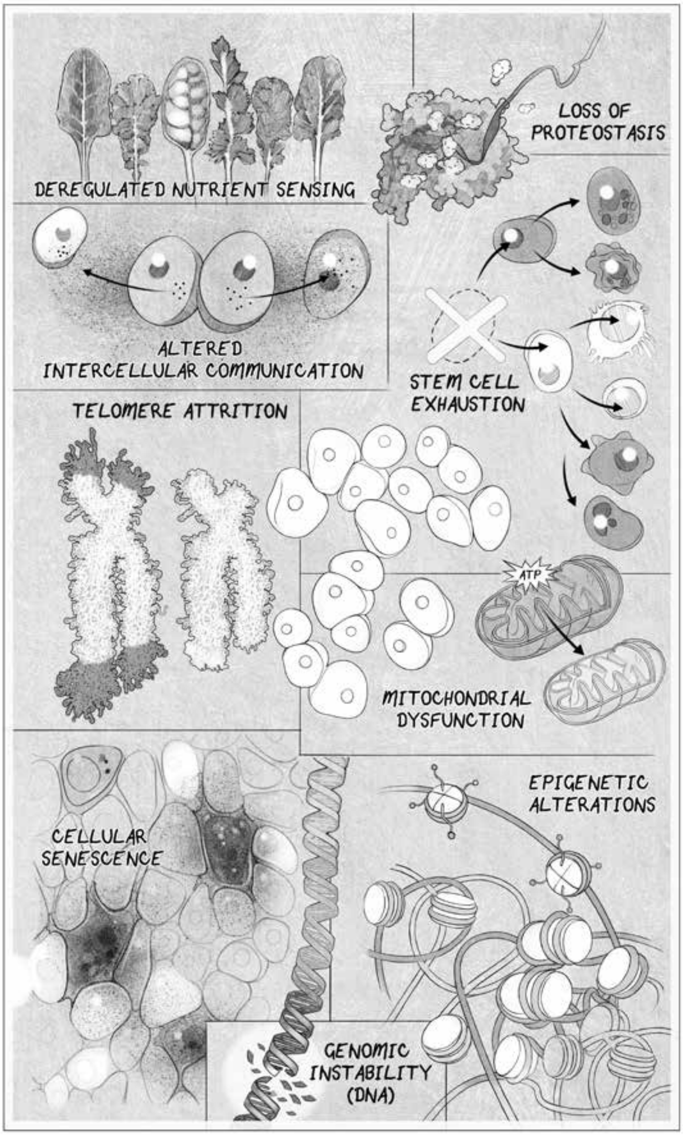
THE BUSH. In the wild and wonderful world of the Garigal clan, waterfalls and saltwater estuaries wind through ancient sandstone escarpments, under shadowy canopies of charred bloodwoods, angophoras, and scribbly gums that kookaburras, currawongs, and wallabies call home.



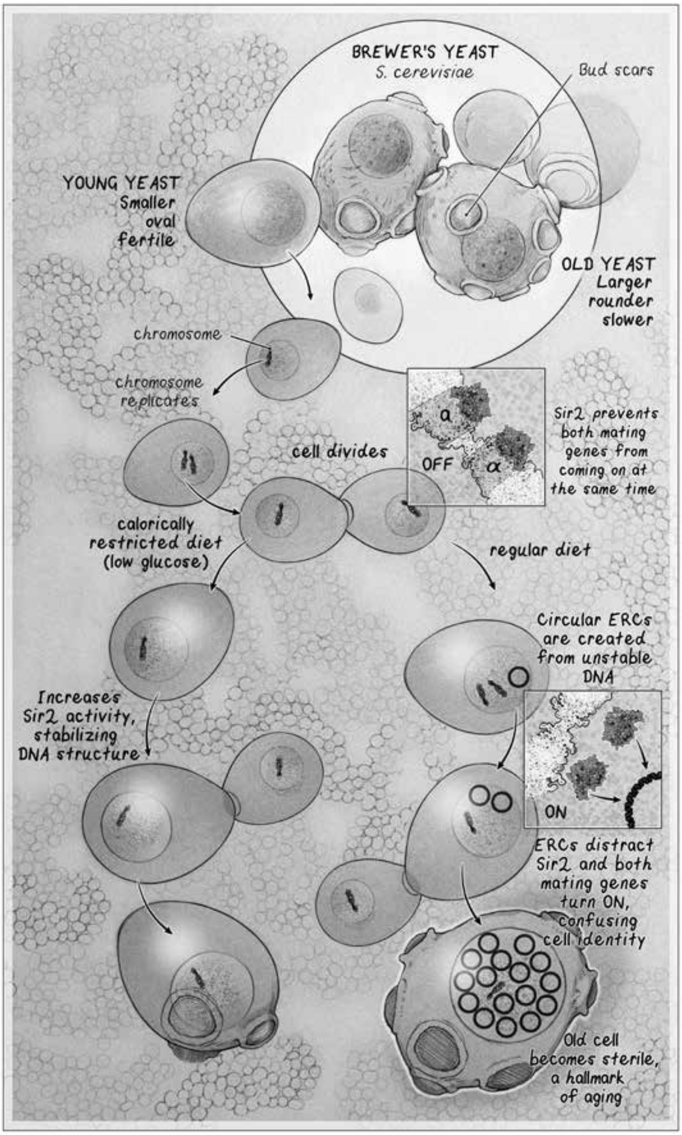
A "GOOD, LONG LIFE." My grandmother "Vera" sheltered Jews in World War II, lived in primitive New Guinea, and was removed from Bondi Beach for wearing a bikini. The end of her life was hard to watch. "This is just the way it goes," she said. But the person she truly was had been dead many years at that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



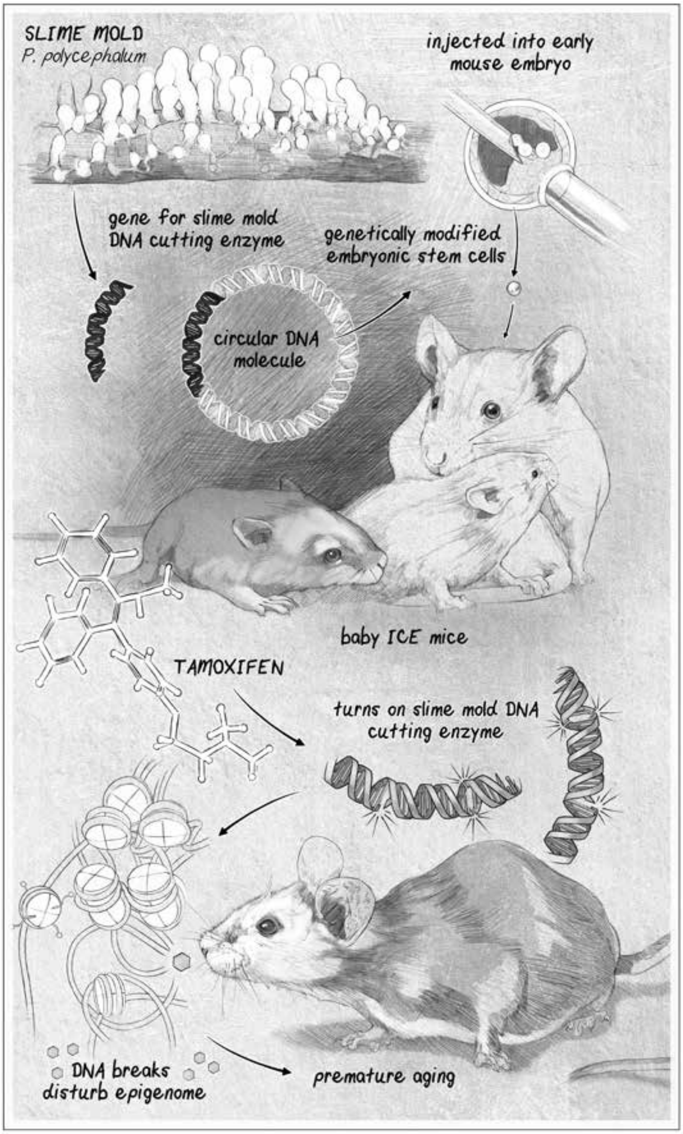
THE EVOLUTION OF AGING. A 4-billion-year-old gene circuit in the first life-forms would have turned off reproduction while DNA was being repaired, providing a survival advantage. Gene A turns off reproduction, and gene B makes a protein that turns off gene A when it is safe to reproduce. When DNA breaks, 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.



