Original Research Article

An Evolutionary Review of Human Telomere Biology: The Thrifty Telomere Hypothesis and Notes on Potential Adaptive Paternal Effects

DAN T.A. EISENBERG*
Department of Anthropology, Northwestern University, Evanston, Illinois 60208-1330

ABSTRACT Telomeres, repetitive DNA sequences found at the ends of linear chromosomes, play a role in regulating cellular proliferation, and shorten with increasing age in proliferating human tissues. The rate of age-related shortening of telomeres is highest early in life and decreases with age. Shortened telomeres are thought to limit the proliferation of cells and are associated with increased morbidity and mortality. Although natural selection is widely assumed to operate against long telomeres because they entail increased cancer risk, the evidence for this is mixed. Instead, here it is proposed that telomere length is primarily limited by energetic constraints. Cell proliferation is energetically expensive, so shorter telomeres should lead to a thrifty phenotype. Shorter telomeres are proposed to restrain adaptive immunity as an energy saving mechanism. Such a limited immune system, however, might also result in chronic infections, inflammatory stress, premature aging, and death—a more "disposable soma." With an increased reproductive lifespan, the fitness costs of premature aging are higher and longer telomeres will be favored by selection. Telomeres exhibit a paternal effect whereby the offspring of older fathers have longer telomeres due to increased telomere lengths of sperm with age. This paternal effect is proposed to be an adaptive signal of the expected age of male reproduction in the environment offspring are born into. The offspring of lineages of older fathers will tend to have longer, and thereby less thrifty, telomeres, better preparing them for an environment with higher expected ages at reproduction. Am. J. Hum. Biol. 23:149–167, 2011.

"The perishable and vulnerable nature of the soma was the reason why nature made no effort to endow this part of the individual with a life of unlimited length."
—August Weismann (1889 pg 154)

Telomeres are repetitive DNA sequences (5′-[TTAGGG]$_n$-3′ in vertebrates) that cap both ends of linear chromosomes and form complexes with specific proteins (Blackburn and Gall, 1978; Meyne et al., 1989). Telomere DNA sequences shorten in dividing human cells as they proceed through the cell cycle (Olovnikov, 1971; Watson, 1972). As a result, telomeres decrease in length with age in some human tissues (e.g. Kimura et al., 2008a). This shortening is associated with diminished cell proliferation capacity, which is believed to contribute to senescence. In particular, telomere lengths measured in human blood are thought to reflect previous immune system activation and current/reserved immune function (Goronzy et al., 2006; von Zglinicki et al., 2005).

While telomeres have been studied extensively from a biomedical perspective, evolutionary and comparative cross-population studies have been limited. Here the patterns of telomere length and telomerase expression over the human life course are examined, and the possible functional significance of these patterns is explored. This leads to a consideration of the evolutionary constraints on human telomere lengths. It has previously been suggested that long telomeres are selected against because of the high cancer risk associated with them (e.g. Weinstein and Ciszek, 2002). However, there are reasons to doubt this explanation given that cancers occur late in life when the force of selection is reduced, and because much empirical evidence suggests instead that shorter telomeres are associated with higher rates of human cancer. As an alternative hypothesis, it is suggested that telomere length regulates the energy invested in cell repair and growth. Finally, the well replicated finding that offspring of older men have longer telomeres (e.g. Kimura et al., 2008a) is considered. The longer telomeres that older men pass on to their offspring are postulated to be an adaptive means by which information about average age at male reproduction in recent generations is conveyed to offspring, allowing adjustment of offspring energetic and life history priorities to local conditions.

TELOMERE SHORTENING, CORRELATES, AND INHERITANCE

Telomeres shorten with age and with each round of mitosis because of the inability of the DNA replication machinery to read and copy to the ends of linear chromosomes (the "end replication problem": Olovnikov, 1971; Watson, 1972) and also from oxidative stress induced DNA damage (e.g. Oikawa and Kawanishi, 1999; Richter and Zglinicki 2007). Ancestral circular chromosomes that occur in most prokaryotes and mitochondria do not have ends and thus do not face the end replication problem or have telomeres (Casjens and Huang, 2008; Gregory, 2005b). Each cell division and its corresponding DNA replication event marks a slight decrease in telomere lengths of linear chromosomes. The telomere sequence presumably functions as a buffer of expendable DNA to prevent

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: National Science Foundation Graduate Research Fellowship.

*Correspondence to: Dan T.A. Eisenberg, Department of Anthropology, Northwestern University, 1810 Hinman Ave., Evanston, IL 60208-1330, USA. E-mail: dtae@dtae.net

Received 5 February 2010; Revision received 3 August 2010; Accepted 30 September 2010

DOI 10.1002/ajhb.21127

Published online 17 December 2010 in Wiley Online Library (wileyonlinelibrary.com).

the loss of coding DNA as a cell lineage replicates and chromosome lengths are reduced. When telomere lengths drop below a threshold (reviewed in Mayer et al., 2006; Meier et al., 2007; Zou et al., 2004), the cell has substantially decreased proliferative potential and may go through programmed cell death (Counter et al., 1992; Harley et al., 1990) or cellular senescence (p53 tumor suppressor protein induced), wherein cellular proliferation ceases and cellular metabolism is altered (reviewed in Campisi, 2005b). Many studies have shown that telomere lengths tend to decrease with age in humans in most of the tissues that have been examined, particularly highly proliferative cells such as leukocytes (e.g. Harley et al., 1990; Ishii et al., 2006; Kimura et al., 2008a; Rampazzo et al., 2010).

Shorter telomeres are associated with increased cell senescence (e.g. Allsopp et al., 1992), Type 2 diabetes (e.g. Adaikalakoteswari et al., 2005; Salpea et al., 2010), overweight (e.g. Fitzpatrick et al., 2007), cardiovascular disease (e.g. Benetos et al., 2001; Brouilette et al., 2008; Demerath et al., 2004; Salpea et al., 2008; Wilson et al., 2008), and increased mortality (e.g. Cawthon et al., 2003). Demerath et al. have proposed that catch-up growth early in life shortens telomere lengths, which might account for later-life development of chronic diseases such as cardiovascular disease (Cameron and Demerath, 2002; Demerath et al., 2004). Furthermore, large magnitude psychosocial stressors are associated with decreases in blood telomere lengths (e.g. Damjanovic et al., 2007; Epel et al., 2004; Tyrka et al., 2010). These psychosocial stress related decreases in telomere length might be due to stress influencing immune cell proliferation or susceptibility to infections (Finch, 2007). With each round of lymphocyte proliferation, the end replication problem is expected to shorten telomeres.

Several studies have reported high heritabilities for telomere lengths in human blood (between 0.36 and 0.82; Andrew et al., 2006; Bakaysa et al., 2007; Bischoff et al., 2005; Hunt et al., 2008; Slagboom et al., 1994; Vasa-Nicotera et al., 2005). Heritability seems to be substantially higher between father and child than between mother and child (Nawrot et al., 2004; Njajou et al., 2007; Nordfjäll et al., 2005, 2010). Other evidence, however, suggests an X-linked inheritance pattern to telomere lengths (Kliegman and Nelson, 2007; Nawrot et al., 2004). Linkage and genome-wide association analysis have identified telomere length associated regions on chromosomes 3, 18, 14, and 10 (Andrew et al., 2006; Codd et al., 2010; Levy et al., 2010; Mangino et al., 2009).

Thus, telomere lengths clearly have genetic determinants, and are characterized by the heritable variation that is necessary for natural selection to occur (reviewed in Demerath et al., 2004). As necessary background for a review of proposals for the adaptive function of telomere length, the next section outlines what is known about developmental changes in telomere lengths over the human life course.

HUMAN DEVELOPMENTAL PATTERNS OF TELOMERE LENGTH AND TELOMERASE ACTIVITY

Most information on age-related changes in telomere lengths comes from cross-sectional studies of blood, which find that telomere lengths decline with age. This decline is presumed to reflect telomere attrition due to the end replication problem at each round of cell division and oxidative stress, together with the rebuilding of telomeres that occurs as the result of telomerase actions. Telomerase, a reverse-transcriptase enzyme, that is thought to have evolved from retrotransposons (Eickbush, 1997), is a principle factor responsible for extending telomere lengths in humans (Greider and Blackburn, 1985; Shay and Wright, 2007). Telomerase extends/maintains telomere lengths in gametes, in prenatal tissues, and in cancerous cells, but is generally inactive in somatic cells. When telomerase is active in proliferative somatic cells it is usually not expressed at levels high enough to maintain stable telomere lengths (Hiyama and Hiyama, 2007; Plunkett et al., 2001), although this is being called into question by recent longitudinal evidence (see below). A simplified illustration of the age-related changes in telomere length and telomerase activity is given in Figure 1. These trends are generally consistent with our understanding of human hematopoietic stem cell dynamics (Sidorov et al., 2009). As illustrated in Figure 1, there is some evidence that the *rate* of age-related decline in telomere lengths also decreases with age.

