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SPECIAL REVIEWS IN ORNITHOLOGY

A BIRD'S-EYE VIEW OF AGING: WHAT'S IN IT FOR ORNITHOLOGISTS?

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ORGANISMAL AGING, OR senescence, can be defined as a progressive, irreversible loss of function that results in declines in fertility and survival. This definition restricts "aging" to age-related deterioration that occurs after organisms reach maturity, including processes that can be detrimental to reproductive success and, hence, relevant to fitness tradeoffs. The biology of aging, or "biogerontology," is broadly focused on understanding basic processes responsible for variation in animal life spans and aging patterns, including evolutionary forces as well as physiological and molecular mechanisms (Finch 1990, Rose 1991, Kirkwood and Austad 2000). Much of the research in this field is couched in terms of preventing aging-related disease or extending human life span, and most biogerontological researchers use short-lived, inbred laboratory model species for which molecular tools are very well developed (e.g., mice, flies, and roundworms) rather than wild, free-living animals. Because longevity and sustained health are a primary focus of the biology of aging, there is also intense interest in animals, including many bird species, that are exceptionally long-lived for their body sizes or metabolic rates and that may have interesting physiological or molecular mechanisms for long-term maintenance of somatic integrity and reproductive capacity. Along with a push to adopt longer-lived, outbred animal models for aging studies, there is growing appreciation of the utility of comparative and evolutionary approaches to understanding basic aging processes (Austad 2001, Holmes et al. 2003a, Buffenstein 2005, Hulbert et al. 2007, Holmes and Kristan 2008).

"Bird studies offer a rich resource for exploring the biochemical and molecular mechanisms that underlie variation in aging and longevity within and between species, as well as the genetic, developmental, and physiological bases of life-history tradeoffs."

Improvements in marking and monitoring techniques now furnish a wealth of demographic data from wild bird populations that are very valuable for addressing predictions of evolutionary aging and life-history theory. Various researchers are seeking reliable physiological correlates of senescence-related changes in birds (Monnier et al. 1999, Holmes and Austad 2004, Monaghan and Haussmann 2006, Palacios et al. 2007), refining clinical immune assays and other aging "biomarkers" for application to studies in both wild and captive populations. Bird studies offer a rich resource for exploring the biochemical and molecular mechanisms that underlie variation in aging and longevity within and between species, as well as the genetic, developmental, and physiological bases of life-history tradeoffs. Research is already underway that is geared specifically toward the discovery of "anti-aging" mechanisms in birds and other extremely long-lived animals that hold special promise as animal models. However, although great potential exists for dialogue across disciplines, much of the biogerontological literature that would be useful for facilitating innovative, interdisciplinary

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research on avian aging and related areas remains unfamiliar or inaccessible to ornithologists.

Avian biologists are currently making exciting research contributions that are directly relevant to the field of aging (reviewed in Holmes and Ottinger 2006, Monaghan et al. 2008, Ricklefs 2008). But communication and collaboration between ornithologists—particularly those working with wild birds in the field—and more biomedically oriented researchers of aging are still rare. Here, we highlight some central research issues in the biology of aging that are of particular relevance to avian biology as a whole. We review recent findings that could be particularly interesting for ornithologists working in aging and related areas. We discuss the importance of developing more meaningful proximate measures of avian aging, and identify some aging measures and "biomarkers" that have special promise for bird studies. Finally, we suggest ways to build a more comparative and ecologically based "avian biogerontology," integrating research priorities of ornithologists, comparative zoologists, and biogerontologists.

Avian Aging and Longevity: An Overview

The biology of aging is focused on how "ultimate," evolutionary forces shape variation in life spans and aging patterns between and within groups of animal species, as well as on the "proximate" physiological, cellular, and molecular mechanisms underlying these patterns. Central questions in the field currently include why some kinds of animals, such as birds or bats, live longer and age more slowly than others with similar body sizes and metabolic rates, and whether diverse animal taxa share key genes or metabolic pathways that shape life spans and aging rates (Kirkwood and Austad 2000, Promislow et al. 2006, Ricklefs 2008).

Comparative explanations for the wide variation in animal life spans and aging patterns include a long-standing idea that animal life spans are constrained primarily by their metabolic rates and resulting cellular wear and tear. This idea is typically referred to as the "rate of living" theory. This proximate, mechanistic theory was based on a strong, positive correlation between body size and maximum documented species longevities within vertebrate classes, coupled with a strong, inverse, relationship between species life spans and basal metabolic rates (Pearl 1928, Austad and Fischer 1991, Speakman 2005a). Currently, a more robust theoretical scenario for the evolution of variation in life span is provided by evolutionary senescence and life-history theory (Stearns 1992, Kirkwood and Austad 2000, Promislow et al. 2006, Monaghan et al. 2008, Ricklefs 2008). Tenets of this body of theory include the central concept of adaptive, genetically based tradeoffs between current and future survival and reproduction. Animal populations subject to higher mortality from predation, disease, or accident generally are expected to evolve more rapid maturation rates, earlier reproductive investment, and higher fecundity. A corollary prediction of this tenet is that in the absence of higher mortality risk, natural selection should favor organisms with slower aging rates and adaptations that ensure long-term somatic maintenance (Williams 1957, Edney and Gill 1968, Partridge and Barton 1993, Kirkwood and Austad 2000, Martin 2001). Evolutionary and more mechanistic ideas for explaining basic aging processes are continually being integrated, and proximate developmental, metabolic, and oxidative processes undoubtedly play major roles in organismal senescence.

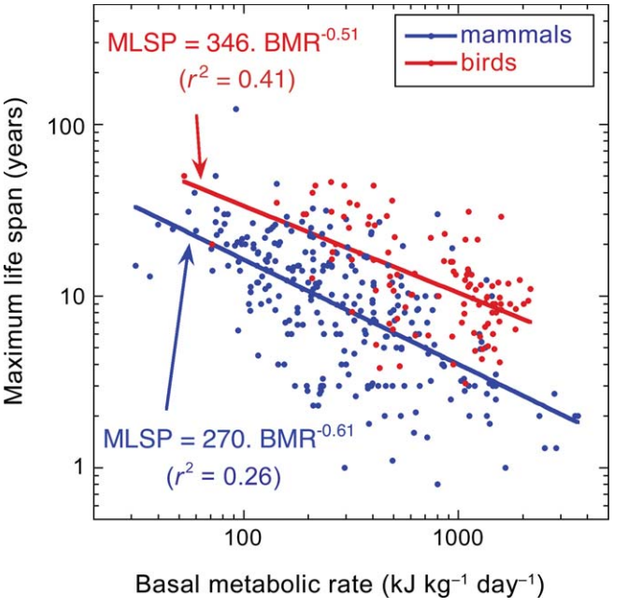

Fig. 1. Comparison of relationships between maximum documented species life spans and basal metabolic rates for birds (upper line) versus mammals (lower line). Although birds have higher metabolic rates, on average, than mammals of similar body mass, many avian species live longer and age more slowly. For birds, n = 108 species; for mammals, n = 267. (Reproduced from Hulbert et al. [2007] with permission of A. Hulbert and American Physiological Society.)

Birds as exceptionally long-lived animals.—Birds exhibit a wide range of life spans and aging patterns (Bennett and Owens 2002, Gill 2007). In general, however, avian species live 1.5 times longer than similar-sized mammals, on average, despite much higher (2–3 times) mass-specific metabolic rates and lifetime oxygen expenditures (3–4 or more times higher) (Figs. 1 and 2; reviewed in Holmes and Austad 1995b, Speakman 2005a, Ricklefs 2008). Maximum species longevities derived from banding records for wild bird populations show that even small songbirds often survive for more than five years in the wild, and that reproductive senescence in many birds occurs at under half the rate of that in similar-sized rodents in captivity (Newton 1989; Holmes et al. 2001, 2003b; Brunet-Rossinni and Austad 2006; Ricklefs 2008). Avian species that mature and reproduce extremely slowly—including seabirds (some with documented life spans of ≥50 years)—are among the longest-lived homeotherms for their size. Slow aging and long life spans in avian species are generally correlated with slow declines in reproductive success (e.g., Pugesek and Diem 1983, Ottinger et al. 1995, Nisbet et al. 1999).

Taken in comparative context, observations about the apparently slow aging rates of birds are intriguing to biogerontologists—and may also be of greater significance to ornithologists than is generally recognized. In the field of aging, there is a continual search for animal model strains or species that appear to be particularly resistant to aging and aging-related diseases. A growing number of specific "longevity assurance" genes have been identified in inbred laboratory animals over the past two decades,

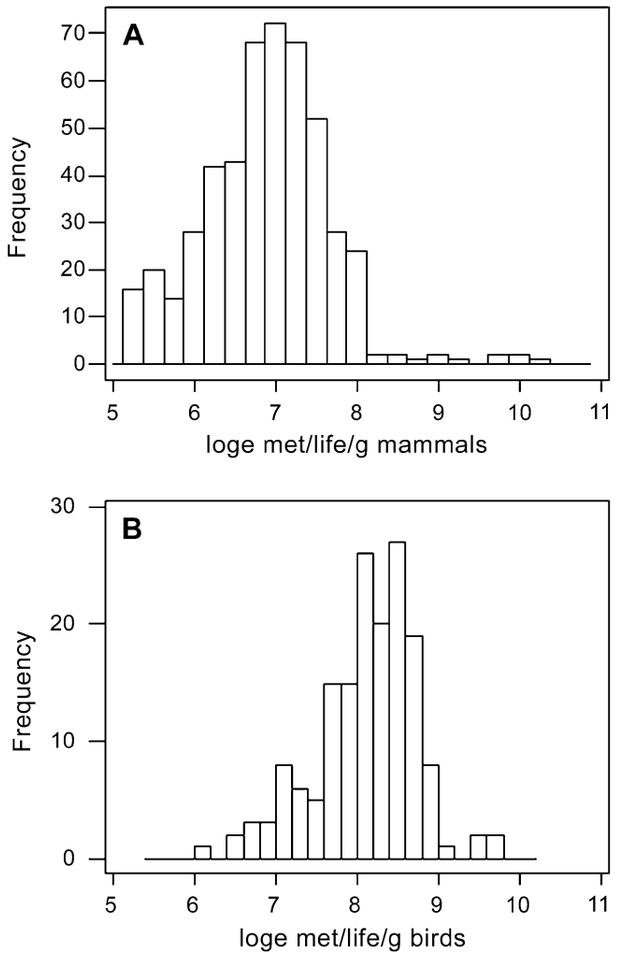

FIG. 2. Comparison of loge (lifetime energy expenditures [kJ/g] of tissue) for (A) mammal (n = 249) and (B) bird (n = 164) species. Birds tend to have higher average metabolic rates for their body masses, than mammals and to expend more energy over the course of a lifetime. (Reproduced from Speakman [2005a] with permission of author and The Company of Biologists.)

and there is an intense effort underway to identify the biochemical and physiological processes controlled by these genes. Some exceptionally long-lived laboratory strains of worms, flies, and mice that possess genes for slow aging also have demonstrably enhanced defenses against certain stressors and types of cellular and molecular damage and, in particular, against damage caused by normal oxidative metabolism. There is also great interest in developing additional animal model species and systems for investigating aging processes, including wild, outbred animals like birds, bats, snakes, fishes, and mole-rats (Brunet-Rossinni and Austad 2004, Buffenstein 2005, Gerhard 2007, Bronikowski 2008).

