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Review article

Ageing studies on bats: a review

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Abstract

Bat biologists have long known about the exceptional longevity of bats (Order: Chiroptera), which is unusual for mammals of such a small size and a high metabolic rate. Yet relatively few mechanistic studies have focused on this longevity. On average, species of Chiroptera live three times longer than predicted by their body size. In addition, bats have other life history traits that are characteristic of large, long-lived mammals such as few and large offspring and slow growth rates. Bats fit the evolutionary theory of ageing, as their extended longevity is predicted by their ability to escape extrinsic mortality through flight and, in some species, hibernation. They also show tradeoffs between longevity and reproduction, as predicted by the disposable soma theory of ageing. From a physiological perspective, bat longevity reportedly correlates with replicative longevity, low brain calpain activity, and reduced reactive oxygen species production. As long-lived and physiologically interesting organisms, bats may prove to be an informative model system for ageing research.

Introduction

In his novel 'Dracula,' Bram Stoker cemented the well-known association between vampires and the often misrepresented bat. Ironically, Stoker probably did not know about the exceptional longevity of bats. He based his connection on a New York newspaper clipping describing the feeding habits of the common vampire bat (which was named after the blood-sucking creature of folklore and not vice versa). However, the association was serendipitously appropriate – the immortal prince of darkness is now linked forever to these long-lived mammals.

There are approximately 1100 species of bats worldwide, accounting for almost one-fourth of all mammal species. Only the order Rodentia contains more species. Body sizes of bats vary from the 2-g hog-nosed or bumblebee bat (*Craseonycteris thonglongyai*) to the 1200-g large flying fox (*Pteropus vampyrus*). Bats are found in every continent except Antarctica and occupy a variety of ecosystems from deserts to temperate forests to rainforests. On many oceanic islands, bats are the only native mammal species. Bats roost in caves, mines, tree canopies and hollows, abandoned and occupied buildings, under leaves and bark, and even under rocks (Kunz 1982). They exploit almost every feeding niche available to them, with different species specializing in insectivory, frugivory, nectivory, piscivory, carnivory, and sanguinivory. Behaviorally, bats show a gamut of different social systems from solitary tree bats to harem-forming fruit bats to enormous colonies comprised of millions of individuals.

The order Chiroptera is divided into two suborders, the Megachiroptera which include the flying foxes and fruit bats of the Old World, and the Microchiroptera which include some bats of the Old World and all bats of the New World. At one time, there was a discussion regarding whether the Chiroptera represented one or two independent

evolutionary lineages (Pettigrew et al. 1989; Pettigrew 1994; but see Van den Busche et al. 1998; Simmons 2000). Some researchers proposed that Megachiroptera were more closely related to primates and dermopterans (flying 'lemurs') than to Microchiroptera. The evidence they adduced included similarity to primates and dermopterans in penis morphology (Smith and Madkour 1980) and in possessing a binocular retinotectal visual pathway. The pathway is monocular in microchiroptera (Pettigrew 1986; Pettigrew et al. 1989). However, today most bat systematists believe the order represents a single evolutionary lineage as evidenced by extensive morphological and molecular data (Simmons 2000).

Similar to birds, the bodies of bats are powered by high metabolic rates, which may increase up to 20-fold during flight (Racey and Speakman 1987). Yet, these rates can vary extensively seasonally and among species. Species living at latitudes with large seasonal temperature fluctuations are typically heterothermic, using hibernation to survive long winters without food, and daily torpor to reduce energy expenditure while roosting (Lyman 1970). During hibernation, bats' metabolic rate may drop to one-hundredth of waking rate. The extent of daily torpor depends on ambient temperature but metabolic rate may drop to one-tenth of waking rate (Hill and Smith 1984). Early gerontologists attributed the exceptional longevity of bats *entirely* to this reduced metabolism (Bourliere 1958; Sacher 1977).

Species living in tropical areas or that migrate to warmer regions during the winter are considered homeothermic as they do not hibernate. Nonetheless, there is a wide range of thermoregulation among tropical bats. Most megachiroptera are true homeotherms while many other species show daily fluctuations in body temperature with low temperatures during inactivity and others enter daily torpor (Lyman 1970; Speakman and Thomas 2003).