It should be noted that while telomere length from blood is generally referred to as 'leukocyte telomere length' (LTL), under the reasonable assumption that the majority of nucleated cells in mammalian blood are leukocytes, in an effort to be more precise, the term "blood telomere length" (BTL) is used here. BTL is used because umbilical and peripheral blood of newborns normally have high levels of nucleated red blood cells (Hermansen, 2001) and increasing levels of nucleated RBCs are associated with many severe diseases throughout the human life course (Constantino and Cogionis, 2000; Schwartz and Stansbury, 1954; Stachon et al., 2004). Given this, further caution must be used in interpreting the age-related patterns of telomere lengths reviewed here.

Beginning with gamete formation, mature spermatozoa and oocytes have no detectable telomerase activity, but soon after fertilization and throughout gestation, telomerase levels are high compared with adult levels (Fig. 1; Schaetzlein et al., 2004). Correspondingly, telomere lengths seem to be first extended and then maintained at a consistent level across tissues throughout gestation, despite the massive cellular proliferation that is inherent to prenatal development. Newborns show differences in telomere lengths across tissues, but few differences by sex, gestational age, birthweight, size for gestational age, maternal health, gravidity, or parity (Akkad et al., 2006; Okuda et al., 2002; but see Friedrich et al., 2001). Weinstein and Ciszek (2002) have suggested that these early high telomerase levels might be acting to "synchronize senescence across the soma," at a time when the reproductive value of the offspring is low, and the fetus is buffered from mutagens.

Very soon after birth infants show a generally lower pattern of telomerase expression and BTL rapidly decreases (Fig. 1). This rapid decrease corresponds with rapid growth rates and high production and turnover of immune cells in the process of developing acquired immunity. Based upon experiments in rat models it has been suggested that catch-up growth following growth restriction in utero causes telomere length shortening which results in later chronic disease development (Cameron and Demerath, 2002; Demerath et al., 2004; Jennings et al., 1999; Tarry-Adkins et al., 2009).

BTL attrition rates in childhood and adolescence are not well characterized, but appear to be similar to adult rates (Vaziri et al., 1993). In adulthood, telomere length attrition averages roughly 60 base pairs per year (bp/year) at 20 years of age, but the attrition rate appears to

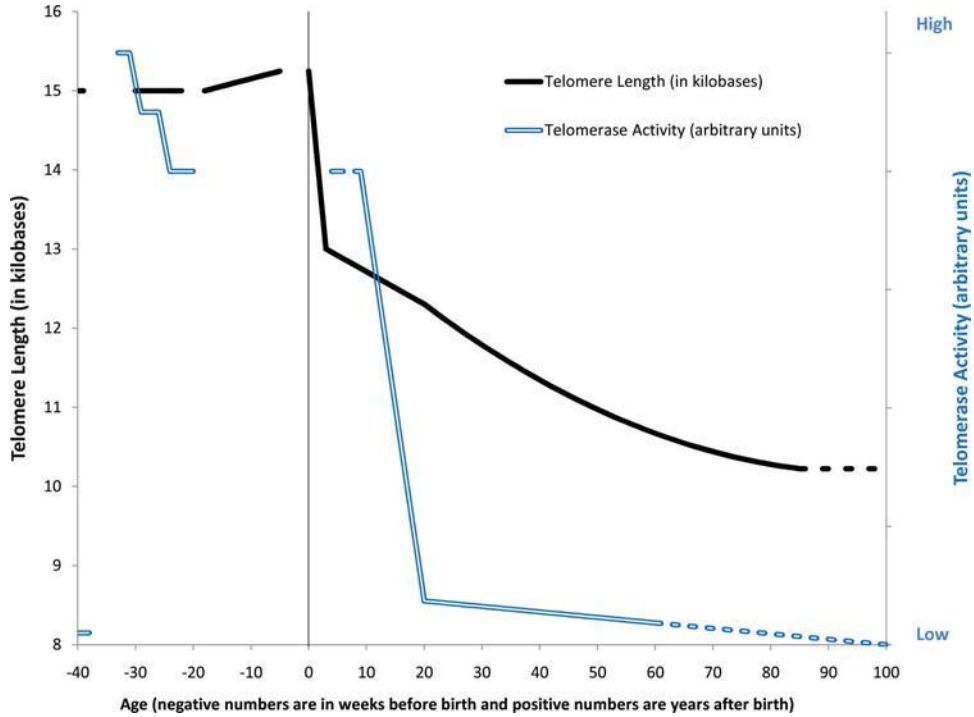

Fig. 1. Age-related changes of telomere length and telomerase activity. Negative numbers on the *x*-axis are weeks before birth, while positive numbers are years after birth. Postnatal data are based on telomere length and telomerase activity from blood. Prenatal values tend to vary less by tissue, and are from available tissues. This figure is meant to give a rough characterization of age-related telomere length shortening and telomerase activity changes and masks considerable population and individual level variability in both inherited telomere length and age-related dynamics. Survival biases might alter the observed patterns, and the dotted lines in old age signify this uncertainty. Almost all sources are based upon individuals from western, wealthy, and industrialized countries. Because of multiple methods of measurement of telomerase, and sparse data, telomerase activity is given without units. Data sources: Cawthon et al., 2003; Holmes et al., 2009; Iwama et al., 1998; Mariani et al., 2003; Martin-Ruiz et al., 2005; Schaetzlein et al., 2004; Ulaner and Giudice 1997; Unryn et al., 2005; Vaziri et al., 1993; Wright et al., 1996; but see Krunic et al., 2009). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

decrease to about 20 bp/year by age 80 and to nondetectable levels in the oldest old (but see Valdes et al., 2005). However, it is difficult to rule out the possibility that survivor bias contributes to this observed decreasing attrition rate with age (see Ehrlenbach et al., 2009; Martin-Ruiz et al., 2005). It has been suggested that, like in early life, this adult pattern might be due to the rates of cell turnover in the immune system (Salomons et al., 2009; Unryn et al., 2005). In this case, the decreased attrition rate could reflect a slower rate of proliferation and less flexible immune system in late life that depends more on innate than adaptive immunity (Dorshkind and Swain, 2009; Finch 2007, p 150; Macallan et al., 2005).

Sexual dimorphism in telomere length attrition

BTL attrition rates tend to be about 3 bp greater per year in adult men than women (Benetos et al., 2001; Kimura et al., 2008a; Mayer et al., 2006; Nawrot et al., 2004; Woo et al., 2009). A similar sex difference is also observed in rats (Cherif et al., 2003), mice (Coviello-McLaughlin and Prowse, 1997; Ilmonen et al., 2008), snakes (Ujvari and Madsen, 2009), and ants (Jemielity et al., 2007). A greater attrition rate in men is consistent with human males' generally higher morbidity, mortality and variance in reproductive success than females (e.g. Kruger, 2004). It should be noted that the direction of causality is not clear here: higher morbidity in males could be a cause and/or a consequence of the telomere attrition rates. Dizygotic human twins with hematopoietic chimerism provide a novel window into telomere biology, because a fraction of the leukocytes of each twin are derived from stem cells of the other twin shared prenatally via blood vessel anastomoses. A recent study of a pair of young adult different sexed twins found that male leukocyte cell lineages in the female twin had relatively longer telomere lengths than the same lineage in the male, while female cell lineages in the male had relatively shorter telomere lengths than those of the same female lineages in the female (Bruderlein et al., 2008). This suggests that the greater BTL attrition rate of males emerge across the life course under the influence of physiologic, metabolic, or other characteristics that vary by sex or gender (e.g. perhaps hormonal milieu or infection). Estrogens are a good candidate mechanism to decrease the rate of telomere attrition in females because of their antioxidant effects and stimulatory effects on telomerase expression (Demerath et al., 2004; Kaszubowska 2008; Lee et al., 2005).

However, in an Amish population, where life expectancies of men and women are the same, mean BTL was found not to differ by sex (Njajou et al., 2007). It must be noted that this study did not directly test whether the BTL attrition rate differed by sex, only whether mean (cross-sectional) BTL differed by sex (Hsueh, personal communication). Interestingly, Alpine Swifts (*Apus melba*), a socially monogamous bird species with limited

sexual dimorphism, also show no sexual dimorphism in mortality rates, telomere length, or telomere attrition rates (Bize et al., 2005, 2009).

Longitudinal patterns of telomere length attrition

Longitudinal studies of BTLs have resulted in the surprising finding that a substantial portion of individuals show either no BTL attrition or BTL extension with age (Aviv et al., 2009; Ehrlenbach et al., 2009; Nordfjäll et al., 2009; Roelofs et al., 2003; Zeichner et al., 1999). This pattern is also evident in birds and snakes (Bize et al., 2009; Ujvari and Madsen, 2009). Environmental/lifestyle factors have also been associated with changes in telomere lengths over time. Weight loss has been related to gains in telomere lengths in rectal mucosa (O'Callaghan et al., 2009). Perhaps demonstrating the mechanism for such changes, a program of dieting, counseling, and stress management was associated with increased peripheral blood mononuclear cell telomerase activity in one study (Ornish et al., 2008). The chronic stress of caring for disabled relatives has been associated with decreased telomere lengths, although the underlying mechanisms accounting for this are less clear as these stressors may be accompanied by either decreased or increased telomerase activity (Bechter et al., 1998; Damjanovic et al., 2007; Epel et al., 2004; Kotrschal et al., 2007; but see Parks et al., 2009).

