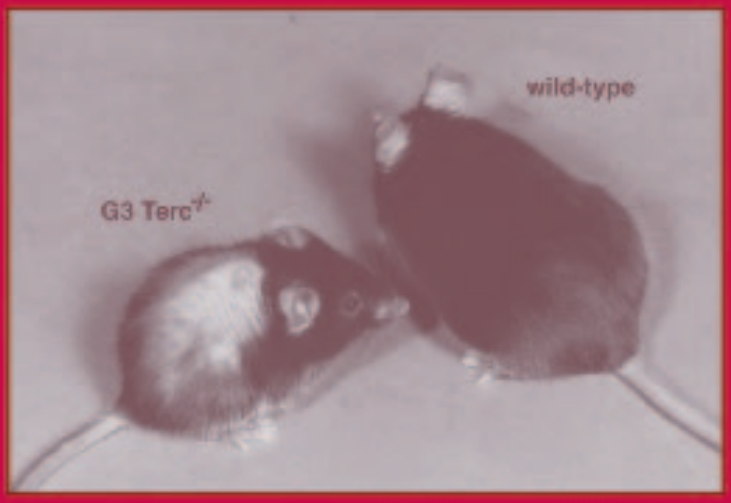
Chromosomal Instability and Aging

Basic Science and Clinical Implications



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To those who have helped me along the way: my parents, Kay and Toshi, my teachers, and my husband, Rusty.

And to Mr. William T. Comfort, Jr., and the John A. Hartford Foundation, whose kindness and interest in this project were a constant source of inspiration.

—FMH

To our many hardworking and imaginative trainees and young colleagues, especially FMH. They will serve as our "cultural germ lines" to carry forward an unbroken lineage of scientific progress.

—SMW and GMM

Foreword

Most of us avoid thinking about the established fact that we are mortal. We know that essentially all organisms, including humans, must ultimately succumb to death, but until we face that immediate reality, we choose to ignore it. Of course, there are the hallmarks of aging that we know so well: graying and loss of hair, wrinkling skin, stiff and painful joints, loss of short-term memory (but often an amazing retention of long-term memory!), cataracts, hearing loss, diabetes, slow wound healing, cardiovascular failure, appearance of tumors, etc.—the list goes on and on. Most if not all of these clinical manifestations are consequences, not causes of aging. Wrinkling skin is caused by many years of sunlight exposure, but wrinkles are not fatal. Nor does gray hair contribute to our ultimate demise.

Are these symptoms of aging programmed through some sort of molecular clock that is set as the embryo develops, or are they the inevitable consequence of the cumulative wear and tear on our genomes, as we face a plethora of environmental chemicals and radiation that damage our DNA? If DNA damage is responsible, then what is the contribution from the reactive oxygen species that are generated in our metabolizing cells and that also cause genomic damage? We don't yet have the definitive answers, but the full armamentarium of modern molecular biology has now been recruited to address these questions and others in laboratories throughout the world.

Much of the current excitement in the field of aging has been captured in this comprehensive volume, which features chapters prepared by scientists at the cutting edge of research on the relationships between genomic instability and aging. A thorough treatment is provided of the human hereditary syndromes that express phenomena of aging, including those that cause premature death. A number of chapters deal with the role of chromosomal telomere shortening as a contributor to aging. Cell senescence and its validity as a model for aging are critically evaluated. Important systems for studying aging are described with their special features that may or may not be relevant models for human aging, including yeast, roundworms, fruit flies, and rodents. Although the editors have cautioned that this volume is not intended to be encyclopedic, it clearly provides a valuable and stimulating reference for anyone wishing to learn about current research in this fascinating field. Furthermore, the chapters are generally quite accessible to the nonspecialist as the various model systems are introduced.

The most prominent human hereditary disease that exhibits a premature aging phenotype is Werner syndrome. It is provocative that the gene now known to be responsible for Werner syndrome is one of five human homologs of the *recQ* gene from the bacterium *Escherichia coli*. The *recQ* gene was originally discovered in a search for genes responsible for the loss in viability that accompanies thymine starvation in bacteria. Thus, seemingly esoteric revelations from the study of these single-cell organisms (which do not age!) may give us important clues to the mechanisms of aging in humans. It is curious that defects in only one of those five *recQ* homologs result in premature human aging, although deficiencies in at least three of them predispose to cancer. What could be the connection?