It has been suggested that the apparently slow aging rates seen in homeotherms that fly (birds and bats) are an evolutionary correlate of low adult mortality rates afforded by efficient modes of escape from predators and accidental death (Williams 1957; Edney and Gill 1968; Partridge and Barton 1993; Ricklefs 1998, 2008; Kirkwood and Austad 2000). Long life spans and slow aging in birds could, alternatively, be a result of the metabolic demands and intensity of selection for flight performance, rather than a straightforward outcome of life-history evolutionary forces (Speakman 2005a, Hulbert et al. 2007, Ricklefs 2008). In either case, the basic biology of aging in birds is worthy of more focused research.

DEMOGRAPHIC PATTERNS AND THE MEASUREMENT OF AVIAN AGING

Demographic measurement of aging.—Detecting and measuring rates of senescence in captive or free-living animals, including birds, depends on the collection of data on age-specific rates of survival or reproduction from mature adults. Long-term, longitudinal studies of large numbers of individuals in wild bird populations have provided a great deal of data suitable for testing ideas from evolutionary aging and life-history theory, including predictions about tradeoffs between reproduction and long-term survival (Newton 1989, Promislow 1991, Stearns 1992, Newton and Rothery 1997, Bennett and Owens 2002, Roff 2002, Monaghan et al. 2008, Ricklefs 2008). Usually, relatively few individuals of a given population reach extreme old ages in the wild, but gradual increases in mortality and declines in reproduction consistent with senescence have now been documented for many avian populations (Ricklefs 1998, Holmes et al. 2001, Ricklefs and Scheuerlein 2003, Brunet-Rossinni and Austad 2006). An increasing number of studies of relatively shorter-lived songbirds and grouse show quite strong declines in survival and reproductive success among birds in older age classes (Wiebe and Martin 1998, Sandercock et al. 2005a, Brommer et al. 2007, Keller et al. 2008). Conventional analytical approaches to demographic studies of aging typically include calculation of age-specific probabilities of death or infertility using survivorship, mortality, or morbidity plots (Fig. 3; Finch 1990, Tatar et al. 1996, Pletcher 1999, Kirkwood and Austad 2000, Bronikowski and Promislow 2005). In studies of wild bird populations, senescence is generally inferred from statistically reliable age-related declines in adult survival or reproductive success, after discounting effects on these traits attributable to specific diseases or terminal illness.

For the most part, the proximate mechanisms responsible for patterns of "demographic senescence," or aging-related changes in various vital rates in wild bird populations, remain undetermined. But a few studies of seabirds and raptors have documented declines in the foraging success of very old individuals compared with that of middle-aged birds (Newton and Rothery 1997, Reed et al. 2008). Age-related variation in various parameters relevant to animals' health, condition, or specific aging-related physiological syndromes (e.g., fertility declines, changes in immune measures, cardiovascular function, or accumulated products of oxidative damage to cells) can also be used to test the hypothesis that senescence is actually occurring. Given adequate numbers of known-age individuals in a range of age classes, demographic analyses of senescence patterns can be useful for (1) testing the hypothesis that reliable aging-related declines are occurring in adult survival, reproduction, or other specific functional measures; (2) comparing patterns of aging-related declines of different physiological

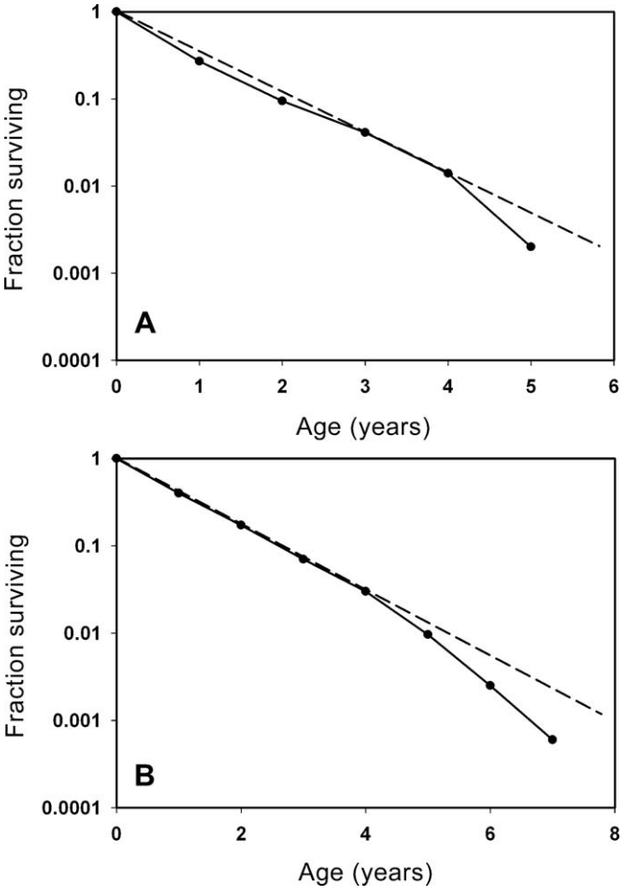

Fig. 3. Declining survivorship consistent with aging in wild populations of (A) European Barn Swallow and (B) Collared Flycatcher. Survival rates that fall below the dashed lines reflect age-related increases in mortality consistent with aging. Data from both populations represent band–recapture records from thousands of individuals. (Reproduced from Holmes and Austad [2004] with permission of the authors and Highwire Press [adapted from original data from Møller and Szép 2002 and L. Gustafsson pers. comm.].)

systems such as immunocompetence or stress responses; and (3) comparing aging patterns between closely related taxa, populations, or experimental groups across different environmental types and conditions (Promislow 1991, Rose 1991, Stearns 1992, Roff 2002, Ricklefs 2008, Wilson 2008, Bears et al. 2009).

Detecting avian aging in the wild: Probability can obscure ability.—Variability in ecological factors or stochastic trends present statistical and other kinds of challenges to gathering the demographic data needed for senescence studies in the wild. Avian aging studies must consider that adult birds often show age-related increases in reproductive success before they reach prime reproductive maturity and undergo subsequent senescence; thus, the performance of old birds is most appropriately compared with that of middle- or prime-aged birds. Declining survivorship with age produces smaller numbers of individuals in older age classes, resulting in increased statistical variance in estimates of vital rates at the oldest ages. Older age classes may not be phenotypically or genetically representative of the entire populations under study but may consist of subsamples of adult individuals, depending on whether or how longevity traits covary with other demographic traits and on the presence or strength of tradeoffs at different ages (Rose 1991, Kirkwood and Austad 2000, Keller et al. 2008, Ricklefs 2008). Another challenge to detection and measurement of senescence is that aging processes may drive steady declines in physiological function of individuals, whereas stochastic, ecological processes such as predation, disease, or extreme weather can abruptly remove individuals from populations for reasons not related directly to senescence. Alternatively, relaxation of harsh ecological or environmental conditions may actually improve the apparent fitness of senescent individuals as measured by other functional capacities (Laaksonen et al. 2002).

Detecting senescence using survival data for birds may be particularly complicated by aging patterns wherein individuals have prolonged good health and performance followed by a catastrophic death, which makes it difficult to detect diminished function and intrinsic aging processes (Ricklefs 2008). Thus, ecological studies of aging may require many years or many study sites to acquire sufficiently large samples for assessing both the ability and the probability of reproductively mature individuals to survive and reproduce as they age (e.g, Brommer et al. 2007). Discrepancies between ability and probability of survival and reproduction of senescent individuals may also vary with species life-history type, such that declines in ability may be more easily discerned in raptors and pelagic seabirds with specialized foraging or other behaviors that require exceptionally high physical performance, and less apparent in herbivorous or omnivorous birds with predation-driven life histories that may show gradual or no declines in performance. Further field studies are needed to determine the role of life-history type in shaping patterns of senescence and the key mechanisms involved (e.g., declines in performance of individuals or selective removal by predators). These studies could be most productively done on populations of bird species that exhibit strong life-history variation or are subject to particularly variable ecological conditions (Martin 2001, Martin and Wiebe 2004).

Avian reproductive aging.—In birds, reproductive vital rates show great variation among species in pattern of onset and degree of apparent senescent declines (Martin 1995). For example, White-tailed Ptarmigan (*Lagopus leucura*), and many other birds, show a strong pattern of senescence in the timing of egg-laying with consequent declines in clutch size, but no declines in either nest failure or the probability of replacing a clutch after failure of the first attempt as birds shift from prime breeding to older age classes (Sandercock et al. 2005a). Other aging-related reductions in fecundity may be compensated for by improvements in another trait (e.g., older birds are able to raise proportionately more of the offspring they hatch); thus, parental experience can compensate for reduced ability to produce eggs (Wiebe and Martin 1998, Velando et al. 2006). There can also be great variability among individuals in the onset and strength of senescence, possibly attributable to strong cohort effects, early breeding experience, population density, or environmental variation (Rockwell et al. 1985, Wilson et al. 2007, Nussey et al. 2008, Reed et al. 2008). In general, relationships among individual fitness, reproductive

success, and senescence in birds are likely to be inherently complex, and the predicted tradeoffs between reproductive investment and longevity remain difficult to assess in natural populations that may or may not exhibit stable population characteristics. These complexities notwithstanding, longitudinal field studies of vital rates in birds, in concert with measurement of physiological or other functional aging measures, can provide invaluable opportunities for examining these processes in natural populations of vertebrates.

Reproductive senescence has been well characterized in domestic poultry and includes changes in ovarian function, declines in gamete production, and changes in reproductive hormone titers, parental care behaviors, and numbers of offspring fledged per breeding episode (reviewed in vom Saal et al. 1994, Holmes et al. 2003b). Age-related changes in reproduction, reproductive endocrinology, and mating behaviors can be particularly sensitive biomarkers of aging. In domestic Japanese Quail (*Coturnix japonica*), for example, changes in courtship behavior are under the control of gonadotropin-releasing hormone (GnRH) secreted by the hypothalamus; hence, changes in GnRH and these behaviors can be used to accurately forecast later reproductive declines in males (Ottinger 2001, Ottinger et al. 2004). As in mammals, patterns of reproductive senescence in birds often differ substantially from patterns of survivorship. But for the reasons stated above, it is generally easier to measure declines in reproductive function than declines in survival. Elucidation of senescence patterns is further complicated by the fact that declines in reproduction are presumably driven only by intrinsic factors, whereas declines in survival are considered to be influenced by either intrinsic or extrinsic factors or both.