For biogerontologists, the most interesting aspect of bats is their truly exceptional longevity (see Table 1). To take a particularly spectacular case, the 7-g Brandt's bat (*Myotis brandtii*) has been documented to live at least 38 years in the wild (Wilkinson and South 2002). Once adjusted for body mass, bats are the longest lived mammal order (Bourliere 1958; Austad and Fischer 1991; Wilkinson and South 2002). On average, species of Chiroptera live three times longer than non-flying eutherian mammals of comparable size and metabolic rate (Austad and Fischer 1991). Bat biologists have known about this exceptional longevity for over 30 years (Tuttle and Stevenson 1982), but ageing research has almost entirely overlooked this order of mammals. A key element to understanding the biology of ageing will be to determine differences and similarities in ageing patterns among species and to uncover the molecular, cellular, and physiological mechanisms underpinning the variation in species longevity. Bats should be key subjects for these studies.

Table 1. Longevity records of bats mentioned in this article and some non-flying mammals for comparison.

Species	Body mass (g)	Maximum lifespan (years)
Chiroptera		
Myotis brandtii	7	38
Myotis lucifugus	8	34
Eptesicus fuscus	22	19
Myotis daubentonii	9	28
Rosettus aegyptiacus	146	22.9
Tadarida brasiliensis	11	10
Rhinolophus ferrumequinum	23.5	30.5
Vespertilio murinus	16	12
Non-flying mammals		
Peromyscus leucopus	25	8
Blarina brevicauda	6	2
Mus musculus	30	4
Rattus norvegicus	350	5

We could not find a longevity record for the bat *Murina leucogaster*. Source: Wilkinson and South (2002) and mammalian longevity database from S. Austad.

In this article, we review trends and correlations in life-history traits of bat species relative to other mammals and summarize the current state of ageing research on bats. We then discuss some advantages and disadvantages of using bats as model organisms for ageing. Finally, we present future research ideas in a number of fields relevant to gerontology, which may benefit from the use of bats as study organisms.

Bat life-history traits: the constraints of flight

Bats defy some of the basic trends in life-history traits that characterize mammals in general. De-

spite having a small body size and consequent high metabolic rate, bats produce few and large young, reminiscent of much larger mammals such as elephants, and like birds, their anatomy, physiology, and life-history are constrained by flight. These life-history traits are very consistent among bat species despite the great ecological diversity of the order (Barclay and Harder 2003).

Based on life-history traits such as age of maturity and reproductive rate, mammalian species can be placed along a fast–slow continuum (Read and Harvey 1989). The fast extreme is characterized by species of a small body size which develop and reach sexual maturity rapidly, produce a large number of small offspring, and are short lived. At the slow extreme, species tend to be large, have long gestation and developmental periods, produce few large offspring, and are long lived. Extrinsic mortality rates play a critical role in the evolution of these life-history trait patterns (Harvey and Zammuto 1985; Promislow and Harvey 1990, 1991). Species at the fast extreme experience high extrinsic mortality making it evolutionarily advantageous to invest in high and rapid reproductive output. Species at the slow extreme experience low extrinsic mortality which allows them to spread out their reproductive output and produce fewer young but invest more heavily in their survival and competitive ability.

Bats are somewhat paradoxical in that they lie at the slow end of this continuum despite their small body size (Barclay and Harder 2003). In addition to their long life, they produce few large offspring (Kurta and Kunz 1987; Hayssen and Kunz 1996; Barclay and Harder 2003). Of 133 species, 62% have one offspring per litter, 23% have one offspring with occasional twins, and 15% have more than two offspring in a litter (Hayssen et al. 1993). Newborn bats weigh 15%–30% the mass of the postpartum mother (Tuttle and Stevenson 1982). Producing such large offspring logically requires a long gestation period, and fetal development rates in bats are generally slow. Gestation periods of 66 species range from 35 to 205 days with a mode of 120 days (Hayssen et al. 1993). Pregnancy length of heterothermic species can also vary in response to environmental conditions (Racey 1982). Postnatal development is also slow (Jones and MacLarnon 2001; Barclay and Harder 2003). Bat offspring take relatively long to reach full adult size (3–4 months for many species; Tuttle and Stevenson 1982), and the age at sexual maturity is typically later than the age at adult size, an unusual characteristic among mammals (Tuttle and Stevenson 1982; Jones and MacLarnon 2001).