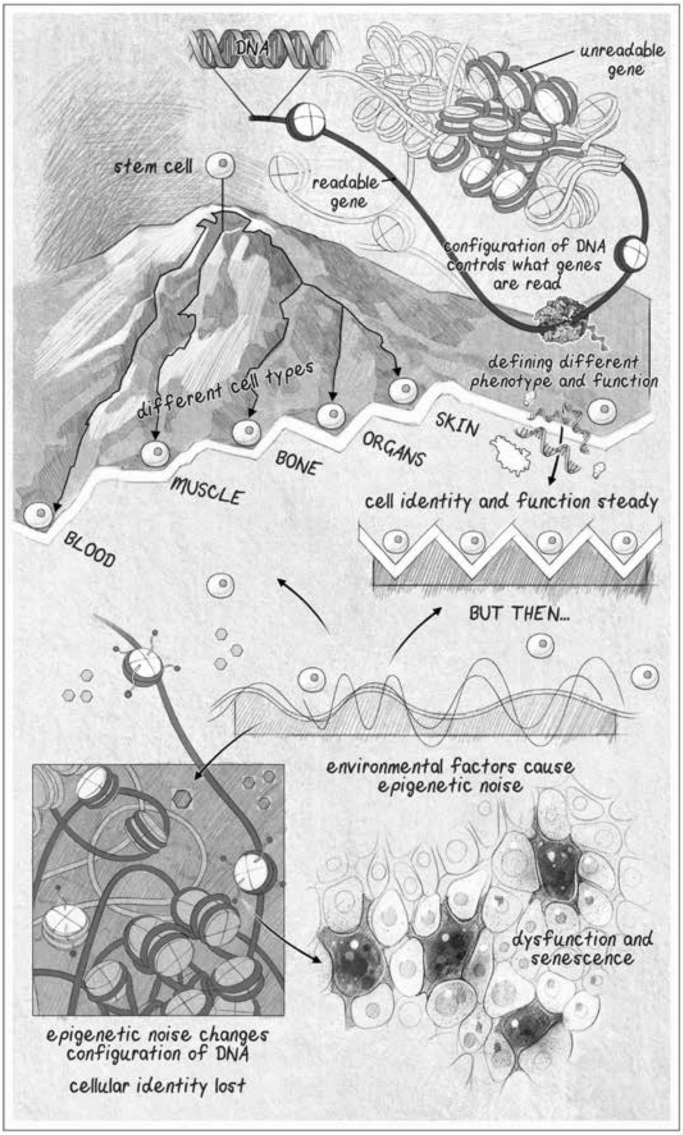
THE HALLMARKS OF AGING. Scientists have settled on eight or nine hallmarks of aging. Address one of these, and you can slow down aging. Address all of them, and you might not age.



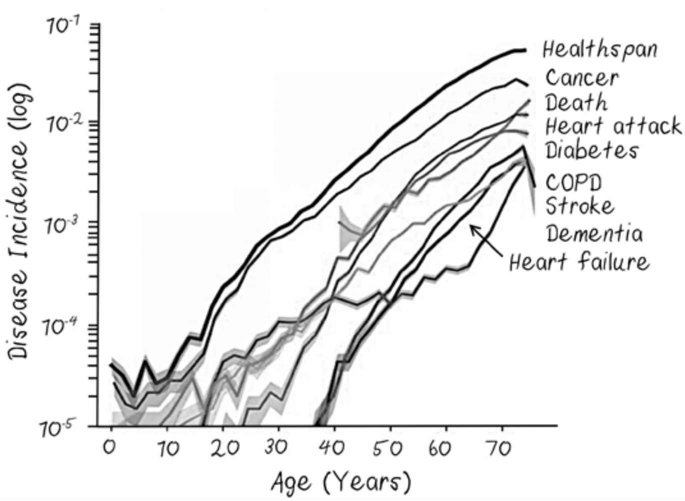
LESSONS FROM YEAST CELLS ABOUT WHY WE AGE. In young yeast cells, male and female "mating-type information" (gene A) is kept in the "off" position by the Sir2 enzyme, the first sirtuin (encoded by a descendant of gene B). The highly repetitive ribosomal DNA (rDNA) is unstable, and toxic DNA circles form; these recombine and eventually accumulate to toxic levels in old cells, killing them. In response to DNA circles and the perceived genome instability, Sir2 moves away from silent mating-type genes to help stabilize the genome. Both male and female genes turn on, causing infertility, the main hallmark of yeast aging.



THE MAKING OF THE ICE MOUSE TO TEST IF THE CAUSE OF AGING MIGHT BE INFORMATION LOSS. A gene from a slime mold that encodes an enzyme that cuts DNA at a specific place was inserted into a stem cell and injected into an embryo to generate the ICE mouse. Turning on the slime mold gene cut the DNA and distracted the sirtuins, causing the mouse to undergo aging.

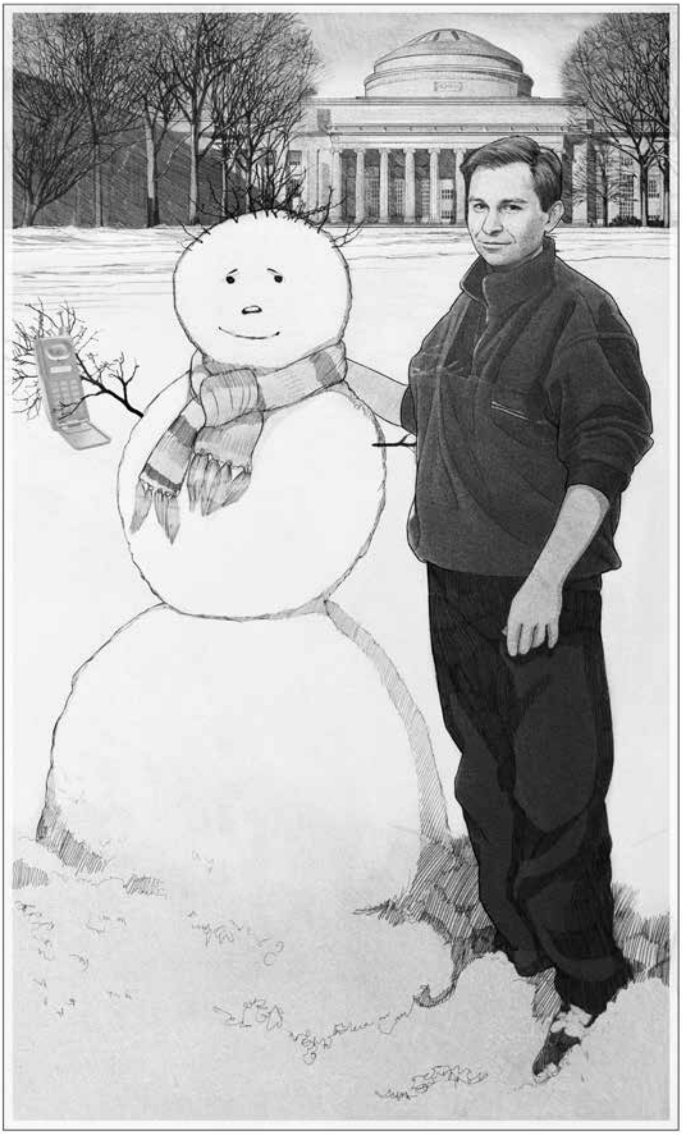


THE CHANGING LANDSCAPE OF OUR LIVES. The Waddington landscape is a metaphor for how cells find their identity. Embryonic cells, often depicted as marbles, roll downhill and land in the right valley that dictates their identity. As we age, threats to survival, such as broken DNA, activate the survival circuit and rejigger the epigenome in small ways. Over time, cells progressively move towards adjacent valleys and lose their original identity, eventually transforming into zombielike senescent cells in old tissues.

