

*Feature Article***A Reassessment of Sexual Dimorphism in Human Senescence: Theory, Evidence, and Causation**

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ABSTRACT Age-specific mortality rates of men are higher than those of women, and men have shorter average life spans than women. This has been interpreted as evidence of sexual dimorphism in rates of senescence. However, because mortality can be caused by numerous factors in addition to senescence, higher mortality rates do not necessarily indicate more rapid senescence. In this paper, we (1) emphasize the necessity of decoupling mortality and senescence when considering sexual dimorphism in senescence, (2) present a theoretical framework for the hypothesis that selection affects senescence in human males and females differently due to different life history characteristics, (3) consider phenotypic evidence from the literature that human males show a later onset of senescence than human females, despite exhibiting higher mortality rates, and (4) discuss the potential roles of mutation accumulation and antagonistic pleiotropy in the evolution of sexual dimorphism in senescence. *Am. J. Hum. Biol.* 18:161–168, 2006. © 2006 Wiley-Liss, Inc.

Virtually all sexually reproducing organisms exhibit increasing probabilities of mortality with increasing age (Carey, 2003), and such demographic patterns have come to be considered a primary indicator of senescence patterns within species (e.g., Comfort, 1979; Crews, 2003). Mortality rates of men are higher and average lifespans are shorter than those of women (Crews, 2003; Olshansky and Carnes, 1994; Promislow, 2003). This has been taken as evidence of sexual dimorphism in rates of senescence among humans (Promislow, 2003; Rose, 1991). However, relative mortality rates of males and females vary considerably across cultures and time periods (Gavrilov and Gavrilova, 1986; Hazzard, 1986; MacIntyre et al., 1996), leading some authors to conclude that differences between human male and female mortality rates are proximate effects of other aspects of sexual dimorphism, rather than products of evolutionary forces acting on senescence directly (Carey, 2003; Crews, 2003). Still, the idea that females exhibit consistently greater life expectancy as a result of slower senescence rates relative to males is widely accepted in gerontology (Aldwin and Gilmer, 2003; Carey, 2003; Perlo and Fretts, 2001). Other than these limited considerations, there has been little discussion of whether sexual dimorphism in human senescence occurs, what phenotypic patterns should

be expressed, or the evolutionary forces that would shape them.

In this paper, we (1) emphasize the need to quantify senescence itself (i.e., physiological decline), rather than a correlated effect (i.e., mortality rate) when considering sexual dimorphism in senescence, (2) present a theoretical framework for the hypothesis that selection affects senescence in human males and females differently due to different life-history characteristics, (3) consider phenotypic evidence from the literature that supports the hypothesis that human males show a later onset of senescence than human females, despite exhibiting higher mortality rates, and (4) discuss the potential roles of the two most widely accepted mechanisms (mutation accumulation and antagonistic pleiotropy) in the evolution of sexual dimorphism in this trait.

SENESCENCE AND MORTALITY

Gompertz (1825) showed that mortality rates increase exponentially with age and hypothe-

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sized that an increasing probability of death should occur "if mankind be continually gaining seeds of indisposition." Gompertz called this consistent mathematical relationship between age and mortality his "law of mortality," and it has become central to demographic studies of senescence (Carnes et al., 1996; Olshansky and Carnes, 1996). Indeed, the rate at which mortality increases is a primary way that biologists measure the rate at which senescence increases (Ricklefs and Finch, 1995) and, in many cases, has been used as a definition of senescence (Kirkwood and Holliday, 1986; Partridge, 2001; Promislow, 1991; Sibly et al., 1997). Although this approach has been extremely useful for comparative studies and testing of life-history theory, we argue that overemphasis of such demographic indicators has led to misinterpretation of sex differences in senescence patterns.

Olshansky and Carnes (1997) reviewed the history of Gompertz's law of mortality in studies of demography and senescence. Although the model has been useful in diverse scientific disciplines, it has also been controversial because many researchers have been unable to find consistent patterns of increase in mortality rates between various life stages, and between various taxa (e.g., Pakin and Hrisanov, 1984). A primary approach to increasing the accuracy of the model has been to partition sources of mortality into extrinsic forms (resulting from something that originates outside of an individual's body such as accidental death, homicide, or predation, rather than senescence) and intrinsic forms (presumably more closely reflecting the effects of senescence) (Carnes and Olshansky, 1997; Olshansky and Carnes, 1997). When deaths from extrinsic factors are removed from mortality data, there is greater consistency in the geometric progression of mortality rates with age, both within and between species (Carnes and Olshansky, 1997).