Studies of bat life-history traits propose that the uniqueness and general consistency of life-history traits among bat species are due to constraints imposed by flight (Jones and MacLarnon 2001; Barclay and Harder 2003). Most bat species have one reduced ovary and uterine horn, likely to reduce body mass for flight. This anatomical constraint likely limits litter size. Flight may also impose anatomical constraints that necessitate near adult skeletal development at fledging. Forearm length at fledging is >90% that of the adult (Barclay 1994). Twisting stresses and the necessity to maintain wing shape may preclude flight until limb and digit bones are fully ossified. This may explain why the age of sexual maturity in bats is later than that of adult size (Jones and MacLarnon 2001). Also, calcium, required to produce bones capable of withstanding the physical strains of flight, may be a limiting factor to bat reproduction as their diets are typically calcium-poor (Barclay 1994, 1995). Finally, flight is energetically costly per unit time (not distance) relative to terrestrial locomotion (Thomas 1987), especially so after the weight gain associated with pregnancy. Hayssen and Kunz (1996) found that litter mass of 15 species of Megachiroptera is reasonably predicted by female body mass, but among Microchiropteran species, aerodynamic constraints (e.g. wing loading) influenced litter mass more than female body mass. The expense of flight appears to limit litter mass and may translate to fewer net resources available for reproduction relative to a non-flying mammal.

Why do bats live so long?

Few studies have addressed bat longevity, and the few that *have* reached sometimes conflicting conclusions as a consequence of steadily improving data on chiropteran longevity. Most bat longevity records are obtained by the fortuitous recapture of tagged individuals in the wild, so our knowledge of their lifespan changes over time and our records

are likely underestimates of maximum lifespan (Austad and Fischer 1991; Wilkinson and South 2002).

Some authors have argued from the standpoint of the rate of living theory (Pearl 1928; Sacher 1959; Sohal 1986) that the extreme longevity of bats is nothing more than a consequence of reduced metabolism during hibernation (Bourliere 1958; Sacher 1977). This observation fails to consider bats that do not hibernate, such as tropical species. Jürgens and Prothero (1987) found that after accounting for torpor and hibernation, lifetime basal energy consumption and body mass reasonably predict the maximum lifespan of hibernating bats, but not of non-hibernating bats. Later studies comparing maximum longevity records of hibernating and tropical bats concluded that hibernation could not be the explanation for bat longevity, as hibernating bats do not live longer than non-hibernating bats (Herreid 1964; Austad and Fischer 1991). However, using an extensively updated data set, Wilkinson and South (2002) found that the maximum lifespan of hibernating bats averaged about 6 years longer than that of non-hibernating species. Hibernation may extend longevity in the wild by concealing bats from predators as well as retarding physiological deterioration (Barclay and Harder 2003), but it does not account for the fact that *all* bat species live significantly longer than non-flying mammals of the same size, including non-flying mammals that hibernate (Jürgens and Prothero 1987; Austad and Fischer 1991).

As originally formulated, the rate of living theory proposed the existence of a constant mass-specific lifetime energy expenditure for all mammals (Sacher 1959). Bats, however, expend on average double the amount of energy in a lifetime compared to non-flying eutherian mammals (Austad and Fischer 1991). Reworked, the theory attributes ageing to imperfect physiochemical processes which lead to the accumulation of biochemical mistakes and damage to an organism's tissues (Sohal 1986). This implies that, all other things being equal, longevity should be inversely correlated with metabolic rate, and thus body size. The longevity quotient (ratio of observed longevity to longevity predicted by body size) for the Chiroptera is 3.0. This means that on average bats live three times longer than expected based on body size (Austad and Fischer 1991), contradicting the rate of living theory. There are conflicting conclusions regarding whether longevity correlates with body mass within the Chiroptera. Austad and Fischer (1991) and Jones and MacLarnon (2001) found no correlation. However, Wilkinson and South (2002) found a correlation when using an analysis of phylogenetically independent contrasts, which accounts for phylogenetic relationships among the species analyzed.

