

CONTENTS

Acknowledgments ix

Abbreviations xi

Introduction	1
1 Ethics and Economics of Longevity: Is It Right to Study Aging?	6
2 Why Do We Age?	15
3 Studying the Genetics of Human Longevity: Centenarians and What We Can Learn from Them	37
4 Long-Lived Species and Longevity Mutants of Model Organisms	51
5 What Is Aging (and How Can We Measure It)? Biomarkers of Aging and “Quality of Life” Metrics	71
6 Insulin Signaling, FOXO Targets, and the Regulation of Longevity and Reproduction	87
7 Dietary Restriction: Nutrient and Genetic Regulation of Longevity and Reproduction	107
8 Taking out the Trash: Molecular Homeostasis in the Regulation of Longevity	137
9 Powering Longevity: Mitochondria’s Role in Aging and Longevity	152
10 Dracula and Wolverine: How DNA Repair and Cell Replacement Can Help Us Live Long	173

viii CONTENTS

11	Use It or Lose It: Reproductive Aging, the Germline, and Longevity	193
12	Sex, Flies (and Worms), and Videotape: The Battle of the Sexes	214
13	I See Dead Flies: Neurons and Sensory Regulation of Longevity	237
14	Don't You Forget about Me: What We Are Learning about Cognitive Aging and How to Slow It	250
15	Lamarck's Revenge? Transgenerational Inheritance, the "Molecular Clock," and the Epigenetic Regulation of Longevity	279
16	Gut Feelings: The Microbiome and Aging	303
17	Long Life in a Pill? The Future of Longevity: From Bench to Biotech	319
	<i>Notes</i>	349
	<i>Index</i>	417

Introduction

What doesn't fit is often what is getting at something exciting!

—DR. EVELYN WITKIN, AMERICAN GENETICIST
WHO TURNED 100 ON MARCH 9, 2021

IN THE LATE 1990S, I was a graduate student in the lab of Jim Spudich, in the Department of Biochemistry at Stanford University. I studied how the motor protein myosin—the molecular motor that powers our muscles and makes our hearts pump—works, by swapping parts from myosins of “slow” and “fast” organisms, and then testing how those swaps affected its activity. I loved that protein; understanding how a sequence of amino acids arranged the right way could take energy and turn it into movement by swinging its “lever arm” a small distance was one of the most interesting questions I could imagine at the time. But when I explained my research to people at parties who asked me, “What do you do?” they would nod and politely smile, then ask when I would graduate. That would be the end of the discussion.

That all changed a few months later after I heard a fantastic talk by Dr. Cynthia Kenyon, a professor from the University of California, San Francisco (UCSF). Cynthia is a lively, engaging speaker and she told the audience about her lab's work on aging and longevity in a small worm, the nematode *Caenorhabditis elegans*. Her lab had found that changing a *single gene* could double the lifespan of these animals,¹ and she showed movies of the mutant worms crawling around at an age when normal worms were already decrepit and dying. This was an “Aha!” moment that made it clear that she wasn't talking about extending the end of life, but rather the youthful, healthy part of life, an outcome that we would all like to experience. That gene, called *daf-2*, turned

out to encode an insulin/IGF-1 receptor, meaning it could matter for people, too, since our bodies also have insulin. After hearing her talk, I knew what I wanted to do: find out how those mutant worms were so healthy. Soon after, I asked Cynthia if I could come to her lab for my postdoctoral research,² and she agreed. At that point, when people asked me what I was going to do, there was a noticeable difference. It turns out that almost everyone is interested in aging research, and everyone has an opinion about it. It quickly became obvious that one's likelihood of supporting the idea of aging research is generally correlated with one's age, and I got several exhortations to "work faster!"

I decided to write this book after developing a class at Princeton, "Molecular Mechanisms of Longevity: The Genetics, Genomics, and Cell Biology of Aging," to teach students about my research field. While preparing for that class, I realized that we (the royal We, being researchers in the field of aging and longevity) have made many molecular insights in the past two decades that would be good to convey to the general public. While the popular science market for longevity books is saturated—no one needs another celebrity's viewpoint on aging or another diet book, and several excellent introductory books already exist—at least a few people might want to have a molecular explanation of the exciting work that has been done in this arena. As I will explain, we have found out a LOT in the past two decades about how longevity is regulated, which can give us clues about how we might slow aging. We now have a better grasp of the genetic pathways and cellular processes that communicate from one cell to another how to tune the rate of aging, and we also better understand the reasons that longevity is regulated at all. These insights have then led to ideas about how to slow age-related decline, and we have some good candidates for those medicines now. Some of this excitement has recently been turned into serious biotech development, with many companies focused on longevity and aging springing up in the past few years.

I have been lucky enough to be right in the middle of things since 2000, since new genes that control longevity had just been revealed. The millennium was a real turning point: after bacteria and yeast, *C. elegans* was the first multicellular organism whose genome was sequenced, and *Drosophila* quickly followed. Those large-scale projects were a direct benefit of the approaches developed for the Human Genome Project and allowed biologists to carry out experiments that had not been previously possible on a genome-wide scale. RNA interference (RNAi), a mechanism that causes the messenger RNA (mRNA) of a gene of interest to be degraded, was first described in detail by Craig Mello and Andrew Fire in *C. elegans* in 1998,³ and it was quickly

employed by the worm field to test *all of the genes in the genome* for every characteristic of interest—including aging—through new tools to easily knock down gene expression levels.⁴ This ability to rapidly test many genes in worms quickly led to an explosion of functional genomics (that is, testing of all genes in a genome for a particular activity), and the field has been expanding in many directions ever since.

I got into the aging field because I was fascinated with the question of how longevity and aging are controlled genetically and biochemically. The tools that were newly available at the time, genomic expression microarrays and RNAi, allowed a previously unimaginable ability to probe long-lived mutants (that is, animals with changes to their DNA that affect a gene) and to learn what was going on inside them. The existence of complete genome sequences for all of these organisms also ushered in new genomic approaches, such as DNA microarrays and later next-generation sequencing, allowing the analysis of every gene simultaneously and giving us unprecedented insights into the inner workings of cells as they age. The amount of data available to researchers has been exploding ever since. Genetic and genomic methods have led the way in longevity research, and large-scale studies of metabolism have added to our understanding. Meanwhile, new molecular tools, particularly the gene-editing tool CRISPR and stem-cell approaches, offer the exciting possibility that we might even modify ourselves to achieve better health.⁵

Because of the nature of the question—understanding how aging works—the field is extremely broad. One can attack the aging question from many different viewpoints: demography, population genetics, evolution, model-system genetics, molecular biology, cell biology, nutrition science, and pharmacology. All of these perspectives are helpful in understanding how aging works and whether we can slow it down. While I will tell you about my lab's work (and I'll try not to *only* talk about our work), I will also explain the latest work throughout the field. It's a fast-moving field, with new discoveries all the time, and inevitably a few things will be missed, but I'll try to give you a good understanding of not only what we know but *how* we know it—the work that was done to figure things out.

What you will not find in this book are descriptions of what I or other scientists eat, or weigh, or how often we exercise—all information that has somehow become the norm for pop-sci books and articles on aging and the researchers who work on aging. As a scientist, I can't stand reading this information—those are all “*n* of 1” experiments whose results we don't yet know, so I won't report them—it's just bad science. Additionally, I've noticed

an odd cult-of-personality air about some aging books, and those cults usually leave out the contributions of female scientists. And I'm not a longevity evangelist; I'm not trying to sell you something, no supplements or drugs or diet plans. I just want to tell you what we know about aging and how we came to these conclusions.

Finally, I won't be using the popular phrase, ". . . , *at least in worms and flies*," which seems to pepper most books on aging. I am an unapologetic model-system advocate, for one simple reason: almost everything we know at the molecular level about the underlying mechanisms controlling (regulating) longevity is because of the work that was done first in invertebrate model systems, and then *tested later* in higher organisms (mammals like mice), a fact that is often overlooked and underreported. Beyond that, the tools that allow us to do the work, all the way up through human cells, have been identified, characterized, and tested in these simpler model systems before being adapted for use in mammals. (The most powerful yet may be CRISPR, which was first discovered in bacteria.) Without model systems, our understanding of longevity regulation would be very poor indeed. For that reason, I won't just be talking about studies of humans with some verification in mice, but I'll try to describe how we really learned about the molecular goings-on inside all of our cells, which relies on studies in small invertebrate systems. For the Sarah Palins of the world, who do not acknowledge the contributions of fundamental ("basic") research to medicine,* this will be a shock, but for the rest of you I hope it will give a fairer insight into how scientists actually learn how things work, and how we might apply what we've learned to help people live better, longer—as Palin would say, *I kid you not*.

In this book, I hope to let you know what we've discovered about longevity in recent years. But before diving into the science, I'll discuss *why* we should study aging—it's not always immediately obvious, but understanding aging could help our whole society in the long run, even economically (chapter 1)—longevity is not just for billionaires. There are many evolutionary theories about *why* we age (chapter 2), but molecular techniques are now helping us better understand this question and adjust our theories accordingly. In

* "You've heard about some of these pet projects, they really don't make a whole lot of sense and sometimes these dollars go to projects that have little or nothing to do with the public good. Things like fruit fly research in Paris, France. I kid you not" (Sarah Palin quoted in Adam Rutherford, "Palin and the Fruit Fly," *Guardian*, October 27, 2008, <https://www.theguardian.com/commentisfree/2008/oct/27/sarahpalin-genetics-fruit-flies>).

chapter 3, we'll start to see how modern genetic and genomic techniques can reveal the secrets of centenarians' long lifespans; but to experimentally test them we need to use model organisms—that is, well-studied animals we can grow in the lab and genetically manipulate so that we can test hypotheses (chapter 4). Of course, in order to study aging, we have to establish some definitions of what it means, and how we can measure these changes with age (chapter 5). In later chapters, I'll describe what we currently know about longevity pathways (chapters 6–10) and interventions in detail, so that you'll recognize the molecules that are being targeted for clinical treatment (chapter 17). Reproduction and mating are intimately linked with longevity, as I'll describe in chapters 11 and 12. What we can sense can also influence how long we live (chapter 13), while aging can affect what we can sense and our cognitive function (chapter 14). Some of the newest thoughts in the field concern how we might inherit factors from our ancestors that affect aging (chapter 15), and that what we eat and the microbes that inhabit our gut might also influence aging (chapter 16). Finally, I'll discuss the current state of longevity biotech, and how we might go about finding treatments for age-related decline (chapter 17).

We are right in the middle of the business of understanding the processes that regulate aging, and it is an exciting time because we are still in that era of discovery. I don't want to imply that we know all of the answers at this time. Instead, what I hope to convey is what we do know and, more importantly, *how* we know it, and what we might be able to do with that wealth of data. With this information at our disposal, we should all be able to make wise decisions about how to manage our own longevity.

INDEX

Page number in *italics* refer to figures.