While senescence occurs along a continuum, mortality for individuals is definitively categorical. Even after removing extrinsic causes of mortality, whether any individual dies at any specific point in the lifespan is a function of its state of senescence and the multitude of other factors that lead to intrinsic mortality. Carnes and Olshansky (1997) emphasize that "any partitioning of mortality, no matter how well justified, must remain imprecise and inaccurate in practice." When considering sexual dimorphism in senescence rates, variation within the sexes is likely to be high, and many

intrinsic sources of mortality are likely to vary between the sexes independently or synergistically with their relationships to senescence. Hence, relatively small differences between sexes in the slope of mortality rates as a function of age are likely to be masked by variance resulting from factors other than senescence. This is evidenced in humans by the variation in relative mortality rates of men and women between cultures and periods in history (Gavrilov and Gavrilova, 1986; Hazzard, 1986; MacIntyre et al., 1996).

Mortality is an event that sometimes accompanies senescence, but oftentimes does not. For example, in sexually reproducing organisms, it is common for females to invest considerable resources in offspring production, while males allocate considerable resources to intrasexual and intersexual competition for mates. Such expenditures can increase mortality rates independent of the processes of senescence. For example, van Poppel (2000) demonstrated female-biased mortality from 1850 until World War II among Dutch people between the ages of 25 and 45 and attributed this primarily to maternal mortality. Increased mortality rate as an effect of increased investment in reproduction is apparent in other female mammals as well (Promislow, 1991; Sibly et al., 1997). Similarly, male secondary sexual characters may increase mortality due to their physiological costs, as well as their unintended attraction of predators (Magnahagan, 1991; Promislow et al., 1992; Sibly et al., 1997; Stuart-Fox et al., 2003). The immunosuppressive effects of testosterone may be a particularly important cost to males, ultimately increasing male mortality rates (Buchanan et al., 2003; Folstad and Karter, 1992). Similarly, large body size relative to conspecifics may reduce life span, and sexual dimorphism in this character could influence mortality rates independent of senescence (Miller et al., 2002; Promislow, 1992; Prothero and Jurgens, 1987). Mortality is correlated with senescence, but when investigating sexual dimorphism in senescence, there are simply too many factors that are confounded with sex that also affect mortality to use this as an indicator of senescence. For example, two studies that used changes in mortality rates as indicators of the onset of senescence found no evidence of senescence in more than half of 56 mammal species (Promislow, 1991; Sibly et al., 1997). This does not indicate that these species do not senesce, but rather that mortality rates provide a gross approximation of the aging process.

Senescence has been defined by Abrams (1993) as “the decrease in physiological functioning that results in a decrease in age-specific components of fitness (e.g., period survival or reproductive rates) with increasing chronological age.” While characteristics like increasing mortality rates are easily quantifiable indicators of senescence (Partridge and Prowse, 1994), such characteristics are only secondary effects of senescence (age-related physiological failure) rather than true measures of senescence itself. Our goal is to identify evolved senescence patterns in human males and females, rather than environmentally induced patterns or effects of other sexually dimorphic traits. Thus, we propose that to identify sexually dimorphic patterns, senescence should be quantified more directly by measures of physiological deterioration. Furthermore, to reduce confounding effects of non-senescence related factors, the physiological indicators of sexual dimorphism in senescence should be phenotypes that are not sexually dimorphic prior to the effects of senescence.

We do not wish to imply that demographic data have not been useful in studying the evolution of senescence; for interspecific comparisons and life history theory, they provide the best data. That is because it is difficult to compare physiological processes across species; variation between species results in comparison of apples and oranges, in a manner of speaking. In contrast, death is death in any species, and across large sample sizes and relatively constant environmental conditions, these are justifiably considered to reflect general patterns of senescence. However, when making intraspecific comparisons of death rates in highly variable environments (temporally and across cultures in the case of humans), sex differences in evolved senescence patterns can be masked or even reversed. Our argument is that just such a situation has led to incorrect conclusions that are contrary to evolutionary theory, as well as direct measures of physiological decline in humans. Still, the idea that men senesce earlier than women is retained by many because of the historically important role of demographic mortality patterns as an indicator of senescence.