Many demographic studies have documented aging-related changes in reproduction in wild birds, but relatively few studies have focused intensively on the physiological basis of these changes (for an exception, see Ottinger et al. 1995). Newton and Rothery (2002), for example, concluded that old female Eurasian Sparrowhawks (*Accipiter nisus*) raised fewer offspring because they were less effective at feeding and protecting their young, given that most nestling mortality was attributable to nestling starvation and depredation. Saino et al. (2002) reported some effects of maternal age and senescence on indicators of offspring quality in Barn Swallows (*Hirundo rustica*), including nestling body mass, morphology, and T-cell-mediated immunity. The ability to sustain reproduction may vary with species and life-history type, such that very old individuals of herbivorous species raising precocial young can maintain reproduction or mitigate declines via behavioral compensation or increased experience. On the other hand, species that must meet the higher demands of feeding altricial young may show more dramatic patterns of reproductive senescence, especially when provisioning of offspring requires high levels of physical performance or specialized foraging skills.

Other phenotypic correlates of aging in wild and captive birds.—In both wild and captive bird populations, aging-related phenotypic variation or changes have been documented for an assortment of other measures, including higher parasite loads, declines in immune function, changes in telomere dynamics, and the accumulation of molecular oxidative damage. Documented clinical signs of aging in captive birds (pets or zoo animals) include fertility loss, osteoarthritis, kidney disease, diabetes, and cancers (Holmes and Austad 1995a, Ricklefs 2000b, Ricklefs et al. 2003, Ottinger et al. 2004, Holmes and Ottinger 2006). Again, particularly interesting to biogerontologists is the fact that even small songbird species appear to exhibit senescence and lose reproductive potential much more slowly than laboratory rodents, which suggests that birds may be particularly resistant to some kinds of deteriorative processes. Although quantification of aging-related changes using clinical aging "biomarkers" in birds is still relatively rare, some measures like these are now being adopted for use in studies of captive and wild birds.

Potential contributions of ecological field studies of birds.—Recent reviews of the ecology and evolution of senescence in vertebrates call for field studies that can contribute particular insights into relationships between environmental conditions or gradients and patterns of lifetime fitness, longevity, and senescence (Monaghan et al. 2008, Nussey et al. 2008, Ricklefs 2008). Some songbirds show remarkable within-species shifts from fast to slow life histories across elevational or geographic gradients; some congeneric grouse species, as well, exhibit striking life-history variation between and within species (Sandercock et al. 2005b, Wilson 2008, Bears et al. 2009). If individuals in some populations of a species live longer than those in others, then such questions arise as which vital rates are modified to achieve differences in life spans, and how much do ecological factors such as predation risk or environmental variation modulate these demographic responses. Although longevity may be generally linked to slower aging or lower vital rates, aging rates may not be uniform among adult age classes. Species that show significant life-history shifts across environmental or geographic gradients provide an ideal opportunity to examine how frequently and how strongly patterns of longevity and senescence are linked, and whether these are related to different reproductive investment patterns or to direct environmental effects on reproductive rates. More generally, there is the intriguing question of how bird populations achieve these life-history shifts, particularly when the mortality is age-independent in large part and presumably attributable to extrinsic factors.

Global warming and the effects of increasing climate variability on different-aged cohorts of breeding birds are a concern for which senescence could be particularly relevant, because populations and species with slow and fast life histories may vary in their vulnerability to environmental perturbation, perhaps depending on whether the patterns of warming influence annual survival or reproduction of individuals (Sandercock et al. 2005b, Wilson 2008). For example, climate warming in winter or severe episodes of weather during the breeding season that depress breeding success may have disproportionate effects on populations with fast life histories, whereas other environmental stressors that influence survival will be expected to have greater effects on populations with high survival. However, if birds that live longer have more prolonged good health until shortly before they die (Ricklefs 2008), they may be more resistant to increasingly severe environmental stress, at least in the short term.

KEY PROXIMATE MECHANISMS IMPLICATED IN AGING

The ability to target specific genes that control aging patterns in laboratory animals has facilitated the identification of key metabolic processes, cell-signaling pathways, and transcription factors

that are likely to underlie differences in life span (Tatar et al. 2003, Partridge et al. 2005, Sonntag et al. 2005, Carter and Sonntag 2006). Genes for longevity and slow aging are of particular interest and have been identified in laboratory mice, fruit flies, roundworms, and yeast (Brown-Borg et al. 1996, Hekimi and Guarente 2003, Johnson 2006a, Pinkston et al. 2006). For example, alterations in single genes (e.g., daf-1 and age) can increase population life spans in roundworms more than seven-fold, and some genes like these are remarkably well conserved across eukaryote taxa.

"Aging genes" also play key roles in regulating apoptosis (adaptive, programmed cell death) and preventing tumorigenesis and cancer (Campisi 2001, Krtolica et al. 2001). Some are associated with homeostatic responses to particular stressors, including heat, cold, oxidative processes, and food restriction. Much current research is focused on the relationship between aging and oxidative damage to cells and macromolecules and on understanding how key aspects of mitochondrial function and energy metabolism are controlled by genes for long life span. Once again, this focus makes long-lived homeothermic vertebrates (e.g., birds, bats, and mole-rats) a particular target as animal models, and the development of molecular tools for use of these species is of growing interest.

Oxidative damage.—Reactive oxygen species (ROS) are unstable oxygen molecules generated by mitochondria during oxidative metabolism. The production of ROS at higher rates by organisms with high metabolic rates and lifetime oxygen expenditures is a central prediction of the free-radical and oxidative-damage theories of aging (Harman 1956, Martin et al. 1996, Beckman and Ames 1998). This proximate prediction drives much current research geared toward a better understanding of the cellular and molecular mechanisms that underlie organismal senescence. Reactive oxygen species and their byproducts are implicated in a growing assortment of aging-related diseases and associated damage to specific tissues, cellular structures, and macromolecules (Martin et al. 1996, Yu and Yang 1996, Finkel and Holbrook 2000, Van Remmen and Richardson 2001, Muller et al. 2007). The long life spans of many avian species despite high metabolic rates and lifetime oxygen expenditures (Figs. 1 and 2) make aging in birds particularly intriguing in this context. Some authors have suggested that birds either have better cellular defenses against oxidative damage or produce fewer ROS during oxidative metabolism than shorter-lived mammals of comparable size and weight (Holmes and Austad 1995a, b; Barja 1998; Hulbert et al. 2007).

Caloric restriction, carbohydrate metabolism, and growth factors.—Another active research area in biogerontology concerns relationships between aging and caloric intake, somatic growth rates, insulin signaling, and other processes regulating cell growth and proliferation. Specific genes and metabolic pathways that control growth, development, and aging via growth hormone (GH) and insulin-like growth factor (IGF-1) are now implicated in a number of aging-related diseases (e.g., diabetes, cardiovascular disease, and inflammatory syndromes) and linked to genes for life-span variation in inbred mice, worms, and flies (Brown-Borg et al. 1996, Flurkey et al. 2001, Tatar et al. 2003, Partridge et al. 2005, Sonntag et al. 2005). In humans and laboratory animals, IGF-1 is a nonspecific regulator of cell proliferation and growth; it is secreted primarily by the liver under the influence of GH. Normal aging-related decreases in GH and IGF-1 have been shown to be correlated in some species with declines in lean body mass, bone density, immune function and cognition, and various other functional declines.

Experimental caloric restriction (CR) while simultaneously controlling for nutritional quality and micronutrient intake has been shown to be a reliable intervention in aging in a wide range of vertebrate and invertebrate species. Reduction of caloric intake of 20–30% below normal (ad libitum feeding) extends the normal life span in laboratory rodents 30–40%, and retards onset of a wide array of aging-related diseases (Weindruch and Walford 1988, Masoro 2001, Partridge et al. 2005). The anti-aging effects of CR may occur in part through altered carbohydrate and insulin metabolism, as well as via specific changes in transcription pathways regulated by IGF-1 and GH. Short-term food restriction has also been shown to reduce egg production and alter reproductive endocrinology in poultry species (Holmes et al. 2003b, Ottinger et al. 2005), but the effects of long-term CR on avian aging over the full course of the lifespan remain unexplored.

The effects of CR are likely a result of physiological and evolutionary tradeoffs between investment in reproduction and long-term somatic maintenance, and between dormancy states and long-term survival during environmental stress. This idea has been subjected to few direct tests using outbred animal models (Martin 1995a, Kirkwood and Austad 2000, Austad and Kristan 2003, Tatar et al. 2003, Ricklefs 2008). Although avian laboratory models (e.g., quail, Domestic Chicken [*Gallus gallus domesticus*], and songbirds) have long been a mainstay of developmental biology and neuroendocrinology, little research has directly addressed relationships among nutrition, development, growth, carbohydrate metabolism, and aging processes in birds. Given our common interests in evolutionary and developmental tradeoffs, there is potentially a great deal of intellectual common ground to be shared by biogerontologists and bird biologists interested in the nutritional and endocrine bases of evolutionary tradeoffs (reviewed in Monaghan et al. 2008; see, e.g., Alonso-Alvarez et al. 2007).

Aging Biomarkers and Avian Senescence

Field ornithologists obviously need robust, noninvasive methods for determining the concordance between age-related physiological changes and chronological ages of birds in the wild. Concurrently, biogerontologists are striving to develop reliable biomarkers of physiological senescence, other age-related functional changes, and disease susceptibility (Cristofalo 1988, Miller 2001, Butler et al. 2004, Johnson 2006b). Ideal measures of senescence, or aging biomarkers, would reliably predict an organism's future life expectancy or risk of mortality from intrinsic, aging-related causes (Table 1) or serve as a measure of the deterioration of particular functions or physiological systems. In addition, good biomarkers should allow repeated and non-invasive measurements without affecting the survival of individuals.

Aging measures currently used in work with laboratory animals include clinical blood parameters, incidence of pathological lesions, cellular markers of cancer and inflammation, and specific byproducts of oxidative metabolism and glycosylation implicated in disease states. Although many of these measures have been shown to correlate with changes in mortality, no biomarker or

TABLE 1. Ideal characteristics of an aging biomarker (adapted from Harper et al. 2004).

An ideal biomarker of aging should
(1) vary reliably with age and predict the future life expectancy of individuals in a given population when 90% of the population is still alive;
(2) predict the future deterioration of particular essential functions or physiological systems, or the probability of occurrence of specific aging-related diseases (i.e., provide a measure of fitness declines), and do so more reliably than chronological age;
(3) correlate with measurable aging-related declines in other physiological functions; and
(4) be measurable repeatedly so as not to influence future life expectancy or other age- or fitness-related traits.

combination of these measures, other than mark–recapture and monitoring methods, has been found that can accurately reflect an individual bird's chronological age, even in the laboratory.

