

# Birds as Models of Aging in Biomedical Research

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## INTRODUCTION

The remarkably long lives of birds have been recognized for centuries (Bacon 1638). Like mammals, birds exhibit a rough positive correlation between body mass and maximum recorded life span (Sacher 1959; Lindstedt and Calder 1976). However, at any specific body mass, birds average some 2 to 3 times the longevity of mammals (Holmes and Austad 1995a,b). Specific avian groups are even longer-lived than this overall average. Even the shortest-lived bird species, the common quail (*Coturnix coturnix*), survives 7 to 8 years in captivity (Woodard and Abplanalp 1971; Ottinger and others 1983), which is longer than at least 20% of described mammal species (Austad unpublished data). Long-lived birds such as macaws, which weigh 500 to 1000 g, may occasionally live as long as 100 years (Etchepare 1990).

Recently it has become apparent that birds achieve these remarkable life spans despite possessing several traits that modern theories of aging suggest should make them substantially shorter-lived than mammals. First, reactive oxygen species, which are highly damaging molecules produced as a normal by-product of aerobic metabolism, are now thought to contribute substantially to the generalized degenerative changes of aging across a wide spectrum of species (recent reviews in Sohal 1993; Martin and others 1996). An index of exposure to such molecules is thought to be lifetime oxygen consumption per cell in an organism. Yet oxygen consumption *per unit time* per cell of birds can range as high as 2 to 2.5 times that of mammals (Calder 1984). So when this level of oxygen consumption is combined with the long lives of birds, one may postulate that lifetime exposure to reactive oxygen species in long-lived avian cells may be 10 to 20 times that of short-lived mammals such as mice and 2 to 5 times that of even long-lived mammals such as humans (Table 1). Clearly birds have evolved some type of especially effective mechanisms for protecting against the accumulation of oxidative damage. The details of these protective measures remain elusive. It may be that because of more effective electron scavenging in avian mitochondria, birds produce fewer reactive oxygen species per unit of oxygen

consumption (Conlon and others 1991; Ku and Sohal 1993; Barja and others 1994) or that birds have more active enzymes for detoxifying these molecules (Schweigert and others 1991; Ku and Sohal 1993). However, research into these areas has so far been limited, and evidence has been somewhat conflicting.

A second significant contributor to aging in tissues rich in long-lived proteins is hypothesized to be the formation of irreversibly glycosylated proteins via Maillard-type reactions (Cerami 1985; Monnier 1990). The Maillard reaction, long known to food chemists, consists of the nonenzymatic attachment of reducing sugars (that is, glycosylation) to susceptible amino acid residues of proteins, which causes "browning." Cooked meat is an example of a Maillard reaction. "Browned" proteins may have differing chemical and physical traits than their unbrowned precursors, or the glycosylation itself may interfere with the active site of enzymatic proteins. In either case, glycosylated proteins would be expected to be less effective at performing the tasks they evolved to perform. Accumulation of the advanced glycosylation products may even be facilitated by oxidative reactions (Kristal and Yu 1992; Sell and Monnier 1995).

Birds should be especially prone to the formation of glycosylated proteins, because the Maillard reaction is accelerated by increasing the concentration of glucose, which is the primary reactant, or by increasing the temperature of reaction. Birds have blood glucose concentrations 2 to 4 times higher, and body temperatures 3 to 5° C warmer, than mammals (Ritchie and others 1994). Because birds apparently avoid problems due to accumulated glycosylation products for much longer than mammals, they are likely to possess some type of especially effective defenses against the accumulation of Maillard reaction products. Superior defenses against these hypothesized aging mechanisms make birds particularly valuable models for aging research in that study of the design of avian defenses may illustrate how we might improve human defenses against these processes.