While cancer incidence is a conspicuous feature of the senescent phenotype in mammals, it is not really a stage in the normal aging process. It results in shortened life spans for many people, but it surely does not impact the maximum life span. However, we might ask whether some of the same phenomena that lead to genomic instability and eventual cancer could participate in other processes leading to the termination of life. In that sense the maximum life span might indeed be a consequence of accumulating genomic instability that eventually becomes incompatible with life.

There are two fundamental issues in relation to aging and the termination of life: (1) maximum life span and (2) health during the aging years. If it were our choice, how long should we be able to live? And would we wish that all humans on the planet should be able to live that long, or just you and me? And would we wish to live an "extra" 50 years, if we would likely be blind or otherwise incapacitated for the final 40 of those years? For many of us the practical question is how to ensure that our terminal years are more comfortable and rewarding in good health, rather than how to extend the human life span. Of

course, most of us would like to live to an age that approaches the maximum life span, whatever that is.

Finally, there does indeed appear to be a significant hereditary component to life span, so if you desire a long life then you should be very careful in choosing your parents.

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Preface

Understanding the biological basis of aging has fascinated people throughout recorded history, and is one of the great remaining scientific questions. The question has never been more important than now, as we anticipate the impact that a rapidly growing older population will have on the social, political, and medical landscape over the next 50 years. There is increasing evidence that aging involves damage to the genome, and it is certainly the case that such damage explains much of the coupling of most cancers to aging. This volume brings together expert reviews on issues related to the role of chromosomal instability in the modulation of life span and health span.

The primary aim of this book is to provide the scientific community with a current treatise on the cellular and molecular bases of aging and chromosomal instability in human diseases and model organisms. We intend this book for students, scientists, and physicians interested in the biology of aging and human genetics, and for those studying genomic instability in the fields of biochemistry, genetics, therapeutic radiology, oncology, and pathology. The realization that aging could be studied by using the methods of modern molecular biology and genetics has led to an explosion of knowledge in the field. Indeed, one of the difficulties of beginning a career in aging research has been how widely scattered the information is, with relevant publications appearing in numerous and diverse scientific journals. In this sense, the biology of aging is a "supraspecialty" encompassing many other fields, rather than a narrow subspecialty. This text will pro-

vide readers with a background for understanding a wide range of the most important work, and a context for future discoveries.

This book is not intended to be encyclopedic, nor the final word on the subjects presented. Progress in research on chromosomal instability and aging continues at a remarkable pace, and we apologize for the inevitable lapses between this publication and the most current literature. This book is well referenced through the beginning of 2002, and we are extremely grateful to our contributors and colleagues who made sure that the latest possible information was included within the time constraints of the publishing process. Fortunately, the Internet has emerged as a means of rapid dissemination of scientific information. One of us (GMM) has been crucial in launching a site devoted to aging research. At present, the site (http://sageke.sciencemag.org) is freely available.

We have assembled a group of leading investigators to contribute to this book. Their individual scientific contributions have been remarkable, and it is a pleasure to acknowledge our indebtedness to them. Their generosity in contributing to this enterprise has been inspiring. We thank Professor Phil Hanawalt for graciously agreeing to write the Foreword for this volume. We also wish to thank our colleagues who anonymously reviewed and commented on the chapters. Their collective expertise and individual thoughtful criticisms and suggestions are greatly appreciated. The responsibility for any errors or inaccuracies that remain, however, lies with us.

We received special assistance from many individuals throughout the writing and editing of this book. We owe a special debt of gratitude to Mr. William T. Comfort, Jr., whose generosity and timely support made this book indescribably easier to produce. We also gratefully acknowledge the support and encouragement of the John A. Hartford Foundation, especially by Mr. James F. O'Sullivan.

We also wish to thank Jinnie Kim, Annie Cok, and their colleagues at Marcel Dekker, Inc., for their commitment to this project from its inception. Student workers Kristin Felice and Anne Lincoln made countless trips to the library and provided cheerful, patient secretarial assistance. Carl Richmond provided exemplary, enthusiastic editorial support, without which this book could not have been completed. At last count, during the production of this book, four children were born to individuals who participated in creating it. We are especially grateful to all eight of their parents for their tolerance and support. Finally, we thank our families for their encouragement.

