Aging
The Longevity Dividend

A subject collection from *Cold Spring Harbor Perspectives in Medicine*

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Front cover artwork: This illustration exemplifies the mechanical nature of the human body; the fact that there is no aging or death clock, which means that aging is inherently modifiable; and the excitement for the future of aging science as many in the field now recognize that a therapeutic intervention to modulate aging may be in sight. (Artwork © 2002 J.W. Stewart, used with permission.)

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Foreword

With the general realization that the population of our planet is rapidly becoming older, economists, population health experts, epidemiologists, policy planners, physicians, scientists, and others have started considering implications of this "silver tsunami" for the society. At the level of physiological functioning and health maintenance in old age, it became apparent that this increase in longevity will be accompanied by multiple comorbidities in a significant proportion of the older population (Goldman et al. 2013). In many countries, particularly in the United States and others where the currently prevalent health-care delivery model is pay-for-service, rather than the more goal-oriented and holistic pay-for-outcome/health approach, this can be equated with a significantly higher future cost to care for an increasingly dependent, disabled, and unhealthy segment of the population. More importantly, in the current U.S. health-care delivery model, the care does not necessarily result in improved health posttreatment. The result is an inefficient and hugely expensive model of care for older adults.

Therefore, developing strategies to maintain optimal health in an increasingly aging population is becoming a global strategic imperative. This book represents the latest concerted and broad effort to shine a light on the potential of biology of aging research to implement what could be a revolutionary change in improving the health span of older adults. It is a culmination of more than 25 years of effort by the editors of this volume (Olshansky et al. 1990, 2007; Butler et al. 2008) to draw broader attention to this issue. Specifically, beginning in 1990, Olshansky and colleagues, many of them coauthors of this volume, started to make a powerful case for why and how research into life-span and health-span extension, as part of the larger field of biology of aging, may have a unique potential to provide broad and far-reaching benefits to the aging human population. The effort, aptly named the Longevity Dividend Initiative, has already made substantial headway in the larger community of researchers and is beginning to extend to policy makers and society overall. This book is part of a groundswell of recent activities (reviewed in the chapter by Sierra and the chapters by Olshansky; also, see Nikolich-Žugich et al. 2015) to help scientists and public advocates of science reach the tipping point and bring about a coherent, conceptually innovative, scientifically based, and publicly as well as industry-supported and sponsored strategy to deal with health issues central to older adults from a revolutionary standpoint.

The argument for the Longevity Dividend is that the payback to society and individuals from extending health span via fundamental interventions based on knowledge of biology of aging will be considerable and broad. This case is made in great detail throughout the volume, but summarized best in the introductory article by Felipe Sierra and the two articles by S. Jay Olshansky. This argument, in its entirety, seems intuitively appealing to the point of being a "no-brainer": The current approaches to treating age-related diseases that produce the highest morbidity and mortality in the older adult population are only incrementally effective at increasing life span and minimally effective in increasing health span, defined as the fraction of life span spent in good health and prosperity. In fact, curing all cancers, for example, although desirable, merely replaces cancer with other chronic morbidities such as Alzheimer's, cardiovascular diseases, metabolic diseases, and so on (Olshanky et al. 1990; Miller 2002). By contrast, in numerous laboratory animal models, including some studies in nonhuman primates and humans, interventions based on manipulations of nutrient sensing and cellular metabolism have shown not only longevity extension but also significant postponement of multiple age-related diseases (including cancer, Alzheimer's, cardiovascular, and metabolic diseases). This, therefore, is close to, or achieves, health-span extension.

The promise of translating these interventions to human subjects, then, starkly contrasts with current, disease-specific research and treatment approach. Simply put, the choice would come down to the two extremes: (1) the current health-care approach, with most individuals enjoying a relatively long life span but reduced health span with multiple comorbidities and increased, ballooning health-care costs; or (2) the biology-of-aging-based health-span extension, which, if successfully translated to humans, would provide increased health span at a fraction of today's health-care cost, with a vigorous and engaged older adult population and even a potentially productive older workforce. One of the key strengths of this book is its further exploration of demographic and economic consequences of biological interventions aimed at modulating the aging process (see the chapters by Goldman and Beltrán-Sánchez et al.). The data provided in these chapters represent further, powerful arguments for biological modulation of the aging process. Other important chapters in the book discuss basic, fundamental physiological levers one could manipulate to modulate aging and increase health span (Part I of the book).