Longitudinal studies of telomere length changes in humans and birds have found a faster pace of BTL attrition with age among individuals with longer telomere lengths at baseline (Aviv et al., 2009; Bize et al., 2009; Ehrlenbach et al., 2009; Farzaneh-Far et al., 2010; Hall et al., 2004; Nordfjäll et al., 2009). In fact, over half of the variance in telomere length change over time is predicted by baseline telomere length (Ehrlenbach et al., 2009; Nordfjäll et al., 2009). The mechanisms explaining this phenomenon are not yet clear, but several candidates have been proposed.

Explanations for longer telomeres having greater attrition rates: Oxidative stress, preferential telomerase action, and/or cell proliferation rates?

One explanation for the more rapid age-related decline in telomere length among individual with longer baseline telomeres proposes that longer telomeres provide a larger target for oxidative stress related telomere shortening (Aviv et al., 2009). Closer inspection of the *in vitro* studies used to support this hypothesis, however, indicate otherwise. In particular, the telomere length attrition rate of cells in the presence of oxidative stress is not appreciably greater for cells with longer telomeres (Forsyth et al., 2003; Harley et al., 1990; Potter and Wener, 2005; Sitte et al., 1998; Tchirkov and Lansdorp, 2003; but see Nordfjäll et al., 2005).

The oxidative stress target hypothesis also does not clearly explain why shorter telomeres at baseline are also associated with more BTL *extension* with age (not only less attrition). This observation led Nordfjäll et al. (2005, 2009) to suggest that telomere length changes are inversely proportional to baseline telomere length because telomerase acts more efficiently on short telomeres. There is a large literature in support of such a homeostatic mechanism (e.g. Hemann et al., 2001; Hug and Lingner, 2006; McEachern and Blackburn, 1995; Samper et al., 2001; Smogorzewska and de Lange 2004). However, whether telomerase activity is actually increased at short telomeres in humans remains uncertain (Hug and Lingner, 2006). Further, the relevance of the largely *in vitro* experimental evidence for normal *in vivo* physiology is in question. While telomerase does act preferentially on short telomeres in yeast (*Saccharomyces cerevisiae*), this only occurs with telomeres so short that they are unlikely to occur in wild-type cells (Teixeira et al., 2004). Similarly, presumed more efficient telomerase activity at short telomeres is observed in human fibroblast cells *in vitro* that have been transfected with telomerase; however, this only occurs after the cells have been cultured for over twice the number of population doublings that normal cells are capable of (Ouellette et al., 2000).

Another possible explanation for the age and baseline telomere length dependent pattern of telomere length change is that proliferation rates are slower in cells with shorter telomeres, which then causes lesser observed telomere length losses. Change in the proliferation rate, together with relatively constant telomerase activity/efficiency, might explain the observed patterns. Since cell proliferation rates are rarely reported, it is difficult to assess this hypothesis with the extant literature.

Does telomere length matter? Evidence for effects on morbidity and mortality

The consensus biomedical view of telomeres is that their length is reduced with aging, stress, smoking and the metabolic syndrome, and that shorter telomeres impair health. Shorter telomeres result in decreased proliferative potential of cell lines (Allsopp and Harley, 1995; Blackburn et al., 2006; Counter et al., 1992; Harley et al., 1990), which is thought to cause senescence. Several studies have found that shorter telomeres predict later mortality in humans (Bakaysa et al., 2007; Cawthon et al., 2003; Ehrlenbach et al., 2009; Honig et al., 2004; Kimura et al., 2008b; Martin-Ruiz et al., 2006), although this finding has not been universal (Bischoff et al., 2006; Harris et al., 2006; Martin-Ruiz et al., 2005; Njajou et al., 2009). The heterogeneity in results might be explained by telomere length being less predictive of mortality at older ages (Cawthon et al., 2003; Kimura et al., 2008b), decreased telomere length attrition in the elderly (reviewed above), and/or survival bias. Shorter telomeres seem to be associated with mid- to late-life mortality, perhaps due to the inability of cell lines to replace themselves (especially resulting in cardiovascular and infection-related mortalities; Bakaysa et al., 2007; Brouilette et al., 2007; Cawthon et al., 2003; Ilmonen et al., 2008). At least some of the correlation of short telomeres with morbidity and mortality probably represents noncausal relationships where telomere length is a biomarker of past immune activation and oxidative stress that resulted in greater telomere length attrition. These past stressors, though correlated with telomere length, likely have independent effects on health. Nonetheless, a large body of literature encompassing many species and methods suggests that the relationship of short telomeres with morbidity and mortality is also causal (e.g. Bize et al., 2009; Ilmonen et al., 2008; Salpea et al., 2008).

Summary

Telomere shortening clearly does occur, on average, with increasing age. However, the dynamics and rates of

these phenomena are complex and have multiple determinants. There are reasons to believe that the BTL attrition rate reflects the rate of immune system cellular proliferation, and there is tentative evidence that telomere length itself plays a part in determining cellular proliferation rates. The heritable nature of BTLs, coupled with their functional relevance, suggests that natural selection has likely helped shape telomere lengths. The negative influence of short telomeres begs the question: Why haven't longer telomeres been selected for to eliminate the negative influence of short telomeres? It is to this question of selective forces that we now turn.

TELOMERE FUNCTION REVISITED: DOES INHERITING SHORTER TELOMERES PROTECT AGAINST CANCER?

The most common suggested cost of having long telomeres is that they provide tissues with more proliferative potential, which increases the opportunity for precancerous mutations to build up in a cell lineage before the lineage goes extinct due to replicative senescence (Aubert and Lansdorp, 2008; Crews, 2003, p 160; DePinho and Kwok-Kin, 2003; Hornsby, 2006; Shay and Wright, 2005, 2007; Weinstein and Ciszek, 2002; Wright and Shay, 1995). The majority of cancers overexpress telomerase (Bechter et al., 1998; Bryan et al., 1997; Kim et al., 1994). Since telomerase maintains telomeres, the finding of high telomerase activity in cancers might have helped lead to the belief that longer inherited telomere length is causally related to human cancer. While this hypothesis has sound theoretical underpinnings, evidence that inheriting long telomeres (as opposed to developing long telomeres), places humans at increased risk for cancer is lacking.

In fact, in humans, longer blood and epithelial cell telomere length are rarely associated with increased cancer rates (see Supp. Info., File 1). To the contrary, shorter telomeres are more often associated with increased prospective or cross-sectional risk of a variety of cancer types and cancer mortality. Of the studies reviewed in Supporting Information File 1, those that showed a positive association between long telomeres and increased cancer rates made up only 1 of 10 case–control studies and 2 of 8 prospective studies. These studies were across a broad variety of cancer types. The high heritability values of telomere length, coupled with the correlation of telomere lengths across tissues and cell types in the same individual (Friedrich et al., 2000; Lin et al., 2010; Lukens et al., 2009; Nakamura et al., 2002; Spyridopoulos et al., 2009; Takubo et al., 2002; Thibeault et al., 2006; von Zglinicki et al., 2000; Wilson et al., 2008), suggests that blood and epithelial cell telomere lengths substantially reflect inherited telomere lengths—and are visible to natural selection. Together, this suggests that inheriting longer telomeres may well be protective against, not a risk factor for, cancer in humans. Consistent with this interpretation, humans with inherited poorly/nonfunctioning telomerase and resultant shortened telomeres face *increased* cancer risks (Cecil et al., 2008, chapter 171; Kliegman and Nelson, 2007; von Zglinicki et al., 2005), even though the conventional theory suggests they should show less cancer development than the normal population (Shay and Wright, 2005).

It has been suggested that the association between shorter telomeres and cancer, even in prospective studies, might be an artifact of precancerous states which induce more rapid telomere attrition in individuals who will ultimately develop clinically detectable cancers (Hastie et al., 1990; Rampazzo et al., 2010). If this were so, long telomeres might still be a catalyst of cancer development, with the association clouded by undetected precancerous states that result in greater telomere length attrition. Contrary to this hypothesis, a recent longitudinal study found no association between telomere attrition rates and new tumor development (Nordfjäll et al., 2009).

Regardless of these findings, most evidence to date suggests that telomeres are involved in regulating cellular proliferation. As such, the most likely explanation for why longer telomeres are not clearly associated with increased cancer risk lies in other effects of telomeres. First, shortened telomeres are associated with chromosomal instabilities that can result in mutations that are cancerous (Aida et al., 2010; Tchirkov and Lansdorp, 2003). Second, senescent cells may have a "secretory phenotype" which promotes growth of neighboring premalignant cells (reviewed in Campisi, 2005a). Third, the immune system, which requires rapid and persistent proliferation of cells for proper function (i.e. needs longer telomeres), acts to fight against cancers (reviewed in Campisi et al., 2001; Effros, 2004). Infectious agents that are thought to cause over 13% of all human cancer cases (Herrera et al., 2005) will also have a greater likelihood of infecting an immunocompromised host. Among individuals diagnosed with cancers, shorter telomeres in bone-marrow and blood are related to poorer outcomes (Bechter et al., 1998; Nordfjäll et al., 2009; but see Svenson et al., 2008). This is consistent with immune function having antimalignancy effects. Finally, given that shorter telomeres are associated with increased telomere length extension (reviewed above), it might be that shorter telomeres increase telomerase activity and other telomere extending mechanisms (i.e. alternative lengthening of telomeres [ALT]), which in turn increases cancer risk (Bechter et al., 1998).