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1
Introduction

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I. INTRODUCTION

A useful approach to the introduction of any book about the biology of aging (after first clarifying the essential terminology) is to consider three traditional questions that have always driven biogerontological research. In keeping with that philosophy, we first shall give a brief summary of what can be referred to as *senescent phenotypes* (*What* is aging?). We will conclude that there is a remarkable range of senescent phenotypes that impact physiological functions at all levels of analysis and in all body systems. Next, we will consider what is surely the most fundamental of all gerontological questions (*Why* do we age?). The evolutionary biological theory of why aging occurs remains by far the most satisfying explanation, although there have been certain challenges to that idea. Finally, we will very briefly introduce the third—and by far the most difficult—question, one to which the modern tools of molecular biology and genetics have only recently begun to be successfully applied (*How* do we age?).

There is little doubt that genomic instability—the theme of this book—is a major pathway toward senescent phenotypes, particularly of the numerous neoplastic proliferations that emerge during the last half of the life spans of mammalian species. The mitochondrial genome and the nuclear genome are important targets of such instability. A recent surprise is the evidence that mitochondrial dysfunction also may participate in the pathogenesis of disorders of proliferative homeostasis, probably including atrophies as well as hyperplasias, as they are among the cell's generators of signals to implement apoptosis (1,2). The equations that ensure a healthy, steady state of cell numbers within our various tissues include factors for the determination of cell death as well as cell birth. Mitochondria are important generators of signals that lead cells to commit suicide; the alterations

of such signals by dysfunctional mitochondria may thus alter the balance of these equations.

These components of DNA damage are not likely to be the only pathways modulating life span and the rates of development of senescent phenotypes. Several other classes of gene action can contribute to the pathobiology of aging, including those that modulate posttranslational alterations to proteins, such as glycations (3).

II. DEFINITIONS

In this book, as in most of the literature that deals with the biology of aging, the term *aging* is used more or less synonymously with the term *senescing* or *senescence*. These terms are meant to encapsulate the slow, insidious, and progressive declines in structure and function of an organism after it has attained sexual maturity and the adult phenotype. As such, it is distinct from what happens in development. Gene action in development, however, is clearly of great significance for what happens in the later half of the life span. Let us consider the metaphor of a protein-synthesizing factory to describe a living organism. The life span of that factory depends on how well it is constructed and how well it is maintained after construction has been completed. The latter involves a variety of quality control mechanisms to maintain macromolecular integrity and proliferative homeostasis.

Not all alterations that occur in old organisms are deleterious. Some are compensatory—adaptive responses to specific types of declines in structure and function. An example is the Starling phenomenon—the increased end-diastolic filling to maintain cardiac output in many old people (4). Such compensation has been referred to as *sageing* (5). But these compensations eventually fail, allowing the full emergence of senescent phenotypes.

Rates of aging are typically measured by the speed at which the probability of organismal death increases as a function of postmaturational age. These are exponential functions and often are referred to as Gompertz curves, named after the 19th century actuary who first described this relationship. Recent studies of the life tables of very large numbers of fruit flies, medflies, roundworms, and people, however, have shown that those rates appear to slow in extremely aged individuals (6). The underlying mechanisms are not yet understood.

Genetic loci that play major roles in the modulation of life span and senescent phenotypes have been referred to as *gerontogenes* (7). This term is becoming well entrenched in the gerontological literature, but it is perhaps an unfortunate choice, as its literal interpretation is that these are genes whose primary functions are to lead directly to senescence. As we shall see in Sec. V. Why Do We Age?, such an interpretation is not consistent with evolutionary biological explanations of the nature of aging. The term *gerontogens* has been coined to refer to

putative *environmental* agents that have the potential to accelerate features of senescence (8). We have mutagens, carcinogens, and teratogens, so why not gerontogens? The best candidate for a "global gerontogen" (one that can essentially advance all features of senescence and thus shorten the life span) is gluttony! We shall learn more about the role of calories in modulating life span in Sec. VI. How Do We Age?

