Preface

The sun rises and sets, seasons change, leaves fall to the ground, the Earth revolves around the Sun, the North Star always points north, and creatures like humans, dogs, mice, and elephants are born, grow up, grow old, and eventually die. The laws of nature that drive the biological functioning of our bodies operate with regularity, like clocks ticking in the background or the beat of our heart beneath our chest.

— *A Measured Breath of Life*
Olshansky and Carnes (2013)

THE QUESTION OF HOW LONG HUMANS CAN live and whether humanity can influence the processes that contribute to the duration and quality of our lives is a foundational question in science. This is not a new inquiry. When Michelangelo painted the *Creation of Adam* on the ceiling of the Sistine Chapel in Rome in the sixteenth century, he portrayed humanity as having been molded by the hand of its creator, in his image, as a "perfect" physical specimen—with alleged 900+ year life spans according to the Old Testament. Biblical scholars suggest that a fall from this idealized notion of "perfection" is the reason the life spans of humans have grown shorter. By contrast, Darwin's theory of evolution in the late nineteenth century emphasized the opposite message by focusing on the imperfections in the anatomic structures and functions of humans and other living things as the strongest evidence for his theory. Alfred Russell Wallace, in the time of Darwin, suggested that aging and death are programmed as a way to remove the old to make way for the young.

As familiar as Michelangelo and Darwin may be to us today, speculation about human longevity and health dates back millennia. Aristotle speculated that aging is caused by the loss of an innate moisture in the body, and that the loss of functioning was nature's ingenious way of preparing us for death—as if aging was an organized and purposeful phenomenon. Galen from the second century AD and Avicenna from the eleventh century AD both believed that aging was an inevitable and natural part of the order of the universe, which led them to believe that the daily pursuit of a healthy life was a far more productive way of living rather than engaging in a constant battle against death. Fatalists dominated early thinking about why we live as long as we do.

Others were not so fatalistic. The Chinese philosopher Ko Hung advocated for the use of Taoist methods of extending life through controlling one's breath—with immortality as the ultimate goal. Roger Bacon from the thirteenth century and Luigi Cornaro from the fifteenth century believed that life-prolonging chemicals, foods, other substances, and even caloric restriction would enable humanity to achieve much longer life spans. Perhaps most relevant to today was the view from French zoologist Georges Buffon, who suggested that "physical laws" regulate the duration of life in humans and other species. These laws, according to Buffon, link the biological clocks that govern growth and development to similar clocks that he thought influenced duration of life. Buffon argued that the duration of life of species is calibrated, as a ratio, to the timing and length of each species' reproductive window—as if a biological clock is ticking for one set of events early in the life course, but which has an inadvertent influence on the timing of death and the diseases that precede it. This should sound familiar to evolutionary biologists familiar with twentieth century concepts of antagonistic pleiotropy, mutation accumulation, and disposable soma and to demographers familiar with the "law of mortality" first discussed by British actuary Benjamin Gompertz in 1825.

It appears that most of these historical figures who considered life span determination were each right in their own way. The artistic-like perfection of the human body is exemplified by the near

flawless maintenance and repair mechanisms of our nuclear DNA, and the perpetuation of the immortal germ line through sexual reproduction. Public health and modern medicine have made it possible for most people born today to survive to older ages, allowing humanity to experience the aging of our bodies for the first time with great regularity. However, our extended lives came with a Faustian bargain.

Our bodies are a complex web of pulleys, pumps, levers, and hinges, woven together by a living, breathing, suite of anatomic structures and functions that deliver nutrients to and remove waste products from every cell in the body—every moment of every day in our lives. When our bodies are used beyond what may be thought of as their biological or Darwinian warranty period (e.g., beyond the end of the reproductive window), the diseases and disorders now commonly associated with aging or senescence appear with clock-like regularity—governing the duration of our lives in the absence of genetic programs to make them operate. The variation observed in disease expression and length of life is expected in a world in which inherited and acquired risk factors dominate longevity determination, but, overall, the age pattern of death in humans has stayed remarkably constant since vital statistics were first collected more than 200 years ago.

Humanity achieved its goal of life span extension for most people during the public health revolution of the twentieth century, although disparities remain and are a central focus of public health today. Now we are left to deal with the consequences of our success. Using the poetic words of Sir Peter Medawar, aging is revealed "only by the most unnatural experiment of prolonging an animal's life by sheltering it from the hazards of its ordinary existence." Now that we live these unnaturally long lives and our aging bodies are experiencing more health challenges than we bargained for, what's next?