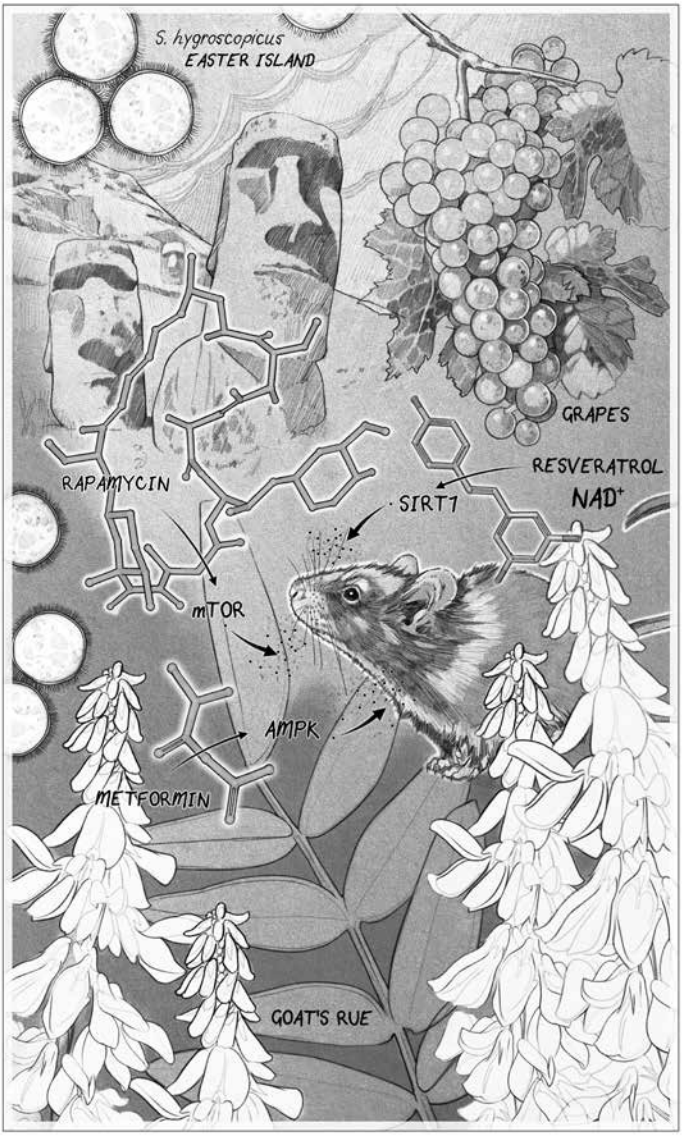


WHY TREATING ONE DISEASE AT A TIME HAS LITTLE IMPACT ON LIFESPAN. The graph shows an exponential increase in disease as each year passes after the age of 20. It's hard to appreciate exponential graphs. If I were to draw this graph with a linear Y-axis, it would be two stories tall. What this means is your chance of developing a lethal disease increases by a thousandfold between the ages of 20 and 70, so preventing one disease makes little difference to lifespan.

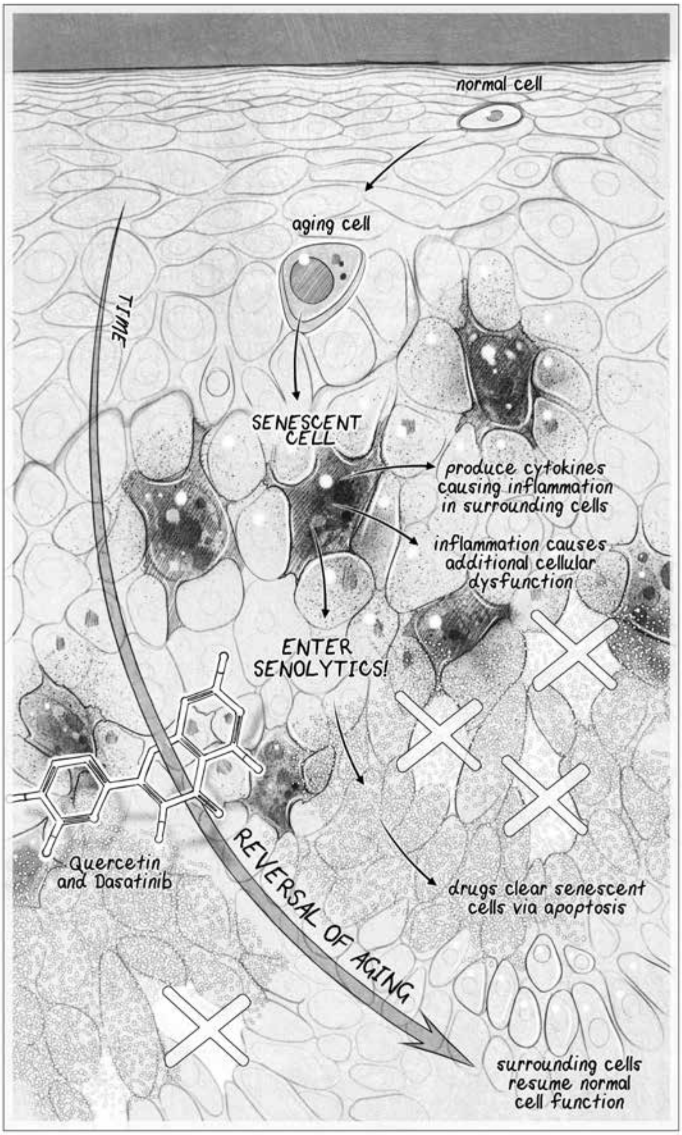
Source: Adapted from A. Zenin, Y. Tsepilov, S. Sharapov, et al., "Identification of 12 Genetic Loci Associated with Human Healthspan," *Communications Biology* 2 (January 2019).



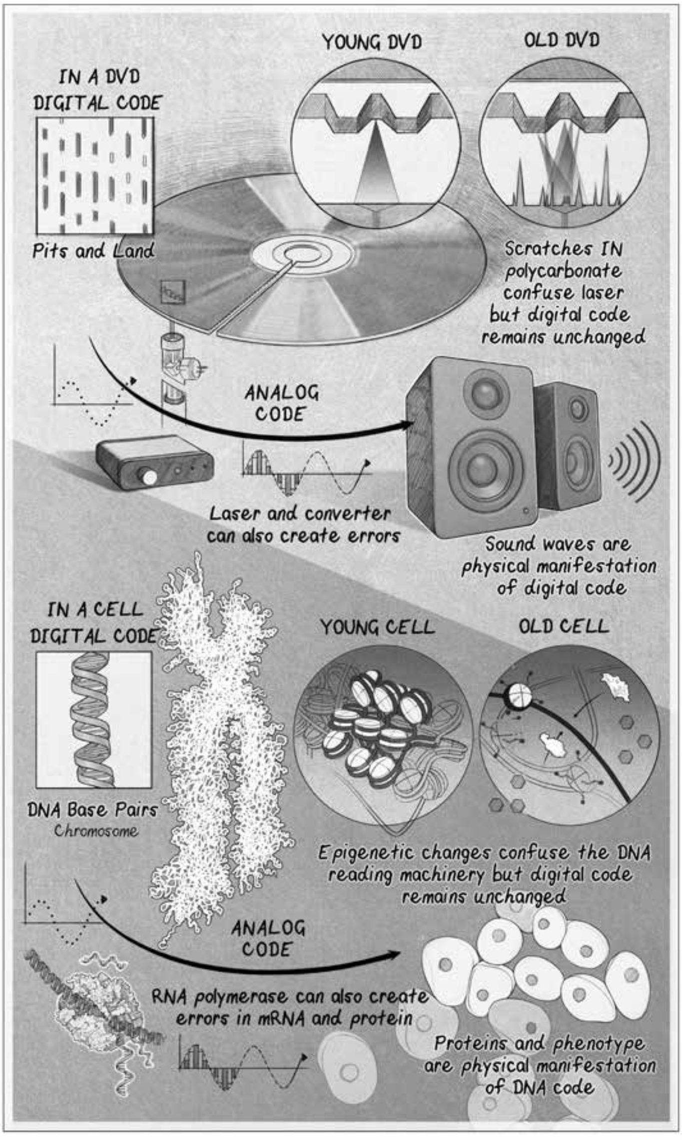
COLD ACTIVATES LONGEVITY GENES. Sirtuins are switched on by cold, which in turn activates protective brown fat in our back and shoulders. Image: The author enduring "cold therapy" at the Massachusetts Institute of Technology in 1999.