Despite the lack of a single measure of aging that can meet an ideal set of criteria, parameters have been identified that show biologically meaningful, reasonably reliable variation with age in inbred laboratory animals under controlled conditions; some of these are potentially very useful to bird biologists. They include clinical measures of immune function, cardiovascular health and inflammation; cumulative oxidative damage to macromolecules (including nuclear and mitochondrial DNA); changes in reproduction and endocrine function (Cristofalo 1988; Meites 1988; Hamilton et al. 2001; Harper et al. 2003, 2004; Chaudhuri et al. 2006; Bentley and Muttukrishna 2007); and measures of physiological performance, strength, or frailty.

Some measures of functional aging are more meaningful for comparisons between species than for comparing individuals within a population or species (Harper et al. 2004, Speakman 2005a). Within species, even in highly inbred strains of animals maintained under pathogen-free conditions, there is much individual variation in rates of aging; offspring from a single litter or breeding attempt can have very different "agedness" profiles at a given chronological age (reviewed in Finch and Kirkwood 2000). Aging-related death and disease rates can be affected dramatically by nutritional status, infectious diseases, exercise, and other factors, as well as reproductive activity and effects of sampling error for older age classes (reviewed in Weindruch and Walford 1988, Finch 1990, Finch and Kirkwood 2000, Masoro and Austad 2005, Conn 2006). In laboratory studies, caloric restriction strongly influences aging and results in statistically reliable changes in aging biomarkers at the population level. Hence, nutritional and other forms of environmental variability are likely to be powerful influences on intrinsic aging rates in the wild, as well as in captivity.

Different physiological and functional systems are expected to have evolved under different selection pressures and constraints and, therefore, to sometimes show different rates and patterns of aging-related deterioration (Martin et al. 1996, Bronikowski and Promislow 2005, Promislow et al. 2006). To complicate things further, aging-related changes in health or condition (e.g., specific aspects of mobility or physiological function) in inbred laboratory animals may not be generalizable to outbred, free-living animals in natural environments that impose selection via predation, disease, and variation in food availability (Lithgow and Walker 2002, Austad and Kristan 2003, Baldal et al. 2006). Some aspects of aging in outbred, free-living animal populations may, in fact, more closely resemble aging in humans than that in inbred laboratory animals that are protected against disease and stress (Partridge et al. 2005, Lithgow 2006, Holmes and Kristan 2008, Monaghan et al. 2008, Ricklefs 2008).

Some of the most interesting aging measures currently being used in wild bird studies include declines in survivorship or reproductive output, neuroendocrine changes, changes in telomere dynamics, and functional immune measures (summarized in Table 2). Although most must be obtained invasively, measures of the accumulation of products of oxidative damage to avian cells and molecules also show promise, both in the laboratory and in the field. In the following sections, we discuss recent research employing such measures in bird studies that should be of interest to ornithology as a whole.

OXIDATIVE DAMAGE AND RESISTANCE MEASURES

Are avian cells exceptionally resistant to oxidative damage?—Healthy animal cells are thought to employ a variety of defenses against ROS-inflicted damage, including both structural features (e.g., oxidation-resistant lipids in mitochondrial membranes) and active molecular defenses (like antioxidant enzymes and other molecules) and repair systems. Several possible mechanisms for slowing the production and accumulation of oxidative damage have been suggested to exist in bird species. These mechanisms include better constitutive or inducible ROS defenses, like antioxidants, and more efficient ways of repairing cellular damage. In addition, some researchers have suggested that avian mitochondria may be especially efficient or produce fewer ROS during oxidative metabolism, creating less potential for cellular damage in the first place (Barja et al. 1994a; Holmes and Austad 1995a, b; Brand 2000; Hulbert et al. 2007; Lambert et al. 2007).

Several labs have begun to explore putative protective mechanisms of avian cells against oxidative damage (Table 3). They have employed a variety of methods from biochemistry, toxicology, and mitochondrial physiology—assessing the survival of isolated cells with respect to oxidative damage, for example, or measuring the production of ROS by isolated respiring mitochondria. These methods usually require *in-vitro* approaches. With few exceptions, they use samples from a variety of tissues from a few individuals that represent only a few bird species, comparing data from a small pool of vertebrate species with markedly different maximum documented life spans. Phylogenetic methods now widely accepted in evolutionary and comparative zoology, in which traits of interest are compared in large numbers of species from diverse taxa while statistically incorporating effects of shared ancestry (i.e., "phylogenetic independent contrasts"; Bennett and Huey 1990, Harvey and Pagel 1991, Promislow 1991), have not been used until very recently for testing specific predictions of the free-radical or other mechanistic aging theories

Table 2. Promising functional measures or correlates of aging in birds.

Correlate or functional measure of aging	References
Age-related declines in survivorship (detectable at population level)	Ricklefs 1998, 2000b; reviews in Holmes et al. 2001, Brunet-Rossinni and Austad 2006, Ricklefs 2008
Age-related declines in reproductive performance (e.g., courtship behaviors, sperm production, ovulation, oviposition, hatching and fledging success; at population or individual level)	Ottinger 1991, Ricklefs et al. 2003; reviews in Holmes et al. 2001, 2003b, 2006; Brunet-Rossinni and Austad 2006; Ricklefs 2008
Neuroendocrine changes correlated with age-related reproductive declines (e.g., brain levels of GnRH, sex steroid levels; photorefractoriness)	Ottinger et al. 1997, 2004; Nisbet et al. 1999; Angelier et al. 2007
Resistance of cells to oxidative damage *in vitro* (for tissues with high cell-turnover rates in adults)	Ogburn et al. 1998, 2001
Accumulation of oxidative damage to macromolecules (proteins, membrane lipids, DNA)	Pamplona et al. 1999, 2005; Liu 2004; Portero-Otín et al. 2004
Accumulation of advanced glycosylation end-products (AGEs) (e.g., pentosidine, carboxymethyllysine, etc.)	Beuchat and Chong 1998, Iqbal et al. 1999, Monnier et al. 1999, Klandorf et al. 2001, Pamplona et al. 2005, Fallon et al. 2006
Deterioration of mitochondrial membranes, DNA, and metabolism	Barja and Herrero 1998; Herrero and Barja 1998, 1999; reviewed in Pamplona et al. 2005
Changes in telomere dynamics, telomerase activity, or cell replicative capacity in differentiated, postmitotic tissues in adults	Venkatesan and Price 1998; Taylor and Delany 2000; Delany et al. 2000; Haussmann et al. 2003, 2007; Hall et al. 2004; O'Hare and Delany 2005; Swanberg and Delany 2006; Juola et al. 2006; Pauliny et al. 2006
Declines in disease resistance or functional immunity	Apanius and Nisbet 2003, Cichoń et al. 2003, Lozano and Lank 2003, Saino et al. 2003, Lavoie 2006, Palacios et al. 2007

(Austad and Holmes 1999; for exceptions, see Promislow 1991; Speakman 2005a, b; Hulbert et al. 2007; Lambert et al. 2007). Despite their sometimes limited taxonomic scope, studies like those we describe below have yielded valuable and provocative results and have refined thinking about the role of oxidative metabolism in aging.

Avian mitochondrial metabolism.—Several labs, using avian species from several different orders (Budgerigar [*Melopsittacus undulatus*], Rock Pigeon [*Columba livia*], Common Canary [*Serinus canaria*]), have reported that mitochondria of long-lived bird species either generate ROS more slowly or generate fewer ROS per oxygen molecule than mitochondria of short-lived laboratory rodents (e.g., Ku and Sohal 1993, Lopez-Torres et al. 1993, Barja et al. 1994a, Herrero and Barja 1998; Table 3). Some have also gathered data consistent with the idea that lower ROS production is localized to avian mitochondrial complex I (Barja and Herrero 1998, Lambert et al. 2007). Moreover, it has been suggested that avian mitochondria undergo metabolic "uncoupling" during oxidative phosphorylation, adaptively leaking protons across mitochondrial membranes and reducing ROS generation and oxidative damage (Barja 1998, Herrero and Barja 1998, Lesnefsky and Hoppel 2006, Hulbert et al. 2007). This idea has been related to *in-vitro* evidence of mitochondrial uncoupling in cells from calorically restricted laboratory rodents (e.g., Gredilla et al. 2001; Bevilacqua et al. 2004, 2005) and of lower ROS production rates by mitochondria of mammals with longer maximum life spans (Brunet-Rossinni and Austad 2004, Lambert et al. 2007). It remains unclear, however, whether the observed species differences in *in-vitro* mitochondrial ROS production can be generalized to living systems, whether uncoupling is directly implicated in the aging process (Brand 2000, Lesnefsky and Hoppel 2006, Lambert and Brand 2007), and whether this type of uncoupling occurs in an adaptive context in living animals.

Antioxidant levels.—Lowered production of ROS by avian cells could, in turn, require lower antioxidant levels to protect against oxidative damage. Several studies (Table 3) have compared levels of various antioxidant enzymes, as well as nonenzymic antioxidants like ascorbate, in avian and mammalian tissues. Most have reported lower levels of some endogenous antioxidants (superoxide dismutase, catalase, glutathione, and glutathione peroxidase) in birds and mammals with longer life spans (Lopez-Torres et al. 1993; Barja et al. 1994a, b; Perez-Campo et al. 1998; Jaensch et al. 2001). Others, by contrast, have shown higher levels of superoxide dismutase, glutathione, and glutathione peroxidase in tissues from these same bird (vs. mammal) species (Ku and Sohal 1993, Ku et al. 1993). In the most comprehensive comparative study of endogenous antioxidant levels in birds to date, Cohen et al. (2008) measured total antioxidant capacity, antioxidant response to stress, and levels of uric acid, vitamin E, and four carotenoids in 95 avian species in relation to life-history patterns. Most of these species were passerines, and the study included tropical and temperate-zone representatives. Higher antioxidant levels were generally found to be associated with smaller body size, higher mass-specific metabolic rates, more rapid development, larger clutches, and lower survival rates. Antioxidant–life history associations also showed some differences between tropical and temperate species, but these statistical relationships were by no means straightforward. As in previous studies with fewer vertebrate species, no simple relationships emerged between levels of specific antioxidants and species' life spans or other particular life-history traits. This is consistent with the lack of evidence of predictable relationships between constitutive antioxidant levels and longevity found in similar comparative studies of mammals, even including mammalian species within a single order with very different life spans (e.g., rodents; Buffenstein et al. 2008).

TABLE 3. Summary of studies comparing putative oxidative defenses in tissues of birds and mammals of similar body sizes and contrasting maximum life spans.