Even assuming that inheriting longer telomeres is associated with increased human cancer risk, there is further reason to doubt that evolution has shaped telomere length primarily for their role in cancer. The mortality resulting from most human cancers occurs relatively late in life (Fig. 2; although this mortality is probably deferred somewhat in industrialized populations due to good medical care). However, in late life residual reproductive values—and thus the strength of natural selection—is reduced (e.g. Fig. 2; Fisher, 1930; Stearns, 1992; Tuljapurkar et al., 2007). Cancer rates in industrialized contexts likely overestimate the importance of cancer as a force of selection on human ancestors, because cancer rates are thought to have increased in recent history due to factors like decreased physical activity, dietary changes, changed reproductive/lactation patterns, and smoking (e.g. Ellison, 1999; Greaves, 2007; Hecht, 2006; Hill et al., 2007; Trevathan, 2007).

Several scholars have postulated a more complex relationship between inherited telomere length and cancer that incorporates differential effects by age (e.g. Campisi, 2005a; Weinstein and Ciszek, 2002; Wright and Shay, 1995). In particular, it is acknowledged that short telomeres are a risk factor for adult onset cancers (for reasons elaborated above), but suggested that long telomeres are a risk factor for childhood cancers. That is, it is thought that the cancer promoting effects of short telomeres are limited in early life, where instead the cancer promoting

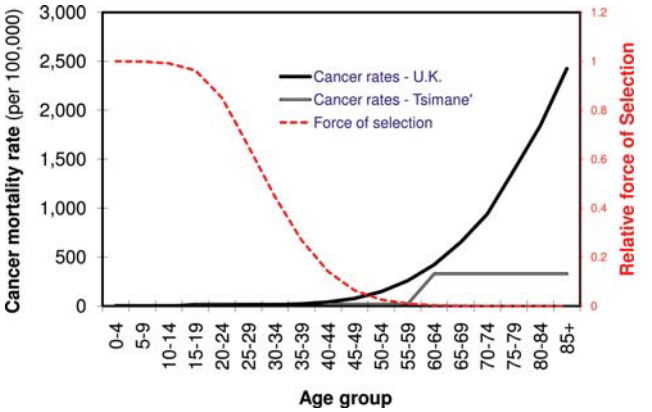

Fig. 2. Cancer mortality rates and the force of natural selection over the life course. Age-specific mortality rates are given from all malignant neoplasms in the United Kingdom in 2006 (modified from Cancer Research, UK) and from an analysis of indigenous Tsimane' forager/horticulturalist's of Amazonia (Gurven et al., 2007). United States age-related patterns are similar to those in the United Kingdom (Heron, 2007). Tsimane' data must be interpreted cautiously given the small sample sizes and difficulties in differential diagnosis necessarily involved in studying such small populations in nonindustrialized contexts. Nonetheless, current evidence suggests that rates of cancer in our preindustrial/preagricultural ancestors were less than today (reviewed in text). The force of selection is derived from an analysis by Tuljapurkar et al. (2007) of demographic characteristics of a forager population. The relative force of selection is defined as the fraction of force of selection at birth or $S_{(x)}/S_{(0)}$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

effects of long telomeres predominate. This is a difficult hypothesis to test because of the very low frequency of childhood cancers in humans (Fig. 2). As Weinstein and Ciszek (2002) note, the low frequency of childhood cancers might be due to effective selection against long telomeres. The only studies I am aware of that are informative about the relationship of inherited telomere lengths and childhood cancer development suggests that shorter telomeres are associated with increased cancers (Tabori et al., 2007; Trkova et al., 2007). However, both of these studies look at rare genetic disorders which might not be representative of childhood cancers generally.

At the population level, there is no association between mean BTL across Europe (from Eisenberg et al., in press) and cancer incidence rates in 0- to 20-year-olds (see Supp. Info., File 2 for details of analysis and results). Further, in most studies, African-Americans have been shown to have longer BTLs than European-Americans (Aviv et al., 2009; Hunt et al., 2008; but only nonsignificant trends in Okuda et al., 2002; Honig et al., 2004; and contrary results in Diez Roux et al., 2009), but European-American children have substantially higher rates of cancer than African-American children (Bleyer, 1993; Gurney et al., 1995).

Summary of evidence for the relationship between cancer and inherited telomere lengths

While long telomeres are commonly thought to be selected against because they are a cause of cancer, there are reasons to doubt this explanation. First, positive associations between long telomeres and adult cancer incidence have been found only infrequently, whereas many studies have documented negative associations. Second, there are several likely phenotypic effects of long telomeres which might protect against cancer. Third, most cancers occur late in life when their selective importance is low. Finally, although selection against childhood cancers could in theory help explain human-specific telomere lengths and represent a constraint on the adaptive length of telomeres, the very low incidence of childhood cancers, and lack of evidence that long telomeres are indeed a risk factor for childhood cancer, argue against this having played an important evolutionary role in shaping human telomere lengths. In light of these facts, consideration of other possible evolutionary constraints on telomere lengths is warranted.

A NEW MODEL OF TELOMERE FUNCTION: THRIFTY TELOMERES

A chief purpose of telomeres is thought to be to regulate cell proliferation by providing limits on the number of replications a cell line can go through. Here it is proposed that telomere lengths serve to regulate maintenance effort, in particular cell turnover and replication in proliferating tissues, such as the immune system. Less maintenance effort frees up resources for growth and reproduction, but at a cost to long-term function or somatic durability.

There are theoretical and empirical reasons to believe that telomeres are involved in programming the allocation of limited resources over the life-course. The proliferation of cells and replacement of damaged cells in normal tissues is an energetically costly endeavor. However, without repair and replacement of cells, errors build up over time and result in dysfunction and senescence (Kirkwood and Holliday, 1979; Weismann, 1889). Tradeoffs between proliferation and senescence are determined by the evolutionary forces shaping the organism, as described in the "disposable soma" theory (Kirkwood and Holliday, 1979). A higher extrinsic mortality rate (mortality due to nonhealth and nonsenescence related causes such as predation, disease, and accidents) decreases life-expectancy and decreases future payoffs associated with maintaining a durable soma (Stearns, 1992). The investment of cellular proliferation/replacement to maintain the soma should be limited so average survival does not considerably exceed the average extrinsically determined lifespan; intrinsic mortality rates are thus expected to be adjusted to match extrinsic mortality rates.

In light of the need for cell turnover and replacement to slow senescence, the role of telomere length in regulating cell proliferation suggests that telomere length might regulate resources devoted to maintaining the soma. As residual reproductive value decreases a prudent strategy would be to progressively decrease long term maintenance efforts, i.e. investing in a durable soma less as the number of future years of likely reproductive payoffs decline. Telomere length might thus be interpreted as a marker of the "disposability of the soma," with telomere lengths limited to reduce the energetic costs of cell replacement, particularly preceding and during the reproductive lifespan. Following this logic, it is proposed that shortened mean telomere lengths are associated with slower rates of cellular proliferation across the lifecycle.

This *thrifty telomere* model suggests at least three key factors should determine the optimum telomere lengths for an individual. *First*, demographic factors, particularly the extrinsic mortality rate, determine the relative costs and benefits of the pacing of growth, sexual maturation, maintenance and reproduction. If extrinsic mortality

rates are high, all else equal, life expectancy is reduced and the payoff of investing in future reproduction is reduced (Hill and Hurtado, 1996; Kirkwood and Holliday, 1979). In turn, maintenance efforts, or investments in a durable soma, are reduced, and shorter telomere lengths would thus be an optimal strategy. That is, if an organism does not have historically selected precedent to live long, then telomere lengths should be relatively constrained in length in order to conserve energy for more immediate use rather than long term investments in durable repair, replacement and maintenance. If lifespan is relatively long then, all else being equal, telomeres should be of increased length to increase the durability of the body so it can be used effectively for reproduction for this longer duration.

Second, nutritional constraints will determine the amount of energy available for an organism to allocate towards growth, maintenance and reproduction (Gadgil and Bossert, 1970; Stearns, 1992). If the nutritional resources in the environment are less of a limiting factor (and intrinsic or extrinsic limits on intake, incorporation or use of nutrients are not a factor: Speakman and Król, 2005), then the relative energetic costs of proliferating tissues will be decreased. In an energetically unconstrained context, selection for shorter telomere lengths will be reduced and telomere lengths will tend to increase in length across generations.