- abortion rights, 9–10
acarbose, 218, 221, 337
acetylcholine, in Alzheimer's disease, 269
acetylcholine receptors: hearing sense of
 C. elegans and, 249; nicotinic, 44, 46, 54,
 121, 269
acetylcholinesterase inhibitors, 269
ADAR proteins, 150
aducanumab (Aduhelm), 270, 271
African Americans: childhood mortality in,
 10, 273; Covid-19 pandemic and, 7n, 8;
 environmental factors in cognitive aging
 of, 272–74; health care inequality and,
 10; historical trauma suffered by, 282;
 maternal mortality in, 10; men's decrease
 in life expectancy, 8; shortened telomeres
 in men, 185
age-1, encoding PI3 kinase, 93
age-1 mutants, 80, 88, 89, 90
age-related diseases. *See* diseases,
 age-related
AGEs (advanced glycation end products),
 75, 78, 85, 143–44
aging: autophagy impairment in, 147; be-
 ginning only in adulthood, 17; beyond
 reproductive span, 30 (*see also* post-
 reproductive lifespan); cause/effect con-
 fusion with, 99–100; cellular damage in,
 138; circular RNAs and, 150–51; DNA
 damage theory of, 177; early theories of,
 16–21; facial features and, 75–77, 341;
 free radical theory of, 155–56 (*see also*
 reactive oxygen species); gait and, 74, 77,
 82; as loss of homeostasis, 15; meno-
 pause accelerating rate of, 199–200,
 201–2; meta-analysis of GWAS and,
 48–49; not regulated itself, 213; sex
 differences in, 214–22; as side effect
 of post-reproductive survival, 15, 33,
 106. *See also* biomarkers of aging;
 longevity; reproductive aging; sex
 differences in aging
aging research: economics of, 12; ethics
 of, 11–12; goal of, 74; lack of focus on
 reproduction in, 196–97; longitudinal
 studies in, 72–73
aging treatments. *See* therapies,
 life-extending
Aguilaniu, Hugo, 68, 124–25, 135, 135n,
 146, 324
Ahringer, Julie, 64, 95n, 98, 157
AICAR, 323, 327
air pollution, and cognitive aging, 272–73
Akey, Joshua, 48
Albert Lea, Minnesota, 41
Alcedo, Joy, 241
alcohol and drug use, 8–9
ALS (amyotrophic lateral sclerosis): dietary
 restriction and, 120; mitochondrial func-
 tion and, 155; protein aggregation in,
 142, 263; retrotransposon activation
 and, 291; trial of antiretrovirals for, 267

- Alzheimer's disease, 262–74; aducanumab for, 270, 271; air pollution and, 272–73; antiretroviral therapy and, 267; autophagy enhancers for, 322; behavioral map approach to, 86; *CETP* gene and, 45; current treatments for, 269; failure of drug trials for, 14, 269–72; gene therapy trial for, 335–36; increasing incidence of, 14; infection and, 265; insulin signaling factor in vitro and, 162; microbiota-gut-brain axis and, 314–15; mitochondrial function and, 155; protein aggregation in, 141–42, 292; racial disparities in, 272–74; transposable element activity in, 266–67; women's higher rate of, 215. *See also* APOE (apolipoprotein E); dementia
- amino acids: branched-chain (BCAAs), 115, 116, 120, 134, 170; diets restricted in, 113, 115
- Amon, Angelika, 185
- AMPK (AMP kinase), 128, 131, 134, 163; FGF21 and, 312; in neuronal signaling, 242, 245
- AMPK activators: dietary restriction mimetics, 323; exercise mimetics, 172, 326–27; metformin, 278, 323
- amyloid-beta plaques, 142, 262, 263–65, 268, 292
- amyloid hypothesis, 262, 264–65, 269
- amyloid precursor protein (APP), 264, 267
- Ancestry.com, 49
- Anderson, Rozalyn, 110–11, 149–50
- Andreasson, Katrin, 277
- androdioecious species, 221, 230, 231
- androstenone, 233
- androstasis, 231
- anorexia nervosa, 107
- antagonistic pleiotropy theory, 19–20, 44, 257, 325
- Antebi, Adam, 133, 149, 171
- antibiotics, 304–5
- anti-inflammatory drugs, 322
- antimicrobial peptides, in *daf-2*, 97, 99
- anti-Mullerian hormone, 197
- antioxidant genes, 22, 23. *See also* catalase; superoxide dismutase (SOD)
- antioxidants, 21, 321–22; blunting hormetic stress response, 24; preventing benefits of exercise, 164; pterostilbene as, 171, 342; rescuing premature aging phenotype, 156
- antiretroviral therapy, and Alzheimer's disease, 267
- antisense oligonucleotide treatment, 336
- apelin receptor J, 340
- Apfeld, Javier, 237–38, 241
- Aplysia*, 143, 258, 259, 292
- APOE (apolipoprotein E), 44–45, 47, 267–68, 272; $\epsilon 4$ allele of, 44, 47, 267–68, 272, 315, 335; gene therapy trial with, 335–36; microbiome and, 315; *TOMM40* and, 44, 47, 48–49
- Arctica islandica*, 23, 53
- Aricept (donepezil), 269
- ART (artificial reproductive technology), 208. *See also* IVF (in vitro fertilization)
- ascarosides, 227, 229
- Ashraf, Jasmine, 103
- Asian Americans, Alzheimer's disease in, 273
- aspartame, and microbiome, 308
- aspirin, 321–22, 323, 337
- astrocytes: APOE and, 268; neural stem cells and, 182
- ATFS-1, 160, 161, 169
- ATP generation, 154–55; cognitive aging and, 277
- Austad, Steve, 23, 29, 55
- autism spectrum disorder (ASD), and microbiomes, 305, 316, 317
- autonomous signaling, neuronal, 247
- autophagy, 146–48; *daf-2* upregulated genes for, 97, 139; DAF-16 and, 103; in dietary restriction, 133, 145; different types of, 147; enhancers of, 322; of mitochondria, 166–67, 168; mitochondrial dysfunction and, 161–62; nighttime fasting in flies and, 117; therapies to increase, 321; in yeast cells, 69
- Avery, Oswald, 287, 300

- bacteria: fed to *C. elegans*, 243, 306; replicative senescence in, 66; small RNAs made by, 300–302. *See also* microbiomes
- Baltimore Longitudinal Study of Aging (BLSA), 72
- Bargmann, Cori, 100, 239–40, 241, 299
- Barlow, Denise, 279
- Barr, Maureen, 231–32
- Barzilai, Nir, 343
- bats: anal microbiome in, 309; longevity compared to mice, 29, 55–56; ROS theory of aging and, 156–57; species with longer-lived males, 217
- Batten's disease, 336
- Baudisch, Annette, 31
- bees: epigenetic programming in, 293; microbiomes of, 307, 309. *See also* eusocial animals
- Benzer, Seymour, 128
- Bert, Paul, 188
- beta-amyloid aggregates, 142, 262, 263–65, 268, 292
- biogenic amines, 242, 244
- biological age: companies selling diagnostics of, 341–42; DNA methylation and, 199–200, 293–95, 342; single-cell transcription and, 295
- biological clock, for having children, 193
- biomarkers of aging: in *C. elegans*, 77–79; companies selling information on, 341–42; DNA methylation, 293–95; facial imaging correlated with, 341; in humans, 73, 74–75, 77; microRNAs (miRNAs), 150; nucleolar size, 86, 141; progerin expression, 178; in TAME metformin trial, 343–44; transcriptional heterogeneity, 148
- biotech companies, 320, 321; diagnostics sold by, 341–42; plasma factors and, 332–33; resveratrol and, 328, 329; searching for new drugs, 337–38, 339; senolytics and, 333; stem cells and, 334, 337; telomeres and, 334–35
- Birney, Ewan, 285
- Blackburn, Elizabeth, 184, 185
- Blagosklonny, Mikhail, 20–21
- blood-borne factors, 188–92, 261–62. *See also* plasma factors
- blood-brain barrier: in cognitive aging, 256, 275; as obstacle to treatments, 336
- blood pressure regulation, 45
- Bloom syndrome, 177
- Blue Zones, 40–41, 43; Mediterranean diet in, 41, 317; telomere length and, 185
- Bodmer, Rolf, 85
- body mass index (BMI), 46
- Bogdanov, Alexander, 188
- bombykol, 232
- Booth, Lauren, 227
- Botstein, David, 68, 93
- bovine spongiform encephalopathy, 142–43, 292
- bowhead whales, 54
- Braak's hypothesis, 315–16
- brain function: caloric intake and, 136; improved by inhibitor of ISR, 323; microbiota-gut-brain axis and, 314–16; plasma factors and, 191. *See also* cognitive aging
- branched-chain amino acids (BCAAs), 115, 116, 120, 134, 170
- Brenner, Charles, 329
- Brenner, Sydney, 62
- Briggs, Margaret, 62
- Brown, Pat, 93–94
- browning of adipose tissue, 35, 162, 244
- Brunet, Anne, 70, 110, 128–29, 131, 226–27, 228, 295, 296–97
- Buettner, Dan, 41
- Buffenstein, Rochelle (Shelley), 23, 56, 157
- Bussemaker, Harmen, 102
- butyrate: bacterial groups producing, 316–17; fecal transplants from aged mice and, 312; FGF21 and, 312–13; future studies needed on, 318; from young microbiome, 310–11

- Caenorhabditis elegans*: aging phenotypes in, 77–79; arrest states in, 239, 298 (*see also* dauer); cellular structure of, 62; death in, 79–80; dietary restriction in, 130–31, 221–22; disposable soma theory and, 24–27, 26, 32; DNA damage in, 187; early development of, 25; forced to exercise, 171; germline and gonad controlling longevity in, 200–201; gut microbiota of, 305, 306, 307; hearing of, 248–49; histone modifications regulating lifespan of, 296–97; insulin signaling and, 63 (*see also* insulin/IGF-1 signaling pathway); intestinal proteostasis in, 150; learning in, 81, 120–21, 258–60, 268; mating in, 205, 220, 225–31; memory in, 81, 85, 120–21, 171, 254, 254, 258–60, 268, 274–75; microarray studies of, 95–97; mitophagy booster in, 327; as model system, 52, 62–65, 87, 90; motility characteristics of, 82–85; mutants bought for \$7, 206; mutations that stop development of, 34–35; nonlethal stresses increasing lifespan of, 23–24; oxygen sensing in, 245–46; parental age in, 87; post-reproductive lifespan in, 209–10, 210; proteostasis in, 97, 103, 139–40, 150; rejuvenating oocyte proteins, 16, 68, 125, 144, 146; reproductive aging in, 204–5, 206–8; resveratrol and, 126, 127; RNA interference (RNAi) in, 2–3, 64–65, 300; RNA splicing in, 149; sensory regulation of lifespan, 237–38, 247; sequenced genome of, 2, 95; Sir-2 in, 125–26, 330; starvation survival in, 133, 298; stochasticity of aging in, 78–79; testing candidate drugs in, 337; transgenerational effects in, 298; velocity of, 82–85; vitellogenins in, 21, 229–30; wild type vs. lab mutants, 35, 94. *See also* hermaphroditic *C. elegans*; longevity mutants of *C. elegans*; male *C. elegans*
- CALERIE trial, 118
- Calico, 49
- Calment, Jeanne, 11, 38, 40
- caloric restriction. *See* dietary restriction (DR)
- Caloric Restriction Society, 119
- Cambodian refugees, 282
- Campisi, Judith, 47, 186, 187–88
- cancer: autophagy enhancers for, 322; autophagy impairment in, 147; as biotech target, 340; cellular damage and, 174; genes involved in suppression of, 48, 54, 55; mTOR inhibitors for, 323; performance-enhancing drugs and, 327; PI3 kinase and, 63; PTEN phosphatase and, 90; regeneration therapies boosting risk of, 336; senescent cells and, 187, 192; stem cells' limited lifespan and, 186; suppressed in naked mole rats, 56–57; telomerase boosting risk of, 334, 336; transposable element in, 291
- Cannon, Walter, 17
- capsaicin, 245
- carbon dioxide sensing, 245, 247
- cardiomyopathy, 190
- cardiovascular disease: as biotech target, 322, 340; genes involved in, 45, 48, 59; menopause after age 55 and, 199; protein in diet and, 115; statins for, 339; sugar and, 114–15; in utero starvation and, 280–81
- Carroll, Sean, 30
- Case, Anne, 8
- catalase, 22, 97, 98, 156, 161
- cathepsin B proteases, 207–8
- Caulobacter crescentus*, 66
- CCL11, 190
- cell culture, 59
- cell cycle checkpoints, 176, 186
- cell cycle/senescence regulator, 48
- cellular damage, 137–38
- centenarians: age-related diseases and, 49, 73; in Ashkenazi Jewish population, 43, 46, 334; athletic achievements of, 152–53; dietary restriction and, 108; DNA methylation in, 294; eunuchs among, 24, 202;