One agreement among researchers is that the exceptional longevity of bats is consistent with the evolutionary theory of ageing, and flight is implicated once again. This theory attributes ageing to the decreasing strength of natural selection with increasing age (Medawar 1952; Williams 1957; Charlesworth 1980). Under reduced selective pressure, late-acting deleterious alleles and alleles that are beneficial early in life but deleterious late in life can accumulate in the genome. Organisms that escape extrinsic mortality (e.g. starvation, predation, disease, accidents, etc.) with exceptional success then evolve to be long lived because natural selection remains powerful until later ages. Although adult bats are vulnerable to predators and the weather and infants are additionally vulnerable to falling from the roost and abandonment (Tuttle and Stevenson 1982), this exposure is low compared with other mammals, as bats are able to fly away from predators and many species adjust their body temperatures, metabolic rates, and movement patterns to survive severe weather conditions and low food supplies (Wilkinson and South 2002; Barclay and Harder 2003). This reduced mortality risk leads to the evolution of increased longevity as evidenced by the long lifespan of birds, bats and gliding mammals (Holmes and Austad 1994) and by the positive correlation between longevity of bats and their use of protected caves for roosting and hibernation (Wilkinson and South 2002).

Bat longevity patterns also support the disposable soma theory of ageing (Wilkinson and South 2002). According to this theory, organisms face an inevitable evolutionary tradeoff between using limited energy and resources for somatic maintenance or to increase reproductive output. Organisms that experience high extrinsic mortality benefit from investing in a high and quick reproductive output, whereas organisms experiencing

low extrinsic mortality can invest in somatic maintenance and extend their reproductive output over a longer lifespan (Kirkwood 1977, 1996). Among bats, longevity is lower in species with high reproductive rates (Rachmatulina 1992; Wilkinson and South 2002; Barclay and Harder 2003) and early sexual maturation (Rachmatulina 1992). For example, the 4-g black myotis (*Myotis nigricans*) produces three offspring per year and has a maximum longevity of 7 years, compared to the slightly larger fringed bat (*Myotis thysanodes*) which produces one offspring per year and has a maximum longevity of 18 years (Wilkinson and South 2002). Additionally, Ransome (1995) found that female horseshoe bats (*Rhinolophus ferrumequinum*) that bred later in life had higher survival rates than females breeding early in life.

How do bats live so long?

Few studies address the molecular or physiological mechanisms involved in the extreme longevity of bats. One recent study investigated bat longevity from the perspective of oxidative stress, or the free radical theory of aging. According to the free radical theory, ageing is a consequence of the accumulation of unrepaired oxidative damage due to the production of reactive oxygen species (ROS) mainly during mitochondrial respiration (Harman 1956; Sohal 1986). The rate of ageing would then in principle be related to oxidative stress – the rate of ROS production relative to the organism's capacity for ROS scavenging or repairing ROS-induced damage. Analyses of oxidative stress both across and within species have suggested that reduced production of ROS is a more reliable correlate of increased longevity than is activity of various endogenous antioxidants (Barja 2002). Bats appear to be consistent with this trend. Brunet-Rossinni (2004) measured hydrogen peroxide production of mitochondria isolated from tissues of little brown bats (*Myotis lucifugus*), short-tailed shrews (*Blarina brevicauda*) and white-footed mice (*Peromyscus leucopus*). Mitochondria of *M. lucifugus* produced significantly lower levels of hydrogen peroxide per unit of oxygen consumed by the individual than mitochondria of either shrews or mice. Brunet-Rossinni also tested the activity of superoxide dismutase (SOD) in tissue homogenates of these three species and found no differences. While not an all-inclusive assessment of antioxidant defenses, this research suggests that bats mitigate oxidative damage by producing low levels of ROS despite high metabolic rates.

The limited replicative lifespan of fibroblasts in culture has also been hypothesized to be causally involved in aging, although this is an intensely disputed hypothesis (Cristofalo and Pignolo 1995). A more recent form of this theory attributes some functional aspects of aging to telomere dynamics (Blasco 2003).

In a comparative study of eight mammals, Röhme (1981) found a positive correlation between species' maximum lifespan and replicative lifespan of cultured fibroblasts. Röhme included in this analysis one bat, *Vespertilio murinus*, and because longevity data were not available for that species, he used as a measure of maximum lifespan the average reported maxima (13.8 years) of the subfamily Verpertilioninae, to which *V. murinus* belongs. He observed that bat fibroblasts underwent an average of 18 population doublings, more than rats and mice but fewer than rabbits and horses. Rabbits are substantially shorter lived than most bats; horses are probably somewhat longer lived than most bat species. Of possible relevance to this observation, telomere length as measured as the terminal restriction fragment in liver from *Tadarida brasilensis*, a short-lived bat (maximum longevity 8 years in the wild, 10 years in captivity) averaged 13.5 kb (range: 11.3–16.6), substantially shorter than in mice (Dudek, Kunz and Austad, unpublished data).