Finally, *third*, the rate of damage accrual will be a determinant of the need for repairs and maintenance. If an organism has a greater metabolic rate, is more stressed, or must combat more high risk infectious agents, then the need for repairs and maintenance costs will generally be greater. The *thrifty telomere* model predicts that a new environment entailing new selective pressures can result in a telomere length mismatch—with either too little or too much of the organism's energy budget devoted to maintaining somatic durability relative to local conditions and thus likely reproductive payoffs. An organism with telomeres too long for its environment is likely to experience more extreme energetic deficits (e.g. malnutrition and delayed maturation) due to miss-allocation of resources. Conversely, an organism with telomeres that are too short is likely to experience premature aging and increased intrinsic mortality in an environment which might otherwise make a slower rate of senescence adaptive.

Extending the thrifty telomere model to explain interspecific patterns

It should be noted that this hypothesis might help explain variation within species, but may not be easily be translated to explain variation between species. *First*, telomere size is strongly correlated with chromosome size in humans ($r = 0.79$; Graakjaer et al., 2003). Similar patterns of correlation between chromosome and telomere sizes seem to also exist in three strains of laboratory mice (Zijlmans et al., 1997), in Chinese hamsters (*Cricetulus griseus*) (Slijepcevic and Hande, 1999), across species of angiosperm plants (Cox et al., 1993), and across species of grasses from the same genius (Sridevi et al., 2002; but see O'Meally et al., 2010). Since average chromosome length varies considerably across species (Gregory, 2005a, 2006) and telomere lengths are expected to be related to chromosome length, this should be considered when comparing mean genomic telomere lengths across species.

Second, at least in rodents, larger animals have decreased expression of telomerase (Seluanov et al., 2007), and fibroblasts of larger, but not smaller, rodents exhibit replicative senescence and telomere shortening *in vitro* (Seluanov et al., 2008). Thus, a given telomere length in an organism that expresses high levels of telomerase and no replicative senescence might have very different significance than in an organism that does not. Further, the lifespan of animals tends to associate with aspects of cellular replicative physiology, including the rate of cell proliferation (Haussmann et al., 2003; Seluanov et al., 2008). Together, this suggests that comparing telomere length and life history characteristics across species, without considering the evolved replicative physiology of the species, may not be informative. That is, telomere length does not seem to exist in isolation, but within a context of other evolving mechanisms which adjust replicative physiology to improve life history allocations of resources, and fitness.

Finally, issues of variations in metabolic rate, related variation in damage (e.g. oxidative stress) and costs of forgoing maintenance efforts, differing reproductive strategies and ecologies, coupled with the statistical nonindependence of species (e.g. Nunn and Barton, 2001) make informative comparisons of telomere lengths between species a complex endeavor. For example the costs and benefits of maintenance efforts, cellular senescence, and a unit of telomere length likely varies substantially between iteroparous continual breeders, iteroparous seasonal breeders, and semelparous breeders—each of which must preserve their somas in rather different ways (Kirkwood, 2005). The degree of sexual dimorphism in a population could also serve as a constraint resulting in sexually disruptive selection. The food availability in natural environments can bear a strong relationship with metabolic rates (Mueller and Diamond, 2001). This, together with whether, and for how long, a population has lived in domestication, should also be considered as the size of energy budgets, and rate of damage accrual likely play a role in determining the costs and benefits of forgoing maintenance efforts. Comparisons between recently diverged sister species or populations, or species of similar size and life history pressures might permit more productive progress.

Evidence for thrifty telomeres

The *thrifty telomere* model predicts that the costs of longer telomeres are mainly in increasing energy/resource expenditures. Below, evidence from general molecular, epidemiological and telomere attrition patterns are first reviewed, followed by a discussion of evidence from a natural experiment with a rodent model. Finally, the case is made that telomeres play an especially important role in regulating immune function.

The most common model of telomere dynamics conceives of telomeres reaching a critically short length late in life which induces cellular apoptosis or cellular senescence (d'Adda di Fagagna et al., 2003). This model predicts that any regulatory effects of telomeres would occur late in life, or in rare pathological conditions that induce premature aging. However, recent evidence shows that the effects of cellular senescence are continuously acquired and that senescent cells exist in tissues even early in life (reviewed below). Given this gradual acquisition of cellular senescence, telomere length could have a dynamic and continuous regulatory role to play throughout the life-course.

By measuring gene expression patterns *in vitro* and *in vivo,* it has been observed that cellular senescence is a

trait which is continuously acquired with increasing cycles of mitosis, not via a threshold relationship as often assumed (Wagner et al., 2008, 2009). In particular, older cell lineages tend to repress DNA repair and mitosis functions (Wagner et al., 2009)—consistent with a less frequent occurrence of cellular division. Cell proliferation/replacement in normal tissues is costly as energy and chemical building blocks (e.g. lipids: Cuthbert and Lipsky, 1987; Schoknecht et al., 1994, amino acids, and micronutrients) are needed to build new cells. The limited mitosis of an older cell lineage, with shorter telomeres, likely causes decreased maintenance investments. Consistent with this idea, senescent T lymphocytes are resistant to apoptosis (Spaulding et al., 1999), suggesting effective replacement of cycling cells with senescent cells and a canalization (loss of plasticity) of immune function. While shorter telomeres and cellular senescence might canalize immune function and result in a less flexible immune system, they are also likely to free up energy for other competing needs.

Senescent cells are present at low, but detectable levels in even young primates (baboons: Herbig et al., 2006; Jeyapalan et al., 2007; humans: Dimri et al., 1995). Since senescent cells do not replicate, their existence (instead of still proliferating cells) is predicted to make tissues less energetically expensive (but see Campisi, 2005a). If a senescent cell dies off, it is thought to be replaced by a nonsenescent cell lineage (Weinstein and Ciszek, 2002). During this process, however, the telomeres of the replacement lineage will be shortened, causing the replacement to exhibit a more senescent phenotype (Drummond et al., 2007; but see Roelofs et al., 2003). The presence of fully senescent cells at low levels *in vivo* suggests the existence of a variety of cells at different stages of proximity to a fully senescent cellular phenotype. Thus, telomere length might serve as a continuous regulator of maintenance efforts, even in early life.

Cell sizes also tend to increase with increasing rounds of mitosis *in vitro* (Enomoto et al., 2002; Greenberg et al., 1977; Wagner et al., 2008), with age (Pendergrass et al., 1999), and with telomere shortening (Damm et al., 2001; Riha et al., 2001). Conversely, slowing telomere length attrition by decreasing oxidative stress results in prevention of cell size enlargement (Furumoto et al., 1998). Across species, greater cell size is related to slower metabolic rates and slower cell growth/division rates (Gregory, 2002, 2005a, p 50; Starostová et al., 2009). There is some evidence that greater cell size results in reduced proliferative capacity in humans as well (Barrandon and Green, 1985; Paiva et al., 2006). This pattern is consistent with the fact that, all else equal, as a cell increases in size, the ratio of surface area to volume decreases. Since much of metabolism may be linked to transmembrane processes (reviewed in Hulbert and Else, 2005), a larger cell is expected to have less membrane activity and energy expenditure per unit volume. Given this, there are further converging reasons to suspect that shorter telomeres are related to decreased energy expenditures.

As reviewed above, telomere length attrition is nonlinear with respect to age (Fig. 1) and baseline telomere length. Longer telomere length at baseline is related to greater prospectively measured telomere length attrition. While increased effects of oxidative stress with longer telomere lengths and increased telomerase activity with shorter telomeres have been postulated to explain this phenomenon, there are reasons to question both explanations (see above). Another possible explanation for the nonlinear attrition phenomenon is that cellular replication rates progressively decrease with shortened telomeres. This would provide yet another mechanism by which telomere lengths have phenotypic effects on cellular proliferation rates, and thus maintenance efforts. This explanation is consistent with the gene expression patterns of aging cells, increasing cell size with aging and slightly decreasing organismal level metabolic rates with adult aging (even after controlling for changes in body composition with aging: Broggi et al., 2010; Roberts and Rosenberg, 2006). This suggests that inheriting shorter telomeres is expected to cause a more thrifty investment in maintenance efforts—shorter telomeres are thrifty telomeres.

Evidence from a rodent model: A case of inadvertent artificial selection

Compared with humans, laboratory strains of mice have extremely long telomere lengths, increased telomerase activity and, correspondingly, their cells easily immortalize when cultured (Davis and Kipling, 2005; Dimri et al., 1995 Hemann and Greider 2000; Manning et al., 2002; Prowse and Greider, 1995). While some of these traits seem to be common to short lived, small rodents (Seluanov et al., 2008; Shay and Wright 2007), when strains of mice of various genera and species that have only recently been taken from the wild were examined, their telomere lengths were not radically elongated as in their cousins that have been reared in labs for many generations (Bickle et al., 1998; Hemann and Greider, 2000; Prowse and Greider, 1995; Seluanov et al., 2008). The reasons for this difference between wild and domesticated populations is not clear, but is likely due to the artificial pressures of laboratory breeding colonies inadvertently selecting longer telomere lengths. Weinstein and Ciszek (2002) cautioned that these long telomeres in lab mice might severely compromise their utility as model organisms.

