

# Contents

Contributors .....	ix
Foreword.....	xxvii
Preface.....	xxix

## Part I

<b>Principles of Gerontology</b> .....	<b>1</b>
1 <b>Biology of Aging and Longevity</b> .....	<b>3</b>
David B. Lombard, Richard A. Miller, Scott D. Pletcher	
2 <b>Demography and Epidemiology</b> .....	<b>23</b>
Michelle C. Odden, Kendra D. Sims, Anne B. Newman	
3 <b>Immunology and Inflammation</b> .....	<b>47</b>
Albert C. Shaw, Thilinie D. Bandaranayake	
4 <b>Psychosocial Aspects of Aging</b> .....	<b>65</b>
Steven M. Albert, Cynthia Felix	
5 <b>Sex Differences in Health and Longevity</b> .....	<b>83</b>
Steven N. Austad	
6 <b>Social Determinants of Health, Health Disparities, and Health Equity</b> .....	<b>95</b>
Laura Block, W. Ryan Powell, Andrea Gilmore-Bykovskiy, Amy J. H. Kind	

## Part II

<b>Principles of Geriatrics</b> .....	<b>107</b>
---------------------------------------	------------

### SECTION A: Assessment

7 <b>Decision Making and Advance Care Planning: What Matters Most</b> .....	<b>109</b>
Daniel D. Matlock, Hillary D. Lum	
8 <b>Principles of Geriatric Assessment</b> .....	<b>117</b>
David B. Reuben, Ryan J. Uyan, Valerie S. Wong	
9 <b>Mental Status and Neurologic Examination</b> .....	<b>133</b>
James E. Galvin, Michelle M. Marrero	
10 <b>Assessment of Decisional Capacity and Competencies</b> .....	<b>151</b>
Margaret A. Drickamer, Sarah Stoneking	
11 <b>Prevention and Screening</b> .....	<b>157</b>
Ashwin A. Kotwal, Sei J. Lee	

### SECTION B: Age-Friendly Care Across Settings

12 <b>Age-Friendly Care</b> .....	<b>171</b>
Terry Fulmer, Maryama Diaw, Chaoli Zhang, Jinghan Zhang, Wendy Huang, Amy Berman, Tara Asokan, Kedar S. Mate, Leslie Pelton	
13 <b>Geriatrics Around the World</b> .....	<b>179</b>
Hidenori Arai, Jacqueline C. T. Close, Len Gray, Finbarr C. Martin, Luis Miguel Gutierrez Robledo, Stephanie Studenski	

14 <b>Models of Hospital and Outpatient Care</b> .....	<b>191</b>
Jonny Macias Tejada, Michael L. Malone	
15 <b>Emergency Department Care</b> .....	<b>207</b>
Christopher R. Carpenter, Ula Hwang	
16 <b>Institutional Long-Term and Post-Acute Care</b> .....	<b>221</b>
Joseph G. Ouslander, Alice F. Bonner	
17 <b>Community-Based Long-Term Services and Support, and Home-Based Medical Care</b> .....	<b>237</b>
Jessica Colburn, Jennifer Hayashi, Bruce Leff	
18 <b>Transitions of Care</b> .....	<b>249</b>
Elizabeth N. Chapman, Andrea Gilmore-Bykovskiy, Amy J. H. Kind	
19 <b>Value-Based Care</b> .....	<b>263</b>
David J. Meyers, Heidi Wold, Joseph G. Ouslander	
20 <b>The Role of Social Workers</b> .....	<b>277</b>
Ruth E. Dunkle, Jay Kayser, Angela K. Perone	
21 <b>The Patient Perspective</b> .....	<b>287</b>
Preeti N. Malani, Erica S. Solway, Jeffrey T. Kullgren	

### SECTION C: Special Management Issues

22 <b>Medication Prescribing and De-Prescribing</b> .....	<b>301</b>
Paula A. Rochon, Sudeep S. Gill, Christina Reppas-Rindlisbacher, Nathan M. Stall, Jerry H. Gurwitz	
23 <b>Substance Use and Disorders</b> .....	<b>317</b>
Benjamin H. Han, Alexis Kuerbis, Alison A. Moore	
24 <b>Integrative Medicine and Health</b> .....	<b>329</b>
Julia Loewenthal, Gloria Y. Yeh, Darshan H. Mehta, Peter M. Wayne	
25 <b>Patient-Centered Management of Chronic Diseases</b> .....	<b>345</b>
Caroline J. Blaum, Aanand D. Naik	
26 <b>Legal Issues</b> .....	<b>361</b>
Marshall B. Kapp	

### SECTION D: Surgical Management

27 <b>Perioperative Care: Evaluation and Management</b> .....	<b>371</b>
Shelley R. McDonald	
28 <b>Anesthesia</b> .....	<b>383</b>
Leanne Groban, Chandrika Garner	
29 <b>Surgical Quality and Outcomes</b> .....	<b>399</b>
Hiroko Kunitake	