- FOXO3A* variants in, 45, 93, 216; genetic studies of, 42–47; genomes of 2000 Han Chinese, 47, 215–16; giving birth later in life, 195, 209; health of, 39–40, 73–74; IGF-1 receptor mutations in, 45–46, 93; maximum lifespan and, 11; microbiome diversity in, 309; mostly women, 215–16; RNA editing and, 150; telomeres and, 334. *See also* supercentenarians
- central dogma, 138, 139, 174
- cephalopods, 29
- cerebral amyloid angiopathy, 268
- CETP*, 45, 59, 268
- cGAS-STING, 186–87, 253
- chaperones, 139, 141, 147
- Chase, Martha, 287
- chemotaxis, transgenerational inheritance of, 284
- chemotaxis assay, 258–59
- chico* mutant of *Drosophila*, 64, 92
- childbearing: after 45 without ART, 208; maternal age and, 194–96; maternal lifespan and, 194–96, 195; number of children and, 195; planning for, 196–97, 213; post-reproductive lifespan and, 210, 211. *See also* maternal mortality; pregnancy
- childhood mortality, 7–8; in Black population, 10, 273
- Chinese emperors, 234–35, 235, 236
- cholesterol metabolism, 44, 45, 47, 268.
See also high density lipoprotein (HDL)
- cholinesterase inhibitors, 269
- CHRNA3/5 nicotinic acetylcholine receptor, 44, 46, 54
- CHRNA10 nicotinic acetylcholine receptor, 54
- chromatin, and pathogenic tau, 267
- chromosome location *Sq33.3*, 44, 45, 47
- chromosomes, 174
- chronological age, 199, 293–94
- chronological lifespan (CLS), in yeast, 67, 123–24, 125, 128
- Church, George, 47
- ciliated neurons, 238
- circadian rhythms: eating and, 117, 135–36; FGF21 and, 131; sex differences in, 219
- circular DNA, mitochondrial, 155
- circular RNAs, 150–51
- clams, long-lived, 23, 53, 156
- Clement, James, 47–48
- climate change, 347
- clk* mutants in *C. elegans*, 63, 64, 80, 184
- clofibrate, 338
- Clostridium difficile*, 305, 307, 312
- clusterin, 262
- Cockayne syndrome, 177
- cockroaches, pheromones of, 232
- cognitive aging: air pollution and, 272–73; biotech drug candidate for, 340; blood-brain barrier in, 256, 275; dietary restriction and, 276; fecal transplants from young mice and, 314; IGF-1 levels in mammals and, 275; longevity mutants of *C. elegans* and, 274–75; Mediterranean diet and, 317; in model systems, 257–61; normal, 251, 252, 262, 278; plasma factors and, 191; prospect for real treatments, 347; racial inequality affecting, 272–74; slowing of, 255, 262, 274–78; systemic regulators of, 261–62; in utero starvation and, 281; vasculature in, 256. *See also* dementia; neurodegenerative diseases; neuronal aging
- cognitive function: companies selling tests of, 341; exercise and, 262, 333; of pet dogs, 344
- COMPASS histone modifiers, 296–97, 298, 300
- compression of morbidity, 13–14, 40, 42, 56, 73
- Conboy, Irina and Michael, 189
- congestive heart failure, 75
- conserved mechanisms, 161, 162; AMPK regulation of mTOR, 245; germline activation upon mating and, 236; of germline-mediated longevity, 201; histone modifications changing with age, 296;

- conserved mechanisms (*continued*)
 insulin signaling pathway and, 93, 240; of learning and memory, 258, 259–60; neuronal gene expression in aging and, 254; neuronal signaling pathways, 242; oxidative damage and, 156; TGF-beta pathway and, 240
- cosmeticeuticals, 342–43
- Cota, Vanessa, 167–68
- Covid-19 pandemic: demographics of mortality and, 7n; inflammation in, 341; life expectancy in minorities and, 7n, 8; long Covid and, 256, 341, 347; Paxlovid treatment in, 267; PCR test for, 179; sex disparity in life expectancy and, 215; vaccines for, 7n, 13
- CREB transcription factor: in *eat-2* mutants, 276; higher in *daf-2* mutants, 274–75; levels declining with age, 260–61; in long-term memory, 258, 259, 260, 274; reversal of cognitive impairment and, 191; thermosensation and, 244
- Creutzfeldt-Jakob disease, 142–43, 292
- Crimmins, Eileen, 8, 12
- CRISPR: first discovered in bacteria, 4; gene therapy and, 336; in killifish, 69, 70; in model systems, 59; possibly used to modify humans, 3; possibly used to prevent progerias, 192; primate models and, 66
- Cryan, John, 314
- Curran, Sean, 20, 325
- cyanobacteria, 179
- cytochrome P-450s, 269
- DAF-2 insulin/IGF-1 receptor, 27, 80, 104, 105; late-life degradation of, 325–26
- daf-2* mutants: aging phenotypes and, 78; *eat-2*' lifespan and, 122, 122n; gene expression in, 95, 97–99; increased lifespan of, 63–64, 88–89, 90–91, 94; insulin/IGF-1 receptor and, 1–2, 22, 22n, 63, 89–90, 94; memory ability with age in, 254, 254, 274; naming of, 22n, 63; neuronal functions and aging in, 85; neurons' transcriptional targets in, 275; oocyte mitochondria in, 168; proteostasis in, 139, 145; regulation of longevity in, 104; reproductive span of, 206–7, 208, 212; RNA editing and, 150; SOD and catalase in, 157; staying healthy longer, 40, 80–82, 82n, 94; synaptic traffic system in, 253; transcription quality control in, 149; ubiquitin-proteasome system and, 144–45; wild type winning out over, 94
- DAF-7, 240
- DAF-9/DAF-12 nuclear hormone signaling pathway, 244, 247
- DAF-16: DNA sequences bound by, 100–102; as FOXO homolog, 45, 63, 90, 93 (*see also* DAF-16/FOXO); insulins in the intestine and, 247; intermittent fasting and, 94; many genes regulated by, 98–99; in neuronal signaling, 242–43; in neuron-specific *daf-2* targets, 274; in nonautonomous regulation of lifespan, 242; in regulation of longevity, 104, 104–6; Sir2 and, 124
- DAF-16 associated element (DAE), 101–2; PQM-1 binding to, 102–3, 104, 105
- DAF-16 binding element (DBE), 101–2, 101n
- DAF-16/FOXO, 95; dietary restriction and, 128–29, 130; germline anti-longevity signal and, 200–201; histone modifications and, 296; in hypoxia sensing, 246; in proteostasis, 140; sensory neurons affecting lifespan and, 241; in sexual conflict, 227. *See also* FOXO; insulin/IGF-1 signaling pathway
- daf-16* mutants, 63; *daf-2* mutants and, 89, 97; dying early, 80–81; *eat-2*'s lifespan and, 122, 122n
- daf-22* mutants, 229
- daf-23* mutants, 89, 90
- Daf-d mutants, 89
- DAMPs, 163
- dauer, 62–64; advantages for genetic studies, 122; availability of food and, 88, 105;

- daf* mutants and, 22n, 88–89; decision to go into, 239–40; extending lifespan, 87; function of, 88; not needed for longevity, 64, 90–91; sensory neurons and, 239–41; strong mutations stopping development in, 35; TGF-beta pathway and, 91–92, 206, 240
- Deaton, Angus, 8
- Deinococcus radiodurans*, 179
- dementia: APOE $\epsilon 4$ allele and, 268; *CETP* gene and, 45; decreased in diabetic patients on metformin, 278; historical trauma and, 282; increasing incidence of, 14; microbiomes in, 315; racial disparities in onset of, 272–74; vascular, 256; women's higher rate of, 215. *See also* Alzheimer's disease
- DeRisi, Joe, 93–95
- development: hyperfunction quasi-program and, 20–21; mutations that slow or stop, 34–35, 34n
- diabetes: AGEs and, 143; Alzheimer's disease and, 265, 273, 277; cognitive aging and, 277–78; drugs with life-extending benefits, 339–40 (*see also* metformin); exercise mimetic and, 326; fecal transplants in mice and, 311; insulin/IGF-1 signaling pathway and, 94; in utero starvation and, 280–81
- diapause: in *C. elegans*, 22n, 34, 35, 87, 298, 299; function of, 238–39; in killifish, 69–70; longevity and, 240. *See also* dauer
- diet: changes in Western diet, 114–15; healthy, 41; inconsistent messages on, 116; Mediterranean, 41, 317, 318; sugar link to cardiovascular disease, 114–15
- dietary restriction (DR): aging slowed by, 133–36; autophagy in, 147; brain function and, 112–13, 136; in *C. elegans*, 130–31, 221–22 (*see also eat* mutants of *C. elegans*); cell biology of, 129–33; cellular repair mechanisms and, 138; cognitive aging and, 276; diets used in study of, 113, 115–16; different types of, 110; difficulty of defining, 109–11; in *Drosophila*, 85, 111–12, 113, 130, 135, 243–44; early research on, 59–60, 108–9; extending lifespan and reproduction, 32; fleeting benefits of, 111–12; gender in studies of, 118, 119; genetics of, 121–29; health-span increased by, 108; human populations experiencing, 108; human studies and choosers of, 118–20; insulin signaling pathway and, 122, 129, 131–32, 134; longevity effect in all animals tested, 109; longevity effect in humans, 108; longevity regulation in, 127–29; metabolic shifts responding to, 133–34; mitochondria and, 167; mood and, 119–20; multiple pathways affecting longevity in, 134; neuronal regulation of lifespan and, 242; nucleolar size and, 86; post-reproductive effect of, 324–26; protein translation inhibition in, 132; retrotransposon activation slowed by, 291; in rhesus monkeys, 65–66, 149–50; RNA splicing and, 149–50; sex differences in, 219, 220, 222; therapies targeting pathways of, 321; timing of, 116–18; in yeast, 67. *See also eat* mutants of *C. elegans*
- dietary restriction mimetics, 134–35, 136, 323–26; acarbose as, 218, 221, 337; in men versus women, 326; post-reproductive effect of, 324–26
- dietary supplements, 342
- Dillin, Andrew, 27, 91, 96n, 128–29, 158, 159, 160, 245
- DiLoreto, Rose, 82
- diseaseQUEST*, 170
- diseases, age-related: accelerated by stress, 8; autophagy impairment in, 147; genes involved in growth and, 55; genetics of supercentenarians and, 48; GWAS associations and, 42–50; hyperfunction quasi-program and, 20–21; longer lifespans leading to increase in, 8; in long-lived individuals, 49, 73; nutrient-deprived rats and, 109; as proxy for longevity drugs,