SELECTION THEORY AND SEXUAL DIMORPHISM IN HUMAN SENESCENCE

Mortality rates are higher for human males than females throughout human life spans,

but causes of such mortality are often independent of senescence (Owens, 2002; van Poppe, 2000). Consequently, over-reliance on demographic data as indicators of senescence can result in misinterpretation of patterns of sexual dimorphism in this trait. In contrast, evolutionary theory clearly predicts that human females, although enjoying lower mortality rates than human males across their life spans, should senesce at earlier ages than males. Four lines of reasoning support this.

First, the Antagonistic Pleiotropy Hypothesis (Partridge, 2001; Reed and Bryant, 2000; Reznik, 1985; Williams, 1957; see below) for evolution of senescence suggests that genes with positive effects on early reproduction may also have negative effects on somatic maintenance later in life. Therefore, early reproductive investment would result in early senescence. In this regard, sexual maturity is attained at earlier ages in women than in men (Mace, 2001; Money and Ehrhardt, 1972). Consequently, genes that provide early-life reproductive benefits to females would concomitantly have negative pleiotropic effects on senescence at earlier life stages than senescence is exhibited in males (Partridge, 2001; Reed and Bryant, 2000; Reznik, 1985; Williams, 1957).

Second, differences in age-specific reproductive success suggest that selection against senescence should be stronger in males than in females. Although the mean fitness of males and females is essentially equal (Fisher, 1930; Maynard Smith, 1978), the distribution of fitness across the lifespan varies between the sexes. Specifically, the direct reproductive output of women peaks soon after the age of first reproduction and declines with age. In contrast, male reproductive success is low during early stages of adulthood and peaks at later ages (Dinkle and Milenovic, 1993; Mace, 2001). Reproductive success is mirrored by the strongly differing patterns of reduction in reproductive capacity summarized by Austad (1994). Patterns of mate choice in humans (Buston and Emlen, 2003) also provide evidence that males achieve peak fitness at older ages than females. Hence, genes expressed later in life should have greater effects on male fitness than female fitness, which would increase selection against late-acting detrimental genes in males and postpone male senescence.

Third, menopause marks the end of human female direct reproductive output (Austad, 1994; Hawkes et al., 1998). The only fitness

benefits females continue to accrue after menopause are through indirect mechanisms (e.g., providing resources to kin). This termination of direct reproductive output further reduces the negative fitness effects of senescence genes expressed late in the lives of females.

Fourth, it has been proposed that women have relatively long life spans as a result of their postmenopausal contributions to individuals sharing their genes (i.e., “the grandmothering hypothesis”; Hawkes et al., 1998). However, while males and females may aid kin in different ways, they are equally capable of nepotistic behaviors (e.g., Crocombe, 1978; Wiessner, 2002) that can contribute to inclusive fitness late into life.

Whatever the mechanism by which senescence evolves, it is accepted that the process results from declining strength of selection with age (Charlesworth, 2000). Furthermore, fitness results from genetic contributions to future generations rather than from long lifespan alone. It is clear from the points outlined above, that contributions to male fitness at late ages are greater than those of females at late ages. Therefore, it should be equally clear that the strength of selection against senescence should be greater in males than in females.

PHENOTYPIC INDICATORS

To assess sexual dimorphism in senescence from an evolutionary perspective, one must separate the effects of genotypes that cause a decline in physiological functions from proximate environmental effects on such processes (Abrams, 1991). Similarly, traits that are sexually dimorphic prior to senescence and those that are affected by other sexually dimorphic characters (e.g., immune function, mortality, athletic performance) are not the best candidates for dependent measures of senescence to be used for intraspecific comparisons between sexes. For example, excess male mortality generally results from behaviors associated with risk taking (accidents, smoking-related cancer, and cardiovascular disease) and violence, or increased parasitic and infectious diseases, which may result from the immunosuppressive effects of testosterone (Owens, 2002; van Poppel, 2000). Sex differences in mortality rates resulting from these factors are likely not related to senescence. Additionally, characters expressed at very late ages are often quantified, even though such characters are rarely expressed (Kirkwood and Austad,

2000). In contrast, Abrams (1991) concluded that predictions about the evolution of senescence are best tested using data from middle-aged individuals, because the fitness costs of senescence are greatest at such ages. Indeed, Abrams (1991) found that in human populations, 99% of the fitness effects of aging occurred before the age of 45, and the fitness effects of aging were greater between the ages of 15 and 30 than between the ages of 30 and 45.