THE THREE MAIN LONGEVITY PATHWAYS, mTOR, AMPK, AND SIRTUINS, EVOLVED TO PROTECT THE BODY DURING TIMES OF ADVERSITY BY ACTIVATING SURVIVAL MECHANISMS. When they are activated, either by low-calorie or low-amino-acid diets, or by exercise, organisms become healthier, disease resistant, and longer lived. Molecules that tweak these pathways, such as rapamycin, metformin, resveratrol, and NAD boosters, can mimic the benefits of low-calorie diets and exercise and extend the lifespan of diverse organisms.



DELETING THE ZOMBIE SENESCENT CELLS IN OLD TISSUES. Thanks to the primordial survival circuit we've inherited from our ancestors, our cells eventually lose their identities and cease to divide, in some cases sitting in our tissues for decades. Zombie cells secrete factors that accelerate cancer, inflammation, and help turn other cells into zombies. Senescent cells are hard to reverse aging in, so the best thing to do is to kill them off. Drugs called senolytics are in development to do just that, and they could rapidly rejuvenate us.



WE ARE ANALOG, THEREFORE WE AGE. According to the Information Theory of Aging, we become old and susceptible to diseases because our cells lose youthful information. DNA stores information digitally, a robust format, whereas the epigenome stores it in analog format, and is therefore prone to the introduction of epigenetic "noise." An apt metaphor is a DVD player from the 1990s. The information is digital; the reader that moves around is analog. Aging is similar to the accumulation of scratches on the disc so the information can no longer be read correctly. Where's the polish?

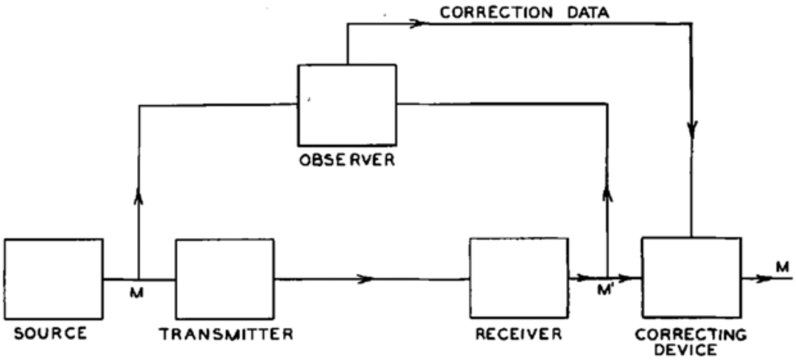
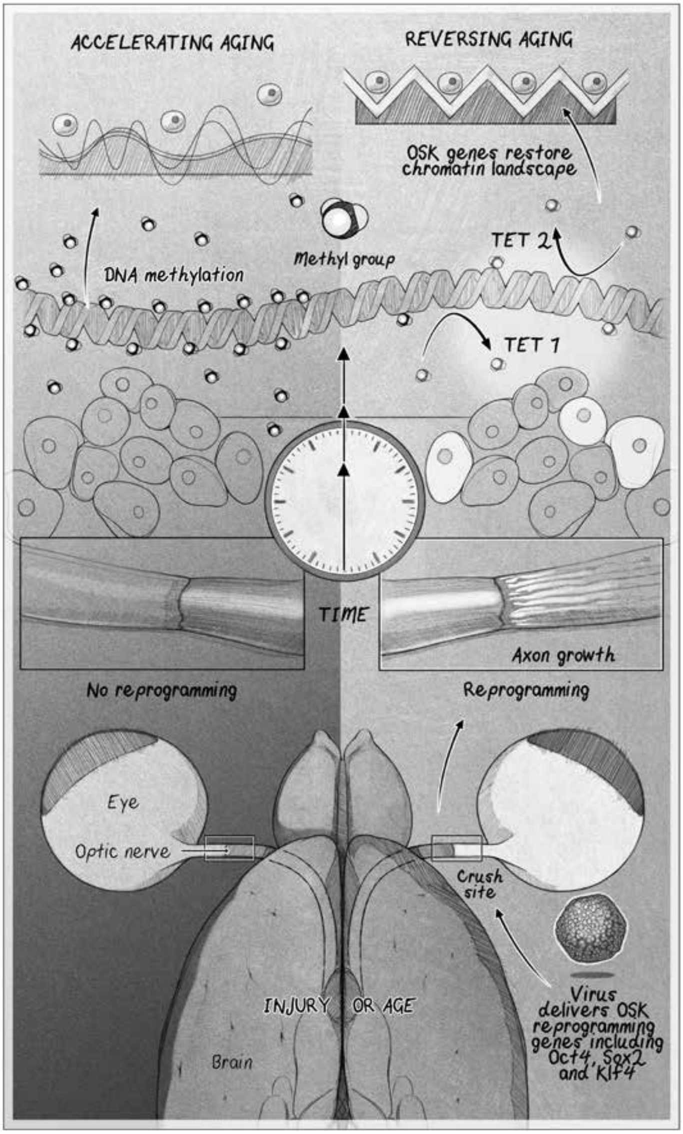


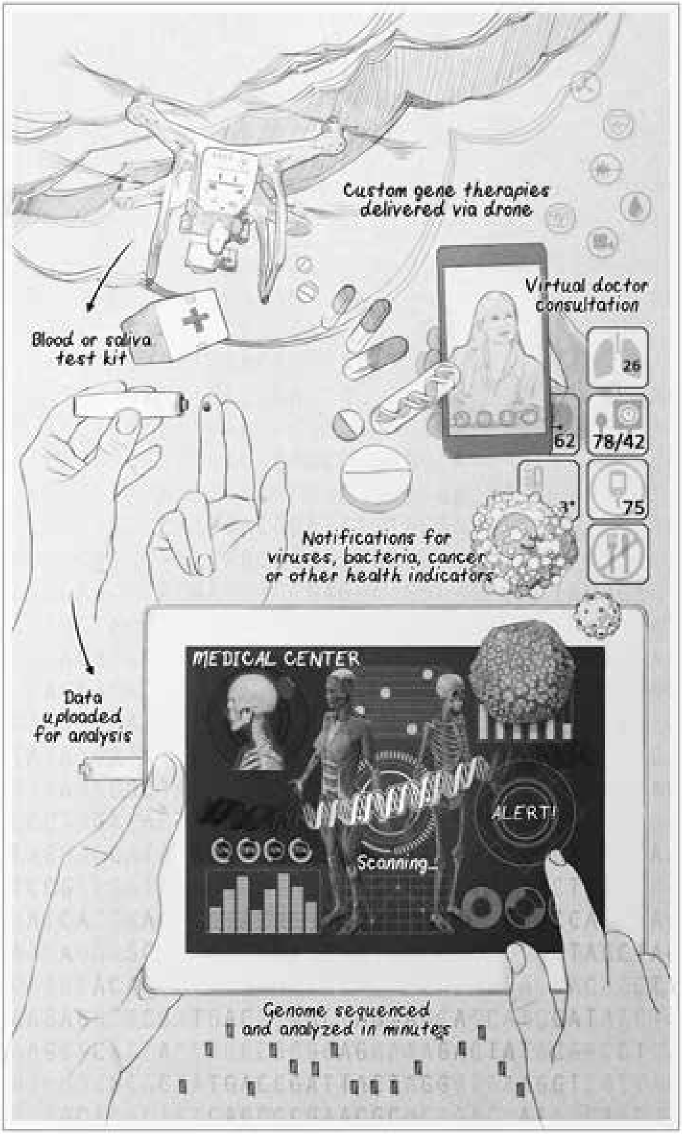
Fig. 8—Schematic diagram of a correction system.