### SECTION E: Nutrition

30 <b>Nutrition Disorders, Obesity, and Enteral/Parenteral Alimentation</b> .....	<b>405</b>
Dennis H. Sullivan, Larry E. Johnson, Jeffrey I. Wallace	

vi	<b>31 Disorders of Swallowing</b> .....	437
	<i>Nicole Rogus-Pulia, Steven Barczy, JoAnne Robbins</i>	
	<b>32 Oral Health</b> .....	453
	<i>Joseph M. Calabrese, Judith A. Jones</i>	

**SECTION F: Sensory Function**

<b>33 Low Vision: Assessment and Rehabilitation</b> .....	469
<i>Gale R. Watson, Katharina V. Echt</i>	
<b>34 Hearing Loss: Assessment and Management</b> .....	489
<i>Su-Hua Sha, Kara C. Schwartz-Leyzac, Jochen Schacht</i>	

**SECTION G: Gender and Sexuality**

<b>35 Sexuality, Sexual Function, and the Aging Woman</b> ....	503
<i>Monica Christmas, Kaitlyn Fruin, Stacy Tessler Lindau</i>	
<b>36 Gynecologic Disorders</b> .....	527
<i>Thomas Clark Powell, Russell Stanley, Holly E. Richter</i>	
<b>37 Sexuality, Sexual Function, and the Aging Man</b> .....	547
<i>J. Lisa Tenover, Alvin M. Matsumoto</i>	
<b>38 Benign Prostate Disorders</b> .....	555
<i>Catherine E. DuBeau, Christopher D. Ortengren</i>	

**Part III**

**Geriatric Conditions 573**

<b>39 Systems Physiology of Aging and Selected Disorders of Homeostasis</b> .....	575
<i>George A. Kuchel</i>	
<b>40 Applied Clinical Geroscience</b> .....	593
<i>Sara E. Espinoza, Jamie N. Justice, John C. Newman, Robert J. Pignolo, George A. Kuchel</i>	
<b>41 Managing the Care of Patients with Multiple Chronic Conditions</b> .....	605
<i>Stephanie Nothelle, Francesca Brancati, Cynthia Boyd</i>	

**SECTION A: Geriatric Syndromes**

<b>42 Frailty</b> .....	615
<i>Luigi Ferrucci, Jeremy D. Walston</i>	
<b>43 Falls</b> .....	633
<i>Stephen R. Lord, Jasmine C. Menant</i>	
<b>44 Sleep Disorders</b> .....	643
<i>Armand Ryden, Cathy Alessi</i>	
<b>45 Syncope and Dizziness</b> .....	665
<i>Ria Roberts, Lewis A. Lipsitz</i>	
<b>46 Pressure Injuries</b> .....	679
<i>Joyce M. Black</i>	
<b>47 Incontinence</b> .....	699
<i>Camille P. Vaughan, Theodore M. Johnson, II</i>	
<b>48 Elder Mistreatment</b> .....	719
<i>Mark S. Lachs, Tony Rosen</i>	

**SECTION B: Mobility**

<b>49 Muscle Aging and Sarcopenia</b> .....	729
<i>Alfonso J. Cruz-Jentoft</i>	
<b>50 Mobility Assessment and Management</b> .....	741
<i>Valerie Shuman, Caterina Rosano, Jennifer S. Brach</i>	
<b>51 Osteoporosis</b> .....	759
<i>Gustavo Duque, Mizhgan Fatima, Jesse Zanker, Bruce R. Troen</i>	

<b>52 Osteoarthritis</b> .....	779
<i>Michele R. Obert, Ernest R. Vina, Jawad Bilal, C. Kent Kwok</i>	
<b>53 Hip Fractures</b> .....	793
<i>Ellen F. Binder, Simon Mears</i>	
<b>54 Therapeutic Exercise</b> .....	805
<i>Kerry L. Hildreth, Kathleen M. Gavin, Christine M. Swanson, Sarah J. Wherry, Kerrie L. Moreau</i>	
<b>55 Rehabilitation</b> .....	817
<i>Cynthia J. Brown</i>	