One phenotypic character that meets these requirements for a good dependent measure of intraspecific variation in senescence is the progressive loss of elasticity in the lens of the eye, which prevents near-vision accommodation and results in presbyopia (Glasser and Campbell, 1998). The lens is remodeled continuously throughout life, with the loss of elasticity resulting from degeneration of molecular repair mechanisms and the progressive accumulation of insoluble crystalline molecules and high molecular weight aggregates (Bron et al., 2000). This degenerative trait is exhibited by virtually all humans (Carter, 1982). It is genetically based and is not a result of pathologies (Pierscionek and Weale, 1996). Accommodation begins to decline by adolescence (Atchison, 1995), which coincides with the expected decline in the strength of selection soon after the onset of reproductive maturity (Abrams, 1991). The loss of accommodation increases rapidly up to about age 40 and then levels off at ages in the 50s (Blystone, 1999; Kalsi et al., 2001). This is in agreement with empirical and theoretical evidence for late-life plateaus in senescence and mortality rates (Rose et al., 2002). Of particular interest with regard to sexual dimorphism in senescence, it is clear that females become presbyopic earlier and faster than males (Duarte et al., 2003; Pointer, 1995a,b, 2002).

Other physiological changes suggest a similar pattern of sexual dimorphism in senescence. Five of six eye diseases that increase in frequency with age in a Gompertzian (exponential) manner occur at younger ages in women than men (Weale, 1998); only cancer occurred earlier in men, which may be related to the immunosuppressive effects of testosterone. Crews (2003) notes the changes in reproductive physiology associated with menopause, and suggests that “Few other aspects of human physiology fit as well the criteria and definition of senescence as does cessation of reproductive function.” That these occur at much earlier ages in women than men is well established (Austad, 1994). Furthermore,

Snowden et al. (1989) show that declining reproductive function is a senescent process closely associated with general somatic senescence. Interesting evidence can also be derived from population genetics. Among humans 50 years of age and older, the heritable component of variation in survival is substantially larger for daughters than sons (Cournil et al., 2000), which would occur as a result of decreased selection against senescent genotypes in women relative to men.

Other traits that change with age also suggest earlier senescence in women than men. While these phenotypes have greater potential for being influenced by other sexually dimorphic traits or cultural differences between the sexes than preceding phenotypes, they reflect a pattern of sexual dimorphism in physiological decline. Motor-evoked potentials in human hand muscles induced by transcranial magnetic stimulation are more variable in older subjects and are more variable in females relative to males of the same age (Pitcher et al., 2002). Manual reaction times to auditory stimuli decline continuously with age and decline faster in women than men (Fozard et al., 1994). As women age, the number of osteoblastic progenitor cells decreases significantly, although such a pattern is not evident in men (Muschler et al., 2001). Although women have greater age-specific survivorship than men, it is a well-known paradox that within age groups, health status is almost invariably better for older men than older women (Baltes et al., 1998; Deeg, 2001; Gold et al., 2002; Verbrugge, 1989). Frailty has been identified as a clinical syndrome defined by unintentional weight loss, self-reported exhaustion, muscular weakness, slow walking speed, and low physical activity that increases with age; it occurs at earlier ages in women than men (Fried et al., 2001; Goggins et al., 2005). Similarly, exercise capacity is an independent predictor of mortality in both sexes, and declines more rapidly with age in women than men (Gulati et al., 2005).