They also suggested that the longer lengths of telomeres in laboratory rodents is due to the antagonistic relationship between cancer risk and cell repair (Weinstein and Ciszek, 2002). They point to a reproductive ecology where lab mice are "retired" early from breeding at 8 months and suggest that breeding strategies select for individuals who reproduce early and often. They further point to selection for high reproductive output and a minimal cost of tumors in small bodied and short lived mice. Weinstein and Ciszek postulate that this relaxes selection against long telomeres, which normally act as a "fail-safe" against the development of malignancies (Weinstein and Ciszek, 2002). Contrary to Weinstein and Ciszek's hypothesis, an 8-month retirement is probably a longer reproductive lifespan than most mice face in the wild (Berry and Bronson, 1992). Further, there are reasons to doubt that long telomeres are actually a risk factor for cancer, as reviewed above.

Nonetheless, Weinstein and Ciszek's focus on how laboratory mice are bred for rapid reproduction is likely a key to understanding the evolution of long telomeres. Wild mice tend to have smaller bodies, reduced reproductive rates, smaller litters, and more seasonally-entrained breeding patterns than laboratory strains (reviewed in Austad and Kristan, 2003; Berry and Bronson, 1992; Miller et al., 2002). It is also important to note that laboratory mice face decreased energetic constraints compared with their wild cousins, a result of generally *ad libitum* feeding (Hedrich and Bullock, 2004; p 470; Koteja et al.,

2003). By removing virtually all environmental limitations on nutrient consumption, housing in rooms at constant temperatures that are probably closer to their thermoneutral zone, and low energetic demands (Austad and Kristan, 2003; Berry and Bronson, 1992), breeders are likely artificially selecting for *spendthrifty genotypes,* and specifically *spendthrifty telomeres*, as opposed to thrifty genotypes that are generally selected for in the wild (see Berry and Bronson, 1992). Further, inbreeding, by exposing harmful homozygous mutations compromises the physiology of the animal and causes depression in fecundity which could select for telomere length extension relative to outbred strains (Fox, 2007; Manning et al., 2002).

The spendthrift strategy that has been selected for is hypothesized to use long telomeres in order to maximize cell proliferation. With such high energy availability, trade-offs between maintenance and growth efforts become less pressing or virtually nonexistent, so investments in both can be simultaneously increased. Thus, the problem of phenotypic correlation becomes more prominent (see McDade, 2003 for a review of phenotypic correlation), and this increased rate of cell proliferation increases growth rates *and* maintenance efforts. Since maturation and subsequent reproduction are dependent upon growth, reproduction rates are also expected to increase (Stearns, 1992). The higher maintenance effort also fits the longer reproductive lifespan of laboratory mice. Consistent with this theory, successive generations of telomerase knockout mice with concomitant telomere shortening exhibit increasingly impaired reproductive function (Lee et al., 1998)–although this might in part reflect direct disruptions of meiosis (de La Roche Saint-Andre, 2008). Importantly, there is evidence that selection for less restrained metabolism, early maturation and larger body size are general characteristics of organisms that face more nutritionally rich and stable environments and selection for rapid production—probably many human domesticated populations (Austad and Kristan, 2003; Boutin, 1990; Jackson and Diamond, 1996; McNab, 1988; Mueller and Diamond, 2001). Although the association of domestication with telomere lengths has been little studied in other species, it has been observed that cultivated lines of pearl millet have longer telomeres than lines from uncultivated species in the same genus (Sridevi et al., 2002; but see Seluanov et al., 2008).

Tissue turnover and expensive immune systems

Telomeres exist in every nucleated cell in the human body. However, they probably have the greatest phenotypic effects in tissues and cell lineages that turnover rapidly. Tissue turnover rates vary considerably in humans, with some cell lineages under a constant state of turnover (e.g. neutrophils) while others are set early in life and barely turnover at all (Table 1; e.g. neurons). It seems likely that telomere length will have fitness effects, and influence energetic expenditure, primarily through effects on those tissues with highest proliferation rates. Therefore, the immune system, with its high energy costs and reliance upon rapid proliferation of leukocyte cell lines (Table 1), is a prime candidate to consider when trying to understand the energetic implications of telomere length. Since telomere lengths are generally measured in white blood cells because of their easy accessibility, the extant literature is particularly applicable to the immune system.

There are reasons to believe that immune function is tightly regulated to increase fitness (e.g. Kuningas et al., 2009). While immune function is critical in combating infectious agents which exert a considerable mortality toll on extant hunter-gatherers (Hill et al., 2007), immune defenses are energetically expensive to develop and deploy (e.g. Coors et al., 2001; McDade, 2003), and infections can increase basal/resting metabolic rates (e.g. Careau et al., 2010; Cutrera et al., 2010; Hommes et al., 1990; Long et al., 1979; Muehlenbein et al., 2010; Steuber, 2007). Decreased energetic stores apparently decrease energy expended on immune responses (reviewed in Alaux et al., 2010; Ardia et al., 2010; Cutrera et al., 2010; Garcia et al., 2010; Steinman et al., 2003) and conversely, immune activation is associated with reduced childhood growth (Careau et al., 2010; McDade et al., 2008). In mice and humans, short telomeres seem to result in more infections (Cawthon et al., 2003; Ilmonen et al., 2008). Because adaptive immune systems are energetically expensive to develop, but relatively cheap to deploy once developed, previous investigators have suggested that populations with high mortality and reproduction should invest relatively less in adaptive immune function and more in inflammatory and nonspecific responses (Lee, 2006; Martin et al., 2006; Shanley et al., 2009).

Effects of shortened telomeres on infectious morbidity

A strong example of the *in vivo* influence of telomere length on host immune response comes from the experimental infection of recently wild derived mice (F2 *Mus musculus musculus*) with *Salmonella enterica*. Infection with *S. enterica* caused shorter BTL in the mice compared with noninfected controls. More importantly, those mice with longer BTLs at baseline were better able to clear the infection and had lower *S. enterica* loads than those with shorter BTLs. Shorter BTLs at baseline were also non-significantly related to increased mortality ($N = 11$, $P = 0.16$; Ilmonen et al., 2008).

Similarly, the human disease *dyskeratosis congenita*, which is caused by mutations impairing telomere maintenance, is characterized by symptoms including bone marrow failure, deficiencies in the number of all blood cells, infections, and death before the second decade of life (Cecil et al., 2008; chapter 171; Kliegman and Nelson, 2007). Other relevant markers of the disease include reduced peripheral blood mononuclear cell telomere length, reduced T-cell and B-cell numbers and reduced T-cell responsiveness (Akbar et al., 2004). Importantly, "anticipation" occurs in the autosomal dominant form of *dyskeratosis congenita* (Armanios et al., 2005). 'Anticipation' is when a genetic disease becomes more severe with earlier onset in successive generations as the gene is passed on (often due to DNA repeat expansions across generations). This anticipation strongly suggests that the symptoms are primarily due to inherited reductions in telomere lengths. The shortening of telomeres and anticipation with successive generations are thought to be due to the inability of telomerase or ALT mechanisms to extend telomere length during reproduction and early development. However, other pleiotropic transgenerational epigenetic effects of telomerase cannot be definitively ruled out.

Phenotypes similar to *dyskeratosis congenita* are seen in telomerase knock-out mice (Chiang et al., 2010; Lee et al., 1998). These mice also display anticipation, with

TABLE 1. Estimated turnover rates in various human tissues

Tissue (infection state and age if applicable)	Turnover	Method	Reference
Neutrophils	19 h	H	Dale et al., 1998
Intestinal epithelium (from GI patients)	34 h	B	Potten et al., 1992
Epidermis	39 d	T	Weinstein et al., 1984
B lymphocytes (in young adults)	53 d	D	Macallan et al., 2005
B lymphocytes (in elderly)	67 d	D	Macallan et al., 2005
Memory B lymphocytes	38 d	D	Macallan et al., 2005
Naive B lymphocytes	217 d	D	Macallan et al., 2005
Killer T lymphocytes (infected by acute EB virus)	9 d	D	Asquith et al., 2007
Killer T lymphocytes (infected by chronic HIV-1)	10 d	D	Asquith et al., 2007
Killer T lymphocytes (infected by HTLV-1 virus)	28 d	D	Asquith et al., 2007
Killer T lymphocytes (non-infected)	77 d	D	Asquith et al., 2007
Helper T lymphocytes (infected by HTLV-1 virus)	40 d	D	Asquith et al., 2007
Helper T lymphocytes (noninfected)	50 d	D	Asquith et al., 2007
Leukocytes	<1 yr	C	Spalding et al., 2005
Adipocytes	9.8 y	C	Spalding et al., 2008
Atherosclerotic plaques	10 yr	C	Goncalves et al., 2010
Intestine (jejunum)	10.7 yr	C	Spalding et al., 2005
Intercostal skeletal muscle	15.1 yr	C	Spalding et al., 2005
Intestine (jejunum) without epithelial cells	15.9 yr	C	Spalding et al., 2005
Cardiomyocytes at 25 yr of age	100 yr	C	Bergmann et al., 2009
Cardiomyocytes at 75 yr of age	220 yr	C	Bergmann et al., 2009
	Age when cell lineage established		
Neurons in neocortex	perinatal	C	Bhardwaj et al., 2006
Gray matter of cerebellum	2.9 y/o	C	Spalding et al., 2005
Non-neuronal cells in neocortex	5 y/o	C	Bhardwaj et al., 2006
Gray matter from occiptal-cortex	8 y/o	C	Spalding et al., 2005

Turnover is the estimated time for all of the averages cells in the tissue or cell type to be replaced. For tissues which do not discernibly turn over, estimated time in life when they are laid down is given.
Rate: h: hour; d: day; y: years; y/o: years old; H: ^{3}H-diisopropylfluorophosphate labeled; B: bromodeoxyuridine labeled; T: tritiated thymidine; D: deuterated glucose labeling; C: carbon-14.

symptoms increasing with increasing generations as telomere lengths decrease (Hao et al., 2005). In those later generation individuals with shortened telomeres, having wild type telomerase function restored does not eliminate the symptoms (Hao et al., 2005; but see Chiang et al., 2010). Shortened telomeres in knock-out mice appear to cause decreased stem cell mobilization and proliferative ability (Flores et al., 2005). Hematopoietic cells in the bone marrow and spleen (important in immune function) also show impaired proliferative capacity (Lee et al., 1998). Later generations of knock-out mice show skin ulcerations and poorer wound healing, which correlate with decreased telomere lengths (among other phenotypes; Rudolph et al., 1999).