## AGING IN SELECTED AVIAN GROUPS

In both birds and mammals, flying species are considerably longer-lived than nonflying species of similar body size (Pomeroy 1990; Austad and Fischer 1991; Holmes and Austad 1995b). One reason for this may be that flight assists animals

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**TABLE 1** Longevity, body mass, and lifetime metabolic expenditure in humans, mice, and several bird species (modified from Holmes and Austad 1995a)

Species	Maximum longevity (years)	Body mass (g)	Body temperature (°C)	Fasting blood glucose (mg/dl)	Lifetime metabolic potential (kal/gl)
House mouse	4+	30	37	80-120	250
Human	120	50,000	37	80-120	800
Raven	69	1,200	?	?	1,400
Zebra finch	12	12	38-44*	291-391	1,450
Budgerigar	21	30	41.7	254-399	1,900
Canary	35	250	39.8-43.3	232-369	2,300
Pigeon	24	22	?	291-391	3,200
Eurasian goldfinch	27	16	?	?	400

\*The body temperature of many birds varies somewhat with environmental temperature, state of excitement, or activity.

in escaping various environmental dangers such as predators or local habitat deterioration (Pomeroy 1990). An evolutionary history of low mortality from nonsenescent causes is considered to lead to the evolution of retarded aging rate (Edney and Gill 1968; Charlesworth 1980).

A corollary of the notion above is that weakly flying species might be expected to age more rapidly than strongly flying species. Although data sufficient to critically evaluate this notion are lacking, birds of the order Galliformes (grouse, pheasants, quail, chickens, turkeys), a group of weak fliers, do appear to be exceptionally short-lived (Holmes and Austad 1995b and unpublished data). By contrast, the acrobatically flighted swifts (order Apodiformes) have exceptionally low mortality rates for their body size and the biogeographic region in which they live (Pomeroy 1990). Also particularly long-lived are the parrots (order Psittiformes), in which some captive individuals of large species have been reasonably well-documented to approach or exceed the 100 year mark (Etchepare 1990), although reproductive senescence may be reached much earlier (Clubb and Karpinski 1992). Also notable for their exceptional longevity are oceanic seabirds of several orders (Holmes and Austad 1995a), some of which show no decline in reproductive activity to at least 40 years of age (Ollason and Dunnet 1988). Some hummingbirds, in spite of body masses less than 5 g, have survived more than a decade in nature (Calder 1990).

It must be emphasized that any apparent patterns in the taxonomic distribution of avian aging must be accepted as provisional. Except for a handful of cage bird species, virtually every demographic analysis of avian longevity comes from mark and recapture studies, the validity of which will depend on initial banding and subsequent recapture effort. Since many recapture studies are opportunistic rather than systematic (for example, Klimkiewicz and Fitcher 1989), the reliability of conclusions about field longevity of individual species will be extremely variable.

However, as they age, birds display many of the same degenerative changes as mammals. For instance, aged macaws exhibit weight loss, muscle atrophy, reduced activity, stiffening joints, increased incidence of dermal dysplasia, generalized thinning of skin, and senile cataracts (Clubb and Karpinski 1992). A wide range of age-related pathologies have also been reported in birds, and many of these are specifically analogous to human diseases. For instance, congestive heart failure commonly occurs in mynahs and poultry. Atherosclerotic lesions are common in aged parrots, pigeons, ducks, and geese and occur in many other species less frequently (Lumeij and Ritchie 1994). Atherosclerosis of the myocardial vessels is detected most commonly in parrots (Johnson and others 1992).

Birds are also susceptible to a wide range of neoplasias, which are catalogued in a centralized database for most commonly kept companion species. Budgerigars appear to be particularly susceptible, with an overall incidence of 17 to 24% (Beach 1962; Blackmore 1966; Latimer 1994), whereas passerine birds have among the lowest incidence of tumors of any order of bird or mammal (Macwhirter 1994).

## CANDIDATE SPECIES FOR DEVELOPMENT AS AGING MODELS

Some wild passerines adapt readily to captivity and have been used successfully in studies of avian endocrinology and nutrition (for example, Murphy and King 1990). However, probably the most suitable models for aging research occur among small pet bird species. These species as a group have been domesticated and thus bred in captivity for generations, having likely undergone significant artificial selection for traits that allow them to thrive in captive conditions. Each of these species also has reasonably well-developed husbandry and at least some available information on common patholo-

gies and appropriate commercially available supplies such as feed and nest boxes. Extensive avian pathology records exist for many cage bird species as part of the Veterinary Medical Database currently housed at Purdue University. Information from that database is commercially available.