III. HERITABILITY AND CHANCE IN AGING

Like all phenotypes, the variable features that clinicians and pathologists observe in older human subjects, and that biologists observe in their aging experimental organisms, result from gene–environment and gene–gene interactions. Although some consider chance events as part of the contributions to the environmental variance, the role of poorly defined stochastic elements in the modulation of life span and the rates of development of senescent features deserves special emphasis (9). Gerontologists who work with genetically identical organisms raised under rigorously controlled environments regularly observe evidence of this in their life table determinations. A particularly compelling example is the determination of the distribution of survival for a cohort of genetically identical *Caenorhabditis elegans* worms grown in suspension cultures with a chemically defined medium (10). One must invoke stochastic events to explain the substantial variation in longevities observed in such experiments. For our own species, twin studies have given heritability estimates of only around 25% (11); this is a reflection of the importance of both environmental and stochastic elements in determining the variance of that phenotype and, by inference, in the rates of development of life-shortening senescent phenotypes. There is, however, a strong rationale behind our preoccupation with genetic approaches to our subject, a preoccupation reflected in this book. A genetic analysis has the potential, of course, to get at first principles. Strictly biochemical and physiological approaches typically reveal a plethora of alterations in the tissues of old organisms, many of which could turn out to be epiphenomena.

IV. WHAT IS AGING?

The phenotypic characterizations of aging in such important model organisms as *Drosophila melanogaster* and *C. elegans* are surprisingly superficial. Laboratory animal models of aging have been extremely valuable, but, with the outstanding exception of research by evolutionary biologists (who use genetically heterogeneous wild-type stock), represent highly inbred stocks developed in artificial laboratory environments. Thus, they may present a biased picture of the pathobiology of aging in any given species.

By far the most comprehensive picture of the results of the aging process is given by studies in our own species, mostly by physicians and pathologists. Although space does not permit a thorough review of those findings, let it suffice to say that physiological and pathological alterations can be found in each of the body systems and in all of the organs. At the molecular level, posttranslational alterations in long-lived proteins have been particularly well documented. Among these alterations, glycation is thought to be particularly important (3). Oxidative adducts have been found to accumulate in DNA, particularly in mitochondrial DNA (12). Lipids are also subject to peroxidative change, perhaps contributing to the accumulations of lipofuscin pigments around the nuclei of a number of cell types. Cross-sectional and longitudinal studies have documented declines in a variety of physiological functions, with the most interesting differences being among individuals revealed by longitudinal studies (13). A plethora of pathologies emerge during the latter decades of the human life span, including atrophies (often accompanied by interstitial fibrosis and fatty infiltrates of parenchymal tissues), hyperplasias, benign and malignant neoplasias (especially those of epithelial origins), several types of arteriosclerosis, osteoporosis, osteoarthritis, ocular cataracts, type 2 diabetes mellitus, loss of subcutaneous fat in the extremities, and hypogonadism. Almost half of all urban-dwelling East Bostonians over the age of 85 years have been found to suffer from probable dementia of the Alzheimer type (14). Other dementing disorders, such as frontal–temporal and Lewy body dementias, also begin to increase with age. Fortunately, a type of dementia due to multiple small strokes and known as *multi-infarct dementia* is much less common today, since age-related increases in blood pressure (common in developed societies) have been brought under control with antihypertensive medications. Some argue that the observed monotonic rate of loss of dopaminergic neurons is likely to result in Parkinson's disease in all of us, were we to live long enough to permit its phenotypic expression. Peripheral neuropathies also become rather prevalent in older people. There are declines in the ability to smell and to hear. Glaucoma or retinal degeneration may lead to blindness. But any child can recognize old from young people merely by observing the wrinkling of skin, the graying and the thinning of hair, and the slowing of movements. The last, incidentally, seems to be a universal feature of virtually all aging animals.