**SECTION C: Mentation**

<b>56 The Aging Brain</b> .....	835
<i>Luigi Puglielli</i>	
<b>57 Cognitive Changes in Normal and Pathologic Aging</b> .....	853
<i>Bonnie C. Sachs, Brenna Cholerton, Suzanne Craft</i>	
<b>58 Delirium</b> .....	879
<i>Matthew E. Growdon, Tanya Mailhot, Jane S. Saczynski, Tamara G. Fong, Sharon K. Inouye</i>	
<b>59 Dementia Including Alzheimer Disease</b> .....	893
<i>Cynthia M. Carlsson, Nathaniel A. Chin, Carey E. Gleason, Luigi Puglielli, Sanjay Asthana</i>	
<b>60 Behavioral Symptoms of Dementia and Psychoactive Drug Therapy</b> .....	919
<i>Carol K. Chan, Constantine G. Lyketsos</i>	
<b>61 Parkinson Disease and Related Disorders</b> .....	935
<i>Vikas Kotagal, Nicolaas I. Bohnen</i>	
<b>62 Cerebrovascular Disease</b> .....	953
<i>Nirav R. Bhatt, Bernardo Liberato</i>	
<b>63 Other Neurodegenerative Disorders</b> .....	981
<i>John Best, Howie Rosen, Victor Valcour, Bruce Miller</i>	
<b>64 Traumatic Brain Injury and Chronic Traumatic Encephalopathy</b> .....	997
<i>John C. McKee, Daniel Kirsch</i>	
<b>65 Major Depression</b> .....	1007
<i>Whitney K. Carlson, William Bryson, Stephen Thielke</i>	
<b>66 General Topics in Geriatric Psychiatry</b> .....	1021
<i>Ellen E. Lee, Jeffrey Lam, Dilip V. Jeste</i>	

**Part IV**

**Principles of Palliative Medicine and Ethics 1043**

<b>67 Palliative Care and Special Management Issues</b> .....	1045
<i>Paul Tatum, Shannon Devlin, Shaida Talebreza, Jeanette S. Ross, Eric Widera</i>	
<b>68 Pain Management</b> .....	1055
<i>Roxanne Bavarian, Amber K. Brooks</i>	
<b>69 Management of Common Nonpain Symptoms</b> .....	1071
<i>Christine S. Ritchie, Alexander Smith, Christine Miaskowski</i>	
<b>70 Palliative Care Across Care Settings</b> .....	1077
<i>Lisa Cooper, Laura Frain, Nelia Jain</i>	
<b>71 Effective Communication Strategies For Patients with Serious Illness</b> .....	1089
<i>Brook Calton, Matthew L. Russell</i>	
<b>72 Ethical Issues</b> .....	1097
<i>Timothy W. Farrell, Caroline A. Vitale, Christina L. Bell, Elizabeth K. Vig</i>	

## SECTION A: Cardiovascular System

- 73 The Aging Cardiovascular System**..... 1115  
Ambarish Pandey, George E. Taffet, Dalane W. Kitzman,  
Bharathi Upadhyaya
- 74 Coronary Heart Disease and Dyslipidemia**..... 1133  
Michael G. Nanna, Karen P. Alexander
- 75 Valvular Heart Disease**..... 1149  
Nikola Dobrilovic, Dae Hyun Kim, Niloo M. Edwards
- 76 Heart Failure**..... 1165  
Mathew S. Maurer, Scott L. Hummel, Parag Goyal
- 77 Cardiac Arrhythmias**..... 1193  
Nway Le Ko Ko, Win-Kuang Shen
- 78 Peripheral Vascular Disease**..... 1209  
Jonathan R. Thompson, Jason M. Johanning
- 79 Hypertension**..... 1219  
Mark A. Supiano

## SECTION B: Pulmonary

- 80 Respiratory System and Selected Pulmonary Disorders**..... 1229  
Daniel Guidot, Patty J. Lee, Laurie D. Snyder
- 81 Chronic Obstructive Pulmonary Disease**..... 1235  
Carolyn L. Rochester, Kathleen M. Akgün,  
Jennifer D. Possick, Jennifer M. Kapo, Patty J. Lee

## SECTION C: Nephrology

- 82 Aging of the Kidney**..... 1247  
Jocelyn Wiggins, Abhijit S. Naik, Sanjeevkumar R. Patel
- 83 Kidney Diseases**..... 1277  
Mark Unruh, Nitin Budhwar

## SECTION D: Gastroenterology

- 84 Aging of the Gastrointestinal System and Selected Lower GI Disorders**..... 1299  
Karen E. Hall
- 85 Upper Gastrointestinal Disorders**..... 1315  
Alberto Pilotto, Marilisa Franceschi
- 86 Hepatic, Pancreatic, and Biliary Diseases**..... 1337  
Dylan Stanfield, Mark Benson, Michael R. Lucey
- 87 Constipation**..... 1353  
Gerardo Calderon, Andres Acosta

## SECTION E: Oncology

- 88 Cancer and Aging: General Principles**..... 1381  
Carolyn J. Presley, Harvey Jay Cohen, Mina S. Sedrak
- 89 Breast Disease**..... 1395  
Mina S. Sedrak, Hyman B. Muss
- 90 Prostate Cancer**..... 1409  
Liang Dong, Mark C. Markowski, Kenneth J. Pienta
- 91 Lung Cancer**..... 1421  
Asrar Alahmadi, Ajeet Gajra, Carolyn J. Presley
- 92 Gastrointestinal Malignancies**..... 1435  
Ryan D. Nipp, Nadine J. McCleary

- 93 Skin Cancer**..... 1455 **vii**  
Shreya A. Sreekantaswamy, Suzanne Olbricht,  
Jonathan Weiss, Daniel C. Butler