The advantage of using relatively small birds as opposed to larger pet species is that acquisition, maintenance, and facility costs will all be lower. Also, small birds typically live 1 to 2 decades instead of 5 or more decades like some of the larger parrots. The disadvantage, of course, is that non-destructive sampling of tissues is more difficult and samples must be smaller.

Before considering individual small species, one might consider a larger species, the domestic pigeon (*Columba livia*). Pigeons weigh approximately 250 g and have been domesticated for centuries. They are a popular animal model in comparative psychology and have contributed to considerable research on pigeon neuroanatomy and neuroendocrinology. In fact, a recent search of the current MEDLINE database (1990 to the present) returned more than 1100 papers in which pigeons were the primary animal model.

Pigeons reach sexual maturity in 4 to 6 months and typically lay 2 eggs. The young are fledged in 3 to 4 weeks (Vogel and others 1994). The sexes are distinguishable only by internal examination or by behavioral means during the breeding season. Pigeons have a reported maximum longevity of 35 years, and some breeds (such as the White Carneau) are known to contract cardiovascular disease (NRC 1981). Two recent studies comparing free radical production and antioxidant activity between rats and pigeons have been performed (Ku and Sohal 1993; Barja and others 1994). Many captive colonies exist.

The best candidates for aging research among the small pet birds appear to be the 3 species listed here and discussed below: zebra finches, canaries, and budgerigars.

## Zebra Finches

Zebra finches (*Taeniopygia guttata*) are seed-eating passerine birds found in virtually all the open country of Australia as well as in the Lesser Sunda islands. The Australian subspecies (*T.g. castanotis*) is significantly larger than the Lesser Sunda subspecies (*T.g. guttata*) (12.1 g vs. 11.1 g), and both are somewhat smaller than domesticated animals (12.7 g) (Zann 1996). Zebra finches are by far the smallest of the 3 candidate species considered here. They also have the fastest life cycle, which defines their chief advantage as an avian model for aging studies. Unlike other Australian finches that first breed at 6 to 12 months, zebra finches are capable of breeding within 2 to 3 months of hatching (Zann 1996). Socially, they live in large groups but are behaviorally monogamous. They produce clutches of 4 to 6 eggs at intervals of about 2 months. In nature, zebra finches have a median longevity of 2 to 3 months, with maximum survival of about 4.5 years (Zann and Runciman 1994). In captivity under good conditions, they can live 5 to 7 years (Burley 1985),

with maximum survival reported to be about 12 years (Austad and Holmes 1995a). Zebra finches are sexually dimorphic in plumage, and the sexes can be easily distinguished visually by 1 month after hatching. They exhibit early behavioral differences in their ability to learn songs and have been used extensively for the study of sexually dimorphic brain development (Shen and others 1995; Foidart and Balthazard 1995), so considerable information exists on their behavior and neuroendocrinology.

Zebra finches are one of the most popular cage birds in the world. They have been bred in captivity since at least the mid-19th century, and they breed so readily that it is often necessary to remove nest boxes to prevent continuous reproduction. All domesticated strains outside Australia have derived from the Australian subspecies, and by now domesticated strains probably approach at least 100 generations of captive breeding (Zann 1996). Approximately 30 different plumage color varieties have been developed during this period. Outside Australia, domestication has led to heavier offspring compared with aviary-reared wild-caught birds. Domesticated females also have longer wings, have longer and deeper bills, and take longer to reach adult size than their wild counterparts. Inside Australia, domesticated birds are actually smaller than their wild-caught counterparts (Zann 1996), an interesting contrast due to unknown factors.

Besides having a rapid life cycle, zebra finches have the other requisite advantages of avian aging models. Their lifetime metabolic potential approaches twice that of humans (Table 1). They also have the typically high avian blood glucose (Macwhirter 1994). Their body temperature is somewhat labile, varying considerably with ambient temperature. They are susceptible to overheating at temperature extremes. For instance, a zebra finch will die within an hour if its body temperature reaches 45 to 46°C (Calder 1964). Unfortunately, the distribution of pathologies available for many cage birds via the Veterinary Medical Database is not readily accessible for zebra finches, due to an unfortunate combining of all finch species in that database.