In sum, telomere length appears to have a substantial role in regulating immune function, particularly for the adaptive immune system. Decreased telomere lengths are directly associated with limitations on clonal expansion of antigen-specific T- and B-cell precursors (Goronzy et al., 2006; Katepalli et al., 2008; Steinert et al., 2000; von Zglinicki et al., 2005). In both observational and controlled laboratory experimental conditions, shorter telomeres are related to a less robust immune response, more susceptibility to infection and greater resultant morbidity and mortality.

Immunologically, telomere length seems primarily to influence the adaptive side of the immune system which relies on extreme cell proliferation to function properly. This suggests that longer inherited telomere lengths increase the ability of the adaptive immune system to proliferate and flexibly detect antigens. By this reasoning, inherited telomere lengths might serve to signal the relative investment the organism should place in adaptive immune system development and maintenance. If inherited telomeres are too long relative to the extrinsic mortality rate, the durable soma thereby produced will decrease the available energy to invest in current reproduction and decrease the organism's fitness. Similarly, if inherited telomeres are too long relative to nutritional availability, energetic costs are expected to increase the probability of malnourishment and decrease reproductive output. On the other hand, if inherited telomeres are too short, infectious morbidity and mortality are more likely to increase and fitness will suffer via pre-mature senescence.

THE PATERNAL EFFECT ON TELOMERE LENGTHS

Longer telomeres are found in the children of older men

While shorter telomeres seem to be thrifty telomeres, achieving optimum telomere lengths might not be limited to the conventional and relatively slow processes of natural selection. In the 1980s it was observed that sperm telomeres were longer than leukocyte telomeres in the same men (Cooke and Smith, 1986). Since the early 1990s it has been known that the telomere lengths of human sperm actually increase with the sperm donor's age (Allsopp et al., 1992; Baird et al., 2006; Kimura et al., 2008a). Consistent with this, the offspring of older men have longer BTLs (De Meyer et al., 2007; Kimura et al., 2008a; Njajou et al., 2007; Unryn et al., 2005). A similar effect of maternal age on offspring telomere length has not been found (e.g. Kimura et al., 2008a). This telomere elongation is thought to be due to the need for continued production of male gametes throughout life, while female gametes have already been produced by the perinatal period (but see Edwards et al., 1970; Keefe et al., 2007; Tilly et al., 2009).

Although direct evidence is hard to come by, increasing sperm telomere lengths with age are, by most accounts, thought to be caused by the activation of telomerase in the course of spermatozoa production in the testis (Achi et al., 2000; Bekaert et al., 2004; Fradiani et al., 2004; Gardner et al., 2007; Kim et al., 1994; Wright et al., 1996; Yashima et al., 1998; but see Kimura et al., 2008a). Telomerase

remains expressed in adult testes at high levels even while it is very low or absent in most other tissues (ibid). As suggested by an anonymous reviewer, increasing sperm telomere length with age could be explained by lower sperm counts with older age (Eskenazi et al., 2003; Schwartz et al., 1983) which might equate to a greater amount of telomerase available per developing sperm cell. Steroid hormones including cortisol, androgens, estrogens, and progesterone seem to play a regulatory role in telomerase activity (Choi et al., 2008; Cong et al., 2002; Hapangama et al., 2008; reviewed in De Vivo et al., 2009; Demerath et al., 2004). However, this regulation seems to vary by cell type (Choi et al., 1999; Cong et al., 2002; Guo et al., 2003; Iczkowski et al., 2004; Soda et al., 2000). Given this variability and the dearth of information on how telomerase is regulated in the testes (Weise and Gunes, 2009), it is difficult to make any clear predictions regarding the effects of steroid hormone levels on sperm telomere lengths. Nonetheless, based upon anthropological research which implicates testosterone as a key male life history hormone involved in dominance and immune function and with varying age-related rates of decline in testosterone concentration (Bribiescas, 2001, 2006; Campbell et al., 2006; Ellison et al., 2002; Muehlenbein and Bribiescas, 2005; Muller and Wrangham, 2004), there is reason to evaluate if testosterone plays a role in setting gametic telomere lengths.

Regardless of the specific mechanisms involved, the fact that older fathers transmit longer telomeres to their offspring suggests a means by which paternal experience, specifically lifespan and age at reproduction, alters offspring physiology. Such a system might allow a closer fit of genotype and phenotype to the likely social/ecological environment, as reflected in mortality rates and reproductive scheduling experienced by recent male ancestors. Such a transgenerational signal could result in adaptive changes in life history settings on a timescale more rapid than possible via natural selection.

Parental effects and intergenerational phenotypic inertia

Similar parental effects to those proposed for telomeres have been observed and theorized about. For example, it has been proposed that the correlation of human maternal health characteristics with offspring birth weight and the later physiology and health of the offspring might represent adaptive nongenetic signaling of past environmental conditions (e.g. Bateson, 2001; Gluckman et al., 2007; Kuzawa, 2005). In rats, stress induced maternal behaviors transmit similar behavioral and physiological profiles to offspring via epigenetic mechanisms (Weaver et al., 2004). The logic behind the adaptive interpretation of these phenomena derives from the observation that organisms must adapt to environments at different timescales. Genetic adaptations generally take many generations to form. However, the environment is often dynamic on much shorter timescales, providing an adaptive evolutionary pressure for organisms to develop means of taking advantage of this variability to guide development. Gene expression is quite plastic and responds to local conditions in a variety of complex ways (West-Eberhard, 2003). Over the life course, individuals developmentally and irreversibly adapt to early environments. For example, increased lung capacity results from early exposure to hypoxia in high altitude dwellers (Frisancho, 1993, p 256). On a shorter timescale, homeostatic mechanisms (e.g. glucose-insulin dynamics) and central nervous system mediated behaviors allow responses to finer scale environmental variability with more malleable and appropriate responses. Expanding the timescale of developmental responses, maternal and paternal life experiences might be incorporated into physiological signals that adaptively relay information across generations about the nature of the environment the offspring is likely to encounter. Because maternal mammalian physiology is more closely linked to offspring than that of the father (e.g. time *in utero*, nursing and generally more close parental care even postweaning from mothers), the opportunities for transmission of adaptive information to the offspring is greater in mothers (e.g. Kuzawa 2008; Kuzawa and Quinn, 2009).

Kuzawa's theory of *intergenerational phenotypic inertia* suggests that the signal received by an offspring represents a rolling average of nutritional/environmental experiences of the mother throughout her lifespan and the environment of her ancestors. Altering long-term developmental trajectories based upon a chance event that is unlikely to be representative of the future (e.g. short term macronutrient supplementation during pregnancy) is, all else equal, a poor adaptation. Instead, some method of integrating a signal that is less susceptible to random environmental fluctuations is predicted. In this way, parental effects could bridge a gap between adaptations which proceed via conventional natural selection at the genetic level (information integrated over many generations) and developmental physiological responses (information integrated over one lifespan via phenotypically plastic mechanisms; reviewed in Kuzawa, 2008).

Here, paternal effects on telomere length are hypothesized to be similar in key ways to the maternal effects outlined above, and to provide a mechanism by which paternal life experiences can be physiologically conveyed to offspring. In particular, there is reason to suspect that the paternal effect exhibits a similar quality of intergenerational phenotypic inertia, acting as a rolling average signal of ancestral conditions. Having an older father should predict a higher mean age at reproduction (especially if the individual is a male). To the extent that the father begins his life with his telomere length shaped by his father's age at reproduction—the grandfather of the current generation—then this too should be reflected in the telomere length in the current generation. In this way, telomere length might represent a rolling average of the age of reproduction of the male ancestors of an individual (male ancestors of mother included), and thereby signal average age at paternal reproduction in one's recent lineage. In turn, the average age at paternal reproduction of an individual's male ancestors may be predictive of the average age at reproduction the individual will face in their environmental/social conditions.