## SECTION F: Hematology

- 94 Aging of the Hematopoietic System and Anemia**..... 1473  
Jiasheng Wang, Changsu Park, Jino Park,  
Robert Kalayjian, William Tse
- 95 Hematologic Malignancies (Leukemia/Lymphoma) and Plasma Cell Disorders**..... 1483  
Anita J. Kumar, Tanya M. Wildes, Heidi D. Klepin,  
Bayard L. Powell
- 96 Coagulation Disorders**..... 1509  
Ming Y. Lim

## SECTION G: Endocrinology and Metabolism

- 97 Aging of the Endocrine System and Non-Thyroid Endocrine Disorders**..... 1525  
Bradley D. Anawalt, Alvin M. Matsumoto
- 98 Thyroid Diseases**..... 1545  
Anne R. Cappola
- 99 Diabetes Mellitus**..... 1559  
Pearl G. Lee, Jeffrey B. Halter

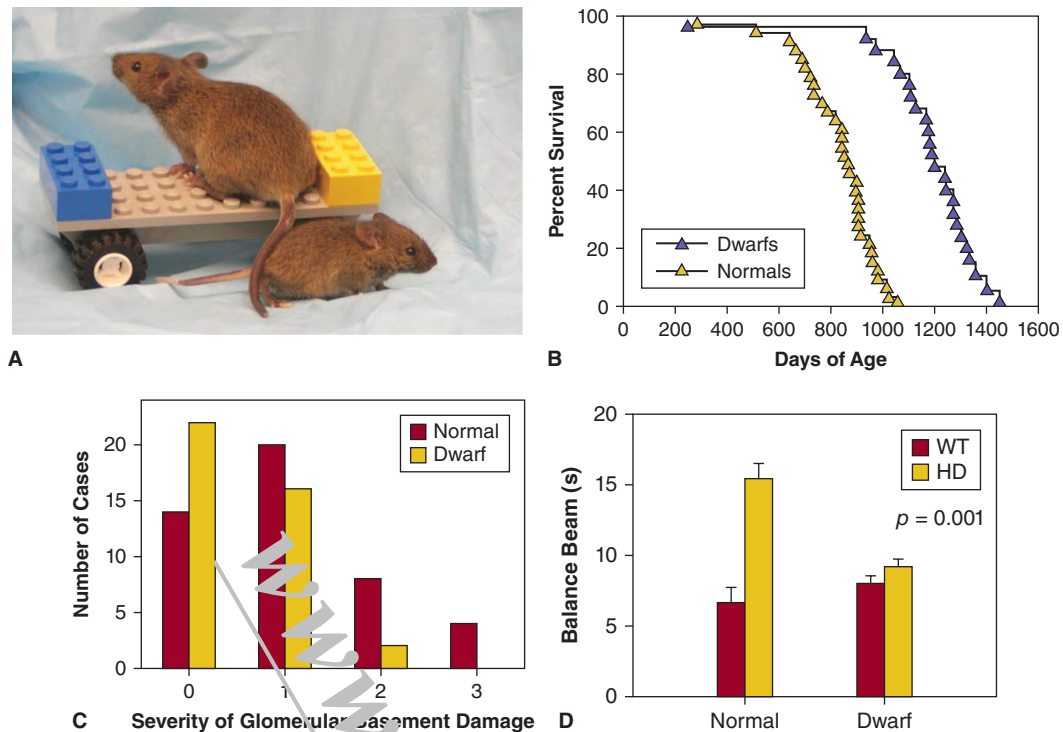
## SECTION H: Rheumatology

- 100 Myopathies, Polymyalgia Rheumatica, and Giant Cell Arteritis**..... 1589  
Vivek Nagaraja
- 101 Rheumatoid Arthritis and Other Autoimmune Diseases**..... 1607  
Jiha Lee, Raymond Yung
- 102 Back Pain and Spinal Stenosis**..... 1629  
Owoicho Adogwa, Una E. Makris, M. Carrington Reid
- 103 Fibromyalgia and Myofascial Pain Syndromes**..... 1643  
Cheryl D. Bernstein, Simge Yonter, Aishwarya Pradeep,  
Jay B. Shah, Debra K. Weiner

## SECTION I: Infectious Diseases

- 104 Infection and Appropriate Antibiotic Selection**..... 1667  
Kevin T. High
- 105 Bacterial Pneumonia and Tuberculosis**..... 1679  
Juan Gonzalez del Castillo, Francisco Javier Martín Sánchez
- 106 Urinary Tract Infections**..... 1699  
Muhammad S. Ashraf, Mandy L. Byers
- 107 Other Viruses: Human Immunodeficiency Virus Infection and Herpes Zoster**..... 1719  
Kristine M. Erlandson, Kenneth Schmader
- 108 Influenza, COVID-19, and Other Respiratory Viruses**..... 1733  
Lauren Hartman, H. Keipp Talbot