It is important to note that some studies have produced results that conflict with the preceding patterns, and they are reviewed in the references cited above. Furthermore, the above is not intended to be a thorough review of the literature on this subject. However, there appears to be a good amount of evidence supporting the pattern of sexual dimorphism in human senescence that is indicated by evolutionary theory. Many studies of physiologi-

cal decline with age are confined to a single sex (e.g., the Massachusetts Male Aging Study: Fonda et al., 2005; the Longitudinal Study of the Gerontology Research Center of the National Institute on Aging: Borkan and Norris, 1980) or do not address sex differences (e.g., from the latest volume (Vol. 60A) of *Journal of Gerontology: Medical Sciences*: Barry et al., 2005; Laufer, 2005; Moody-Ayers, 2005; Ogrin et al., 2005). Studies designed specifically to address sexual dimorphism in human senescence would be useful for testing our hypothesis.

We propose that various phenotypic indicators of senescence, along with a number of theoretical perspectives, indicate that sexual dimorphism in human senescence should be reconsidered. In contrast to the widely held belief that men senesce earlier than women, we argue that the opposite pattern of sexual dimorphism in senescence is supported by both theory and evidence. We hypothesize that, although the average life span of human females is longer than that of male conspecifics in modern societies, women, in fact, exhibit senescence at earlier ages than men.

EVOLUTIONARY MECHANISMS

If we are to suggest that sexual dimorphism in human senescence patterns has evolved in response to selection pressures, then it is important to establish that a viable mechanism for this process occurs. If it does not, then sexual dimorphism in senescence cannot be more than an effect of other processes (reviewed in Crews, 2003). The two most widely discussed theories concerning the evolution of senescence describe the phenomenon as a non-adaptive outcome of the reduced strength of selection against alleles with deleterious effects late in life. The Mutation Accumulation Hypothesis (Medawar, 1952) suggests that random deleterious mutations accumulate in genomes if extrinsic forms of mortality make it unlikely that individuals will live long enough to express them. Alternatively, the Antagonistic Pleiotropy Hypothesis (Williams, 1957) suggests that alleles are selectively advantageous when they increase fitness early in life, even if they also decrease fitness late in life. Because early-life reproduction has a greater influence on fitness than late-life reproduction and the probability of surviving to earlier ages is always greater than the probability of surviving to later ages, positive effects early in life have greater influence on

mean fitness than negative effects expressed late in life.

Except for a relatively small number of genes on the Y chromosome, human male and female genotypes are identical. Genes on somatic chromosomes as well as X chromosomes will necessarily occur in both sexes at similar frequencies as a result of sexual reproduction. When considering interspecific differences in senescence, separate gene pools can diverge independently as a function of mutation rates and the strength of selection. However, sexual dimorphism in senescence results from differential expression of a common genome under the effects of male and female hormonal contexts (Andersson, 1994). Because senescence is a nonadaptive effect of reduced strength of selection, this has important implications for the mechanisms by which sexual dimorphism in the trait can evolve.

If senescence evolves as a result of mutation accumulation, reductions in late-life fitness contributions in women would result in reduced selection against senescence genotypes expressed at later life stages. However, as such alleles are added to female genomes, they would appear in male genomes at essentially the same frequency as a result of sexual reproduction. There is no reason to assume that random mutations that result in senescence should be expressed differently in males or females or that such differences would occur in ways that match differences in lifespan and reproductive potential. Hence, there is no reason to expect sexual dimorphism in senescence to evolve by mutation accumulation.

Alternatively, senescence could evolve as a result of antagonistic pleiotropy. Selection for sexually dimorphic reproductive investment patterns would increase the frequency of relevant alleles only when they are expressed appropriately under male and female phenotypic contexts. Pleiotropic effects of selection for alleles that are differentially expressed in males and females early in life would result in similar patterns of sexual dimorphism in senescence patterns late in life. This would produce a pattern of sexual dimorphism in senescence that is congruous with the theoretical framework and phenotypic evidence described above. Our arguments do not address the relative roles of antagonist pleiotropy and mutation accumulation in the evolution of senescence, and this question remains unresolved (Hedrick, 1999; Partridge, 2001; Promislow and Tatar, 1998). But when sexual dimorphism in senescence occurs, this pattern of

expression should evolve via the antagonistic pleiotropy process, rather than from the mutation accumulation process. This conclusion illustrates our perspective that the evolution of sexual dimorphism in senescence should be considered in different ways from the evolution of senescence itself.

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