CLAUDE SHANNON'S 1948 SOLUTION TO RECOVERING LOST INFORMATION DURING DATA TRANSMISSIONS LED TO CELL PHONES AND THE INTERNET. It may also be the solution to reversing aging.

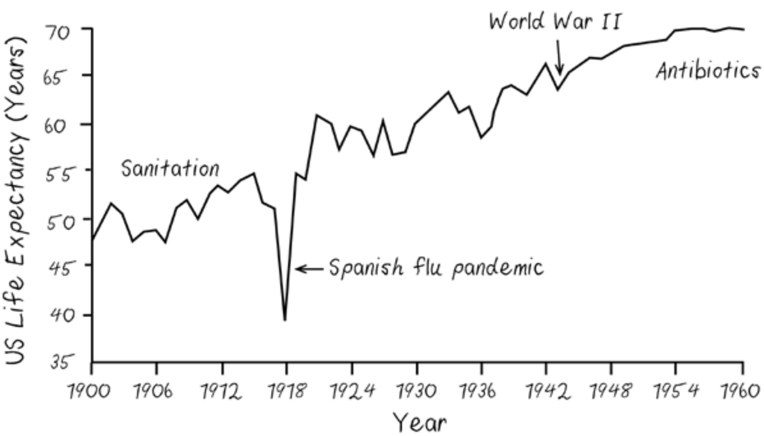
Source: C. E. Shannon, "A Mathematical Theory of Communication," *Bell System Technical Journal* 27, no. 3 (July 1948): 379–423 and 27, no. 4 (October 1948): 623–66.



EPIGENETIC REPROGRAMMING REGROWS OPTIC NERVES AND RESTORES EYESIGHT IN OLD MICE. The Information Theory of Aging predicts that it is a loss of epigenetic rather than genetic information in the form of mutations. By infecting mice with reprogramming genes called Oct4, Sox2, and Klf4, the age of cells is reversed by the TET enzymes, which remove just the right methyl tags on DNA, reversing the clock of aging and allowing the cells to survive and grow like a newborn's. How the enzymes know which tags are the youthful ones is a mystery. Solving that mystery would be the equivalent of finding Claude Shannon's "observer," the person who holds the the original data.

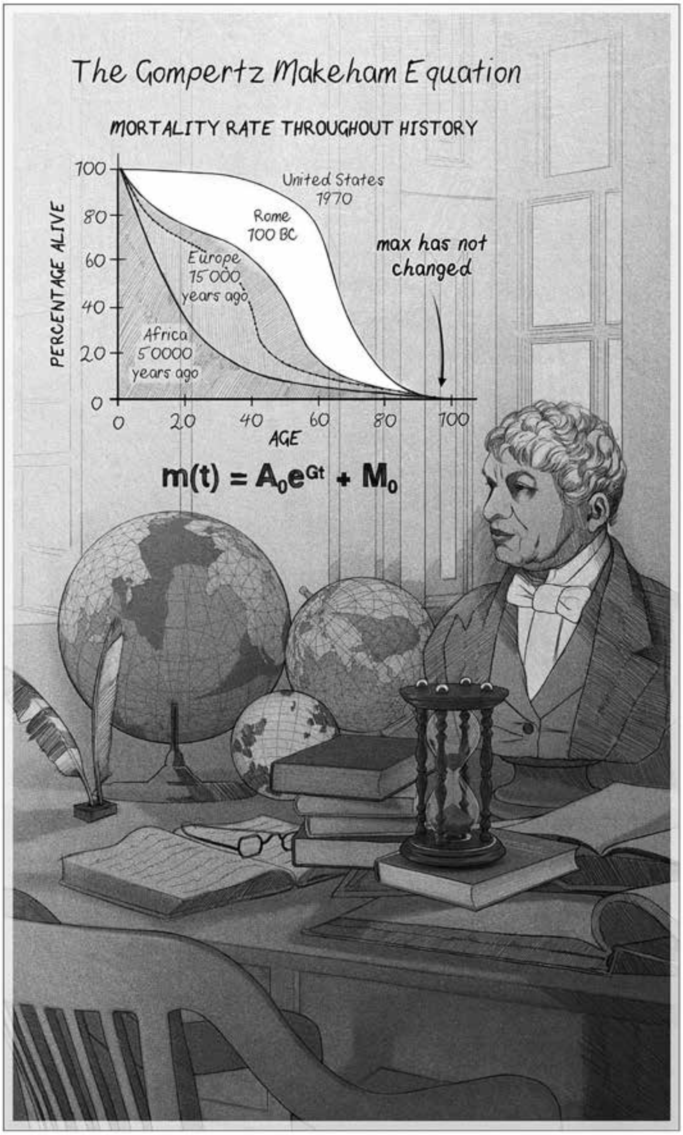


TECHNOLOGIES TO EXTEND OUR LIVES. In the near future, families will be monitored by biosensing wearables, small devices at home, and implants that will optimize our health and save lives by suggesting meals and detecting falls, infections, and diseases. When an anomaly is found, an AI-assisted, videoconferenced doctor will send an ambulance, a nurse, or medicines to your door.



CHANGE IN LIFE EXPECTANCY DURING THE 1918 FLU EPIDEMIC.

Source: S. L. Knobler, A. Mack, A. Mahmoud, and S. M. Lemon, eds., The Threat of Pandemic Influenza: Are We Ready? Workshop Summary, Institute of Medicine (Washington, DC: National Academies Press, 2005), https://doi.org/10.17226/11150, PMID: 20669448.



THE LAW OF HUMAN MORTALITY. Benjamin Gompertz, a self-taught mathematical genius, was barred from attending university in nineteenth-century London for being a Jew yet was elected to the Royal Society in 1819. His brother-in-law, Sir Moses Montefiore, in partnership with Nathan Rothschild, founded Alliance Assurance Company in 1824, and Gompertz was appointed actuary. His tidy equation, which replaced mortality tables, tracks the exponential increase in the chance of death with age. As important as this "law" is to insurance companies, it does not mean that aging is a fact of life.

BUSHWALKING. If you head north from my childhood home, you'll move through hundreds of miles of consecutively larger national parks, a seemingly endless undulation of saltwater estuaries and craggy mountain ridges decorated by ancient rock carvings left by the original inhabitants, the Garigal clan. Dad is now 80, the age his mother, Vera, was when she lost the will to live—aging has that effect on people. Instead, my father hikes mountains, travels the world, and has started a new career, representing hope for all of us.

The Scale of Things

1 grain of sand = 10 skin cells	0.5 millimeter
1 skin cell = 5 blood cells	50 micrometers
1 blood cell = 2 X chromosomes or ~2 yeast cells	10 micrometers
1 X chromosome = 1 yeast cell = 10 *E. coli*	5 micrometers
1 *E. coli* or mitochondrion = 2 *M. superstes*	0.5 micrometer
1 *M. superstes* = 4 ribosomes	0.25 micrometer
1 ribosome = 6 catalase enzymes	30 nanometers
1 catalase enzyme = 5 glucose molecules	5 nanomaters
1 glucose molecule or amino acid = approximately 4–6 water molecules	1 nanometer
1 water molecule = 275,000 atomic nuclei	0.275 nanometer
1 atomic nucleus	1 picometer

1 inch = 25.4 millimeters
1 foot (12 inches) = 0.3048 meter
1 yard (3 feet) = 0.9144 meter
1 mile = 1.6093 kilometers

1 million = 10^6 (1 with 6 zeros)
1 billion = 10^9 (1 with 9 zeros)
1 trillion = 10^{12} (1 with 12 zeros)
milli = 10^{-3} (1 thousandth)
micro = 10^{-6} (1 millionth)
nano = 10^{-9} (1 billionth)
pico = 10^{-12} (1 1,000 billionth, or a trillionth)

32°F = 0°C
212°F = 100°C

Cast of Characters

JOSEPH BANKS (February 24, 1743–June 19, 1820): English naturalist, botanist, and former president of the Royal Society who accompanied Captain James Cook on his voyage round the world. With Lord Sydney a staunch advocate of starting a colony in Australia at Botany Bay on Cape Banks. Namesake of the flower called the *Banksia*.