- Index**..... 1741



**FIGURE 1-3.** Mice carrying the Snell dwarf mutation are one-third of the size of their normal littermates, because the mutation diminishes production of growth hormone by the pituitary (A). This mutation increases mean and maximum lifespan by about 40% (B), and reduces the severity of kidney lesions at death among many other forms of late-life illness (C). Mice carrying a dominant mutation for Huntington disease (HD) perform less well than wild-type (WT) control mice on a balance beam task (D), but the HD gene does not produce corresponding symptoms when it is placed on a Snell dwarf background. (A, Reproduced with permission from Richard Miller; B, Reproduced with permission from Flurkey K, Papaconstantinou J, Miller RA, Harrison DE. Life span extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. *Proc Natl Acad Sci U S A.* 2001;98[12]:6736–6741; C, Data from Vergara MM, Smith-Wheelock JM, Harper R, et al. Hormone-treated Snell dwarf mice regain fertility but remain long-lived and disease resistant. *J Gerontol A Biol Sci Med Sci.* 2004;59[12]:1244–1250; D, Data from Tallaksen-Greene SJ, Sadagurski M, Zeng L, et al. Differential effects of delayed aging on phenotype and striatal pathology in a murine model of Huntington disease. *J Neurosci.* 2014;34[47]:15658–15668.)

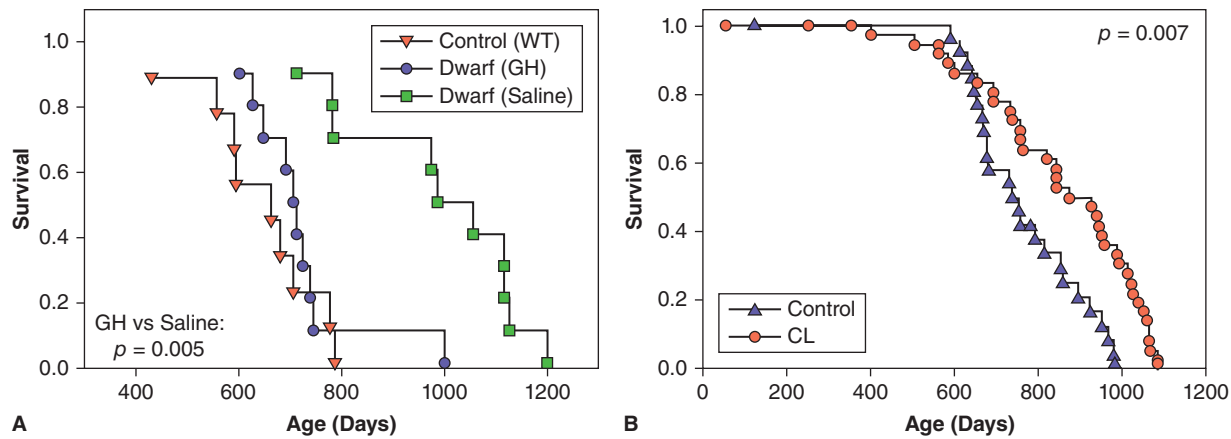
Building on interest in TOR signaling and its effects on protein translation, work in invertebrates and increasingly in mammals has revealed fundamental links between the maintenance of proteostasis and longevity. Proteostasis refers globally to the processes that improve the quality and function of cellular proteins, collectively termed the proteome. It includes regulation of protein translation, folding, damage repair, and degradation. Autophagy is a process by which damaged cellular proteins and even whole organelles such as mitochondria are degraded in lysosomes. In invertebrates, intact autophagy systems are required for longevity extension by essentially all interventions that increase lifespan. Increased expression of the autophagy protein ATG5 extends mouse lifespan and improves neuromuscular function and glucose tolerance in old mice. Rapamycin, which extends lifespan in many different organisms, decreases translation of many cellular proteins, while promoting increased autophagic function. Snell and GHR-KO mice show augmented levels of a specific form of autophagy, “chaperone-mediated autophagy,”

which can affect levels of proteins involved in cell cycling, fat synthesis, and mRNA translation. Collectively, these findings indicate that maintenance of proteostasis is a key requirement of longevity.

### Sirtuins

Sirtuin proteins, which play a major role in aging in yeast, have captured the public interest and sparked robust debate in aging circles. The sirtuins are a family of protein deacetylases that consume the metabolic cofactor NAD<sup>+</sup> during catalysis. Cellular NAD<sup>+</sup> levels increase under conditions of fasting or DR, in a tissue-type specific manner. In light of their NAD<sup>+</sup> requirement, sirtuins have been implicated as energy sensors and potentially as mediators of some of the benefits of DR. In yeast, worms, and flies, sirtuin overexpression extends longevity, albeit more modestly in worms and flies than initial reports suggested. Mammals possess seven distinct sirtuins; these are a diverse protein family, from the standpoint of biochemical activity, protein targets, and localization. Mammalian sirtuins target their protein