V. WHY DO WE AGE?

The evolution of life history strategies is driven by the ecologies in which species evolve. Consider, for example, a population of field mice facing its usual formidable array of predators plus an array of infectious agents, periods of drought and food deprivation, and the ever-present danger of a serious accident. How many such mice are likely to survive even one harsh winter, let alone two such winters? Very few indeed, if any, would survive for more than one year. Thus, al-

leles that only reach some phenotypic level of expression after one year are quite unlikely to contribute to the gene pool of the next generation. These could be good or bad alleles, it makes no difference. The vast bulk of the inherited alleles are those contributed by the much younger, actively reproducing members of the population. The result is a life history strategy that is selected for rapid development and early fecundity. There is no need for selection for elaborate and energetically expensive biochemical means to protect the somatic tissues during a period of years—that energy is best used for the production of progeny. Given the emergence of ecologies with much lower hazard functions, however, there is the potential for natural selection to result in a much different life history strategy—one characterized by slower development, fewer progeny over longer periods of time, and substantial increases in life span that likely would have required enhanced mechanisms for the protection of macromolecular integrity and the maintenance of physiological homeostasis for longer periods of time. These concepts have received strong support from laboratory experiments (15) and from investigations in the field (16). Like all scientific theories, however, this one should also be subject to challenge. I have mentioned above, for example, the peculiar observation that mortality rates actually decrease at very advanced ages for many organisms, including humans. This is not predicted by evolutionary theory, and current explanations are still controversial. There is also still some uncertainty concerning the extent to which grandparents may have contributed to the reproductive fitness of grandchildren among remote ancestors. A recent field study of baboons and prides of lions provides no such evidence of grandmaternal contributions to such fitness in these contemporary populations of those particular mammalian species (17).

One can conclude that the evolutionary theory of why we age is alive and well (18). There is as yet no compelling evidence that aging evolved because "it was good for the species to rid itself of older individuals." Aging, unlike development, does not result from sequential, determinative alterations in gene expression selected to *produce* aging. Instead, aging may be regarded as a *by-product* or as an *epiphenomenon* of gene action that was selected for an entirely different purpose—namely, to enhance reproductive fitness. Evolutionary theory teaches us, however, that life span is plastic. Given the chance, natural selection has shown that nature could do a much better job at keeping our DNA and proteins and proliferating cells in peak working condition for extended periods of time than it has, say, at prolonging the life span of the lowly field mouse. Perhaps we scientists can learn the secrets of these differences!

VI. HOW DO WE AGE?

Now comes the hard part, trying to unravel the underlying fundamental processes of aging. Here we are faced with a fundamental dilemma. Evolutionary theory in-

vokes the possibility of gene actions involving a variety of different genetic loci. One class of actions is known as *antagonistic pleiotropy*, by which alleles, selected for positive effects early in the life span, come to have negative effects late in the life span (19). There are potentially a large number of such loci and thus a large number of common polymorphisms that can influence life span. We might refer to these as leading to "public" modulations of aging. A second idea is that we all carry some number of constitutional mutations that have escaped the forces of natural selection. Although individually rare, there are a great variety of such possibilities. We might refer to these as leading to "private" modulations of aging (20). When viewed collectively, these various genetic modulations provide for a complex array of potential mechanisms of aging. The dilemma, however, results from the extremely well-documented observation in a number of species that the simple intervention of partial caloric restriction can lead to a substantial increase in maximum life span (21). Such a result is consistent with the view that there cannot be a very large number of independent mechanisms of aging. This is supported by the surprising observation that allelic variants leading to increased life span in such diverse organisms as *C. elegans* and *D. melanogaster* affect the same neuroendocrine-mediated pathway involving members of the insulin-like growth factor family of gene products (22). Moreover, these experiments may provide an explanation for the coupling of reproductive behavior with modulation of life span. However, downstream effector mechanisms in those pathways remain to be elucidated. They may address, in part, the free radical theory of aging, which invokes reactive oxygen species as the agents inducing macromolecular damage. The extent to which these results with nematodes and fruit flies, whose somatic cells (with the exception of those within the germ line) are all postreplicative, can be applied to the aging of mammals remains to be determined. As mentioned above, the loss of proliferative homeostasis, including the emergence of cancer, is a conspicuous component of the senescent phenotype in mammals and is not observed in nematodes and flies. Moreover, there can be no doubt that the theme of this book is highly germane to the pathogenesis of the striking coupling between cancer and aging.

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6 Chapter 6. Role of Ku at the Telomere

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8 Chapter 8. Chromatin, Aging, and Cellular Senescence

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11 Chapter 11. Molecular Biology of Rothmund-Thomson Syndrome

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14 Chapter 14. Nijmegen Breakage Syndrome

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15 Chapter 15. Dyskeratosis Congenita

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18 Chapter 18. Down Syndrome

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