Parameters studied or results reported	Tissues and species compared	References
Efficiency of mitochondrial metabolism *in vitro*		
Fewer ROS generated per oxygen molecule; slower peroxide production by mitochondria of long-lived birds vs. lab rodents	Brain, heart, kidney, liver: pigeon vs. rat; canaries and parakeets vs. mice; various vertebrate species	1–4
Localization of lower ROS production by avian mitochondria to mitochondrial complex I; mitochondrial complex I and II content differed in long-lived birds vs. lab rodents	Brain: canaries and parakeets vs. mice	5, 6
Antioxidants		
SOD levels higher in tissues of long-lived birds vs. short-lived lab rodents	Brain, heart, kidney: pigeon vs. rat	1, 7
SOD levels lower in long-lived birds vs. shorter-lived mammals in some tissues; SOD levels uncorrelated with species life span	Brain, liver, lung: ≤7 assorted vertebrate species	2, 3, 8
CAT levels lower in long-lived birds vs. shorter-lived mammals	Brain, heart, kidney, liver, lung: pigeon vs. rat; 6–8 vertebrate species	1–3, 8
GSH and glutathione peroxidase levels higher in longer-lived birds vs. lab rodents in some tissues	Brain, heart, kidney: pigeon vs. rat	1, 7
GSH, glutathione peroxidase, and GSH reductase levels lower in longlived birds vs. short-lived mammals	Blood, brain, liver, lung: parakeet; 6–8 vertebrate species	2, 3, 8, 9
Uric acid uncorrelated with life span in long-lived birds vs. mammals	Brain, liver, lung: parakeet, canary, pigeon	2, 9
Ascorbate levels higher in longer-lived vertebrate species; ascorbate levels uncorrelated with species life span	Liver, blood, lung: parakeets	2, 9
Ascorbate levels negatively correlated with species life span	Brain, lung: 6–7 vertebrate species	3, 8
Measured total antioxidant capacity, antioxidant response to stress, levels of uric acid, vitamin E, and four carotenoids in relation to life-history patterns; higher antioxidant levels generally associated with smaller body size, higher mass-specific metabolic rates, more rapid development, larger clutches, and lower survival rates; some antioxidant–life history associations; some tropical vs. temperate species differences; complex statistical relationships; no straightforward correlations among specific antioxidants and species life spans or other life-history traits	Blood: 95 avian species, mostly passerines, temperate and tropical	18
Resistance of cells or specific macromolecules to oxidative damage, etc.		
Better survival after exposure to oxidants *in vitro* of cells from long-lived birds vs. short-lived birds or rodents; transcription necessary for resistance to damage in avian cells	Kidney epithelial cells: parakeets, starlings, canaries vs. mouse; embryonic fibroblasts: quail, parakeet vs. mouse, human	10, 11
Less protein oxidative damage in long-lived birds vs. short-lived rodents	Brain: canary, parakeet, mouse	6
Less nonenzymatic modification of proteins and proteosome activity in long-lived bird vs. short-lived rodents	Skeletal muscle: pigeon vs. rat	11
Less oxidative damage to lipids in long-lived birds vs. short-lived rodents; lower levels of fatty-acid unsaturation and lipid peroxidation in long-lived birds vs. short-lived mammals	Brain: canary, parakeet, mouse	6, 12
Less DNA unwinding and better DNA repair *in vitro* in cells from long-lived birds vs. short-lived birds or rodents; transcription required for resistance of DNA to oxidative damage in birds	Kidney epithelial cells: parakeets, starlings, canaries vs. mouse; embryonic fibroblasts: quail, parakeet vs. mouse, human	10, 11, 13
8-oxo-dG levels reported to correlate with individuals' age in skeletal muscle and brain of domestic Zebra Finches; skeletal muscle of older individuals of three wild species (Tree Swallows, Common Terns, and Leach's Storm-Petrels) reported to contain less detectable 8-OH-dG than that of middle-aged individuals	Various tissues	13
Compared levels of some AGEs (e.g., pentosidine, glycated hemoglobin) in tissues of short- or long-lived birds (including short-lived chickens, hummingbirds, others) vs. either short- or long-lived mammals; report AGE levels in birds generally lower than in mammals	Various tissues, including erythrocytes	6, 14, 15, 16, 17

Abbreviations: ROS = reactive oxygen species, SOD = superoxide dismutase, GSH = glutathione, CAT = catalase, and AGEs = advanced glycoxidative end-products. References: (1) Ku and Sohal 1993, (2) Lopez-Torres et al. 1993, (3) Barja et al. 1994, (4) Herrero and Barja 1998, (5) Barja and Herrero 1998, (6) Pamplona et al. 2005, (7) Ku et al. 1993, (8) Perez-Campo et al. 1998 (9) Jaensch et al. 2001, (10) Ogburn et al. 1998, (11) Ogburn et al. 2001, (12) Pamplona et al. 1999, (13) Liu 2004, (14) Beuchat and Chong 1998, (15) Iqbal et al. 1999, (16) Monnier et al. 1999, (17) Fallon et al. 2006, and (18) Cohen et al. 2008.

Whole-cell approaches.—Another approach to comparing resistance to oxidative damage of cells from different populations or species of animals involves isolating (and, in some cases, growing in culture) embryonic cells from representative individuals of long- and short-lived avian and mammalian species. Cells can then be exposed *in vitro* to various forms of oxidative stress (e.g., high concentrations of atmospheric oxygen, hydrogen peroxide, or paraquat). Using this approach, cells of longer-lived birds (European Starlings [*Sturnus vulgaris*], Common Canaries, or Budgerigars) have been reported to survive oxidative stress significantly longer and repair damaged DNA better than those of short-lived birds (i.e., Japanese Quail [*Coturnix japonica*]), laboratory rodents, or humans (Ogburn et al. 1998, 2001).

Damage to specific macromolecules.—Specific structural defenses against oxidative damage have also been examined in cells of some bird species. Parameters measured have included variation in structure and unsaturation levels of the fatty acids in mitochondrial membranes. In general, membrane lipids from long-lived birds have been shown to have lower levels of some markers of accumulated oxidative damage than those of short-lived mammals. This apparent resistance to damage also may be associated with lower levels of fatty-acid unsaturation and lipid peroxidation in avian membranes (Herrero and Barja 1999, Pamplona et al. 2005). Variation in fat composition in membranes of long- and short-lived vertebrates may not only enhance the stability of membrane lipids, but could underlie differences in mitochondrial metabolism and species differences in rates of damage accumulation (Hulbert 2003, Hulbert et al. 2007).

Presumably, the maintenance of functional cells—and organismal homeostasis as a whole—depends on sustaining the integrity of DNA. Permanent, irreparable oxidative damage could cause mutation, genomic instability, and the dysregulation of cellular and physiological processes (Beckman and Ames 1998, Hamilton et al. 2001, Cabelof et al. 2006). Hence, DNA oxidative lesions of various types have been adopted as biomarkers of aging and as clinical markers of certain diseases (i.e., cancers) or of exposure to environmental toxins. For example, 8-OH-dG (8-oxo-7,8-dehydro-2'-deoxyguanosine), a widely used marker of oxidative damage to nuclear and mitochondrial DNA, has been shown to accumulate with age in various tissues in humans and laboratory animals (Hamilton et al. 2001, Van Remmen and Richardson 2001, Kujoth et al. 2005). The rate of accumulation of such oxidative biomarkers can be altered reliably via caloric restriction (Ward et al. 2005, Mansouri et al. 2006).

Levels of 8-OH-dG in some tissues also have been reported to be correlated negatively with maximum potential life span in mammals and in a few bird species (reviewed in Pamplona et al. 2005, Muller et al. 2007). Liu (2004) assayed tissues from four bird species across a range of ages and found that 8-oxo-dG levels were correlated with the individuals' age in skeletal muscle and brain of captive Zebra Finches (*Taeniopygia guttata*). Remarkably, however, skeletal muscle of older individuals of three wild species also examined (Tree Swallow [*Tachycineta bicolor*], Common Tern [*Sterna hirundo*], and Leach's Storm-Petrel [*Oceanodroma leucorhoa*]) were reported to contain less detectable 8-OH-dG than that of middle-aged individuals. To our knowledge, this is the only study to explicitly address the hypothesis that this oxidative damage marker either accumulates or decreases with chronological age in birds. A key priority for ornithological researchers is additional, longitudinal characterization of promising biomarkers like this one, along with further development of less-invasive ways of obtaining tissue samples for assays.

"AGEs" and glycoxidative processes in birds.—Under normal *in-vivo* conditions, glucose in living cells interacts with proteins, nucleic acids, and other macromolecules in a complex series of nonenzymatic reactions. These include reactions called "glycosylation" and "glycoxidation," which can produce potentially damaging compounds known as "advanced glycosylation end-products" (AGEs). There is growing evidence that AGEs contribute to aging-related diseases and diabetes, including arthritis, kidney disease, ocular cataracts, and cardiovascular disease. Without effective mechanisms for prevention or repair, given their high metabolic rates and blood-glucose levels, birds might be expected to be more susceptible to accumulated damage from these compounds than their mammalian counterparts (Monnier 1990; Holmes and Austad 1995a, b; Austad 1997). Several recent studies on chickens suggest that birds may produce AGEs (e.g., pentosidine) at slower rates than mammals (Beuchat and Chong 1998, Iqbal et al. 1999, Monnier et al. 1999, Holmes et al. 2001, Klandorf et al. 2001, Fallon et al. 2006). Although limited in taxonomic scope, these data support the idea that birds somehow prevent AGE accumulation despite much higher blood glucose levels, and they are somewhat consistent with slower rates of accumulation of damaging DNA adducts like 8-OH-dG. With careful selection of appropriate tissues and biochemical protocols, AGE accumulation assays might be adapted for use in wild bird populations.

Avian Immunosenescence

Declines in immune function are a well-documented feature of aging in humans, domestic animals, and laboratory rodents and arguably one of the primary correlates of organismal senescence (Grubeck-Loebenstein and Wick 2002, Effros 2003, Miller et al. 2005). Aging-related deterioration of functional immunity, or "immunosenescence," includes increased susceptibility to infectious diseases and diminished responses to immunizations, as well as increased risk of cancers and autoimmune disease. Changes in some subpopulations of T lymphocytes have been identified as predictors of longevity and, hence, as promising aging biomarkers for rodents and other mammals (Harper et al. 2004, Miller et al. 2005).

Although extensive work on the chicken has shown the avian immune system to be similar in its general features to that of mammals, little work has focused specifically on avian immunosenescence (Lavoie 2005). But over the past decade, a few studies have documented some age-related immune changes in wild populations of birds, using either cross-sectional or longitudinal approaches (Table 4). For the most part, these have employed one or a few simple clinical assays of humoral or cellular immune responses; we are aware of no published studies of aging-related changes in avian lymphocyte subsets. The measures currently being developed, however, show definite promise as measures of changing functional immunity and resistance to disease as wild birds age in nature.

In one such study, in conjunction with long-term field studies of Barn Swallow populations, Saino et al. (2003) vaccinated

TABLE 4. Studies of aging-related immune changes in wild and outbred birds (results are for wild populations unless otherwise noted).