**FIGURE 1-4.** Early-life hormonal and nutritional status can have major effects on late-life survival and disease. The left panel shows an experiment in which Ames dwarf mice were given injections of growth hormone (GH) for an 8-week period beginning at 2 weeks of age. The hormone-injected mice had survival patterns similar to that of normal mice (WT controls), and therefore much shorter than Ames mutant mice (green) that had only saline injections at early ages. The right panel shows a complementary experiment, in which genetically normal mice were partially deprived of milk (“CL” for “crowded litter”) by adding extra pups during the suckling phase, from birth to 3 weeks. This transient milk deprivation led to a substantial increase in lifespan in the CL mice. (A, Reproduced with permission from Panici JA, Harper JM, Miller RA, et al. Early life growth hormone treatment shortens longevity and decreases cellular stress resistance in long-lived mutant mice. *FASEB J.* 2010;24[12]:5073–5079; B, Adapted with permission from Sun L, Sadighi Akha AA, Miller RA, et al. Life-span extension in mice by preweaning food restriction and by methionine restriction in middle age. *J Gerontol A Biol Sci Med Sci.* 2009;64[7]:711–722.)

substrates via deacetylation, or removal of other posttranslational modifications, to regulate a wide range of proteins involved in gene expression, DNA repair, metabolism, and many other processes. Three sirtuins are present in the mitochondrial matrix, where they regulate intermediary metabolism and other aspects of mitochondrial function.

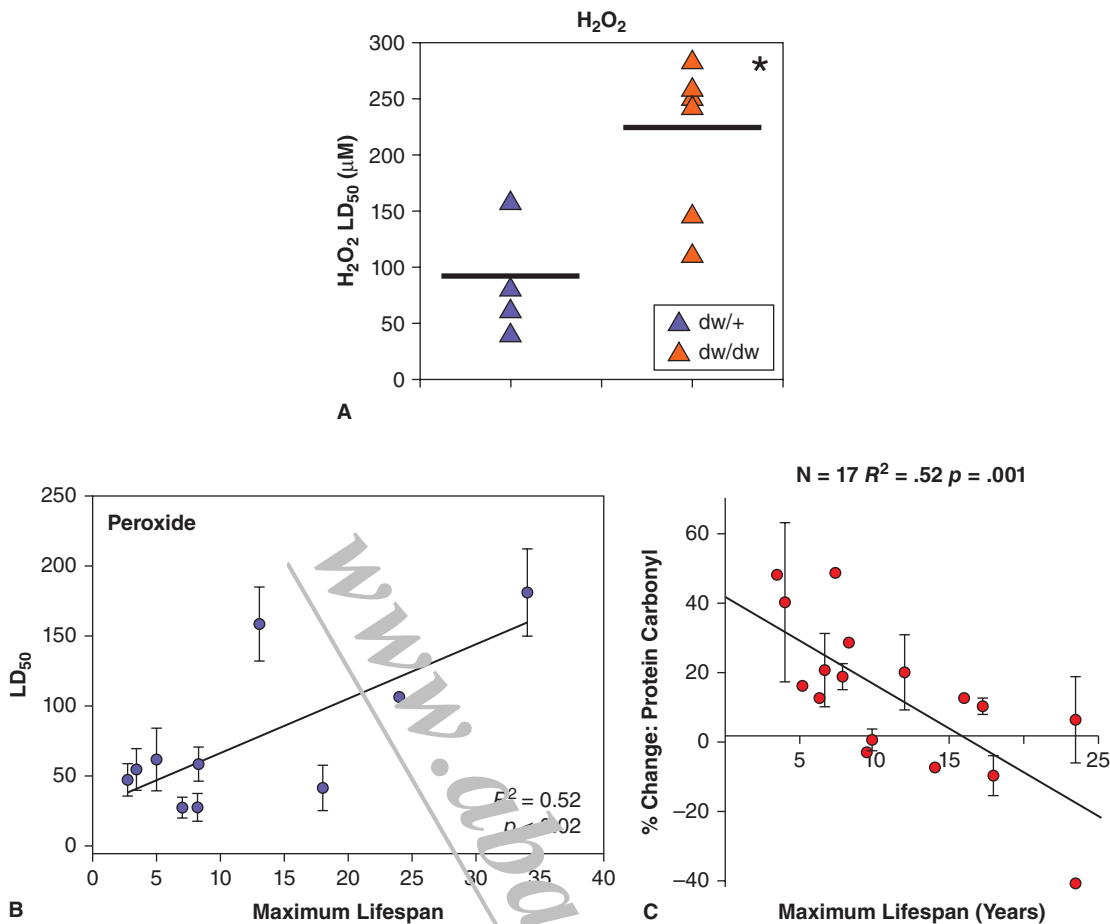
In mammals, most studies have focused on SIRT1, the closest homolog of the yeast SIR2 protein. Whole-body overexpression of SIRT1 does not increase overall lifespan in mice, although it is protective against age-associated metabolic dysfunction and certain forms of neoplasia. Overexpression of SIRT1 in the brain only, however, does extend mouse lifespan. Overexpression of the sirtuin SIRT6 throughout the body also extends lifespan in male mice. SIRT6 promotes metabolic homeostasis and enhances genomic stability; it will be important to elucidate which of SIRT6’s many functions are most important in its pro-longevity role. For example, sequence variations among SIRT6 homologs across different mammalian species may contribute to altered DNA repair efficiencies, and even to differences in lifespan.