Other studies using cell cultures from bat tissues to investigate longevity have not been completed, but are underway in our and several other laboratories. Fibroblast cell cultures from bat tissues are easily established from skin biopsies (Moratelli et al. 2002) and wing membrane. Cell cultures established from whole kidney tissue of little brown bat (*Myotis lucifugus*) and big brown bat (*Eptesicus fuscus*) appear to result in a mixture of cell types (K. Carlberg, personal communication).

In another study of possible significance for mechanisms of aging, calpain activity was measured in two species of bats (Baudry et al. 1986). The calpains are a family of nonlysosomal calcium-dependent cysteine proteases that have been

implicated in a wide range of cellular functions including apoptosis, proliferation, and cell migration. Inappropriate activation of calpain has been been implicated in age-related pathologies of the kidneys, heart, connective tissue, and eyes as well as certain myopathies, Alzheimer's disease and the several degenerative responses to stress (Bahr et al. 1991; Vanderklish and Bahr 2000).

Calpain hydrolyses a broad spectrum of endogenous proteins (Croall and DeMartino 1991). During development, calpain is involved in establishing synaptic organization and plasticity and long-term potentiation. Later in life, calpain activity increases in the ageing brain, perhaps due to deteriorating inhibitory mechanisms. This increased calpain activity appears to break down proteins that are important to the stability and maintenance of neuronal networks (Vanderklish and Bahr 2000; Sloane et al. 2003).

Baudry et al. (1986) tested the hypothesis that because calpain activity is inversely correlated with brain size and brain size is correlated with longevity (Hofman 1983), calpain activity should also be inversely correlated with maximum lifespan. These authors compared calpain activity in brain tissue from mice (*Mus musculus*), pallid bats (*Antrozous pallidus*) and Brazilian free-tailed bats (*Tadarida brasiliensis*). Calpain activity, measured by quantifying degraded proteins in the presence of calcium, was significantly lower in brain tissues from both bat species compared to the mouse. Research on proteins such as calpain may provide an insight into the processes involved in the age-related deterioration of the brain. However, it may be worth noting that the correlation between brain size and longevity does not exist in bats. Bats do not have particularly large brains, and Austad and Fischer (1991) found no correlation between bat maximum lifespan or longevity quotient and encephalization quotient (ratio of actual brain size to brain size predicted by body size).

Bats as model organisms for studies on ageing

Currently, most ageing studies focus on a small set of model organisms: laboratory mice and rats, round worms, and fruit flies (Austad 1997). These organisms have been the workhorses of biological research because they are easy to obtain, genetically uniform lines are available, and there are established husbandry protocols as well as ample information regarding their physiology and pathology. However, ageing and differences in longevity evolved in natural populations molded by their specific environment. Consequently, differences and similarities in patterns of ageing among various organisms, and the inclusion of bats in these comparative studies, are likely to be instructive and yield an insight into specific questions (Austad 1997).

Ageing research would benefit greatly from the use of an 'out-group', a species that is distantly related to the study species. The inclusion of an out-group allows a researcher to assess whether a trait is unique to the study species or is characteristic of a larger taxonomic group (Austad 1997). Bats may be a good out-group as traits shared by rodents and bats are also likely to be shared by other mammalian orders, including primates, and the life-history traits that characterize bats are similar to those that characterize primates: slow reproductive output and lifespan longer than predicted by body size.

Bats can be maintained in captivity and a variety of species – insectivorous, frugivorous and sanguinivorous – have been kept captive for several years. There are several resources for the captive maintenance of bats including books (e.g. Rasweiler 1977; Wilson 1988; Lollar and Schmidt-French 1998) and bat rehabilitators who have extensive experience with the nutritional and medical needs of captive bats. The breeding of bats in captivity is difficult, although not impossible. Bats require very specific environmental conditions for reproduction, especially for species that hibernate as they typically mate in the fall but postpone pregnancy until the spring (Heideman 2000). However, some bat species exhibit high fidelity to roost areas with individuals moving among several roosts in the area (Kunz and Lumsden 2003). Permanent roosts (such as caves and buildings) are often visited by the same species of bats from year to year. This is especially true for species whose females establish large nursery colonies every year. Thus, a captive colony can be established from a known roost, new individuals can be introduced to the captive colony when necessary, and results obtained from the captive colony can be tested in the wild population.