The approach that our modern world has taken to the gift of long life and its accompanying aging-related diseases is a natural response: attack them with the same sense of purpose adopted more than a century ago when communicable diseases dominated the longevity landscape, one at a time, as they arise. This disease-specific model has been successful, but a new Faustian bargain has presented itself in the modern era—and it is not nearly as appealing as the first bargain we agreed to in the middle of the nineteenth century when declining early age mortality was exchanged for longer lives and aging-related diseases. Success today in attacking the diseases of aging leaves behind a suite of less appealing health challenges that are more resistant to traditional interventions because the biological process of aging—which is uninfluenced by changes in the risk of disease—marches on in the background, unaltered by changes in behavioral risk factors and modern medicine.

People reaching older ages may yearn for "extended warranties" on our body parts that wear with time and use, but modern medicine is not delivering like it used to. Instead, we are receiving a continuous flow of band aids that yield short-term benefits, but which may inadvertently deliver the one thing we fear most—an extension of frailty and disability instead of the health span extension we desire. This is likely to happen if we make ourselves live longer without ensuring that the added survival time is accompanied by good health.

The good news is that human ingenuity has once again presented us with a suite of alternative "fixes" designed to attack the underlying source of the maladies associated with survival to older ages—the biological process of aging itself. The rise of "geroscience," or what was first called the "longevity dividend," is a new public health effort designed specifically to address the Faustian bargain of biological aging emerging as the primary risk factor for disease and death. Geroscience is a paradigm shift in the way in which medicine, science, and public health think about and treat the maladies that are present in aging bodies. Geroscience was a fanciful theoretical idea when first presented a half century ago—it is theoretical no more.

In 2015, the three editors of this volume published the first book ever written on the rise of geroscience, its importance to public health, and the various approaches that scientists were taking at the time to advance this nascent field. Thousands of books and scientific articles have since flooded

the scientific literature. We are now beyond the nascent stage of this new field—trying to figure out what we have created, its potential impact on health and longevity, how to fund the science, which pathways to pursue, how to measure and demonstrate safety and efficacy, what happens if we succeed or fail, and, perhaps most important to many, how to communicate what this all means to people not familiar with the promise of geroscience.

Our first book summarized the logic used to support the rise of geroscience, and some of the initiatives pursued at the time that looked most promising. A lot has happened in the last 8 years. The pursuit of health span over life span has become a meme within the vibrant geroscience community, and advances have occurred along multiple fronts. In this new updated volume, we take you with us on the journey this new field is taking as we navigate our way through the initial stages of a major new movement in public health.

The book begins with a dedication to our third editor—Dr. George Martin—who unfortunately passed away in late 2022 after a very long and distinguished career in aging science. While George will be missed as this field progresses, his presence will endure through the powerful influence he has already had on the entire field and the majority of the scientists now pursuing the goals outlined in this book. This volume is dedicated to Dr. Martin.

In a Foreword written by one of the fathers of the modern geroscience initiative—Dr. Felipe Sierra—the logic and background behind this new movement is presented to those less familiar with the field. The heart of the book is the next section, devoted to many, but certainly not all, of the various pathways that researchers are pursuing to modulate the biological process of aging for the purpose of extending health span.

Driving the development of the latest science in the field is a more thorough understanding of the health and economic consequences if geroscience is successful. There have only been a few papers ever written on this topic, but the importance of understanding what will happen to national economies and personal health care costs, if successful, is at the heart of geroscience's appeal to many.

One of the more interesting stories that has developed regarding the rise of geroscience is how the science is being funded. In today's world where deep pockets abound, influence is sought, and profits associated with the development of perhaps one of the most valuable commodities that can exist (interventions that manufacture healthy life) are clearly visible. You will learn here how geroscience is coming to life in nontraditional ways.

In the final analysis, this book chronicles a fascinating journey into the launch of something that is rarely seen in public health and medicine—an intervention that has global health and economic consequences that can and will influence most people alive today and all future generations. The scientists that wrote the articles in this book are central figures in this movement—but there are many more who are part of the story and working feverishly to bring this movement to life. We would encourage readers to stay updated on developments in this field because of its potential global impact —this volume is an excellent way to catch up on advances that have occurred within just the last 8 years.

James L. Kirkland
S. Jay Olshansky
George M. Martin