NIR BARZILAI (December 23, 1955–): Israeli-born American endocrinologist and professor at the Albert Einstein College of Medicine in New York best known for his work to elucidate genes that enable members of Ashkenazi families to live over 100, hormones that control lifespan, and the effects of metformin on lifespan.

ELIZABETH BLACKBURN (November 26, 1948–): an Australian American Nobel laureate who, with Carol W. Greider and Jack W. Szostak, discovered telomerase, the enzyme that extends telomeres. In 2004, she was controversially dismissed from the Bush administration's President's Council on Bioethics, allegedly for her advocacy of stem cell research and politics-free scientific enquiry.

ARTHUR C. CLARKE (December 16, 1917–March 19, 2008): British science fiction writer and futurist known as the "Prophet of the Space Age." Spent most of his adult life in Sri Lanka foreseeing the advent of space travel and satellites. Advocate for protection of gorillas. Polio in 1962 led to postpolio syndrome.

ALVISE (LUIGI) CORNARO (1464 or 1467–May 8, 1566): Venetian nobleman and patron of arts who wrote four books of *Discorsi* about the path to health and longevity that included fasting and sobriety.

EILEEN M. CRIMMINS: American demographer at the University of Southern California who was the first to combine indicators of disability, disease, and mortality to predict healthy life expectancy. She showed that the prevalence of dementia in women stems largely from their longer life.

RAFAEL DE CABO (January 20, 1968-): Spanish-born scientist at the National Institutes of Health, an expert in the study of the effects of diet on health and lifespan in rodents and primates.

BENJAMIN GOMPERTZ (March 5, 1779-July 14, 1865): British self-educated mathematician who is best known for the Gompertz-Makeham Law of Human Mortality, a demographic model (1825). He became a Fellow of the Royal Society and then an actuary at Alliance Assurance company, founded by his brother-in-law Sir Moses Montefiore with his relative Nathan Mayer Rothschild.

LEONARD P. GUARENTE (June 6, 1952-): American molecular biologist and professor at MIT, best known for codiscovering the role of the sirtuins in aging and the necessity of NAD^+ for sirtuin activity, linking energy metabolism to longevity.

ALEXANDRE GUÉNIOT (1832-1935): Centenarian and French physician who wrote the book *Pour vivre cent ans. L'Art de prolonger ses jours* (To Live a Century). He attributed great significance to the "hereditary vital force" that he suggested determines the natural duration of human life at no less than 100 years.

JOHN B. GURDON (October 2, 1933-): British biologist who in 1958 cloned a frog using a nucleus from an adult tadpole's cell, demonstrating that aging can be reset, for which he shared the Nobel Prize with Shinya Yamanaka in 2012.

DENHAM HARMAN (February 14, 1916-November 25, 2014): American chemist who formulated the "Free Radical Theory of Aging" and the "Mitochondrial Theory of Aging." Harman was a founder of the American Aging Association, ran two miles a day until he was 82, and eventually died at the age of 98.

LEONARD HAYFLICK (May 20, 1928-): American biologist who invented the inverted microscope; best known for his 1962 discovery that normal mammalian cells have a limited capacity for replication. The Hayflick limit on cell division overturned a long-held belief promulgated by the French surgeon and biologist Alexis Carrel in the early twentieth century that normal cells in culture would proliferate continuously.

STEVE HORVATH (October 25, 1967-): Austrian-born American professor at the University of California at Los Angeles known for his pioneering work on epigenetics and aging and for codeveloping algorithms that predict the age of organisms based on DNA methylation patterns, known as the Horvath aging clock.

SHIN-ICHIRO IMAI (December 9, 1964-): Japanese-born American biologist known for his Heterochromatin Hypothesis of Aging, his work on mammalian sirtuins, and the discovery with Lenny Guarente that sirtuins need NAD^+ for their activity.

CYNTHIA J. KENYON (February 21, 1954-): American geneticist who showed that Daf-2 mutations double nematode worm lifespan, after studying under Nobel Prize winner Sydney Brenner using nematodes as a model organism. Kenyon is a professor at the University of California, San Francisco, and vice president of aging research at Calico.

JAMES L. KIRKLAND: American physician and biologist working at the Mayo Clinic in Rochester, New York; a pioneer in the study of senescent "zombie" cells and the development of drugs called senolytics that kill them.

THOMAS B. L. KIRKWOOD (July 6, 1951-): South African–born biologist and associate dean for ageing at Newcastle University, UK. Proposed the Disposable Soma hypothesis, the idea that species aim to balance energy and resources between reproduction and building a robust, long-lasting body.

PIERRE LECOMTE DU NOÜY (December 20, 1883-September 22, 1947): French biophysicist and philosopher who noticed that the wounds of older soldiers healed more slowly than those of younger ones. His "telefinalist" hypothesis that God directs evolution was criticized as unscientific.

CLIVE M. McCAY (March 21, 1898-June 8, 1967): American nutritionist and biochemist who spent decades at Cornell University researching the soybean and flour. Best known for his early work confirming that calorie restriction extends the lifespan of rats. In 1955, he and his wife published "You Can Make Cornell Bread."

PETER B. MEDAWAR (February 28, 1915-October 2, 1987): British biologist born in Brazil whose work on graft rejection and the discovery of acquired immune tolerance was fundamental to the practice of tissue and organ transplants. Realized the force of natural selection declines with age due to reduced "reproductive value."

ARTHUR PHILLIP (October 11, 1738-August 31, 1814): British admiral of the Royal Navy and first governor of New South Wales who sailed to Australia to establish the British penal colony in Botany Bay that later, after moving one harbor north, became the city of Sydney, Australia.

CLAUDE E. SHANNON (April 30, 1916-February 24, 2001): American mathematician and engineer who worked at MIT and is known as the "father of information theory." His paper "A Mathematical Theory of Communication" (1948) solved problems of information loss and its restoration, concepts that laid the foundation for the TCP/IP protocols that run the internet. His hero was Thomas Edison, who he later learned was his relative.

JOHN SNOW (March 15, 1813-June 16, 1858): English anesthesiologist and leader in the adoption of anesthesia and medical hygiene; best known for his work tracing the source of a cholera outbreak arising from the Broad Street pump in Soho, London, in 1854.

LEO SZILARD (February 11, 1898-May 30, 1964): Hungarian-born American physicist and humanist who proposed the DNA Damage Hypothesis of Aging. Wrote the letter that resulted in the Manhattan Project. Conceived of the nuclear chain reaction, nuclear power, chemostat, electron microscopes, enzyme feedback inhibition, and cloning of a human cell.

CONRAD H. WADDINGTON (November 8, 1905–September 26, 1975): British geneticist and philosopher who laid the foundations of systems biology and epigenetics. His Waddington Landscape was proposed to help understand how a cell can divide to become the hundreds of different cell types in the body.

ROY L. WALFORD (June 29, 1924–April 27, 2004): American biologist who rejuvenated the field of caloric restriction. One of eight crew members inside Arizona's Biosphere 2 from 1991 to 1993. In medical school, reportedly used statistical analysis to predict the results of a roulette wheel in Reno, Nevada, to pay for medical school and a yacht, and sailed the Caribbean for over a year.

H. G. WELLS (September 21, 1866–August 13, 1946): British science fiction writer who foresaw air raids in World War II, tanks, nuclear weapons, satellite television, and the internet. Best known for *The War of the Worlds*, *The Shape of Things to Come*, and *The Time Machine*. His epitaph is from *A War in the Air*: "I told you so. You damned fools."

GEORGE C. WILLIAMS (May 12, 1926–September 8, 2010): American evolutionary biologist at the State University of New York, Stony Brook, known for developing a gene-centric view of evolution and "Antagonistic Pleiotropy," a leading theory about why we age; essentially that a gene that helps young individuals survive can come back to bite them when they are older.