Heterothermic bats are metabolically malleable and a researcher can use this malleability to assess the role of metabolism and its corresponding physiochemical processes in ageing. Bats enter and are aroused from hibernation more readily than other hibernators (Davis 1970). By changing the environmental conditions experienced by a captive bat, a researcher can cause the bat to enter torpor or hibernation, and to arouse from these. There is a large body of literature on the physiology and metabolism of bats, both hibernating and active. It should be noted that this literature (as well as other studies on bats) is biased toward only a few Chiropteran families (Jones and MacLarnon 2001), and not all species within a family can enter torpor. Conversely, this metabolic plasticity can pose a problem for research unless the metabolic state of the study individual is monitored carefully. This would be especially important with caloric restriction studies, as bats may enter torpor in response to low food availability.

The extreme longevity of bats is both an advantage and a disadvantage for ageing studies. On the one hand, it would be beneficial to use an organism that naturally lives long to gain an insight into the physiological mechanisms underlying this extended longevity. On the other hand, organisms that live 20–30 years make lifespan studies difficult. Adding to this problem is the difficulty of determining the age of a field-captured bat. A researcher can assign an individual to age classes such as infant, juvenile and adult based on body size, wing development, and indicators of reproductive status. Yet, current techniques for specific age determination in adults such as assessing tooth wear and counting incremental lines in secondary dentine and cement of teeth, are invasive, cumbersome, and have not been developed for all bat species. Assessing tooth wear on a live animal is difficult, especially with the smaller species, and should be done by investigators experienced with the range of variation in tooth wear seen in a particular species. Incremental line counting cannot be used on live individuals, and its accuracy is questionable (Anthony 1988). These however are not insurmountable hindrances. Not all studies on ageing and longevity require knowledge of the exact age and, if necessary, ageing techniques can be developed for specific species. Furthermore, the cellular mechanisms allowing extended longevity should be present, and thus observable, even (perhaps especially) in young adults. Finally, long-term studies of known bat populations are already underway. For example, Dr. Thomas Kunz and his lab have been monitoring two colonies of little brown bats (*Myotis lucifugus*) in New Hampshire for 10 years and marking newborns in at least one of these colonies (T. Kunz, personal communication); Dr. Robert Barclay and his lab have studied and marked individuals of a colony of big brown bats (*Eptesicus fuscus*) in Alberta, Canada, since 1990 (R. Barclay, personal communication); and Luan and Hanák (2002) recently reported on a long-term study of a marked population of Daubenton's bats (*Myotis daubentonii*) with data collection since 1969.

A final disadvantage of using bats as model systems for ageing research is that only segments of the nuclear and mitochondrial genomes of bats have been sequenced. However, this is really only a temporary disadvantage as bat genomes are small (50–85% the size of other eutherian mammals) and sequencing power is continuing to increase exponentially.

Interestingly, several species of bats have been shown to be heteroplasmic for mitochondrial DNA, i.e. an individual can have more than one mitotype even early in life (Wilkinson and Chapman 1991; Petri et al. 1995, 1996; Wilkinson et al. 1997). The presence of several mitotypes in young animals presents the intriguing possibility that selection for efficient mitotypes might occur within an individual in response to high energetic demands (such as during flight). These efficient mitotypes may have reduced free radical production and consequently might potentially be implicated in bat longevity.

The fact that bats live so long in nature where maintenance of high organismic function is critical to continuing survival suggests that they may also provide an insight into the preservation of function in multiple organs. For instance, microchiropteran bats rely on accurate hearing for navigation and foraging. Insect-eating bats eat 20–50% of their pre-feeding body mass in insects every night, and lactating females can consume 80% of their body mass in insects (Kurta et al. 1989). Because they rely on their echolocation ability for prey capture, these bats are critically dependent on

their auditory sensitivity, which if some individuals survive more than 30 years in nature must be exquisitely preserved. This preservation is particularly remarkable because of the high frequency and intensity of these echolocation calls (Neuweiler 2000). Age-related hearing impairment (ARHI) is the most prevalent loss of sensory acuity among the elderly (Fransen et al. 2003). One form of ARHI is correlated with degeneration of cochlear hair cells (Schuknecht and Gacek 1993). Humans and rodents show no evidence of hair cell proliferation after birth or of hair cell turnover and plasticity in adults (Corwin and Oberholtzer 1997). However, regeneration of auditory cells in the ear of adult vertebrates has been reported in amphibians, fish and birds. Of particular interest, Daubenton's bat (*Myotis daubentonii*) appears to have a continuous turnover of hair cells in the inner ear (Kirkegaard and Jørgensen 2000). At this time, we do not know the extent of this turnover, if it is limited to just cells in the inner ear, if it occurs in all bat species, or if the rate of turnover changes with age.