At present, two key issues stand in the way of broad application of health-span extension to humans. First, we are still not at the point of having applications that are distribution-ready. In that regard, the book provides welcome insights into possible translation of robust findings from model organism into clinical practice (see the chapter by Kirkland) and the review of the exciting, burgeoning literature on pharmacological intervention to extend life span and health span (see the chapters by Novelle et al. and Milman and Barzilai).

Second, serious additional roadblocks exist to implementation, including the omnipresent lack of funding for research and, even more so, advanced-stage clinical testing. There also remain ingrained views in society that aging is immutable and/or that intervening in the aging process will produce deleterious and unwanted consequences such as further overpopulation and shortages of resources (reviewed by Miller 2002). Various chapters in this volume go a long way toward debunking many of these myths and making a strong case for the longevity/health span dividend. I applaud the authors on an excellent job of reviewing the known facts and discussing future needs and actions and the editors for their vision to organize and compile an extremely timely set of contributions from the prominent, respected thought leaders in the field.

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Preface

The increase in human longevity during the last century was one of humanity's most remarkable medical and technological accomplishments. As valuable as oil, gold, diamonds, fresh water, and clean air may seem, life itself is likely to be our most precious commodity—and we managed to manufacture more of it during the last 150 years than during all of humanity's existence prior to the 19th century. At first blush it would therefore seem like a rhetorical question whether we should be trying to extend life even further. After all, it is easy to justify almost all facets of modern medicine and public health as desirable. The answer to this question is no longer simple. A growing faction of scientists are concerned that further life extension in long-lived populations may extend the period of frailty and disability later in life as the biological processes of aging emerge as the most important risk factor for what ails us as we grow older. Living longer sounds good at one level, until it becomes clear that for people who already are expected to live long lives, it is health extension we should be pursuing, not life extension.

This is not a new argument. In the late 1970s, Dr. Bernice Neugarten and Dr. Robert Havighurst from the University of Chicago organized a meeting sponsored by the National Science Foundation in which they set out to answer the question on whether governments should be in the business of making people live longer. Neugarten and her coauthors identified two ways in which life extension could be accomplished: through continuing efforts to conquer disease (referred to as "disease control"), and through an effort to identify the intrinsic biological processes that are thought to underlie aging and that proceed independently from disease processes—that is, to discover the genetic and biochemical secrets of aging, then to alter them (referred to as "rate control"). Amid overly optimistic views by some suggesting that dramatic increases in longevity were forthcoming, Dr. Nathan Shock and others made it clear that life extension is not a legitimate goal of aging science, and that instead we should focus on making the years that we have good years.

Until recently, the idea that aging could be modified was little more than wishful thinking, but enough evidence has emerged just within the last decade to justify the pursuit of "rate control" as a new method of attacking diseases. Modern versions of the rate control idea emerged beginning in 2006 under the banner of the Longevity Dividend Initiative, and more recently, this has been called Geroscience. Scientists are now routinely arguing that modifying aging or its consequences represents perhaps the best opportunity to achieve the primary prevention of both fatal and disabling diseases among long-lived populations.

So, how exactly will this be accomplished? What are the various pathways that scientists in the fields of aging are pursuing to bring about this vision of rate control, morbidity compression, disease reduction, and the extension of healthy life? That is what this book is all about. We set out to put into one place a description of most of the major projects now underway or about to be pursued to achieve this end. Although it must be acknowledged that there are enticing approaches to aging science that are not described in the pages of this book, we are confident that many of the most interesting opportunities are described here.

This movement of aging science in the direction of a major public health intervention has gained significant momentum in recent years, and we expect this book will advance the cause and explain both the rationale for doing so and the consequences of failure. The longer lives we enjoy are a wondrous accomplishment to be sure, but we have placed ourselves in a precarious position by allowing aging to rear its ugly head with increasing frequency and duration. We may very well be on the

precipice of a new public health movement—the seeds of which are most likely to be sown by the authors of this book and their colleagues across the globe now working in this exciting field of aging science.

On behalf of the editors I would like to thank Barbara Acosta, Richard Sever, and their colleagues at Cold Spring Harbor Laboratory Press for their excellent work in helping us to organize this book and for their patience in herding together scientists from a broad range of disciplines—all of whom are busy making history.

S. Jay Olshansky