SHINYA YAMANAKA (September 4, 1962–): Japanese biologist who discovered reprogramming genes that turn regular cells into stem cells, for which he shared the Nobel Prize in Physiology or Medicine with John Gurdon in 2012.

Glossary


ALLELE: One of several possible versions of a gene. Each one contains a distinct variation in its DNA sequence. For example, a "deleterious allele" is a form of a gene that leads to disease.


AMINO ACID: The chemical building block of proteins. During translation, different amino acids are strung together to form a chain that folds into a protein.

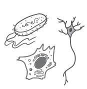

ANTAGONISTIC PLEIOTROPY: A theory proposed by George C. Williams as an evolutionary explanation for aging: a gene that reduces lifespan in late life can be selected for if its early benefits outweigh its late costs. An example of this is the survival circuit.


BASE: The four "letters" of the genetic code, A, C, T, and G, are chemical groups called bases or nucleobases. A= adenine, C = cytosine, T = thymine, and G = guanine. Instead of thymine, RNA contains a base called uracil (U).


BASE PAIR: "Teeth" on the twisted "zipper" of DNA. Chemicals known as bases make up a DNA strand, each strand runs in the opposite direction, and bases attract their opposite partner to make a base pair: C pairs with G, A pairs with T (except for in RNA, where it's a U).


BIOTRACKING/BIOHACKING: The use of devices and lab tests to monitor the body to make decisions about food, exercise, and other lifestyle choices to optimize the body. Not to be confused with biohacking, which is do-it-yourself body enhancement.


CANCER: A disease caused by uncontrolled growth of cells. Cancerous cells may form clumps or masses known as tumors and can spread to other parts of the body through a process known as metastasis.


CELL: The basic unit of life. The number of cells in a living organism ranges from one (e.g., in yeast) to quadrillions (e.g., in a blue whale). A cell is composed of four key macromolecules that allow it to function: protein, lipids,

carbohydrates, and nucleic acids. Among other things, cells can build and break down molecules, move, grow, divide, and die.

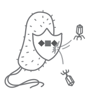
CELLULAR REPROGRAMMING: The changing of cells from one type of tissue to a prior stage of development.

CELLULAR SENESCENCE: The process that occurs when normal cells stop dividing and start to release inflammatory molecules, sometimes caused by telomere shortening, damage to DNA, or epigenomic noise. Despite their seeming "zombie" state, senescent cells remain alive, damaging nearby cells with their inflamatory secretions.

CHROMATIN: Strands of DNA wound around protein scaffolds known as histones. Euchromatin is open chromatin that allows genes to be switched on. Heterochromatin is closed chromatin that prevents the cell from reading a gene, also known as gene silencing.

CHROMOSOME: The compact structure into which a cell's DNA is organized, held together by proteins. The genomes of different organisms are arranged into varying numbers of chromosomes. Human cells have 23 pairs.

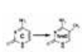
COMPLEMENTARY: Describes any two DNA or RNA sequences that can form a series of base pairs with each other. Each base forms a bond with a complementary partner: T (in DNA) and U (in RNA) bond with A, and C bonds with G.



CRISPR: Pronounced "crisper." An immune system found in bacteria and archaea, co-opted as a genome-engineering tool to cut DNA at precise places in a genome. CRISPR, which stands for "clustered regularly interspaced short palindromic repeats," is a section of the host genome containing alternating repetitive sequences and snippets of foreign DNA. CRISPR proteins such as Cas9, a DNA-cutting enzyme, use these as molecular "mug shots" as they seek out and destroy viral DNA.

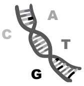
DAF-16/FOXO: An ally of sirtuins, DAF-16/FOXO is a gene control protein called a transcription factor that activates cell defense genes, upregulation of which extends lifespan in worms, flies, mice, and perhaps humans; required for Daf-2 to extend lifespan in worms.

DEACETYLATION: The enzymatic removal of acetyl tags from proteins. Removal of acetyls from histones by histone deacetylases (HDACs) causes them to be more tightly packed, switching off a gene. Sirtuins are NAD-dependent deacetylases. Deacylation is a catchall term that includes deacetylation and the removal of other, more exotic tags such as butyryls and succinyls.



DEMETHYLATION: Demethylation is the removal of methyls and is carried out by enzymes called histone demethylases (KDMs) and DNA demethylases (TETs). Attachment of methyls is achieved by a histone or DNA methyltransferases (DMTs).

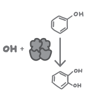
DISPOSABLE SOMA: A hypothesis proposed by Tom Kirkwood to explain aging. Species evolve to grow and multiply quickly or build a long-lasting body, but not both; limited resources in the wild don't allow for both.



DNA: Abbreviation of deoxyribonucleic acid, the molecule that encodes the information needed for a cell to function or a virus to replicate. Forms a double-helix shape that resembles a twisted ladder, similar to a zipper. Bases, abbreviated as A, C, T, and G, are found on each side of the ladder, or strand, which run in opposite directions. The bases have an attraction for each other, making A stick to T and C stick to G. The sequence of these letters is called the genetic code.

DNA DOUBLE-STRAND BREAK (DSB): What happens when both strands of DNA are broken and two free ends are created. May be done intentionally with an enzyme such as Cas9 or I-*Ppo*I. Cells repair their DNA to prevent cell death, sometimes changing the DNA sequence at the site of the break. Initiating or controlling this process with the intent to alter a DNA sequence is known as genome engineering.

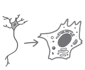
DNA METHYLATION CLOCK: Changes in the number and sites of DNA methylation tags on DNA can be used to predict lifespan, marking time from birth. During epigenomic reprogramming or cloning of an organism, methyl marks are removed, reversing the age of the cell.



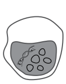
ENZYME: A protein made up of strings of amino acids that folds into a ball that can carry out chemical reactions that would normally take much longer or otherwise never happen. Sirtuins, for example, are enzymes that use NAD to remove acetyl chemical groups from histones.

EPIGENETIC: Refers to changes to a cell's gene expression that do not involve altering its DNA code. Instead the DNA and the histones that the DNA is wrapped around are "tagged" with removable chemical signals (see Demethylation and deacetylation). Epigenetic marks tell other proteins where and when to read the DNA, comparable to sticking a note that says "Skip" onto a page of a book. A reader will ignore the page, but the book itself has not been changed.

EPIGENETIC DRIFT AND EPIGENETIC NOISE: Alterations to the epigenome that take place with age due to changes in methylation, often related to an individual's exposure to environmental factors. Epigenetic drift and noise may be a key driver of aging in all species. Damage to DNA, especially DNA breaks, is a driver of this process.

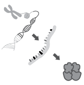


EXDIFFERENTIATION: The loss of cell identity due to epigenetic noise. Exdifferentiation may be a major cause of aging (see Epigenomic Noise).



EXTRACHROMOSOMAL RIBOSOMAL DNA CIRCLE (ERC): The generation of extrachromosomal ribosomal DNA circles leads to the breaking apart of the nucleolus in old cells, and in yeast they distract the sirtuins and cause aging.

GENE: A segment of DNA that encodes the information used to make a protein. Each gene is a set of instructions for making a particular molecular machine that helps a cell, organism, or virus function.



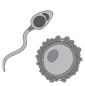
GENE EXPRESSION: A product based on a gene; can refer to either RNA or protein. When a gene is turned on, cellular machines express this by transcribing the DNA into RNA and/or translating the RNA into a chain of amino acids. For example, a highly expressed gene will have many RNA copies produced, and its protein product is likely to be abundant in the cell.

GENE THERAPY: The delivery of corrective DNA to human cells as a medical treatment. Certain diseases can be treated or even cured by adding a healthy DNA sequence into the genomes of particular cells. Scientists and doctors typically use a harmless virus to shuttle genes into targeted cells or tissues, where the DNA is incorporated somewhere within the cells' existing DNA. CRISPR genome editing is sometimes referred to as a gene therapy technique.

GENETICALLY MODIFIED ORGANISM (GMO): An organism that has had its DNA altered intentionally using scientific tools. Any organism can be engineered in this manner, including microbes, plants, and animals.

