This is an important and timely book on an extremely critical subject, and although its technical excellence and depth will challenge those without a formal background in molecular biology, the rewards I believe will be deeply commensurate with the effort. I would not recommend this book to someone without a basic understanding of molecular biology, who is not prepared to struggle or spend considerable time and energy (at least initially) looking up new terms and concepts—and tolerate feeling initially a little bit ignorant and overwhelmed. It is probably originally aimed at the advanced student, graduate student, or researcher in aging, or geriatrician, or someone else who is fairly sophisticated about biology and molecular biology. However, with that qualification in mind, the articles are uniformly of high quality and address critical issues in the science of aging—several, if not many, of these reviews are good enough to be considered benchmark reviews, cogently summarizing the state of the science. There are very good chapters on the network of genes activated by dietary restriction (DR) (the gold standard in terms of environmental manipulations to slow aging and reduce the diseases of aging), the role of the somatotropic axis in mammalian aging (roles played by growth factors such as insulin growth factor and growth hormone), the mechanisms of mitochondrial-free radical production and their relationship with the aging process (the most widely quoted molecular theory of aging which actually has mixed evidence for it), aging and programmed cell death in muscle tissues, aging in adipose tissue, aging of stem cells, leukocytes telomere dynamics (shortened telomeres in white cells predicts mortality at least in men), a reappraisal of the free radical theory of aging, the role of target of rapamycin (TOR) in aging (probably the hottest cellular pathway in the aging and antiaging business currently), comparative genetics of aging, the role of sirtuins in aging and age-related disease, inflammation in aging processes, protein homeostasis and aging, and aging and brain myelination trajectories, and work on cardiovascular (CV) aging in primates, vascular dysfunction in aging, and pulmonary issues and aging, age-related changes in thermoregulation, and last but not least, sex differences in longevity and aging. Although this chapter listing sounds exhaustive, I wish there had been a better chapter on calorie restriction (CR) mimetics (substances that mimic the physiology of CR but without the pain of chronic hunger), and although many chapters addressed the relationship between these various topics and particular diseases of aging, there were no chapters specifically addressing the primary diseases of aging namely cancer, Alzheimer’s disease (AD), CV disease, diabetes, etc. Other than those limitations, the volume coverage is comprehensive and uniformly good to excellent.

I personally have had to struggle to catch up with the emerging biological science in these territories and can appreciate that a detailed discussion of cell signaling (AKA internal cellular regulation and its molecular pathways) is likely to be at least initially intimidating to the average neuropsychologist. However, I can also personally testify that the rewards are quite commensurate; I am increasingly convinced that the unraveling of AD, along with our first truly effective disease modifying treatments, and also a real ability to prevent this disease (and other diseases of aging) will emerge from basic aging science—particularly a much more detailed understanding of cell signaling in aging neurons and aging glial cells. I also believe that this area of basic science will eventually yield insights into how a host of other non-age-related neurological conditions can be more effectively treated, including learning disabilities, head trauma, stroke, and perhaps many other conditions. This is thus an area of basic science with enormous relevance for our discipline, and indeed, as discussed below, for medicine in general. The science of aging is scientifically, economically, and culturally a vital subject for our time (as also
presented below). It is my hope that this review might kindle more interest in this critical area of science on the part of our discipline.

To give first a scientific context for this volume, a brief overview of the science of aging might be useful (abstracted from Watt, 2011—copies available). The study of aging, now the focus of a rapidly expanding if still immature biological science, remains one of the most fundamental and yet mysterious and poorly understood aspects of biology. The science of aging has explored the cellular and molecular basis of aging largely in three target organisms with fully sequenced genomes and short lifespans (yeast, roundworms, and fruit flies) as well as an increasing number of in vivo studies in mammalian (typically mice) animal models. Evidence argues that the network of multiple molecular pathways modulating aging in these three target organisms are all well conserved in mammals, primates, and humans, although perhaps with additional modifications and interactions: insulin and growth factor signaling, other nutrient sensing pathways and their downstream targets, particularly TOR (mammalian TOR [mTOR]), sirtuins (a family of transcription factors), and other protein–sugar bonds—a special class of junk proteins which are particularly pro-inflammatory. Last but not least, even inflammation (which is a primary factor in many of the diseases of aging), but it may not be the primary cellular mechanism for aging as we have believed for many decades (Harman, 1956). An excellent chapter in the Handbook reviews evidence for and against this traditional oxidative stress hypothesis (concluding that the jury is still out but that evidence is quite mixed), while several chapters summarize work on TOR in aging. Indeed, oxidative stress turns out to be one of the secondary activators of mTOR, suggesting that these processes may be interactive versus mutually exclusive. Reducing oxidative stress thus may still pay anti-aging dividends because it may reduce overall drive on mTOR, will also secondarily reduce inflammation and through these pleiotropic effects, and protect against several key diseases of aging. Indeed, inflammation appears to be a major etiological factor in relationship with virtually all of the diseases of aging, but particularly AD, CV disease, diabetes, cancers, and arthritis.