Immune parameter measured	Species	References
Humoral responses *in vivo*		
Decreased primary antibody response to NDV vaccine in breeding females; decreased secondary antibody response subsequent year in both sexes	Barn Swallow	Saino et al. 2003
Decline in antibody response to sheep red blood cells in females feeding nestlings	Collared Flycatcher	Cichoń et al. 2003
No change in acquired antibody response to sheep red blood cells in females; no change in innate immunity (NABs or hemolysis titers)	Tree Swallow	Palacios et al. 2007
No change in IgG levels in breeding males; IgG correlated with reproductive performance	Common Tern	Apanius and Nisbet 2003, 2006
Cell-mediated responses *in vivo*		
Marginally significant aging effect on skin PHA hypersensitivity response in males; higher response overall in nonbreeding males	Ruff (*Philomachus pugnax*)[a]	Lozano and Lank 2003
Declines in skin PHA response in all species studied; rate of decline proportionate to species life span, average 57% decrease over 80% of maximum life span	Zebra Finch (in laboratory), Tree Swallow, Leach's Storm-Petrel	Haussmann et al. 2005
Decreased T-cell proliferation to PHA and conA (up to 84% lower in the oldest females, independent of breeding status or stress of handling); no change in response to LPS	Tree Swallow	Palacios et al. 2007

Abbreviations: NDV = Newcastle disease virus, NABs = natural antibodies, PHA = phytohemagglutinin, conA = concanavalin A, and LPS = lipopolysaccharide from *Salmonella typhimurium,* a B-cell mitogen.

[a]Captive colony.

breeding adults with killed Newcastle disease virus (NDV) and monitored their ability to raise primary and secondary antibody responses during the first year of vaccination and the following breeding season. They found that older (four-year-old) breeding females showed significantly lower antibody responses during the first year of treatment; their secondary responses averaged only about one-third that of two-year-old females. In the second year after immunization, older individuals (2–6 years old) of both sexes showed a trend toward a significantly diminished secondary antibody response. Similar age-related changes in acquired humoral immunity to sheep red blood cells, a nonspecific antigen, were observed by Cichoń et al. (2003) in Collared Flycatchers (*Ficedula albicollis*) that were feeding nestlings, with one-year-old females showing the highest antibody titers. Titers declined with advancing age and were lowest in the oldest (5–6 years) adults.

A more comprehensive picture of age-related immune changes was obtained in a study of female Tree Swallows, in which Palacios et al. (2007) combined measures of cell-mediated acquired immunity (*in vivo* and *in vitro*) with assays for innate humoral immunity. They also performed *in-vitro* assays of T-cell proliferation in response to each of two mitogens, PHA and concanavalin A. *In-vitro* responses to a B-cell mitogen, LPS (lipopolysaccharide from *Salmonella*), did not vary with age; nor did *in-vivo* antibody responses to immunization with sheep red blood cell antigen or two measures of innate humoral immunity. These results seem consistent with work on breeding Common Terns (Apanius and Nisbet 2003) that correlated reproductive performance and serum IgG levels but showed no apparent aging effect on immunoglobin levels.

As these studies suggest, some aging-related immune changes may be exhibited reliably by wild birds, and in some cases these may be detectable rather early in the aging process. Other measures, however, show little aging-related change consistent with senescence in functional immunity. In humans and laboratory rodents, declining T-cell proliferative responses are an important correlate of aging; it is far from clear how these particular types of cellular responses might change with aging in any free-living vertebrate populations. It is a reasonable expectation, however, that older birds should rely and invest differentially in some forms of immunity as fitness tradeoffs and relative costs of specific immune functions change over the course of the life span.

In laboratory studies of immune aging, animals typically are maintained in pathogen-free conditions, and changes in resistance to infectious disease and other parameters relevant to fitness in free-living animals—including humans—generally are not measured (Austad and Kristan 2003, Holmes and Austad 2004, Lithgow 2006). Wild bird populations, by contrast, provide opportunities for exploring specific predictions about aging-related changes in immunity in natural environments where disease and parasites are expected to have significant effects on survivorship and reproductive success (Ricklefs and Wikelski 2002, Haussmann et al. 2003, Holmes and Austad 2004, Martin et al. 2006, Palacios et al. 2007). The progressive effects of aging, including immunosenescence, might be predicted to show stronger or earlier effects on survival or reproduction in wild birds subject to ecological pressures; this possibility has yet to be explored. Few studies, moreover, have directly compared aspects of immunity in short- vs. long-lived birds, or between species with different developmental or life-history patterns (Tella et al. 2002; Matson et al. 2006a, b).

The emerging discipline of "ecoimmunology" has generated an explosion of studies adopting clinical measures of immune function to test evolutionary hypotheses in outbred vertebrate populations. Areas of intense interest include the relationships among immune function, sexual selection, and mate choice;

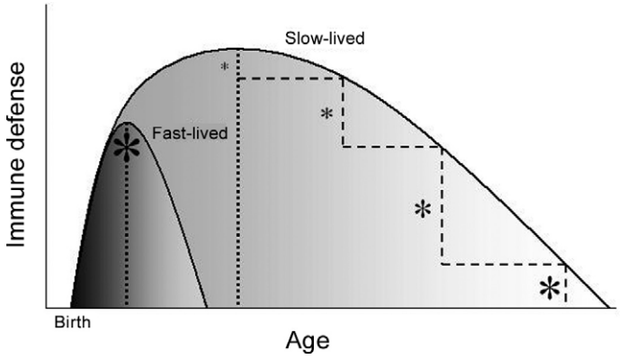

Fig. 4. Predicted patterns of development and senescence of immune defenses in fast- and slow-living species. Dotted line stands for age at first reproduction. Shaded portion of graph represents transition from nonspecific (dark) to specific (light) immune defenses: fast-living species are predicted to rely on nonspecific defenses for most of their lives. "Stair-stepped" part of graph shows predicted variability in rate of aging-related immune declines during seasonal transitions between breeding and nonbreeding conditions: larger decrements per step show bias toward investment in reproduction with advancing age. Asterisks indicate breeding events; asterisk size represents breeding effort per event. (Reproduced from Martin et al. [2006] with permission of L. Martin and Highwire Press.)

the stress response and nutritional status; and defenses against infectious disease and parasites (e.g., Norris and Evans 2000, Alonso-Alvarez and Tella 2001, Martin et al. 2006). An ecoimmunological framework could readily be applied to more directly address evolutionary questions about avian aging, life-history tradeoffs, and reproductive costs. This would require careful experimental integration of immunosenescence measures in wild animals with other biomarkers of aging, such as assays for oxidative damage, inflammation, specific disease states, or other physiological stressors. In addition, we need to know how immune changes in wild birds actually reflect variation in fitness and reproductive success, or how species with different life histories make tradeoffs between immunocompetence and other evolutionary priorities.

Some avian biologists have begun to integrate predictions from life-history theory with ideas about immunosenescence, suggesting that immune-system declines should vary qualitatively along a "fast–slow" continuum of life-history strategies (Lochmiller and Deerenberg 2000, Norris and Evans 2000, Tella et al. 2002, Martin et al. 2006, Matson et al. 2006a; see Fig. 4). Shorter-lived populations or species are predicted to invest less in immune defenses overall and to rely on less expensive, nonspecific immune functions rather than costly acquired defenses against particular pathogens. A vigorous discussion is in progress concerning the need for refinement and better integration of various measures of immune fitness for studies of wild vertebrates (Franceschi et al. 1999, Adamo 2004, Palacios and Martin 2006). This is an area in which studies of wild bird populations hold great promise for a more integrated approach to understanding organismal aging.

Telomere Dynamics and Avian Aging

Telomeres, which are highly repetitive nucleotide sequences located on the ends of eukaryotic chromosomes, are essential for the replication of linear DNA. In healthy tissues undergoing cell replication, telomeres are maintained by telomerase, a reverse transcriptase. Interest in aging-related changes in telomere maintenance and telomerase function arose from the observation that telomeres shorten progressively as somatic cell lines in culture (e.g., human epithelial fibroblasts) undergo repeated rounds of replication and division. These cells typically replicate a finite number of times before the population either dies out or "transforms" to become cancer cells. This loss of replicative capacity or "cellular senescence" *in vitro* is accompanied by telomere shortening and loss of telomerase activity, ostensibly increasing genomic instability. This phenomenon led cell biologists to the concept of a "telomere clock"—the idea that telomere shortening rates (or declining telomerase activity) provide a measure of loss of replicative capacity (and, hence, a marker of aging) in terminally differentiated animal tissues. Critical changes in telomere structure and function have been implicated in the transformation of healthy to cancerous cells in humans and rodents, and evidence is accumulating that telomere dynamics are important in these species in aging and in some aging-related diseases, such as cancer (Blackburn 1991, Hastie et al. 2003, Kujoth et al. 2005, Wright and Shay 2005).

But there is no particular reason, *a priori*, to expect that telomere lengths or other aspects of telomere dynamics will reflect variation in organismal aging patterns—even between species within a vertebrate class—in a straightforward way. Telomeres of cells from adult laboratory rodents, for example, are considerably longer than those of similar cells from adult humans, and replicative senescence in rodent cells *in vitro* does not correlate predictably with telomere shortening as it does in human cells. However, long-lived organisms are expected to have more efficient ways of responding to stressors, preserving healthy capabilities for cell replication and preventing cancers, and these are likely to involve aspects of telomere dynamics (Shay and Wright 2001, 2005; Wang et al. 2001). It is interesting, in this context, that aging-related telomere shortening rates in some tissues have been reported to correlate inversely with documented life spans of some vertebrates, including some bird species (Haussmann et al. 2003, Vleck et al. 2003).

Given that many birds are exceptionally long-lived for their sizes and metabolic rates, it stands to reason that they may have particularly efficient regulation of cell replication. Thus, the concept of an avian telomere clock has received considerable attention recently (reviewed in Taylor and Delany 2000). The measurement of avian telomeres can be complicated by the unusually large size of the avian telomeric genome, and there is considerable variability reported in the lengths of telomere fragments measured from different avian tissues and species (Table 5; Delany et al. 2000, Swanberg and Delany 2006). The chicken telomeric genome, the best-studied of all bird species, includes about 10× more DNA than the human telomeric genome. Avian class-III terminal restriction fragments (TRFs) are the largest described for telomeres of any vertebrate group, with lengths ranging from 40 kilobases to 2 megabases.

In some respects, avian telomere dynamics resemble those in human tissues more closely than those in rodent tissues. As in

TABLE 5. Some key studies of avian telomere dynamics relevant to senescence.