GENOME: The entire DNA sequence of an organism or virus. The genome is essentially a huge set of instructions for making individual parts of a cell and directing how everything should run.

GENOMICS: The study of the genome, all the DNA of a given organism. Involves a genome's DNA sequence, the organization and control of genes, the molecules that interact with the DNA, and the way in which these different components affect the growth and function of cells.

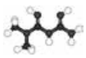


GERM CELLS: The cells involved in sexual reproduction: eggs, sperm, and precursor cells that develop into eggs or sperm. The DNA in germ cells, including any mutations or intentional genetic edits, may be passed down to the next generation. Genome editing in an early embryo is considered to be germline editing since any DNA changes will likely end up in all cells of the organism that is eventually born.

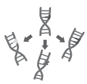
HISTONES: The proteins that form the core of DNA packaging in the chromosome and the reason three feet of DNA can fit inside a cell. DNA wraps around each histone almost two times, like beads on a string. The packaging of histones is controlled by enzymes such as the sirtuins that add and subtract chemical groups. Tight packaging forms "silent" heterochromatin, while loose packaging forms open euchromatin, where genes are turned on.

HORMESIS: The idea that whatever doesn't kill you makes you stronger. A level of biological damage or adversity that stimulates repair processes that provide cell survival and health benefits. Originally discovered when plants were sprayed with diluted herbicide and afterward grew faster.


INFORMATION THEORY OF AGING: The idea that aging is due to the loss of information over time, primarily epigenetic information, much of which can be recovered.


METFORMIN: A molecule derived from the French hellebore used to treat type 2 (age-associated) diabetes that may be a longevity medicine.

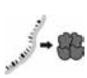

MITOCHONDRIA: Often called the cell's powerhouse, mitochondria break down nutrients to create energy in a process called cellular respiration. They contain their own circular genome.


MUTATION: A change from one genetic letter (nucleotide) to another. Variation in the DNA sequence gives rise to the incredible diversity of species among different organisms of the same genus. Though some mutations have no consequences at all, others can directly cause disease. Mutations may be caused by DNA-damaging agents such as ultraviolet light, cosmic radiation, or DNA copying by enzymes. They can also be created deliberately via genome-engineering methods.


NAD: Nicotinamide adenine nucleotide, a chemical used for more than five hundred chemical reactions and for sirtuins to remove acetyl groups of other proteins such as histones to turn genes off or give them cell protective functions. A healthy diet and exercise raise NAD levels. The "+" sign you sometimes see, as in NAD^+, indicates that it is not carrying a hydrogen atom.

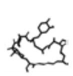

NUCLEASE: An enzyme that breaks apart the backbone of RNA or DNA. Breaking one strand generates a nick, and breaking both strands generates a double-strand break. An endonuclease cuts in the middle of RNA or DNA, while an exonuclease cuts from the end of the strand. Genome engineering tools such as Cas9 and I-*Ppo*I are endonucleases.


NUCLEIC ACIDS OR NUCLEOTIDES: The basic chemical units that are strung together to make DNA or RNA. They consist of a base, a sugar, and a phosphate group. The phosphates link with sugars to form the DNA/RNA backbone, while the bases bind to their complementary partners to form base pairs.

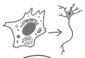

NUCLEOLUS: Located inside the nucleus of eukaryotic cells, the nucleolus is a region where the ribosomal DNA (rDNA) genes are situated and where the cellular machines for stitching together amino acids to form proteins are assembled.

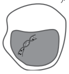

PATHOGEN: A microbe that causes illness. Most microorganisms are not pathogenic to humans, but some strains or species are.


PROTEIN: A string of amino acids folded into a three-dimensional structure. Each protein is specialized to perform a specific role to help cells grow, divide, and function. Proteins are one of the four macromolecules that make up all living things (proteins, lipids, carbohydrates, and nucleic acids).


RAPAMYCIN: Also known as sirolimus, rapamycin is a compound with immunosuppressant functions in humans. It inhibits activation of T cells and B cells

by reducing their sensitivity to the signaling molecule interleukin-2. Extends lifespan by inhibiting mTOR.


REDIFFERENTIATION: The reversal of epigenetic changes that occur during aging.

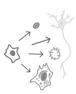

RIBOSOMAL DNA (rDNA): A key component of the manufacture of new proteins within cells; the source of the genetic code for ribosomal RNA, which is the building block of the ribosome. These molecules knit together amino acids that become new proteins.


RNA: Abbreviation of ribonucleic acid. Transcribed from a DNA template and typically used to direct the synthesis of proteins. CRISPR-associated proteins use RNAs as guides to find matching target sequences in DNA.


SENOLYTICS: Pharmaceuticals currently under development that are hoped to kill senescent cells in order to slow down or even reverse aging-related issues.

SIRTUINS: Enzymes that control longevity; they are found in organisms from yeast to humans and need NAD^+ to function. They remove acetyl and acyl groups from proteins to instruct them to protect cells from adversity, disease, and death. During fasting or exercise, sirtuin and NAD^+ levels increase, which may explain why those activities are healthy. Named after the yeast *SIR2* longevity gene, *SIRT1–7* (Sir2 homologs 1 to 7) genes in mammals play key roles in protecting against disease and deterioration.


SOMATIC CELLS: All the cells in a multicellular organism except for germ cells (eggs or sperm). Mutations or changes to the DNA in the soma will not be inherited by subsequent generations unless cloning takes place.


STEM CELLS: Cells with the potential to turn into a specialized type of cell or divide to make more stem cells. Most cells in your body are differentiated; that is, their fate has already been decided and they cannot morph into a different kind of cell. For example, a cell in your brain cannot suddenly transform into a skin cell. Adult stem cells replenish the body as it becomes damaged over time.

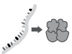

STRAND: A string of connected nucleotides; can be DNA or RNA. Two strands of DNA can zip together when complementary; bases match up to form base pairs. DNA typically exists in this double-stranded form, which takes the shape of a twisted ladder or double helix. RNA is typically composed of just a single strand, though it can fold up into complex shapes.

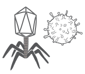

SURVIVAL CIRCUIT: An ancient control system in cells that may have evolved to shift energy away from growth and reproduction toward cellular repair during times of adversity. After response to adversity, the system may not fully reset, which, over time, leads to a disruption of the epigenome and loss of cell identity leading to aging (see Antagonistic Pleiotropy).


TELOMERES/TELOMERE LOSS: A telomere is a cap that protects the end of the chromosome from attrition, analogous to the aglet at the end of a shoelace or a burned end of a rope to stop it fraying. As we age, telomeres erode to the point

where the cell reaches the Hayflick limit. This is when the cell regards the telomere as a DNA break, stops dividing, and becomes senescent.


TRANSCRIPTION: The process by which genetic information is copied into a strand of RNA; performed by an enzyme called RNA polymerase.


TRANSLATION: The process by which proteins are made based on instructions encoded in an RNA molecule. Performed by a molecular machine called the ribosome, which links together a series of amino acid building blocks. The resulting polypeptide chain folds up into a particular 3D object, known as a protein.


VIRUS: An infectious entity that can persist only by hijacking a host organism to replicate itself in. Has its own genome but is technically not considered a living organism. Viruses infect all organisms, from humans to plants to microbes. Multicellular organisms have sophisticated immune systems that combat viruses, while CRISPR systems evolved to stop viral infection in bacteria and archaea.


WADDINGTON'S LANDSCAPE: A biological metaphor for how cells are endowed with an identity during embryonic development in the form of a 3D relief map. Marbles representing stem cells roll down into bifurcating valleys, each of which marks a different developmental pathway for the cells.


XENOHORMESIS HYPOTHESIS: The idea that our bodies evolved to sense the stress cues of other species, such as plants, in order to protect themselves during times of impending adversity. Explains why so many medicines come from plants.

Connect with Dr. David A. Sinclair on

lifespanbook.com

info@lifespanbook.com

@davidasinclair / @mdlaplante

@davidsinclairphd