The recommended density of these birds for captive breeding is 0.3 to 0.4 m<sup>3</sup> per pair (Zann 1996). Unlike most other domesticated species, zebra finches have not become tame. No matter how much they are handled, they still invariably fly when approached and typically cannot be trained to be handled by humans except with some sort of restraint.

## Canaries

Canaries (*Serinus canarius*) are seed-eating passerines that originated in the Canary Islands but have been domesticated since at least the 16th century (Dodwell 1976). For centuries, there has been artificial selection by fanciers for distinctive plumage varieties as well as various body sizes and shapes. Other fanciers have bred birds for distinctive song types. Both male and female canaries sing, although their song structure is substantially different. Neurobiologists have been very interested in the structure and function of

brain regions involved in their song (for example, Gahr and Garcia Segura 1996). Male canaries modify their song each year, which has been associated with the annual death and recruitment of neurons in certain brain regions (Kirn and others 1994; Nottebohm and others 1994), a phenomenon not known to exist in mammals.

Canaries are not as trivially easy to breed as the other species discussed here. They are also considerably more expensive to obtain. Clutch size in canaries is 4 to 6 eggs, laid 1 egg per day. Females begin incubating immediately, causing asynchronous hatching and hatchlings of various sizes in the nest. To avoid mortality due to competition among different sized nestlings, breeders generally remove the first 4 eggs, replace them with dummy eggs, and then put the original eggs back when laying is nearly finished. Young fledge at 3 to 4 weeks, but allowing hens to lay more than 2 to 3 clutches per year is considered deleterious to their health. The sexes are monomorphic with respect to plumage, and the best method for determining sex is to identify their singing during the breeding season.

## Budgerigars

Budgerigars (*Melopsittacus undulatus*), more commonly but improperly called “parakeets,” are small, highly gregarious, seed-eating psittacine birds native to Australia. Like the previously discussed species, they possess all the traits of interest to aging researchers. They are long-lived and consume 2 to 3 times as much oxygen per gram of body tissue per lifetime as humans (Table 1). They also have exceptionally high blood glucose (250 to 400 mg/dl) and a higher than average avian body temperature (41.7° C) (Petrak 1982), conditions that facilitate the formation of advanced Maillard end-products.

Budgerigars have been domesticated since the mid-19th century and are thought to be the most common pet and exhibition bird in the world (Hart 1970). Capable of breeding year-round under the proper conditions, budgerigars are bred by the thousands in both large and small commercial establishments throughout the world. They are fecund (3 to 8 eggs per clutch, up to 10 clutches per year), rapidly developing (sexually mature at 5 to 6 months), and quite tame when handled regularly (Kavanau 1987). In their current role as a darling of fanciers who breed them for specific plumage characters, budgerigars seem oddly reminiscent of house mice just before they were adopted as the laboratory standard for mammalian genetics.

Largely as a consequence of their popularity and small size, budgerigars are inexpensive to purchase and maintain, and an enormous variety of commercially available diets and other maintenance supplies have been developed for them. Also probably due to their popularity as pets, there is more known about their physiology and clinically relevant parameters, such as normal blood chemistry and hematology values, than any avian species besides poultry. Common infectious diseases and other pathologies are also well-described,

as are a variety of invasive veterinary procedures for ill birds (Ritchie and others 1994).

Budgerigars are prone to several age-related pathologies—primarily many types of cancers (Petrak and Gilmore 1982) but also diabetes mellitus (Hockleithner 1994). They are also prone to obesity in captivity and must be given room to exercise or fed a diet of low caloric density (Macwhirter 1994).

## CONCLUSION

Without question, birds have a great deal to teach us about the successful management of factors thought to be centrally involved in aging, such as oxidative load and the long-term toxic effects of glucose. A variety of species suitable for development as animal models exists to investigate these processes, and with relatively little effort, such models could be implemented.

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