- diseases, age-related (*continued*)
339–41, 346; staved off by centenarians, 40; women's higher rate of, 215. *See also* cancer; cardiovascular disease; neurodegenerative diseases
- disposable soma theory, 24–27, 26, 32
- DNA: central dogma and, 174; of extremophiles, 179–80; histones and, 290, 295–97; nucleosome packaging of, 174, 295–96; proved to be hereditary material, 287; replication of, 175–77. *See also* mitochondrial DNA (mtDNA)
- DNA damage: SASP and, 186–88; in stem cells, 185–86; types of, 176; UV-induced, 158–59, 176, 177, 179–80
- DNA methylation: aging clocks based on, 199–200, 293–95; companies selling kits based on, 341–42; as epigenetic mechanism, 290, 293; menopause and, 294–95; S-adenosine methionine and, 283
- DNA repair: aging as slowdown in, 17; bowhead whale genes and, 54; progerias and, 176–77; in semi- and supercentenarians, 48; in thermophilic archaea, 180
- DNP (2,4-dinitrophenol), 35, 327–28
- Dobzhansky, Theodosius, 36
- dod* genes, 97, 99, 101, 101n, 102
- dog lifespans, 19, 55, 185, 339, 344
- Dougherty, Ellsworth, 62
- Dracula* (Stoker), 188
- Driscoll, Monica, 21, 77–78, 80, 171
- Drosophila*: behavioral changes in, 85–86; carbon dioxide sensing in, 247; cardiac function in, 85; circular RNAs in, 150–51; dietary components fed to, 113; dietary restriction in, 85, 111–12, 113, 130, 135, 243–44; food choice in, 244; germline-mediated longevity in, 201; gut microbiomes of, 307; informed GWAS and, 49; insulin signaling pathway in, 64, 92; intermittent starvation in, 109; intestinal barrier assay in, 85; learning and memory in, 258, 292; longevity regulation in, 92; as model system, 52, 60–62; neuronal regulation of longevity in, 243; retrotransposon activation in, 291; seeing dead flies, 248; sequenced genome of, 2; sex differences in, 219; sexual conflict in, 223–24; SOD and catalase in, 156, 157
- DrugAge database, 337, 338
- drugs, life-extending: current excitement about, 319–20; exercise mimetics, 171–72, 326–28; geroprotectors, 337–38; increasing autophagy in model systems, 148; senolytics, 187–88, 333, 340; testing candidate effects on lifespan, 218. *See also* dietary restriction mimetics; therapies, life-extending
- Dubal, Dena, 219
- Dubnau, Josh, 291
- Dutch Hunger Winter, 280–81, 283, 285, 298
- eating disorders, 107, 119
- eat* mutants of *C. elegans*, 62–63, 64, 80–81, 121–22, 128–29, 130, 149, 221; learning and memory in, 113, 275–76
- economics: affecting lifespan factors, 13; potential aging population and, 12
- education, and lifespan, 46
- Eisen, Michael, 93, 96
- embryonic stem cells (ESCs), 181, 182
- endogenous retroviruses. *See* retrotransposons
- endoplasmic reticulum (ER): stress in, 242–43; unfolded and misfolded proteins in, 145
- energy: to maintain functioning cells, 16–17; mitochondrial production of, 154–55
- enrichment analysis, 101, 101n
- enteric nervous system, 310, 314–15
- entropy, 16
- Epel, Elissa, 185
- epigenetic clocks, 199–200, 293–95
- epigenetics: biotech using, 334; dark history of, 284, 286–89; defined, 279; important role of, 289; marks reset in

- every generation, 297, 302; McClintock's contribution to, 288–89; mechanisms of, 289–90; mitochondrial stress signal and, 160–61; silencing mechanisms in, 290–91, 293; in utero conditions and, 283; in yeast, 69. *See also* DNA methylation
- Escherichia coli*: fed to *C. elegans*, 243, 306; replicative senescence and, 66
- estrogen: 17 α -estradiol and mouse lifespan, 218, 337; extreme female longevity and, 216; postmenopausal health problems and, 215. *See also* menopausal hormone therapy
- eugenics, 288
- eukaryotes, 66
- eunuchs, long lifespan of, 24–25, 202, 234, 236
- eusocial animals, 57–58, 217; insects, 34, 293 (*see also* bees); naked mole rats, 56, 57
- Evans, Ron, 172
- evolution: of longevity as a trait, 30, 32; mutations used in, 175, 176; of placenta, 291; post-reproductive lifespan and, 31, 33–34, 213; reproductive success and, 203; successful learning and memory in, 257; transposable elements in, 291. *See also* conserved mechanisms; selective pressure
- Ewald, Collin, 27
- exercise: antioxidants and, 23, 164; blood factors affecting memory and, 191; in *C. elegans*, 171; mitochondria and, 166, 171–72; as mitohormesis, 169; nucleolar size and, 86, 171; plasma factor from exercising mice and, 333; plasma proteins increased by, 262; telomere length and, 334; transcriptional clocks and, 295
- exercise mimetics, 171–72, 326–28
- exons, 149
- extremophiles, 179–80
- eye diseases: autophagy enhancers for, 322; as biotech target, 340; senolytics for, 333; stem cell therapy in mouse model of, 336. *See also* retinal cells, and Yamanaka factors
- facial aging, 75–77, 341
- famine: in Dutch Hunger Winter, 280–81, 283, 285, 298; in Great Chinese Famine, 281, 288; Soviet Lysenkoism and, 288
- fasting-mimicking diet, 117, 317–18, 323
- FDA approval, 343
- fecal microbial transplants, 304, 311–14, 316, 317–18
- Felix, Allyson, 10
- fen-phen, 35
- fibroblast growth factor 21 (FGF21), 131–32, 133, 161–62; in biotech for dogs, 344; butyrate and, 312–13; Klotho and, 190, 312; systemic therapies and, 332
- fibroblasts, SOD in, 156
- Finch, Caleb (Tuck), 272
- Fire, Andrew, 2, 64, 298
- fitness, and reproductive aging, 203, 213
- flatworms. *See* planaria
- Fontana, Walter, 80
- 14-3-3 proteins, 105, 124
- FOXO, 45–46, 64; DNA sequences bound by, 101; in *Drosophila*, 64, 92; microRNAs and, 297; Sir2 and, 123; treatments that use, 321; ubiquitin-proteasome system in mammals and, 145. *See also* DAF-16; DAF-16/FOXO
- FOXO3A, 44, 45, 93, 216
- FOXO3 in bowhead whale, 54
- frailty, 14, 39, 74, 153, 316, 317, 326, 341, 346, 347
- Frankenstein* (Shelley), 173
- Franklin, Rosalind, 175
- Fraser, Andy, 98
- free radical theory of aging, 21–23, 155–56. *See also* reactive oxygen species (ROS)
- Fries, Jim, 14, 40, 42, 73
- functional genomics, 3
- gait, 74, 77, 82
- galantamine, 269
- Gallan, Jessie, 232, 236
- gallic acid, 338
- Garigan, Delia, 21, 77–78, 79, 80

- GDF11, 190, 332
Gelsinger, Jesse, 335
Gems, David, 79–80, 125–26, 220–21, 225–26
gender, as social construct, 214n
gene editing. *See* CRISPR
gene expression: in aging vs. response to aging, 99–100; histone modifications and, 296; inflammation and, 46; knocked down with RNAi, 3; neuronal aging and, 254. *See also* messenger RNA (mRNA); microarrays
gene knockdown. *See* RNA interference (RNAi)
gene therapy, 335–36; in dogs, 344
gene x environment effects, 13, 46, 61
genome wide association studies (GWAS), 36, 42–50, 42n; of ages of menarche and menopause, 198–99, 200; APOE alleles in, 267, 268; candidate disease genes in, 170; of centenarians, 93; FOXO in, 63; SNPs tracked in, 175; testing genes found in, 59, 61, 65
germline stem cells, 181
gerontology, 18–19, 304
geroprotectors, 337–38
Ghazi, Arjumand, 200–201
Glantz, Stanley, 114
glial cells: amyloid precursor protein and, 264; cleaning brain during sleep, 256; declining IGF-1 in aging mammals and, 275; endoplasmic reticulum stress and, 243; from induced pluripotent stem cells, 255; in neuroinflammation, 261–62, 266; retrotransposon activation in, 291; tau and, 266. *See also* microglia
D-glucosamine, 338
glycine, 337
glymphatic system, 256, 262
Goldstein, Dana, 12
gonochoristic species, 221, 229, 230, 231, 232
Gorbunova, Vera, 57
Gottesman, Susan, 158–59
Gottschling, Dan, 69
grandmother hypothesis, 30, 31, 209, 216
Great Chinese Famine, 281, 288
Greenland shark (*Somniosus microcephalus*), 53
green tea, 322
Greer, Eric, 110, 129
Greider, Carol, 184
Griffith, Frederick, 287
group selection, 28–29
growth hormone, 219
growth hormone receptor, 56, 110
Guarente, Leonard (Lenny), 125, 171, 328, 330
Gula, Sharbat, 75
guppies (*Poecilia reticulata*), 29–30, 32
GW1516 (Endurobol), 327
Hagiwara, Masatoshi, 149
Hall, David, 78
Han, Jing-Dong Jackie, 76–77, 130–31
Han Chinese centenarians, 47, 215–16
Hannum clock, 294
Hansen, Malene, 103n, 128
Harman, Denham, 21, 23, 155
Harris, Nadine Burke, 282
Hawkes, Kristen, 209
Hayflick, Leonard, 59, 183–84
Hayflick limit, 59, 184, 334, 341
Haynes, Cole, 169
health-care disparities, 12, 13
healthspan, 14, 71; lifespan of *C. elegans* mutants and, 80–82, 169; metrics in vertebrates, 86. *See also* compression of morbidity
hearing, of *C. elegans*, 248–49
heat shock proteins: in *daf-2* mutant of *C. elegans*, 97, 99, 103, 141; proteostasis and, 139, 140; stress responses and, 79
Heimbucher, Thomas, 246
Hekimi, Siegfried, 22, 64, 121, 122
hematopoietic stem cells (HSCs), 183, 185–86
Henrich, Christy, 107