Focus of study	Species, ages, and tissues	Key findings and references
Characterization of avian telomere structure and TRF shortening in cultured cells *in vitro*	Domestic Chicken and 12 other species from diverse avian orders: adults and embryos; somatic cells (erythrocytes, sperm, embryonic tissues)	Telomeric sequence generally 5–10 times more abundant in birds than in humans; identified three classes of avian telomeric DNA: class I, 0.5–10 kbases (interstitial); class II, 10–40 kbases (detectable in typical TRF smears); and class III, ≤3 megabases; require specialized detection techniques; not present in all species examined; "ultralong" sequence detectable in all but two species; molecular weight varies with tissue type No *in-vivo* age-related changes in average TRF (class II) lengths detected; shortening of class II arrays with age detected in chicken cells cultured *in vitro* (3.2-kbase decrease in average TRF length from early embryo to adult) (Delany et al. 2000, Taylor and Delany 2000, Nanda et al. 2002; reviewed in Swanberg and Delany 2006)
Measured TRF lengths in relation to age in domestic and wild populations (cross-sectional study)	Zebra Finch,[a] Tree Swallow, Adélie Penguin (*Pygoscelis adeliae*), Common Tern, Leach's Storm-Petrel: subadults and adults; erythrocytes	Average TRF length declined with chronological age in Zebra Finch, Tree Swallow, Adélie Penguin, and Common Tern; increased with age in Leach's Storm-Petrel; rate of telomere shortening correlated with species life span (Haussmann et al. 2003)
Measured TRFs in wild populations (cross-sectional and longitudinal studies)	European Shag (*Phalacrocorax aristotelis*), Wandering Albatross (*Diomedea exulans*): subadults and adults; erythrocytes	TRF lengths declined between chick stage and adulthood, but not correlated with age in adults; concluded that rates of telomere loss not constant with age; high inter-individual variation could be attributable to conditions during growth (Hall et al. 2004)
Measured TRFs in wild population (cross-sectional study)	Great Frigatebird (*Fregata minor*): subadults and adults; erythrocytes	TRF length declined more rapidly early in life but continued to shorten in adults; rate of decline not tightly correlated with age (Juola et al. 2006)
Characterization of avian telomerase activity *in vitro* and tissues from living birds	Domestic Chicken: various ages from 1 day old: cultured embryonic fibroblasts, germline cells, assorted somatic tissues (erythrocytes, sperm)	Telomerase active in some tissues of adult chickens; down-regulated in cell cultures established from embryos; replicative senescence in chicken fibroblast cells in culture (Venkatesan and Price 1998, Delany et al. 2000, Taylor and Delany 2000, O'Hare and Delany 2005)
Telomerase activity measured in tissues from living birds	Zebra Finch,[a] Tree Swallow, Adélie Penguin, Common Tern, Leach's Storm-Petrel: adults and subadults; muscle, liver, intestine, kidney, brain, gonad, bone marrow of most species	More activity of telomerase from bone marrow in species with lower rates of TRF shortening and longer life spans; telomerase may not be down-regulated in tissues of adults in some birds (Haussmann et al. 2007)

Abbreviation: TRF = telomere restriction fragment.

[a]Domestic birds.

humans, for example (but unlike in mice), avian telomerase has been shown to be down-regulated in many organs postnatally, after tissues have completed differentiation, remaining active only in tissues with high cell turnover or particular cell lines that have undergone transformation to a precancerous state *in vitro* (Swanberg and Delany 2003, Swanberg and Payne 2004). An initial comparison of erythrocytes and sperm from a few individuals for each of 18 bird species revealed no reliable relationships among TRF lengths and either the age of individuals or documented species life spans (Delany et al. 2000). But more recent cross-sectional studies including considerably larger numbers of individuals from wild populations of a number of avian species (with a wide range of documented life spans) have reported age-associated shortening of TRFs derived from erythrocytes (Haussmann et al. 2003, Vleck et al. 2003, Juola et al. 2006) (Table 5 and Figs. 5 and 6). Moreover, contrary to expectations, these authors reported that telomere fragment lengths from Leach's Storm-Petrels were *positively* correlated with chronological age. A later, longitudinal

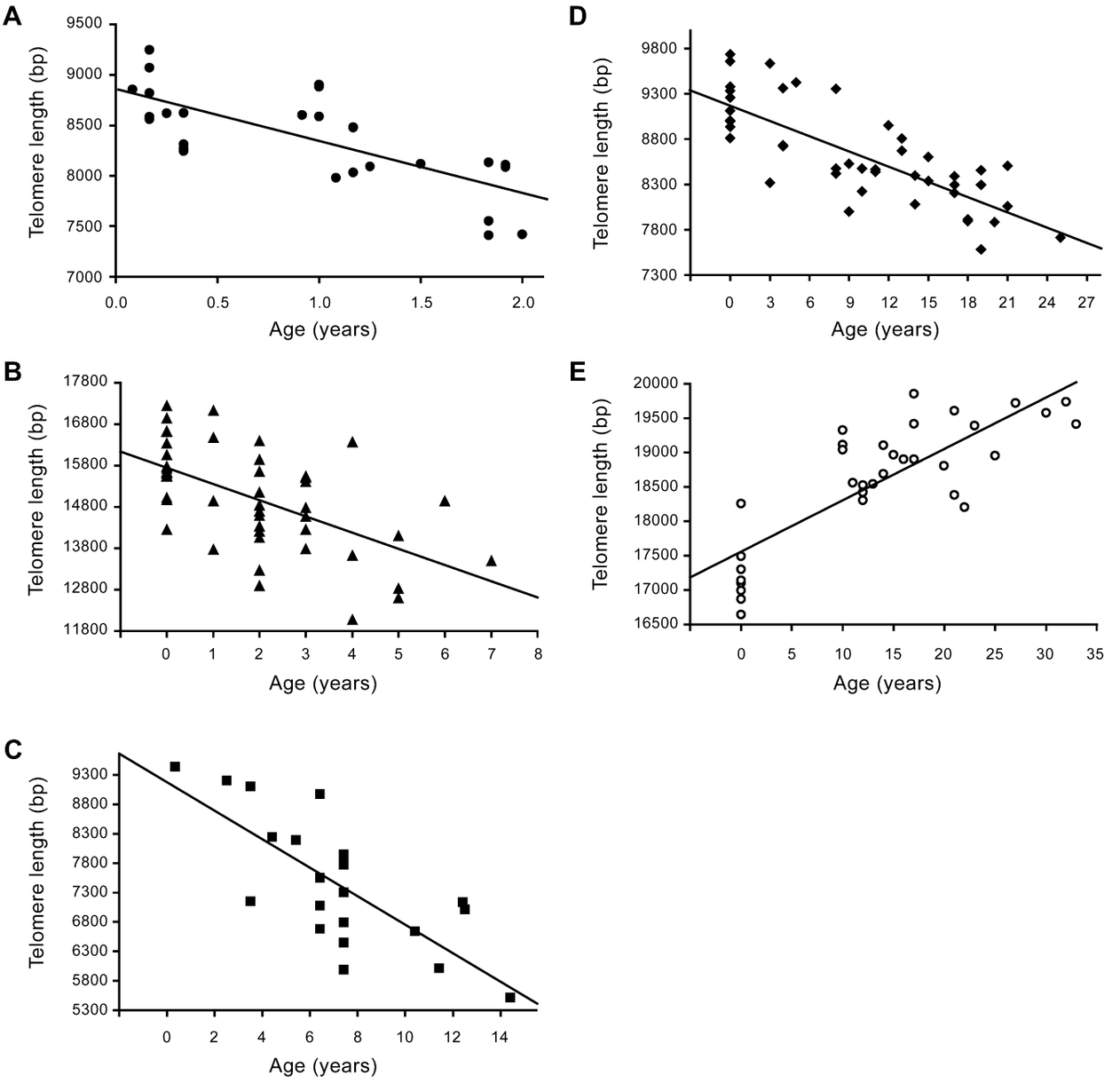

Fig. 5. Cross-sectional examination of relationships between age and telomere (TRF) lengths (from erythrocytes) in one domestic and five wild bird populations: (A) domestic Zebra Finch, (B) Tree Swallow, (C) Adélie Penguin (*Pygoscelis adeliae*), (D) Common Tern, and (E) Leach's Storm-Petrel. Note that subadults are included for all but Leach's Storm-Petrel and that telomere lengths increase with age in this species. (No samples obtained from Leach's Storm-Petrels 1–9 years old; young do not return to breeding site until 3–6 years after fledging.) Lines are best-fit regressions: (A) slope = –515 ± 95 (SE) base pairs (bp) year^{-1}, $F = 29.9$, df = 1 and 26, $P < 0.0001$, $r^2 = 0.54$; (B) slope = –391 ± 65 bp year^{-1}, $F = 23.3$, df = 1 and 47, $P < 0.0001$, $r^2 = 0.34$; (C) slope = –235 ± 48 bp year^{-1}, $F = 23.9$, df = 1 and 21, $P < 0.0001$, $r^2 = 0.55$; (D) slope = –57 ± 7 bp year^{-1}, $F = 67.0$, df = 1 and 43, $P < 0.0001$, $r^2 = 0.61$; (E) slope = +75 + 10 bp year^{-1}, $F = 59.7$, df = 1 and 32, $P < 0.0001$, $r^2 = 0.66$. (Reproduced from Haussmann et al. [2003] with permission of M. Haussmann and the Royal Society.)

study of several different wild bird populations, on the other hand, reported no telomere shortening or lengthening in erythrocytes when younger birds were eliminated from the analysis (Hall et al. 2004). The authors of this last study suggested that aging-related telomere shortening is likely to be overestimated in studies when subadult birds are included (age = 0; Table 5), given that tissues of younger, immature birds may not be composed of terminally differentiated cells.

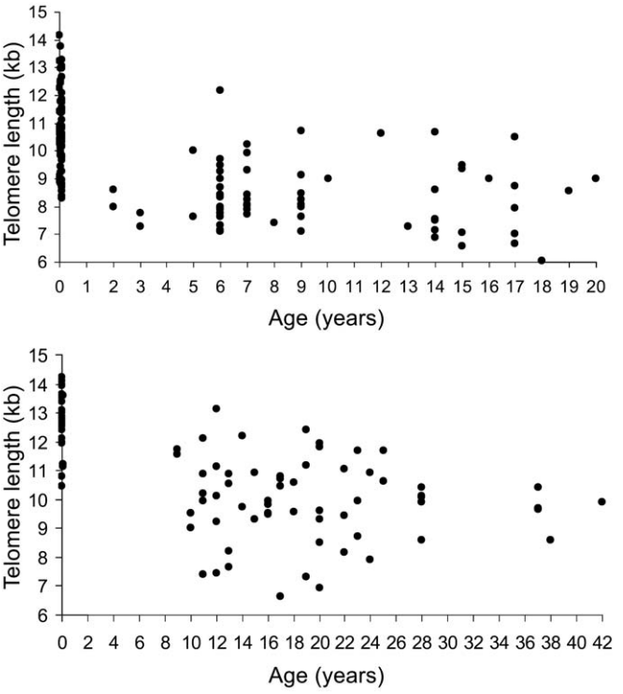

FIG. 6. Cross-sectional comparisons of telomere lengths (from erythrocytes) as a function of age in two wild seabird populations: (A) European Shag and (B) Wandering Albatross. Although telomere length appears to decline with age with youngest age classes are included, no significant associations were detected between telomere length and age in adults. For European Shags, $r = -0.08$, $P = 0.54$, $n = 63$; for Wandering Albatrosses, $r = -0.08$, $P = 0.52$, $n = 61$. (Reprinted from Hall et al. [2003] with permission of P. Monaghan and the Royal Society.)