The science of aging has made progress in describing and analyzing several of these critical phenotypes or components of aging: sarcopenia (the loss of muscle mass which contributes enormously to frailty, one of the best predictors of mortality), inflammation and oxidative stress (as noted above, increasingly seen as first cousins and mutually reinforcing), dysregulation in apoptosis (programmed cell death—which may drive increased atrophy), telomere loss and cellular senescence, genomic damage and instability (leading to cancers), mitochondrial dysfunction and decline, and increasing junk protein and declining autophagy (removal of damaged or “junk” proteins) and glycation (the non-enzymatic or “unintended” creation of protein–sugar bonds)—a special class of junk proteins which are particularly pro-inflammatory. Last but not least, even our stem cells age and eventually become increasingly senescent, preventing rejuvenation of multiple organ systems. Although the relationships between these various aspects of aging remain incompletely mapped, evidence is increasing that they are deeply interactive (and perhaps with multiple synergisms between these factors), reflecting the many linked “faces” or facets of aging. As a great example of this set of interactions, recent work in Nature (Sahin et al., 2011) has shown that telomere dysfunction induces metabolic and mitochondrial compromise, via interactions between declining telomeres, activation of p53 (an anticancer but the pro-senescence molecular pathway that promotes cell-cycle arrest) and failing promotion of PGC-1α (leading to declining mitochondrial function and bioenergetic deficits). Telomere loss itself may be driven by oxidative stress and inflammation, suggesting a large matrix of looping control factors modulating aging. That aging appears driven by a recursive and complex matrix of interactive factors (see Watt, 2011b, for summary) should hardly be surprising, given how all of biological regulation appears similarly non-linear and recursive. Increasing evidence links most if not all of these basic physiological processes (the various phenotypes of aging noted
above) to “all the major diseases of aging and also to most neurodegenerative disorders,” including specifically to AD, Parkinson’s disease, and other neurodegenerative disorders of major interest of neuropsychology. Specifically, declining removal of junk proteins (amyloid and phosphorylated tau and alpha synuclein in AD and PD, respectively), oxidative stress, mitochondrial decline, and inflammation are increasingly seen as primary factors in both AD and PD. Disordered cell cycling is also increasingly seen as a driver of neurodegeneration in AD.

Evolutionary perspectives argue that aging must be a process against which natural selection operates minimally, in a post-reproductive animal. In other words, basic selection processes assure that enough members of the species (absent predation or other accidental death) survive to a period of maximum reproductive competence (or else a species would not exist), but selection does not assure longevity much past a peak reproductive period. Aging is the result of this relative absence of selection for an extended post-reproductive adaptation. In this sense, evolution “does not care too much about aging,” although there may be some partial exceptions to this principle in humans, due to the likely contribution of tribal elders to an extended “group fitness,” which may help explain why humans are longer lived than almost all other mammals, currently poorly understood. Such evolutionary perspectives also suggest that aging (and its deceleration) are likely to be highly polygenic (consistent with the above discussion of the recursive nature of all biological processes), and not easily radically modified, arguing strongly against any wild optimism about improvements to maximum human lifespan beyond its documented maxima (~120 years) being easily achievable. Another basic evolutionary perspective on aging is that it reflects antagonistic pleiotropy—that basic cellular operations promoting reproduction, growth, and fecundity in youth “backfire” in a post-reproductive animal and drive aging. The essential role of mTOR in both growth and reproduction, as well as its increasingly pivotal role in our understanding of aging, offers support for these basic ideas at a molecular level.

Aging research has also extensively probed highly conserved protective effects associated with DR or CR, the clear gold standard in terms of a basic environmental manipulation that slows aging in virtually every species in which it has been closely studied, from yeast to mammals. CR/DR functions as a global metabolic “reprogramming” for most organisms, reflecting a shift of biological priorities from growth and reproduction toward stasis and conservation. CR physiology was presumably selected by allowing organisms to survive times of nutrient shortage and then resume the critical business of growth and procreation, once back into environments more supportive of fecundity. CR (particularly if it includes some degree of protein restriction and not simply CR) appears to intercept every phenotype of aging: it reduces oxidative stress, reduces both nuclear and mitochondrial DNA damage, increases autophagy and the removal of junk proteins, and decreases mTOR (growth drive), inflammation, glycation, and insulin resistance. CR extends lifespan and reduces the penetration of the diseases of aging significantly if not dramatically in almost every species in which it has been studied, but does not appear to be a viable healthcare strategy for the vast majority of individuals (due to the intrinsic stresses of chronic hunger). If anything, the obesity epidemic underlines that we as a species are very poor at restricting calories, even when we are quite painfully aware of the many negative consequences, if tasty foods are easily obtained.