- hermaphroditic *C. elegans*, 27n, 31, 62, 205;
advantages for research, 220; evolution
of, 223, 230; lifespan of, 221; male pher-
omones shortening lifespan of, 226–27;
masculinized, 228n, 229; mating leading
to death of, 225–27; running away from
males, 231; sperm content decreasing
attractiveness to males, 231–32
- Herndon, Laura, 21, 78, 80
- Hershey, Alfred, 287
- heterochronic parabiosis, 188–91, 295
- hibernation, 29, 33, 34, 55, 56, 90, 238
- hidden Markov models, 101
- HIF-1 (hypoxia induced factor), 246, 340–41
- high blood pressure, 8, 273
- high density lipoprotein (HDL), 44, 45,
47, 59
- high-fructose corn syrup, 115
- hippocampus: acetylcholinesterase inhibi-
tors and, 269; of calorically restricted
rhesus monkeys, 276; CREB in, 260–61;
fecal transplants from aged mice and,
312; integrated stress response and, 276;
neurogenesis and, 255; transposable
element activity in AD and, 267
- Hispanics: Alzheimer’s disease in, 273;
Covid-19 pandemic and, 7n, 8
- histone modifications: COMPASS and,
296–97, 298, 300; as epigenetic mecha-
nism, 290, 295–97; sirtuins and, 328,
329
- historical trauma, 281–82, 285, 289
- HLA loci, 46, 49
- Holocaust survivors, 282
- homeostasis: aging as loss of, 15, 17, 36,
137; of autophagy, 148; histone modifi-
cations and, 296; mitochondria and,
169; RNA quality control in, 148–51;
unfolded protein response in, 145. *See also*
proteostasis
- Hoppe, Thorsten, 242–43
- hormesis, 18, 23–24; heat stress in *Dro-*
sophila and, 92; mitochondrial, 163–64,
169, 171
- Horvath, Steven, 199–200, 293–94
- Horvitz, H. Robert, 62, 239
- Hsin, Honor, 25, 200
- humanin, 162
- Huntington’s disease, 142, 263, 336
- Hutchinson-Gilford progeria, 177–78, 305,
308, 316, 336
- Hutterites, 233
- hyaluronic acid, 57, 314
- Hydra*, stem cells of, 181
- hyperfunction quasi-program, 20–21
- hypomorphs, 122n
- hypoxia sensing, 245–46; muscle aging
target and, 340–41
- IGF-1. *See* insulin/IGF-1 signaling path-
way; insulin-like growth factor (IGF-1)
- IL-6 inflammatory cytokine, 46, 47, 265,
301
- immortalists, 345–46
- immortality, universal search for, 6–7
“immortal jellyfish” (*Turritopsis dohrnii*),
18, 181
- immortal organisms, 17–18, 181
- immune system: cognitive aging and, 256,
261, 277; HLA loci and, 46, 49; inflam-
mation and, 46–47, 187, 256, 277; in-
tergenerational response in, 301–2;
mate choice in mealworm beetle and,
233; mitochondrial-derived DAMPs
and, 163; multigenerational effect on,
281; retrotransposon activation and,
291; RNA editing and, 150; RNA splic-
ing and, 149; senolytics and, 333; stem
cells and, 18. *See also* microglia
- immunotherapy, and extracellular tau, 266
- InCHIANTI study, 72, 74
- induced pluripotent stem cells (iPSCs),
182, 255, 294, 334, 337
- inequality, and life expectancy, 8, 9, 10
- infant mortality. *See* childhood mortality
- infertility, female, 193–94, 198, 331
- inflammaging, 187, 261, 291, 296, 310,
316, 341

- inflammation, 46–47; age-related diseases and, 48; AGEs and, 144; in aging brain, 256, 261, 262, 275, 276, 277; Alzheimer’s disease and, 265; drugs that block, 322; fasting-mimicking diet and, 317–18; histone modifications and, 296; lifespan of male mice and, 218; male centenarians and, 215–16; microbiome and, 310, 316; pain receptor in mice and, 245; SASP and, 47, 56, 187; therapies for reduction of, 321
- inflammatory bowel disease (IBD), 317–18
- influenza pandemic of 1918, 7, 215
- informed GWAS (iGWAS), 49
- Ingram, Donald, 111
- insulin/IGF-1 signaling pathway: autophagy induced by, 147; bat longevity and, 56; in bowhead whale, 54; cellular repair mechanisms and, 138; in centenarians, 36, 45–46, 93; chaperones and, 141; cloning of genes in, 63, 90; *daf-2* mutant and, 1–2, 22, 22n, 63, 89–90, 94; DAF-16 transcription factor and, 90, 98–99, 104; dauer decision and, 240–41; diabetes and, 94; dietary restriction and, 122, 129, 131–32, 134; in *Drosophila*, 64, 92; FOXO activity and, 45–46, 63, 64, 90; germline and gonadal longevity signals and, 201; in killifish, 70; Laron syndrome and, 35, 55; longevity benefit to tiny changes in, 36, 46; longevity regulation by, 62, 64, 89–90, 92–93, 104, 104–6; mammalian, 90, 92–93; microbiome and, 310; microRNAs and, 297; mitochondria and, 161, 162, 167, 168, 204; mTOR and, 128; oocyte quality and, 204; PQM-1 and, 102–3, 104, 105; reproductive span and, 208; sense of smell in mice and, 244; sensory neurons affecting lifespan and, 241; sex differences in, 219; sexual antagonism and, 226, 227; Sir2 in *C. elegans* and, 124; Sirt6 and, 219; strong mutations of, in *C. elegans*, 34–35; as therapeutic target, 93, 321, 326, 332; yeast homolog and, 67
- insulin-like growth factor (IGF-1): declining with age in mammals, 275; in extreme human longevity, 46; Fgf21 and, 162
- insulin-like peptides: in *C. elegans*, 242, 243, 244–45, 247; in *Drosophila*, 243
- insulin resistance, 156, 162, 163, 244, 277, 311
- integrated stress response (ISR), 276, 322–23
- intergenerational inheritance, 282–84; trauma and, 281–82
- intermittent fasting (IF), 116–17, 129, 130, 134, 135, 323; Fgf21 and, 162; human sexual differences in, 222; lifespan of *C. elegans* and, 21; mitochondria and, 167
- Intervention Testing Program (ITP), 218, 337
- introns, 149
- ISRIB treatment, 323
- IVF (in vitro fertilization), 196–97, 204. *See also* ART (artificial reproductive technology)
- Izpisua Belmonte, Juan Carlos, 182
- James, Sherman, 8
- “John Henry” effect, 8
- Johnson, Tom, 23–24, 63, 79, 82, 88, 163
- Julius, David, 245
- Just, E. E., 289
- Kaerberlein, Matt, 344
- Kahn siblings, 42, 45
- Kaletsky, Rachel, 169–70, 300
- Kapahi, Pankaj, 128
- kefir, 317
- Kenyon, Cynthia, 1–2, 21, 25, 27, 63, 77–78, 80, 87, 88–89, 95, 157–58, 159, 164, 200–202, 221, 237–38, 241–42, 244, 330
- Kesselheim, Aaron, 270
- keto diet, mimics of, 323
- killifish, 69–70, 86, 126, 313–14
- Kim, John, 95n
- Kim, Stuart, 47, 49, 95n
- Kimura, Jiroemon, 39

- Kirkland, James, 187–88
Kirkwood, Thomas, 24, 195
Klass, Michael, 62–63, 64, 82, 87–88, 121
Klotho, 190, 312, 332, 344
Kluger, Jeffrey, 194
Kopec, Stefan, 109
Kornfeld, Kerry, 80–81, 82, 205
Kreiling, Jill, 291
- Lakota, trauma suffered by, 281–82
Lamarck, Jean-Baptiste, 284, 286
Lamarckian inheritance, 284–85, 286, 287, 288
lamin A, 178, 182, 336
Landsteiner, Karl, 188
Laron syndrome, 35, 55, 94
Lashmanova, Elena, 327
learning: in *C. elegans*, 81, 120–21, 258–60, 268; claimed heritability of, 283, 286–87; fecal transplants from aged mice and, 312; in invertebrate models, 257–61; plasma factors and, 190, 191, 261–62
Lee, Richard, 190
Lee, Seung-Jae V., 148–49, 221, 244
Lee, Stan, 173
Lee, Sylvia, 101, 159
Levine, Morgan, 199, 294, 342
Lewy body dementia, 263, 268
Libina, Natasha, 242
life expectancy: correlated with income in US, 8; Covid-19 pandemic and, 7n, 8, 215; declining in US, 8; demographics of, 7–10; known determinants of, 9, 12–13; menopause after age 55 and, 199; preventable infections and, 304–5; sex difference in, 215; socioeconomic inequality in, 8, 9, 10; twentieth-century US increase in, 7. *See also* childhood mortality; lifespan of humans; maternal mortality
lifespan of humans: lifestyle factors in, 9, 12–13, 41, 46, 49; maximum, 11, 14, 34, 38–39; post-reproductive, 30–31, 33, 209–12, 210, 216; reproductive span and, 208–9; sexual behavior and, 234–35, 235. *See also* centenarians; life expectancy; longevity
lifespans of animals: long-lived, 52, 52–57; nucleolar size and, 86, 133, 141, 185; protein and amino acid restrictions and, 113, 115; as sexually dimorphic trait, 214–16; with shorter lifespans, 19, 21; size dependence of, 54–55, 92–93; as somatic quality maintenance, 33; species with broad range of, 52. *See also* lifespan of humans; longevity; post-reproductive lifespan
lifestyle factors: of centenarians and super-centenarians, 40; lifespan of humans and, 9, 12–13, 41, 46, 49; of longest-lived cultures and populations, 40–41
linkage disequilibrium, 44
lipofuscin, 78
lipoprotein(a) (LPA), 45
lipoproteins: age-related diseases and, 48; high density (HDL), 44, 45, 47, 59; vitellogenin, 21, 229–30
liraglutide, 278
Lithgow, Gordon, 23–24
Liu, Daniel, 132
Liu, David, 178, 336
Logan's Run (film), 28
longevity: genetic component to, 42–50; late-life childbearing and, 194–96; maximum velocity as predictor of, 83–85; mitochondrial regulation of, 171; quality control mechanisms and, 151; regulated for reproductive timing, 212–13; wealth and, 76. *See also* lifespan of humans; lifespans of animals
longevity mutants of *C. elegans*, 14, 62–63, 80–82, 87–88; cognitive aging and, 274–76; gene expression changes in, 99–100; ribosomal proteins reduced in, 132. *See also* *age-1* mutants; *daf-2* mutants
longevity quotient (LQ), 52, 55–56; proteostasis and, 140, 146
long interspersed element-1 or LINE-1 (L1), 187, 291