It is important to recognize that telomere lengths (and any aging-related changes in TRFs) are expected to vary substantially among tissues with different cell-turnover rates. Terminal restriction fragments could fail to reflect either organism age or tissue age (i.e., number of cell replications) in cell lines that are not terminally differentiated (e.g., germ cells, some blood cells, or in tissues from young animals that are still undergoing development). Telomere lengths from a given tissue type can also vary considerably among individuals, even in inbred laboratory animal populations, as well as with organismal health, nutritional state, and history, including exposure to oxidative or other stressors (Levy et al. 1998, Hastie et al. 2003, Shay and Roninson 2004).

Despite the complexity of these issues, and the as-yet-unexplored variability of telomere genomes and dynamics among avian species, the data on telomeres and telomerase activity from wild bird populations are provocative. This emerging area merits additional, careful study and critical analysis—particularly in the context of other aging-related functional changes and fitness tradeoffs (see, e.g., Monaghan and Haussmann 2006). Evolution is expected to produce an array of defenses against molecular stress and damage; the telomere shortening typical of replicative senescence in humans, for example, may represent one, but not the only, kind of adaptation whereby longer-lived species preserve genomic integrity (Shay and Wright 2001). The influence of environmental conditions (e.g., stress and food availability) on telomere dynamics within a species is of particular interest to ornithologists. More controlled, longitudinal studies—both in captivity and in the wild, and using a range of tissue types from a variety of bird species—will be needed to clarify the significance of age-related changes in telomere dynamics and telomerase activity in birds with different aging patterns.

FUTURE DIRECTIONS IN "AVIAN BIOGERONTOLOGY"

Major research priorities for the biology of aging include the identification of molecular, physiological, and evolutionary mechanisms that allow, as well as prevent, organismal senescence, and that promote sustained somatic maintenance and reproduction in exceptionally long-lived species—including many birds. A better understanding of the generality of basic aging mechanisms in a wide taxonomic range of model organisms has obvious utility for intervention in diseases of aging. Current research priorities of avian and evolutionary biologists are quite compatible with those of more medically oriented biogerontologists, given their common strong focus on the roles of genes and the environment in creating and maintaining healthy, integrated animal phenotypes. Below, we summarize several areas we view as potentially ripe for cooperation and shared research contributions by ornithologists and biogerontologists.

Evolutionary aging and life-history theory.—Biogerontology and ornithology have a common investment in evolutionary theory as a framework for understanding the "fast–slow" continuum of development, maturation, and [in] aging patterns seen among living organisms, including the laboratory species commonly used in studies of basic aging processes (Rose 1991, Martin et al. 1996, Reznick et al. 2004, Reznick 2005). For several decades, studies of wild bird populations have focused on the effects of specific ecological variables on life-history evolution and life span, including predation, food supply, latitude, altitude, extreme cold, and migration patterns (e.g., Ricklefs 1973, 1990, 2000a; Botkin and Miller 1974; T. E. Martin 1987; K. Martin 1995; Wiebe and Martin 1998; Ricklefs and Scheuerlein 2003; Møller et al. 2005; Sandercock et al. 2005b; Møller 2006; Dobson and Jouventin 2007; Wilson 2008; Bears et al. 2009). Despite demonstrations that many birds undergo some form of aging in the wild, however, it is unknown how aging-related deterioration varies across populations in relation to environmental conditions and whether such deterioration contributes in a significant way to changes in fitness or lifetime reproductive success. More comprehensive studies of aging-related immune changes in wild, breeding birds should lead to a clearer understanding of how specific aspects of immunity and other physiological functions actually reflect variation in condition or stress resistance and how species with different life histories make tradeoffs between immunocompetence, reproduction, and other evolutionary priorities. Avian ecoimmunology holds particular promise for a more integrated approach to understanding senescence in nature, and this discipline is stimulating the adoption of clinical measures of immune function for testing hypotheses from life-history and sexual-selection theory using both captive and wild populations of birds.

Biogerontologists have expressed particular interest in very long-lived birds, like seabirds, that inhabit insular habitats and are

subject to very low mortality rates (Finch 1990; Ricklefs 1990; Holmes and Austad 1995a, b; Ricklefs and Finch 1995; Holmes 2003). Recent seabird studies have shown little appreciable change in immune function or reproductive endocrinology in older breeding birds (Ottinger et al. 1995; Nisbet et al. 1999, 2002; Apanius and Nisbet 2003) but suggest the intriguing possibility that older birds may compensate for declines in physiological condition with increases in reproductive effort (Velando et al. 2006, Torres and Velando 2007, Keller et al. 2008) or enhanced physiological resistance to stress (Angelier et al. 2007; but see Heidigger et al. 2008). Apart from being intrinsically interesting from ecological or evolutionary standpoints, sustained low rates of reproduction with little apparent aging-related loss of fertility in birds could have implications for understanding basic mechanisms of human reproductive aging and infertility.

Physiological tradeoffs and reproductive costs.—A particularly strong focus of avian biology now centers on potential costs of reproduction accrued from exposure to steroid sex and stress hormones and the relationships between antioxidant defenses, fitness, and reproductive success. Although genetic and physiological tradeoffs are sometimes considered in studies of basic aging processes, a rigorous evolutionary perspective is often lacking; this is arguably one of the most important shortcomings of standard biogerontological approaches currently (Partridge et al. 2005, Lithgow 2006). Sustained fertility and slow, healthy aging are expected to be related in evolutionary terms, and genes responsible for variation in life span probably also control, in many cases, key aspects of reproduction (Kirkwood and Austad 2000, Partridge et al. 2005). Consideration of reproductive costs and the possible evolutionary tradeoffs (e.g., antagonistic pleiotropy) among fertility, somatic fitness, and longevity are relevant to a number of current aging-related medical priorities, including human reproductive aging issues and cancers (Stearns et al. 2008).

Energy metabolism, oxidative stress, and nutrition.—Currently, a primary focus of biogerontology is the relationship between aging and oxidative stress and damage to cells and macromolecules, and how key aspects of energy metabolism and growth rates are related to life span. Ornithologists are likewise engaged in studies of the relationships among nutritional status (particularly in relation to antioxidants), hormonal influences, growth rates, and such fitness parameters as immune function and stress resistance (see, e.g., Alonso-Alvarez and Tella 2001; Metcalfe and Monaghan 2001, 2003; Blount et al. 2003; Alonso-Alvarez et al. 2006, 2007; Criscuolo et al. 2008). Researchers increasingly recognize the importance of studies like these to the biology of aging generally, their implications for human health and developmental biology, and the potential for interdisciplinary collaboration in exploring these issues.

Sexual selection, sexual conflict, and mate choice.—The biology of aging has distinct implications for addressing theoretical questions about sexual conflict, mate choice, and the evolution of mating systems, given that there are strong correlates of sex differences in aging and mortality patterns in many animals, including humans (e.g., Promislow et al. 1992, Promislow 2004, Clutton-Brock and Isvaran 2007). Sex differences in the roles of steroid hormones in long-term health, including immune function, susceptibility to parasites and disease, and the ability to combat oxidative and other stresses have direct clinical relevance. For example, Bonduriansky et al. (2008) suggested that sexual selection and male reproductive strategies may result in elevated mortality and weakened selection on life span in males compared with females. Currently, however, there is little direct discussion or collaboration among evolutionary biologists, behavioral ecologists, and biogerontologists in addressing these issues.

Comparative approaches to studies of basic aging processes.—Comparative approaches of various kinds have long provided important insights into the basic processes underlying senescence in both wild and captive studies (reviewed in Austad and Holmes 1999, Holmes and Kristan 2008). Although natural populations typically show patterns of survival and reproductive investment consistent with predicted survival–fecundity tradeoffs, the mechanisms responsible for these aging patterns remain elusive. For example, rates of aging-related mortality in field studies of birds are often highly correlated with mortality resulting from extrinsic age-independent causes, such as predation, harsh weather, or habitat conditions, rather than from the predicted causes of intrinsic (aging-related) mortality, such as cancer or cardiovascular failure (Ricklefs 2008). Furthermore, in captivity, where resources are plentiful, the life spans of birds and mammals appear to be unrelated to investment in reproduction (Ricklefs and Cadena 2007). More field studies using comparative approaches are needed to determine the cause of death in natural populations and to characterize variation in rates of aging within and across populations, and we need more detailed longitudinal studies of individual health and reproductive success in relation to age at death (Monaghan et al. 2008, Nussey et al. 2008). Such comparative studies should help to quantify differences in aging rates between different physiological systems and reveal how each contributes to fitness at different life-history stages (Promislow et al. 2006). Although multispecies comparisons of aging and life span have long been used by biogerontologists, phylogenetic statistical approaches have been applied only recently for addressing comparative questions about proximate aging mechanisms (Haussmann et al. 2003; Speakman 2005a, b; Hulbert et al. 2007; Lambert et al. 2007). In addition, clinical and genetic markers, as well as other variables, should prove useful for identifying phenotypic traits that contribute to the probability of longevity (Møller and Szép 2002, Priest et al. 2002, Saino et al. 2002, Møller 2006).

Value of reliable aging biomarkers in avian conservation biology.—The development of aging biomarkers for avian populations has wide potential application for both diagnosis and prescription in ecology, conservation, and management. Such biomarkers would allow greater insight into the relationships and the ecological importance between senescence and other cohort effects in response to environmental gradients or stressors. Where population life histories vary with altitude or latitude, intensive, long-term longitudinal studies could be used to assess potential effects of climate change on particular age cohorts. Current field techniques often can distinguish only two or a few "cohorts" of adults—first-time breeders and all older birds—making it difficult to diagnose effects of overhunting or other elevated mortality factors.

Improved physiological or molecular measures of aging might eventually allow earlier diagnosis of populations or cohorts of birds in peril, if such measures reflected environmentally altered patterns of actuarial or physiological senescence that are actually correlated with reduced vital rates. For declining populations of threatened

species, such as the Horned Lark subspecies *Eremophila alpestris strigata* in Washington state (Pearson et al. 2008), such aging biomarkers might be particularly useful. Reliable, biologically meaningful measures of cellular or molecular damage, specific functional declines, or other signs of physiological stress in known-age individuals might eventually be employed to weigh the relative contributions of habitat loss or degradation to intrinsic aging-related changes, as opposed to "normal," extrinsic mortality forces. In critically endangered populations, such as the Northern Spotted Owl (*Strix occidentalis caurina*) in British Columbia, where all remaining birds in the populations are older, a biomarker that could measure reproductive senescence would have wonderful efficacy for identifying those individuals in the best condition to set up a captive breeding program. For threatened species, many of which are long-lived, we might save valuable time and maximize successful breeding attempts in captivity if we could develop biomarker for separating 'chronologically old' from 'physiologically old' individuals.

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