We may also gain an insight into metabolic regulation from the diets of some bats. Let us consider glucose intake. Hyperglycemia and hyperinsulinemia have been observed to mimic a number of aspects of accelerated ageing (Masoro 1996). Frugivorous bats ingest large amounts of sugar. For example, *Rousettus aegyptiacus* can eat its body mass in bananas in one night (120–180 g; Van der Westhuyzen 1976). These bats are then able to absorb those large amounts of sugar in a short period of time. Following a 1.5 g glucose challenge, *R. aegyptiacus* assimilated 765 mg of glucose in 30 min compared to 277 mg assimilated by a rat (Keegan 1977). In an immunocytochemical study, Michelmore et al. (1998) determined that the pancreas of *R. aegyptiacus* has an endocrine structure that differs from that of other mammals. *R. aegyptiacus* has a high percentage of pancreatic endocrine tissue (nine times greater than in humans). This tissue secretes regulatory hormones suggesting that *R. aegyptiacus* maintains blood glucose levels in a narrow range. However, blood glucose levels in these bats rise in excess of 40 mM during an oral glucose tolerance test, compared to the 7.4 mM level observed in rats, and during fasting levels drop to 2 mM (Keegan 1977). Understanding the mechanisms involved in the quick absorption of glucose in these bats and the physiology that allows them to tolerate such a broad range of blood glucose levels may be relevant to studies on diabetes and age-related hyperglycemia.

Humans are particularly vulnerable to high fat diets. Insectivorous bats consume a diet of about 60% fat (Kunz et al. 1995), and some species show hyperphagia on this diet during the fall months in preparation for hibernation. For instance, Brazilian free-tailed bats (*Tadarida brasiliensis*) have reasonably high levels of circulating cholesterol (200–300 mg/dl) but surprisingly low levels of triglycerides despite a high peak in blood triglyceride content immediately after feeding (Widmaier et al. 1996). These bats appear to have a mechanism to rapidly clear triglycerides from general circulation. Widmaier et al. (1996) point out that the quick clearing may be due to triglycerides being incorporated into milk as the bats used in this study were lactating females. However, lipids from this bat's high fat diet must still be metabolized, especially during hibernation when lipid oxidation becomes the primary fuel for metabolism (Holden and Storey 1998). This is particularly interesting when we consider the significant levels of ROS produced during lipid metabolism (St-Pierre et al. 2002). Mitochondria from the little brown bat (*M. lucifugus*), also an insectivorous bat, produce low levels of ROS when respiring on pyruvate and malate (Brunet-Rossinni 2004), but perhaps ROS production increases when respiring on palmitoyl carnitine, a derivative of lipid metabolism. If so, how are cellular constituents in these bats protected from oxidative damage?

Despite this high fat diet, Widmaier et al. (1996) found no evidence of artherosclerosis in *T. brasiliensis*. They found no plaque formation in either the coronary arteries or aortas. Despite its longevity (10 years, Wilkinson and South 2002), elevated circulating cholesterol, and high fat intake, *T. brasiliensis* is protected against the development of artherosclerosis. We do not know the mechanism that affords this protection, but Widmaier et al. suggest it may be related to elevated levels of HDL cholesterol.

Research on muscle disuse atrophy and sarcopenia may also benefit from studies on bats. Immobilization and inactivity result in a reduction