- Long Life Family Study (LLFS), 72–73, 74, 195
- long-lived animals, 52, 52–57; proteostasis in, 139–40, 146; SOD and catalase in, 156
- long-lived people: mostly women, 215–16; reproducing later in life, 194, 208–9; staying healthier longer, 73–74. *See also* centenarians; supercentenarians
- Longo, Valter, 116–17, 317–18
- long-term memory, 258–61; in *C. elegans*, 258–60, 274; differences from short-term memory, 261; evolution of prions for, 292; fecal transplants from young mice and, 314; integrated stress response and, 276. *See also* CREB transcription factor; memory
- Luo, Shijing, 205
- lymphatic system, cleaning brain, 256, 262
- Lysenko, Trofim, 288
- lysosomes, 69, 147, 148, 166, 168, 322
- MacLeod, Colin, 287, 300
- mad cow disease, 142–43, 292
- male animals, in sexual conflict, 223
- male *C. elegans*, 205, 206, 220; damaged by mating, 228–30; dietary restriction and, 221; killing females by mating, 224–27; lifespan of, 220–22, 229; memory assays for, 258n; pheromones of, 226–27, 228–29
- male hormones, and lifespan, 24–25, 202
- Maliha, George, 30, 210–11
- mammals: aging of memory ability in, 260–61; blood-brain barrier in, 256; bowhead whales as longest-lived, 54; FGF21 in response to fasting of, 131; IGF-1 declining with age in, 275; lifespan-regulating genes in, 64; mitokines in, 161–62, 163; oocyte quality in, 205–6; pheromones in, 233–34; post-reproductive lifespan in, 210; sirtuins in, 126–27; transgenerational inheritance reported in, 285–86; ubiquitin-proteasome system in, 145. *See also* mice; primates, nonhuman
- Mango, Susan, 128
- Mansuy, Isabelle, 285, 287
- marmosets, 66
- marriage, and lifespan, 216
- marsupials, 55, 58, 140
- Martin, George, 156
- mate choice, 231–33
- maternal mortality, 9–10, 31
- mating in *C. elegans*: different *Caenorhabditis* species and, 230–31; evolution of longevity pathways and, 227; males' focus on, 220; progeny production in, 205; shortening male lifespan, 228–30; shrinking and death of hermaphrodites caused by, 225–27. *See also* seminal fluid
- mating in *Drosophila*, 223–24
- matricide in *C. elegans*, 91, 207, 210, 211, 232
- Mattison, Julie, 111
- maximum human lifespan, 11, 14, 34, 38–39
- maximum velocity, predicting lifespan, 83–85
- Mazmanian, Sarkis, 315–16
- McCarroll, Steven, 100, 130
- McCarty, Maclyn, 287, 300
- McCay, Clive, 59–60, 109, 188–89
- McClintock, Barbara, 288–89, 290
- McCurry, Steve, 75
- Medawar, Peter, 19, 209
- Mediterranean diet, 41, 317, 318
- Mello, Craig, 2, 64, 298, 301
- memantine, 269
- memory: in *C. elegans*, 81, 85, 120–21, 171, 254, 254, 258–60, 268, 274–75; dietary restriction and, 113, 120–21, 133; fecal transplants from aged mice and, 312; identity and, 250–51; plasma factors and, 190–91, 261–62; prions and, 143; traumatic brain injury and, 323; Yamanaka factors in mice and, 183. *See also* long-term memory; short-term memory
- menopausal hormone therapy, 199–200, 201, 294–95. *See also* estrogen

- menopause, 194, 198–200; aging of non-reproductive tissues and, 199–200, 201–2; DNA methylation and, 294–95; postmenopausal health problems and, 215
- messenger RNA (mRNA): central dogma and, 174–75; maintaining quality of, 148–51; memory and, 259; RNA interference and, 2–3; transcription factors and, 45. *See also* gene expression
- metabolic disease, 45, 48, 49
- metabolism: cognitive aging and, 277–78; facial aging and, 75; mitochondria and, 163; nutrient levels and, 33–34; rate-of-living theory and, 19; of warm-blooded animals, 35
- metal toxicity, and *daf-2* worms, 97
- Metchnikoff, Elie, 18–19, 304, 315, 317, 318
- metformin: adverse effects of, 344; as AMPK activator, 278, 323; bacterial folate metabolism and, 306; biosimilars of, 324; cognitive benefit in diabetic patients and, 278; increasing autophagy in model systems, 148; microbiome and, 306, 310; mitochondrial activity and, 170–71; repurposing of, 337; TAME clinical trial of, 278, 323, 337, 339, 343–44
- methionine, and dietary restriction, 113, 115
- MHC genes, 48, 233
- mice: dietary restriction in, 109, 110, 112, 115, 135, 203; DNA methylation clock for, 294; fasting-mimicking diet in, 117; insulin/IGF-1 signaling pathway in, 92–93; intergenerational immune response in, 301; lifespan-regulating genes in, 64; longevity compared to bats, 29, 55–56; male bias in research on, 217–19; metrics of aging in, 86; as model system, 52, 59, 60, 61; oocyte quality in, 205–6; ovarian transplants extending lifespan of, 201; reproductive aging in, 203; reprogramming brain cells in, 255; rescuing aging memory in, 261, 275; testing candidate drugs in, 337; testing learning and memory in, 258; transgenerational inheritance reported in, 285–86
- microarrays, 3; caloric restriction and, 129–30; on *daf-2* longevity mutant, 22, 93–97, 102; of *dod* genes, 99; late child-bearing and, 208; methylation events and, 199; in SNP studies, 43
- microbiomes: aging of, 308–9, 311–14; antibiotics and, 304–5; bacterial composition of, 307; beneficial effects of, 307–8, 309–11; in *C. elegans* gut, 305, 306, 307; dietary approaches to health of, 316–18; of eusocial insects, 307, 309; factors affecting, 308; in fly intestines, 307; in killifish, 70; Metchnikoff's early ideas on, 18, 303; number of bacteria in, 303; oral, 315; possible healthy mechanisms in, 309–11; sequencing of bacteria and host cells in, 305, 307; untangling cause and effect in, 305, 308, 310, 311, 315
- microbiota-gut-brain axis, 314–16
- microglia: Alzheimer's disease and, 265; APOE and, 268; fecal transplants from aged mice and, 312; neuroinflammation and, 261; Parkinson's disease and, 316
- microRNAs (miRNAs), 150, 151, 187, 242–43, 297
- microtubules, and tau protein, 142, 265–66
- mild cognitive impairment, 262, 272, 335
- Miller, Richard, 218–19, 221
- Mitchell, Kevin, 285, 287
- mitochondria: asymmetric inheritance of, 165; ATP generated by, 154–55, 277; autophagy of, 166–67; biogenesis of, 166, 171; biotech companies working with, 322; dietary restriction in *C. elegans* and, 131; DNA repair disorders and, 177; functions of, 153; fusion and fission of, 166, 167; in germline of *C. elegans*, 167–68; hormetic stress response and, 24, 159; morphological changes in, 166, 167–68; neuronal, 145, 159, 161, 253;

- mitochondria (*continued*)
oocyte quality and, 204, 205; originating in engulfed prokaryote, 154, 160; quality control of, 164–68; RNA quality control and, 149; stress signal from, 160–62; TOMM40 protein in, 44; uncoupled from longevity extension, 157–58, 159; unfolded protein response in, 123, 145, 159–61
- mitochondrial-derived peptides, 162–63, 340
- mitochondrial diseases, 322
- mitochondrial DNA (mtDNA), 155, 162; coordination with nuclear DNA, 164–65; levels of knockdown in, 163–64; lifespan and, 219; MOTS-c encoded by, 340; replication of, 165; toleration of damage to, 166
- mitochondrial mutations, 155; in *C. elegans*, 64, 80, 81, 82, 275
- mitochondrial replacement therapy, 204, 322
- mitochondrial uncouplers, 35
- mitohormesis, 163–64, 169, 171
- mitokines, 161–62, 163
- mitophagy, 166–67, 168
- mitophagy boosters, 322, 327
- model systems, 4, 5, 50, 51–52, 52, 70; *C. elegans* as, 52, 60–61, 62–65, 87, 90; cognitive decline in, 257–61; *Drosophila* as, 52, 60–62; extremely long-lived, 65–66; extremely short-lived, 66–69; killifish as, 69–70; measuring learning and memory in, 257–58; proposed possibilities for, 58; quality of life and, 71; yeast as, 52, 66–69
- Mondoux, Michelle, 221
- Monod, Jacques, 51
- Moore, Rebecca, 299–300
- Mor, Danielle, 170
- Morgan, Thomas Hunt, 61, 287, 288, 289
- mortality: age in naked mole rats and, 56; decreasing by age 105, 11, 39; early menopause and, 199; extrinsic rate of, 32 (*see also* predation); in infancy and childhood, 7–8, 10, 273; maternal, 9–10, 31; of nutrient-restricted *Drosophila*, 112; in utero starvation and, 281
- motility: of aging *Drosophila*, 85; of *C. elegans*, 82–85
- MOTS-c, 162–63, 340
- mTOR inhibitors, 323
- mTOR pathway, 127–28, 185, 220, 227, 245. *See also* TOR (target of rapamycin)
- muscle. *See* skeletal muscle
- muscular dystrophies: activator of PPAR- δ for, 172; transposable elements in, 291
- mutation accumulation theory, 19
- mutation fixation, and post-reproductive lifespan, 31
- mutations, 175. *See also* mitochondrial mutations
- NAD⁺, 124, 330–31; anti-aging supplements based on, 171, 342; disorders of DNA repair and, 177; histone acetylation and, 283
- NAD⁺-dependent protein deacetylases, 124
- NAD⁺/NADH energy metabolism, 67–68, 123, 331
- naked mole rats, 23, 56–57, 140, 157
- Nam, Hong-Gil, 82–85
- Native Americans: Covid-19 and, 8; preventing pellagra, 331, 331n; trauma suffered by, 281–82
- Navajas Acedo, Joaquin, 145
- NDGA (nordihydroguaiaretic acid), 218, 337
- Neill-Dingwall syndrome, 177
- neural stem cells, 182, 190–91, 254–55, 261
- neurodegeneration: behavioral map approach to, 86; biotech drug candidate for, 340; retrotransposon activation and, 291–92
- neurodegenerative diseases, 263; AGEs and, 144; biotech companies working on, 322; blood-borne factors and, 192;

- cellular damage and, 174; *Drosophila* models of, 86; gut dysfunction preceding, 315–16; in GWAS studies, 48, 49; microbiota-gut-brain axis and, 314–16; mitochondrial function and, 155, 166–67; prion-like mechanisms and, 292; protein aggregation in, 141–43, 263; stem cells in therapy for, 182, 255; transposable element activity in, 266–67. *See also specific diseases*
- neurofibrillary tangles (NFTs), 142, 263–64, 266; drugs targeting, 271; prion-like protein aggregation in, 292; transposable element activation and, 267
- neurogenesis: in adult hippocampus, 255; fecal transplants from aged mice and, 312–13, 314; transcription in mouse brain and, 295
- neuronal aging, 252–55; reprogramming in mice and, 255; stem cell replacement in, 254–55; vasculature in, 255–57. *See also cognitive aging*
- neuronal signaling pathways, 242–43
- neurons: APOE and, 268; ciliated, 238; dauer decision and, 239–42; mitochondrial stress in, 145, 159, 161, 253; retrotransposon activation and, 291–92; for sensing temperature, 244–45; for smelling food, 237–38; thermosensory, 244–45; transgenerational inheritance in *C. elegans* and, 300–301
- niacin, 331
- nicotinamide, 330
- nicotinamide adenine dinucleotide. *See* NAD₊
- nicotinamide mononucleotide (NMN), 331
- nicotinamide riboside (NR), 171, 329, 331, 342
- nicotine, 46
- nicotinic acetylcholine receptors, 121; Alzheimer's medicines and, 269; CHRNA3/5, 44, 46, 54; CHRNA10, 54
- nictation, 239
- Nigon, Victor, 62
- NIH-funded research, 196, 218, 262, 265, 337, 345
- Nishida, Eisuke, 221
- nonautonomous signaling: by blood factors, 261; by inflammation, 261; of mitochondrial stress, 163; neuronal, 247; regulating lifespan, 238, 242
- noncoding RNAs, 290, 297–98
- nonsense-mediated decay, 148–49
- Norris, Arthur, 72
- nuclear pore complex proteins, 140
- nucleolar size, 86, 132–33, 133n, 141, 171, 185, 253
- nucleosomes, 174, 295–96
- nutraceuticals, 342, 346
- nutrient availability, and reproduction, 32–33, 105–6, 109, 203
- nutrient levels: aging rates and, 19; metabolic rates and, 33–34; regulation of longevity and, 212–13
- nutrient sensing: epigenetic mechanisms and, 283; by NAD₊, 283; neuronal, 131; regulation of longevity and, 134; reproduction as output of, 194
- obesity: AMPK in mouse models of, 327; as biotech target, 340; fecal transplants in mice and, 311; lipid dysregulation and, 45; mice protected from, 162, 163; tripled in US since 1950s, 114; in utero starvation and, 280
- octopuses, 29
- odor fear, transgenerational inheritance of, 283, 287
- ODR-10 food-sensing receptor, 84, 220
- Okawa, Misao, 39
- olfactory cues to choose mates, 233. *See also* pheromones
- olfactory neurons, 244
- oligoanalysis, 101
- Olins, Don and Ada, 295–96
- Olshansky, Jay, 12
- oocyte proteins, rejuvenated in *C. elegans*, 16, 68, 125, 144, 146