Beginning with resveratrol, a series of small molecule activators of SIRT1 have been developed. In mice, these drugs show some beneficial effects, particularly in the context of dietary challenge such as high-fat feeding. There are continued controversies regarding these agents, particularly focused on the extent to which they target SIRT1 directly, versus exerting indirect effects through other signaling molecules, such as AMPK. Nevertheless, these or

similar agents could conceivably find utility in treating age-associated metabolic dysfunction in humans.

### Stress Response

Mutations that extend lifespan in invertebrates typically render the animals resistant to multiple forms of lethal injury, whether the threat comes from oxidative agents, heat, heavy metals, or irradiation. Genetic dissection of the relevant pathways—which must have evolved very early in the evolutionary tree, that is, prior to the common ancestor shared by worms, flies, and humans—has shown, surprisingly, that in normal, non-mutant worms, the levels of stress resistance, and thus resistance to aging, are actively diminished by inhibition of specific DNA-binding transcription factors, members of the FoxO family (see **Figure 1-5**). These pathways are retained by evolutionary pressures because they provide reproductive advantages in the natural environment, in which animals must be able to quickly take advantage of transient access to nutrients. Activation of FoxO proteins in the laboratory produces mutant animals that are not ideally suited for natural conditions, but which are resistant to many kinds of stress and which age more slowly than normal. Studies of gene expression patterns in the long-lived mutant worms have shown that the FoxO proteins can regulate transcription of over 100 genes that together protect against many different forms of cellular damage. The list includes enzymes that destroy free radicals, heat shock proteins, and other chaperones that guard against misfolded proteins, proteins that protect against infection, and chelating agents that bind toxic metal ions, among others.



**FIGURE 1-6.** Links between exceptional longevity and resistance to stress. (A) Skin-derived fibroblasts from long-lived mutant (red symbols, dw/dw, Snell dwarf) mice are resistant to the lethal effects of hydrogen peroxide, H<sub>2</sub>O<sub>2</sub>. Each symbol is an individual mouse, and the Y-axis shows the amount of H<sub>2</sub>O<sub>2</sub> needed to kill 50% of the cells. (B) Skin-derived fibroblasts from long-lived species are relatively resistant to lethal injury induced by H<sub>2</sub>O<sub>2</sub>. Each symbol represents a different rodent or bat species with the indicated maximum lifespan. Species, left to right, are laboratory mouse, wild-caught mouse, rat, red squirrel, white-footed mouse, deer mouse, fox squirrel, porcupine, beaver, and little brown bat. LD<sub>50</sub> is the amount of hydrogen peroxide that kills 50% of the cells. (C) Cells from long-lived rodent species are resistant to changes in oxidized proteins (“protein carbonyl” on Y-axis) induced by 1-h exposure to H<sub>2</sub>O<sub>2</sub>. Each symbol is a different species, with the species’ lifespan indicated on the X-axis. (A, Adapted with permission from Murakami S, Salmon AB, Miller RA. Multiplex stress resistance in cells from long-lived dwarf mice. *FASEB J.* 2003;17[11]:1565–1566; B, Reproduced with permission from Harper JM, Salmon AB, Leiser SF et al. Skin-derived fibroblasts from long-lived species are resistant to some, but not all, lethal stresses and to the mitochondrial inhibitor rotenone. *Aging Cell.* 2007;6[1]:1–13; C, Reproduced with permission from Pickering AM, Lehr M, Kohler WJ, et al. Fibroblasts from longer-lived species of primates, rodents, bats, carnivores, and birds resist protein damage. *J Gerontol A Biol Sci Med Sci.* 2015;70[7]:791–799.)

idea, DNA lesions, mutations, and aneuploid cells (cells with incorrect chromosomal number or rearranged chromosomes) accumulate with age in mammalian tissues. Because such events occur stochastically on a cell-by-cell basis, it has proven difficult to rigorously identify and quantitate such events. Aging leads, in mice and humans, to increased incidence of aneuploidy. Although evidence that accumulation of DNA damage contributes to aspects of aging other than neoplasia is currently modest, elevated levels of a protein involved in repair of DNA damage, SIRT6, can increase mouse lifespan in males and delay cancer and metabolic dysfunction. Further work in

this and similar models may help to clarify the possible role of genome maintenance in aging and nonneoplastic diseases.