CR mimetics (substances offering at least some of the physiology of CR without the stress of chronic hunger) may eventually offer some or many of the benefits of CR, protective effects of enormous relevance to Western societies as they undergo progressive demographic shifts in the direction of a larger percentage of elderly citizens than at any point in prior human history, with an impending tsunami of diseases of aging. However, clinical and long-term data on CR mimetics are badly lacking outside of animal models, where they show impressive protective effects. CR mimetics (the two most famous and best studied being resveratrol and rapamycin) are currently being examined as potential therapies in multiple diseases of aging, including cancer, heart disease, AD, diabetes, and several others. The hope (unfortunately sometimes accompanied by hype) is that CR mimetics may show ability to protect against these major diseases of aging, including AD, or at least substantially delay onset.

Then, there are the critical cultural and economic contexts for this volume on aging—the impending fiscal implosion associated with our out-of-control healthcare costs, in an aging population, in which multiple aspects of unhealthy living are increasingly ubiquitous. Although everyone in our discipline is painfully aware of the financial constricting facing our field, there is a real sense in which “we ain’t seen nothing yet.” Although we have all been witness recently to a vigorous national “healthcare debate,” little of that debate gets at any of the real problems that are poised to fundamentally collapse the healthcare system in this country. The healthcare debate in this country has been largely analogous to a large group of people on high-speed train accelerating toward a known break in the track, and where everyone on the train is arguing about when and how the track is going to repair itself, instead of insisting that the train slow down, or get onto another, better track. Our current course in health care is completely unsustainable. In 2010, healthcare expenditures in the USA were expected to be ~18% of gross domestic product (GDP), almost twice as much, in terms of percentage of GDP, as any other Western society. Even just within the only next several years, at a current rate of increase of...
roughly 6%–8% a year, by 2018/2019, roughly 20% of the U.S. GDP (1 dollar in every five) could be spent on healthcare expenses, an unprecedented fraction of our national wealth and resources—indeed such multi-trillion dollar healthcare expenditures are unprecedented in human history. Healthcare expense as a proportion of GDP is projected (without substantive changes in practice trends or in penetration of chronic illnesses) to rise to 28% by 2030 (>1 dollar in every four) and to potentially reach 34% by 2040 (>1 dollar in every 3; CEA, 2009). Despite these enormous and escalating financial outlays in health care, overall health may be actually declining in the USA, as measured by several indices (currently the USA ranks around 50th in life expectancy, while other indices, such as infant mortality are also worrisome and rank 46th, behind all of Western Europe and Canada; CIA Factbook, 2011).

How are we getting such poor results for so much money? Although standard answers to this question typically lean heavily on the notion of an aging demographic coupled with fee-for-service private health care as primary escalation factors in these costs, recent work suggests that demographic shifts toward an aging population are only one contributing factor in these accelerating expenditures and are paired with rapidly escalating costs for both first-line drugs and common high-technology interventions, and additionally, the high overhead associated with the burgeoning health care and health insurance bureaucracy itself (CEA, 2009). “Evidence suggests that as much as three quarters of the increasing costs are due to factors other than simply an aging demographic” (CEA, 2009). If we continue on our current course, we will see an increasing fraction of our national wealth going to healthcare expenditures, but with every indication that our quality of life will not be correspondingly improved in any substantive way.