in muscle fiber cross-sectional area and a corresponding loss in muscle strength (Hudson and Franklin 2002). Sarcopenia, age-related muscle mass loss, differs from atrophy caused by disuse, but similar mechanisms may be at play. There appears to be a positive correlation between the amount of muscle atrophy after a period of inactivity and specific metabolic rate. This trend was also found in four hibernating and estivating vertebrates (*Cyclorana alboguttata*, *Ursus americanus*, *Spermophilus lateralis*, *Mesocricetus auratus*), but atrophy was significantly lower than that experienced by non-dormant organisms (Hudson and Franklin 2002). Several hypotheses have been proposed to explain how dormant animals prevent muscle atrophy and the resulting loss in locomotion during estivation and hibernation (Wickler et al. 1991; Tinker et al. 1998; Harlow et al. 2001; Hudson and Franklin 2002). Bats would be good study organisms to test these hypotheses. Heterothermic bats spend several months in hibernation with bouts of continuous torpor lasting up to 90 days (Menaker 1964). Periods of spontaneous arousal comprise only 2% of the time spent in hibernation (Yacoe 1983). In humans, this long period of inactivity would lead to substantial muscle atrophy (LeBlanc et al. 1988), but this does not appear to be the case in bats. Fiber composition of pectoralis muscle of *M. lucifugus* does not change during hibernation (Armstrong et al. 1977). In a study on the bat *Murina luecogaster*, Kim et al. (2000) found some atrophy in pectoralis muscle during hibernation, indicated by an 18% reduction in myofiber size. This atrophy is lower than that observed in hamster after 80 days of torpor (30%; Hudson and Franklin 2002), though the authors do not indicate the exact time interval of inactivity. It has been proposed that frequently used muscle from animals with high metabolic rates is more susceptible to disuse atrophy (Hudson and Franklin 2002). The reduced atrophy observed in *M. leucogaster* is despite their high specific metabolic rates and the heavy use of pectoralis muscle for flight. The atrophy resulting from hibernation does not prevent bats from flying after a short arousal period (15–30 min, Pauziene et al. 2000; Brunet-Rossinni, personal observation) or from flying at body temperatures as low as 22–30 °C (Studier and O'Farrell 1972; Choi et al. 1998). In fact, *M. leucogaster* pectoral muscle retains the same magnitude of tetanic tension (an indication of force) from 10 to 40 °C which allows the bat to bite despite low body temperatures (Choi et al. 1998). Contractile rate, however, is low at low body temperatures, so behaviors requiring speed (such as flight) cannot be performed until body temperatures, are higher (Choi et al. 1998). Studies on the reduced atrophy of bat pectoralis despite long periods of physical inactivity and on atrophy associated with age could provide an insight into the mechanisms underlying, and the prevention of, muscle disuse atrophy and sarcopenia.

The capability of a bat heart to tolerate a broad range of beating rates is exceptional (Pauziene et al. 2000). Like birds, bats have large hearts that pump large volumes of blood to meet the oxygen needs of tissues during flight, beating 700–1000 times per minute (Kallen 1977). Furthermore, these changes in heart rate are extremely rapid. For example, the heart rate of the greater spear-nosed bat (*Phyllostomus hastatus*) increases from 530 to 770 beats/min within 5 s of takeoff. This rate then returns to a resting heart rate of approximately 450 beats/min within 10–12 s of landing (Thomas and Suthers 1972). During hibernation, a bat's heart rate can drop below 10 beats/min (Johansson 1967) and then increase to 450–800 beats/min in a short period of arousal (Kallen 1977). Protection against ventricular fibrillation which can result from high concentrations of catecholamines stimulating myocardial receptors at low temperatures (as would be expected during arousal) may be afforded by the scarce adrenergic innervation of the bat heart (Kallen 1977). During arousal, bats transition from a depressed metabolic and circulo-pulmonary state to an active one. The increasing demand for oxygen requires an increased blood supply, which is satisfied by a continuously sustained increase in the heart rate. The heart itself has a higher oxygen demand during arousal (Kallen 1977) and experiences hypoxia and hypercarbia, which inevitably causes severe metabolic stress. Is this organ protected from the damage that might ensue? Lee et al. (2002) found that the brain of male *Rhinolophus ferrumequinum* experiences a significant oxygen deficiency during arousal from hibernation. Concomitantly, levels of glucose-regulated proteins (GRP) also increase. These proteins may play a role in protecting the brain during

this period of hypoxia. Similar mechanisms may be in place to protect the heart during hibernation and arousal. Understanding the mechanisms that protect the heart of the bat from hypoxia during arousal and allow the organ to perform at such different heart rates may provide key information for treatment of heart disease, arrhythmia, and damage caused by cardiac arrest.

Some of the traits we have described in bats may be shared with other hibernators. What makes bats attractive as a model system for ageing research is that bats are physiologically intriguing heterotherms and homeotherms in addition to having very long life spans and sharing traits with other long-lived organisms, such as life-history traits with primates and flight with birds. Chiroptologists have amassed a wealth of information on these creatures, background knowledge upon which to base future research on ageing. Bats may yet provide us with key information to further our understanding of the processes and mechanisms of ageing.

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