The role of ROS in inducing age-associated genetic damage, or in aging more generally, remains controversial. Resistance to many forms of stress, including oxidative injury, is a common feature of long-lived mutants, as described above. However, many mouse mutations that impair resistance to ROS damage have no detectable effect on lifespan and show no obvious acceleration of age-related pathology. Furthermore, administration of antioxidants to mice or people does not extend lifespan and

may under some circumstances actually increase mortality. Conversely, for the most part mouse strains with increased activity of ROS defense systems show protection from specific toxins that cause oxidative injury, but do not show extended lifespan. The only current exception is a mouse strain overexpressing the antioxidant enzyme catalase in mitochondria. These animals show increased lifespan, and, by some measures, improved health in old age.

### Cellular Senescence, Telomeres, and Cancer

The famous observation of Hayflick that human diploid fibroblasts cease to grow in culture after a limited number of population doublings sparked a line of experimentation that continues to yield important insights into the molecular control of cell growth, differentiation, and neoplastic transformation. Human fibroblasts placed in tissue culture will divide until approximately 50 cell doublings have occurred, after which the remaining cells survive indefinitely in a healthy but nondividing state. In the 1970s and 1980s, this “clonal senescence” model seemed to be an attractive approach to study the genetics and cell biology of aging. It is now clear that growth cessation of continuously passaged human fibroblasts is caused principally by the progressive loss of telomeric DNA at the ends of each chromosome at each mitosis, which occurs in cells that lack a specialized enzyme complex called telomerase. Critically shortened telomeres induce a DNA damage response in the cell, leading to senescence or cell death. Short telomeres can influence intracellular signaling to hamper mitochondrial function, thereby impairing cellular metabolism, suggesting that damaged telomeres might exert effects even in tissues such as the liver that are largely postmitotic.

**Telomeres and cancer** (also see Chapter 82) Telomere-dependent clonal senescence clearly plays a critical role in the protection of humans from many forms of cancer. Telomerase is turned on, and telomere attrition prevented, in approximately 90% of malignant tumors in humans. Genomic sequencing efforts have revealed that individuals with mutations that chronically elevate telomerase activity, or increase the accessibility of telomeres to telomerase, are at increased risk for a variety of cancers.

Studies of the role of telomeres and telomerase in the biology of aging in mice have produced controversial findings. Mice have much longer telomeres than humans, but live much shorter lives. The rate at which telomeres shorten, however, is more rapid in mice than in humans, and mouse strains engineered to have elevated telomerase show increased cancer rates, consistent with a role for telomere length as a contributor to malignancy in mice, as in humans. Paradoxically, elevated telomerase function may improve some aspects of health in mice carrying other alleles that block many forms of neoplasia, though with no effect on maximum lifespan, a provocative observation worth further exploration. As indicated in **Figure 1-7**,

telomere erosion can, in different settings, lead to cellular senescence, or to changes in cell properties related to DNA damage, genomic instability, or neoplastic transformation. The potential role of these changes in late-life human disease is an area of active investigation. Genetic disruption of telomerase can also produce lines of mice with shortened telomeres. These mice are short-lived, but the spectrum of pathology, featuring skin ulceration, infertility, increased frequencies of specific forms of neoplasia, and frequently lethal gastrointestinal lesions, does not closely resemble the pattern of illnesses seen in normal aging mice or humans. Thus telomere attrition, except for its major role in oncogenesis, does not seem likely to represent a major contributor to aging in rodents.

**Senescent Cells** Early work based on histologic assays suggested that senescent cells were rare (< 0.1%), even in biopsies from very old donors, although new methods for detecting other aspects of the senescent phenotype have led to upward revisions of this estimate. Senescent cells in vitro express a suite of secreted enzymes and inflammatory cytokines (not produced by dividing fibroblasts), which may facilitate the growth of cancer cells and could in principle contribute to other aspects of aging at the tissue or organ level. The *p16/INK4a* protein serves to maintain a balance between senescence and oncogenic transformation. P16 is induced as part of the process during which cellular senescence halts cell proliferation. An increase in levels of P16 is observed in many tissues of aging mice, but particularly in stem cells, suggesting that senescent stem cells may indeed accumulate as a consequence of normal aging and may represent an evolved mechanism to prevent early-life neoplasia. P16 accumulation leads to diminished stem cell function in the aging bone marrow, brain, and pancreas. Mice engineered to have reduced levels of p16 retain stem cell activities at ages at which these cells proliferate poorly in normal animals, though these mice are somewhat more cancer-prone than normal controls. In humans, genetic polymorphisms near the *p16/INK4a* gene have been linked to age-associated conditions such as type 2 diabetes, coronary artery disease, and frailty. Interventions that prevent age-related induction of p16 might be an attractive approach to diminishing many forms of late-life illness in parallel, if the intervention did not simultaneously increase cancer risk.

Several research groups have developed genetic methods to delete senescent cells from adult mice, and there is current interest in the possible therapeutic potential of pharmacologically targeting senescent cells. However, thus far there is little evidence for beneficial effects of these drugs, termed senolytics, in humans and little data on possible negative effects of such treatment. A series of ongoing clinical trials will evaluate the possible efficacy of senolytic drugs in the context of many age-associated diseases in humans, including osteoarthritis, Alzheimer disease, and others.