- oocyte quality, 197, 198, 202–8; cathepsin B levels and, 207–8; of exploding *sma-2* mutants, 211–12
- opioid epidemic, 9
- oral microbiome, in dementia patients, 315
- organ regeneration and replacement, 321, 334, 337
- osteoarthritis, 333, 338, 340
- oxidative stress, 17, 21–24; adverse effects of antioxidants and, 164; lifespan increased by low levels of, 164; therapies to reduce, 321. *See also* reactive oxygen species (ROS)
- oxygen sensing, 245–46
- oxytocin, 190, 221, 283
- pain sensation, in mice, 245
- Palin, Sarah, 4
- Panda, Satchin, 117
- parabiosis, 188–91, 295, 334
- parental age: in *C. elegans*, 87. *See also* childbearing
- Parkinson's disease: behavioral map approach to, 86; dementia in, 263, 268; gastrointestinal problems in, 315–16; gene therapy for, 336; induced pluripotent stem cells and, 182; low BCAA signaling and, 120; microbiota-gut-brain axis and, 314–16; mitochondrial damage and, 166; mitochondrial function and, 155, 170–71; mitophagy boosters for, 322; model systems and, 65; protein aggregation in, 141–42, 263
- Parrish, Elizabeth, 335
- Partridge, Linda, 61, 64, 85, 92, 111–12, 130, 223–24
- Patapoutian, Ardem, 245
- Pauling, Linus, 21, 23, 156
- Pavlov, Ivan, 286–87
- Pavlovian associations, 257–58, 274
- Paxlovid, 267
- PCR (polymerase chain reaction), 179
- Pearl, Raymond, 19, 156
- Pearson's syndrome, 322
- pellagra, 124, 331
- Perls, Tom, 194–96, 213
- personalized medicine, 182
- Pes, Giovanni, 40
- Peter, William, 72
- PGE₂, 277
- PHA-4, 128–30, 133
- pheromones, 214, 232–34; of humans, 233–34; of insects, 232–33; of mammals, 233–34; species specificity of, 236
- pheromones of *C. elegans*: female, 227; hermaphrodite's sperm content and, 232; male, 226–27, 228–29, 230–31; of masculinized hermaphrodites, 228n, 229
- PI3 kinase, 63, 80, 90; inhibitor of, 93, 326
- Pincus, Zachary, 133n
- piRNAs, 290, 300, 301
- placenta, evolution of, 291
- placental cell harvesting, 334
- planaria, 18, 58, 178, 223
- plasma factors, 189–90, 261–62; suspect companies selling, 332n; systemic therapies and, 332–33. *See also* blood-borne factors
- plasticity: epigenetic mechanisms and, 279–80; in order to reproduce, 33
- Pletcher, Scott, 109, 113, 130, 227, 243, 244
- pluripotent stem cells, 181; induced (iPSCs), 182, 255, 294, 334, 337
- Portman, Douglas, 84, 220
- Posner, Rachel, 283–84
- post-reproductive lifespan, 30–31, 33, 209–13, 210, 216
- post-traumatic stress disorder (PTSD), 258, 282, 284
- Poulain, Michel, 40
- PPAR β/δ , 327
- PPAR- γ , 166, 216, 326–27
- PPAR- δ , 172
- PQM-1, 102–3, 104, 105, 227, 228, 229n, 246
- prebiotics, 316–17
- predation, 29–30, 32, 53, 55, 56

- pregnancy: psychological stress during, 282–83. *See also* childbearing; maternal mortality
- premature aging phenotypes: mitochondrial mutation in *C. elegans* and, 156; mutations of mtDNA in mice and, 155. *See also* progerias
- presenilin, 267
- primates, nonhuman: caloric restriction in, 65–66, 111, 149–50; sex differences in longevity, 217
- prion diseases, 142–43, 292
- probiotics, 18, 303–4, 310
- progerias, 177–78; CRISPR applied to, 192, 336; DNA methylation in, 294; fecal microbial transplants and, 313; microbiome and, 305, 308, 313, 316
- programmed aging, 18, 304; regulated, 32
- programmed death, of Pacific salmon, 27–28
- Prolla, Tomas, 130
- Promislow, Dan, 344
- prostaglandin signals, 201
- protandim, 337
- proteasome, 144–45
- protein aggregation: age-related, 20; biotech companies working on, 322; combatted by chaperones, 141; microbiota-gut-brain axis and, 315–16; in neurodegenerative diseases, 138, 141–43; prion-associated, 292; therapies to reduce, 321, 322
- protein folding, 141. *See also* unfolded protein response (UPR)
- proteins: central dogma and, 174–75; dietary, 113, 115; oxidative damage to, 17; rejuvenation of, 16, 67–68, 124–25, 144
- proteostasis, 138–41; age-related diseases and, 48; in *C. elegans* intestine, 150; companies aiming to improve, 322; in *daf-2* mutant of *C. elegans*, 97, 103; in dietary restriction, 133; failing with age, 145–46; mechanisms of, 139
- Pseudomonas* in *C. elegans* diet: learning and, 299–302; in the wild, 306
- pterostilbene, 171, 342
- public health efforts, 7–8, 9
- p-value, 43, 48, 49
- quality of life, 8, 14, 41, 71, 81
- quasi-program of aging, 20–21
- racial disparities in dementia onset, 272–74
- RAGE, 75, 144
- Rando, Tom, 189, 190
- rapamycin (sirolimus), 127–28; as AMPK activator, 323; biosimilars of, 324; increasing autophagy in model systems, 148; microbiome and, 310; preventing stem cell growth, 185; repurposing of, 337; trial in aging dogs, 344; trial searching for optimal regimen, 324, 325. *See also* TOR (target of rapamycin)
- rate-of-living theory, 19, 156–57
- rats: male bias in research on, 218; nutrient-deprived, 60, 109; urolithin A in, 327
- Rea, Shane, 163
- reactive oxygen species (ROS), 21–24; cellular damage and, 138; DNA damage caused by, 176, 177; mild mitochondrial stress and, 164; mitochondrial production of, 155–57, 158, 161, 170–71; naked mole rats and, 56; Parkinson's disease and, 170–71; in SASP response, 187. *See also* free radical theory of aging; superoxide dismutase (SOD)
- Rechavi, Oded, 284
- regeneration: of aging heart muscle, 190; blood-borne factors affecting, 190; in normal human tissues, 181; parabiosis and, 189; treatments based on, 321, 336–37. *See also* stem cells
- repair of cells: energy for, 16–17; oxidative damage and, 23. *See also* DNA repair
- replacement of cells: as goal of research, 16; in immortal organisms, 18; in juvenile organisms, 17
- replicative lifespan (RLS), in yeast, 67–69, 123–24, 125, 128
- replicative senescence, 183–84

- reproduction: by animals with shorter life-spans, 19, 21; dauer decision and, 241; disposable soma theory and, 24–27, 26; longevity regulation and, 15, 26–27, 194, 212–13; mitochondria and, 168; mutations accumulating after, 19; nutrient availability and, 32–33, 105–6, 109, 203; predation and, 29–30; quasi-program theory and, 21; as the selected trait, 33; vitellogenins accumulating after, 21
- reproductive aging: fitness and, 203, 213; longevity and, 194–96; in men, 194; menopause and, 194, 198–200; oocyte quality and, 197, 198, 202–8; women's biological clock and, 193–94
- reproductive span, 206–12, 210; extrinsic mortality factors and, 29–30; polygamy and, 216
- restricted tolerance, 34–35
- resveratrol, 67, 123, 126–27, 322, 328–30, 331–32; pterostilbene similar to, 171, 342
- retinal cells, and Yamanaka factors, 255, 336. *See also* eye diseases
- retrotransposons, 267, 291–92; learning in *C. elegans* and, 301
- rhesus macques, caloric restriction in, 65–66, 111, 149–50
- ribosomal components: downregulated in dietary restriction, 133; downregulated in proteostasis, 140. *See also* nucleolar size
- Riddle, Don, 89, 220–21
- Riera, Celine, 245
- Ristow, Michael, 24
- rivastigmine, 269
- RNA: homeostasis of, 148–51; microRNAs (miRNAs), 150, 151, 187, 242–43, 297; noncoding, 290, 297–98; piRNAs, 290, 300, 301. *See also* small RNAs
- RNA editing, 150
- RNA interference (RNAi): evolved as silencing mechanism, 290; library of, 64, 98, 122n, 135, 157; modified by RNA editing, 150; testing antagonistic pleiotropy theory, 20; in testing genes for longevity, 98, 99, 140; transgenerational learning in *C. elegans* and, 300; worm genetics and, 2–3, 64–65
- RNA sequencing, single-cell, 295
- RNA splicing, 149–50; DNA methylation and, 293; in naked mole rats, 57
- Ro, Jenny, 244
- Rose, Michael, 61, 92
- Rosi, Susanna, 276
- r selection, 28
- Rush Religious Orders study, 72
- Ruvkun, Gary, 20, 63, 89–90, 101, 128, 157
- salmon, 27–28, 55, 58
- sarcopenia, 78, 130, 153, 155, 171. *See also* skeletal muscle
- schizophrenia, 46, 280
- sea urchins, 31, 211
- Sebastiani, Paola, 74, 150
- Sedivy, John, 291
- selective pressure: cellular senescence and, 186; on developmental and reproductive rates, 32; on post-reproductive lifespan, 31, 209; on reproductive lifespan, 29–30; for women's longer lifespan, 30. *See also* evolution
- Seluanov, Andrei, 57
- semelparous species, 27–28, 58
- seminal fluid: components in *C. elegans*, 236; peptides in, 214, 224, 236; regulating hermaphrodite's lifespan, 226, 228. *See also* mating in *C. elegans*
- senescence-associated secretory phenotype (SASP), 47, 56–57, 186–88, 333
- senescent cells, 186–88; drugs targeting, 187–88, 192, 321, 333, 340; failing neurons as, 253; inflammation and, 47; short telomeres and, 334; sleep loss and, 256; transposable elements activated in, 291
- senolytics, 187–88, 333, 340