Another basic dimension to our current healthcare environment is the massive failure of meaningful prevention of the diseases of aging (in other words mitigating or reversing unhealthy lifestyles) on a global cultural and unprecedented scale. It is most discouraging that recent evidence suggests that major risk factors for the diseases of aging, including particularly the twin epidemics of obesity and diabetes (dubbed “diabesity”), are still basically spiraling out of control—current estimates suggest that the total worldwide diabetes epidemic has topped 350 million. Recent work suggests that obesity is still on the rise, despite the attention it has received recently, with roughly one third of the U.S. population having a body mass index (BMI) over 30, while another third is overweight (BMI between 25 and 30). Statistics for obesity in children and adolescents are even more frightening. Some estimates suggest that at the current rate of increase that 50% of the U.S. population will be obese by 2030 (Wang et al., 2011). Clearly, diet and lifestyle issues are the primary problem here in relationship with these twin epidemics. Less than 15% of the population exercises regularly, nearly 30% of adults report an average of ≤6 h of sleep per day (mild to moderate sleep deprivation). Fewer than 1 in 10 Americans is thought to be consuming adequate amounts of fruits and vegetables, and a minority of Americans shows a desirable BMI of between 21 and 24 (a typical BMI for our hunter-gatherer ancestors). Many Americans, particularly elderly Americans, report significant and chronic social isolation, increasingly appreciated as a risk factor for virtually all the diseases of aging as well as a classic risk factor for depression (Watt, 2011a). Although prevention in primary care receives increased attention these days, there is very little money spent on it, at least in relative terms. Currently, we spend at most 5% of our healthcare dollar on prevention in any meaningful sense, while somewhere between 75% and 85% goes into the treatment of an established disease of aging, oftentimes emphasizing high-tech tertiary care of an advanced disease of aging (often one at which little truly meaningful prevention was ever aimed). This emphasis on high-tech intervention includes spending roughly $100,000 or more in the last year or so of life. Extrapolating from these trends means that we could easily spend 6–7 trillion dollars on end-of-life care for the Baby Boomers—obviously a crushing set of costs. The evidence suggests that most high-technology care is associated with an advanced disease of aging, or in many cases, care of individuals with several advanced diseases of aging. Many of these elderly patients require both periodic high-technology (acute in-patient) care and chronic long-term care (nursing homes or assisted living). Both of these (acute in-patient and long-term care) are very expensive and constitute the two largest big-ticket items in the current climate of exploding healthcare costs.

There is accumulating evidence that Western lifestyles, and an associated pandemic of obesity, reflecting a radical departure from our evolutionary environment as hunter-gatherers, will expose us to increased penetration by the diseases of aging, despite (or perhaps because of) increasing life expectancy. And most of that increased life expectancy comes from one primary factor—reducing early mortality associated with infections and not from substantive progress in treating the major diseases of aging. Although we tend to think of sleep deprivation, sedentary lifestyle, obesity, and the Western diet pattern as separate issues, recent work in aging suggests that all of these lifestyle factors impact on a shared set of molecular and cellular substrates. These multifactorial lifestyle changes in Western cultures (poorer sleep, little exercise, complex dietary shifts, increased social isolation) may actually increase many of these basic phenotypes of aging, including oxidative stress, inflammation, glycation, insulin resistance, telomere loss, increased junk proteins, and both nuclear and mitochondrial DNA damage. Similarly, although we tend to see so-called healthy lifestyle variables as unrelated (a good night’s sleep, significant intake of plant substances, aerobic exercise, social connection), the evidence is that these are all fundamental characteristics of the ancient hunter-gatherer environment. While we cannot go back to being hunter gatherers, lifestyles that are
closer to hunter-gatherer lifestyles (significant aerobic exercise, “Paleolithic” diet with minimal products of food technology, a good night’s sleep, and intimate social bonds) may reduce has been called an “evolutionary discordance” between our genes and our environment (Konner, 2001). Genetically, we have changed very little in the last 10,000 years but our lifestyles are obviously radically different. This suggests the disconcerting conclusion that Western lifestyles place us in an alien environment from the standpoint of our genome—such mismatches suggest a poor chance at adaptive success. Thus, while the central pro-longevity triumph of Western civilization and medicine, the prevention and treatment of bacterial infection (CDC, 1999), has had a large positive impact on median survival to old age, Western lifestyles may actually accelerate aging and the diseases of aging in a multitude of other ways. Prevention of the diseases of aging therefore has to begin with appreciation for the central importance of lifestyle change, back toward at least some approximation of our evolutionary environment.

Fundamental shifts in healthcare strategy and priorities will be needed in coming decades, away from our current reliance on high-technology interventions aimed at an advanced disease of aging (often one at which little real prevention was ever aimed), toward a re-prioritizing of meaningful prevention, via substantive lifestyle modifications. Such a shift in healthcare priorities is likely to be politically contentious, but the current (and unsustainable) escalation of healthcare spending will eventually force basic changes in both healthcare policy and clinical practice. The science of aging may eventually heuristically integrate much of our currently fragmented approach to the diseases of aging, and merits not only much more attention and review in medical school curriculums but also in basic biomedical research initiatives. Additionally, work on CR mimetics opens up promising avenues for maximizing neuroplasticity and not only protecting against AD, but potentially optimizing recovery from other central nervous system insults and stressors. Neuropsychologists dealing with neurodegenerative disorders will find work on CR mimetics especially intriguing, but given their pro-plasticity effects, they may become treatments for many other neurological conditions. For those interested in a benchmark series of reviews on aging, this volume has much to offer. I recommend it highly. For geriatric neuropsychologists, sophistication about the biology of aging should be considered a required area of competence.

References


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doi:10.1093/arclin/acr108

Advance Access publication on 11 January 2012

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