- senomorphic drugs, 333
- sensory regulation of longevity, 237;
dauer decision and, 239–42; neuronal
coordination of systemic response and,
247; neurons sensing food sources and,
237–38, 241, 243; still unknown in
humans, 249
- sequencing, whole-genome (WGS), 3,
43, 52
- serotonin signaling, 242, 244, 246, 247,
248
- sex, biological definition of, 214n
- sex differences in aging, 214–16; biological
bases of, 217–22; in *C. elegans*, 220–22;
marriage and, 216–17; sons or daughters
and, 217
- sex peptide, 224, 236
- sexual behavior: human lifespan and, 234–35,
235. *See also* mating in *C. elegans*
- sexual conflict, 214; in *C. elegans*, 224–27;
in *Drosophila*, 223–24
- Shaevitz, Josh, 85–86
- Shanahan, Nicole, 197
- Shelley, Mary, 173
- Shi, Cheng, 221, 224–28, 234–35, 235
- Shock, Nathan, 72
- short-chain fatty acids (SCFAs), 310, 315,
316–17. *See also* butyrate
- Short Physical Performance Battery
(SPPB), 74, 82
- short-term memory: in *C. elegans*, 258–59,
274; differences from long-term mem-
ory, 261; first to go in humans, 260; lira-
glutide for diabetic patients and, 278.
See also memory
- Sinclair, David, 67, 126, 127, 328–30
- single genes affecting lifespan, 19–20, 20n,
32; insulin/IGF-1 signaling pathway and,
63, 93
- single nucleotide polymorphisms (SNPs),
36, 42–45, 42n, 175, 176
- Sir2, 123–27; in *C. elegans*, 125–27, 330;
in yeast, 68, 123–25, 144, 328, 329,
331
- SIRT1, 326, 329
- Sirt6, 218–19
- sirtuins, 124, 126, 328–29, 331–32
- skeletal muscle: as biotech target, 340–41;
caloric restriction and, 130; declining
performance with age, 153–54; mito-
chondria in *C. elegans* and, 166, 167, 168;
mitochondrial-derived peptide and,
162–63; mitochondrial dysfunction in
invertebrates and, 161; mitochondrial
dysfunction in mice and, 162; repaired
by heterochronic parabiosis, 189. *See also*
sarcopenia
- Slagboom, Eline, 171
- sleep: functions of, 256–57, 262; telomere
length and, 334
- sleep loss, brain effects of, 256–57
- small RNAs: in neurons, and chemotaxis,
284; personalized therapy based on, 336;
in transgenerational inheritance, 297–98,
300–301, 302. *See also* RNA
- smell, sense of: in *C. elegans*, 237–38, 241,
243; in *Drosophila*, 243–44; in humans,
249; in mice, 244
- smoking, 46, 75
- social castes. *See* eusocial animals
- Social Security, 12
- socioeconomic factors: epigenetic aging
and, 294; inequality and, 8, 9, 10; in life-
span, 49, 76
- Sohrabi, Salman, 170
- SOS response, 158–59, 160
- Soukas, Alex, 128
- Soviet Communism, 284, 288
- spatial memory, 277, 312
- sperm, and epigenetic information, 283
- sperm competition, 224, 226
- spermidine, 311, 321, 338
- sphingosine kinase, 135, 135n, 324
- sports doping, 327
- Spudich, Jim, 1
- Stalin, 288
- starvation hormone, 131–32, 162
- statins, 339

- stem cells: circulating factors affecting, 190;
critical for our health, 18; dividing sym-
metrically or asymmetrically, 165, 181–82;
embryonic, 181, 182; hematopoietic,
183, 185–86; of immortal organisms, 18,
181; induced pluripotent (iPSCs), 182,
255, 294, 334, 337; joint pain treatment
with, 183n; mitochondria in, 165, 171;
modifying humans with, 3, 192; mutations
in, 175; neural, 182, 190–91, 254–55,
261; in normal adults, 181–82; of pla-
naria, 178; prion function and, 143; re-
placing damaged cells, 138; size of, and
proliferative potential, 185; therapies
using, 192, 321, 334; types of, 181. *See also* regeneration
- sterility, and lifespan, 24–26
- steroid hormones: in neuronal signaling,
247. *See also* estrogen; male hormones,
and lifespan
- stress: age-related diseases and, 8; chronic
in childhood, 282; on disadvantaged
populations, 273; facial aging and, 75;
lifespan increased by, 23–24; mitochon-
drial, 145; oxidative damage and, 23–24;
telomere shortening and, 185
- stress resistance: DNA damage in germ
cells and, 184; heat shock proteins and,
79; mitohormesis and, 169; in naked
mole rats, 57; regulation of, 104, 105; in
tardigrades, 58
- stress response: hormesis and, 163–64;
integrated, 276; intermittent fasting
and, 94; longevity pathways utilizing,
164; senses and, 245; in the uterus, 283.
See also unfolded protein response
(UPR)
- Stroustrup, Nick, 80
- Study of Longitudinal Aging in Mice
(SLAM), 86
- sugars: AGEs and, 143–44; cardiovascular
disease and, 114–15; dietary, 143–44
- Suh, Yousin, 48, 93, 268
- Sulston, John E., 62
- supercentenarians, 37–38, 39; exaggerated
instances of, 6, 37; genetic studies of,
47–48; Jeanne Calment as, 11, 38, 40;
mostly women, 215–16. *See also*
centenarians
- superoxide dismutase (SOD), 22, 23, 67,
156
- superoxide radicals, 155
- synapses: of aging neurons, 253; APOE ϵ 4
allele in pathologies of, 268; learning
and, 259; prion form of proteins in,
292; repaired during sleep, 256–57;
short-term memory and, 259; tau and,
266
- synaptic plasticity, 190, 191
- synaptogyrin-3, 266
- α -synuclein, 315–16
- Szostak, Jack, 184
- Taber, Sarah Kendall, 331n
- TAME clinical trial, 278, 323, 337, 339,
343–44
- Tanaka, Kane, 37, 38
- Taq polymerase, 179
- tardigrades, 180
- taste. *See* smell, sense of
- Tatar, Marc, 64, 92, 201
- tauopathies, 265–66
- tau protein, 142, 263–64, 265–66; APOE
 ϵ 4 allele and, 268; drug that targets, 271;
prion-like aggregation of, 292; transpos-
able elements and, 267
- telomerase, 184–85, 186, 334
- telomeres, 183–85; of bats, 55–56; compa-
nies selling information on, 341; later-life
childbearing and, 195–96; mitochondrial
biogenesis and, 165; shortening of, 59,
184–85; SOD expression and, 156; ther-
apies based on, 334–35
- temperature sensation, 244–45
- Tepper, Ron, 102
- TGF-beta pathway: anti-Mullerian hormone
and, 197; dauer and, 91–92, 206, 240;
mitochondria and, 161; in reproductive

- aging, 206–7; reproductive span of Sma/Mab mutants and, 206–7, 211–12; stem-cell maintenance and, 190
- therapies, life-extending: categories of, 321; current excitement about, 319–20; insulin signaling as target for, 93, 326; in a just and sustainable world, 347; mitochondrial distress signals and, 163; mitochondrial mechanisms and, 169; stem cells and, 192, 321, 334; systemic factors and, 332–33; telomeres and, 334–35; testing, developing, and selling, 338–41. *See also* drugs, life-extending
- Thomas, Jim, 89
- Tibshirani, Rob, 93
- Tilly, Jonathan, 203
- time-restricted eating (TRE), 116, 117–18, 136, 323
- Tissenbaum, Heidi, 81, 82, 84, 169
- tissue culture, 59, 61
- TOMM40*, 44, 47, 48, 49
- TOR (target of rapamycin), 54, 67–68; amino acid restriction and, 115, 134; dietary restriction and, 127–29, 130–31, 133, 134, 140; in neuronal signaling, 242. *See also* mTOR pathway
- tortoises, 53–54
- transcriptional clocks, 295
- transcription factors, 45. *See also* DAF-16; FOXO; PHA-4
- transdifferentiation, 18
- transfusions: of blood, 188; of plasma from young to old animal, 189–90
- transgenerational inheritance, 282–84; epigenetic (TEI), 296–98, 302; flaws in reports of mammals, 285–86; historical trauma and, 281–82, 285
- transgenerational learning in *C. elegans*, 301
- translation inhibition: in dietary restriction, 133, 140; in proteostasis, 140
- transposable elements (TEs): in aging cells, 266–67, 291; as epigenetic mechanism, 290–92; McClintock's discovery of, 288–89, 290; silenced by methylation, 293
- transposon theory of aging, 266–67
- trauma: epigenetic mechanisms and, 283, 302; historical, 281–82, 285, 289; inter- and transgenerational, 281–82
- traumatic brain injury, 323
- trees: cell replacement in, 18; as longest-lived organisms, 53
- Troyanskaya, Olga, 169–70
- Trump's vote, and poor health, 8
- ubiquitin-proteasome system, 144–45; ER stress and, 242–43; mitochondrial proteins and, 165
- umbilical cord plasma, and brain function, 191
- unfolded protein, 141
- unfolded protein response (UPR), 123, 145, 146, 159–61, 163, 164, 168; ER stress and, 243; fecal transplants from aged mice and, 312
- uroolithin A, 148, 311, 327
- UV-induced DNA damage, 158–59, 176, 177; survived by some extremophiles, 179–80
- vaccination: against childhood diseases, 8; against Covid-19, 7n, 13, 175; public health efforts for, 9
- vagus nerve, 314–15
- Valenzano, Dario, 70, 313–14
- van Andel-Schipper, Hendrikje, 183
- van Raamsdonk, Jeremy, 22
- vascular cognitive impairment, 268
- vascular dementia, 256; cholinesterase inhibitors for, 269
- vasculature: A-beta plaque accumulations on, 268; APOE and, 272; declining IGF-1 in aging mammals and, 275; in long Covid, 256; in neuronal aging, 255–57
- Vaupel, James, 11, 39
- Vijg, Jan, 11, 38
- Vilchez, David, 201
- Villeda, Saul, 190–91, 261–62, 333

- vision in *Drosophila*, 248
Vitamin C, 21, 23, 156, 164, 322
Vitamin E, 23, 164, 321–22
vitellogenins, 21, 229–30
vomeronasal organ, 233–34
- Wagers, Amy, 189, 190
Walford, Roy, 120, 323
Walker, David, 85
Walter, Peter, 276, 323
warm-blooded animals, 35
Weindruch, Richard, 111
Weismann, August, 18, 286, 294, 300
Weismann barrier, 286, 301
Weiss, Ethan, 117–18
Weissman, Irv, 189
Werner's progeria, 177, 294
Westphal, Christoph, 328
whole-genome sequencing (WGS), 3, 43, 52
Williams, George, 19–20, 32, 63
Williams, Serena, 10
Witkin, Evelyn, 158–59
Wolfner, Marianna, 92, 223–24
women's health, unequal research on, 196
worms. See *Caenorhabditis elegans*
Wyss-Coray, Tony, 190–91, 261, 262, 295
- X chromosome: dietary restriction in
C. elegans and, 221; extra in women, 219;
in male *C. elegans*, 220; methylation of
extra X, 293; XX animals and, 261
xeroderma pigmentosum, 177
Xu, Shawn, 245, 248–49
- Yamanaka, Shinya, 182
Yamanaka factors, 182–83, 255, 336
Yao, Vicky, 169–70
yeast: asymmetric inheritance in, 68, 144,
147, 165; caloric restriction in, 67, 109,
123; cell size and budding of, 185; in
Drosophila diet, 247; longevity regula-
tion in, 125, 128; measuring lifespan in,
68–69, 123–24; microarray experiments
with, 94; as model system, 52, 66–69; new
techniques for replicative aging studies
in, 125; prion functions in, 292; resvera-
trol extending lifespan in, 126, 330; Sir2
in, 68, 123–25, 144, 328, 329, 331; sort-
ing mitochondria when dividing, 165
Yellow Horse Brave Heart, Maria, 281–82
- Zak, Nikolai, 38
Zhang, Yun, 299