Paternal age as an important life history trait

Across species, there is a tendency for females to mate with older males (Brooks and Kemp, 2001) and this pattern persists among humans cross-culturally (Fenner, 2005; Hill and Hurtado, 1996; Hodgson et al., 2004; Tremblay and Vézina, 2000). This is thought to be due to greater variance in reproductive success in males than females, greater male-male competition for mates, and sexual selection by females for mates that have proven

themselves as better able to thrive in the current environment (e.g. Fenner, 2005; Kruger, 2008). In the few species in which males provide parental care or protection, older males might provide larger investments in offspring because of increased experience/resources and/or decreased residual reproductive value which can cause increased parental care effort coupled with decreased mating effort (Brooks and Kemp, 2001). Examination of reproductive schedules suggests that human male reproduction in late life is common enough to be an evolutionarily important occurrence (Tuljapurkar et al., 2007). Average age at reproduction, in addition to being correlated with lifespan, might be correlated with the abilities of members of a lineage to amass resources for reproduction in a particular socioecological context. An individual from a lineage with a lower adult extrinsic mortality rate and higher average age at reproduction would have more to gain by having a more durable soma than an individual from a lineage with higher adult extrinsic mortality and a shorter and earlier reproductive lifespan. Paternal effects on telomere lengths are a plausible candidate mechanism for efficiently tracking this variability.

The provisioning and social abilities of humans males likely improves more rapidly and persistently with age, increasing the salience of reproductive age as an important signal. It has been noted that humans and human ancestors have traditionally learned a suite of elaborate skills including hunting and socializing—which are improved by a lifetime of experience (e.g. Gurven et al., 2006; Kaplan, 1996; Kaplan and Robson, 2002). Many of these skills are likely learned from relatives, contributing to correlations between an individual's ability to utilize the environment (social and nonsocial) and the abilities of that individual's kin. The elaborate use of culture in humans not only provides a robust mechanism for intergenerational transfers of information, but this transmission of information serves as a mechanism by which lineages maintain stable environments across generations (Laland et al., 2001). Evidence across economic systems, including contemporary hunter-gatherers, shows that wealth is reliably transmitted to descendants across generations (Borgerhoff Mulder et al., 2009). As such, this transmission of wealth, social networks and skills from parents to offspring means that the effective environment an individual experiences is likely to be similar to those of one's ancestors (lineage level niche selection and creation). These forces, which stabilize the characteristics of the niches that each individual inhabits, could promote selection for mechanisms for transgenerational adjustment and tracking of these conditions. The paternal effect on telomere length, outlined here, combined with the broad effects of telomere length on somatic allocation, could provide an important means of achieving this.

DISCUSSION AND CONCLUSION

The fact that telomeres are DNA sequences that are stable but change throughout the lifespan underscores the potential insights that telomere biology likely holds for many domains within anthropology and human biology, including developmental plasticity, the modes of adaptability and the developmental origins of health and disease (Cameron and Demerath, 2002; Demerath et al., 2004).

Despite the burgeoning interest in, and recognition of the importance of, telomere biology (Watts, 2009), the evolutionary determinants of telomere lengths are not well understood. Clarifying these evolutionary dynamics will require a better understanding of the fitness implications of both long and short telomeres. It is clear that shorter telomeres are associated with a variety of fitness reducing phenotypes including increased morbidity and mortality from infectious diseases and metabolic syndrome. These observations lead to a consideration of why telomeres have not evolved to be longer to spare us these effects. What are the fitness reducing phenotypes that constrain telomeres from being longer? While cancer rates have been suggested to be increased among those who inherited longer telomeres, the evidence reviewed suggests this explanation is not correct. Instead, I proposed that telomeres are important life history markers that determine how much to invest in maintenance efforts over the life course, particularly in rapidly proliferating tissues with high maintenance requirements, such as the adaptive immune system. Longer telomeres are postulated to increase maintenance efforts via the less restrained cellular proliferation they permit. Conversely, shorter telomeres shunt resources from maintenance functions into other more immediate demands, such as reproduction, and thereby increase fitness when extrinsic mortality rates make the likelihood of dying before reproducing in the future higher.

The paternal effect

The paternal age effect on offspring telomere lengths, where older men have longer telomeres in their sperm, and pass on these longer telomeres to their offspring, is an unexpected finding which, so far as I know, has not been considered from an evolutionary perspective.* (Monaghan, 2010). Paternal age might be an effective signal of the average paternal age of an individual's male ancestors. If individuals with older male ancestors are themselves more likely to face a longer reproductive lifespan, having longer telomeres could be an adaptive means of investing more in maintenance effort. This higher maintenance effort would pay off in a more durable and longer lasting soma, which together with increased life expectancy, would increase fitness.

The hypothesized telomeric system of paternal effects might seem to be a violation of central precepts of biology, mainly the inalterability of the germ-line ("Weismann's barrier") and the "central dogma of biology" (Weismann, 1883 cited in Crick, 1958; West-Eberhard, 2003, p 86). However, what is proposed here incrementally builds upon accepted biological knowledge by fitting within a body of research which shows the complexity of inheritance and mutation patterns (reviewed in Jablonka and Lamb, 2005; Jablonka and Raz 2009; Kuzawa, 2005).

Predictions derived from the thrifty telomere and paternal effects hypotheses

The thrifty telomere hypothesis leads to predictions about the allocation of energy into somatic maintenance versus growth and reproduction. There is reason to believe that, as has been observed in multiple species of laboratory mice, domestication will often be associated with artificial selection for telomere length extension. This will likely depend upon the energetic constraints

*While this manuscript was in press an excellent review by Pat Monaghan (2010) was published which briefly addressed the possible evolutionary importance of this phenomenon.

placed on the animal (in terms of nutrition and energy expenditures), reproductive lifespan, age at paternal reproduction, infectious disease loads and the particularly cellular replicative physiology and telomere biology characteristic of the species (Haussmann et al., 2003, 2005; Mueller and Diamond 2001; Seluanov et al., 2007, 2008).

Since thrifty telomeres are proposed to be involved in allocating limited energetic resources, testing the hypothesis in humans will likely be more straightforward in non-industrialized contexts characterized by nutritional instabilities, chronic physical activity, infectious disease and generally greater energetic demands. In particular, inheriting longer telomeres is predicted to be disadvantageous in nutritionally marginal environments. The more active immune systems permitted by longer telomeres are expected to provide effective responses to pathogen loads; however, these responses are predicted to be hyperreactive such that resources will be wasted and growth and maturation rates will be decreased. In turn, those with too short telomeres are expected to be hyporeactive to pathogen challenges and to face fitness reducing morbidity and mortality as well as reduced growth and maturation rates. Adequately controlling for infectious disease exposures as well phenotypic correlations (see McDade, 2003) will be critical to overcome confounding.

The telomere paternal effect, in which inherited telomere length is related to paternal age at conception, is predicted to exhibit a multigenerational character. That is, an older age of both maternal and paternal grandfathers at father's and mother's conception will result in longer telomere lengths in ego. This would allow the paternal effect to convey stable information on typical conditions in recent generations, consistent with Kuzawa's theory of intergenerational phenotypic inertia (reviewed in Kuzawa, 2008). In humans, differences in paternal ages over multiple generations might explain differences in telomere length across populations (Eisenberg et al., in press; Salpea et al., 2008). The telomere paternal effect is also expected to be greater in species with more variable reproductive ages in their adaptively relevant environments.

Alternative hypotheses to the thrifty telomere

There are few alternative theories to the thrifty telomere hypothesis to explain why telomere lengths are not longer (Kappei and Londono-Vallejo, 2008). One alternative that deserves further consideration states that longer telomeres might cause mal-adaptive gene regulation via altering the position of the genome in the nucleus, thereby altering the expression of the genome (telomere position effects; Kappei and Londono-Vallejo, 2008). Long telomeres might also cause disruption of proper telomere capping functions, including T loop formation and associated telomeric binding proteins (Di Donna et al., 2003), which could cause cell cycle and gene expression dysregulation. Shorter telomere length might also disrupt proper chromosome pairing during meiosis as well as the meiotic recombination process (de La Roche Saint-Andre, 2008; Keefe et al., 2007). Regardless, complex regulatory pathways exist which serve to keep telomere length from being too long or too short (reviewed in Shore and Bianchi, 2009). Given that multiple species of mice extend their telomere lengths by 3-20 fold in laboratory conditions and continue to survive and reproduce, it seems unlikely that telomere position effects or telomere capping are the primary limiting factors preventing human telomeres from evolving to longer lengths.

CONCLUSION

Anthropology and human biology have critical roles to play in elucidating the function and evolutionary significance of telomeres. Further research and theoretical efforts from comparative and evolutionary perspectives are sure to improve our understanding of telomere biology, life-history theory, and inheritance patterns more generally. The *thrifty telomere hypothesis* proposed here provides a theoretical framework to view the evolutionary biology of telomeres which articulates with research on the developmental origins of health and disease (DOHaD) and yields testable predictions. The effect of paternal age on telomere length raises intriguing hypotheses of adaptive developmental intergenerational programming of physiology.

ACKNOWLEDGMENTS

Chris Kuzawa provided mentorship, intensive feedback, discussions, and big questions which were fundamental to coming to and refining the ideas in this manuscript, as well as improving their presentation. Geoff Hayes, Jerry Shay, Bill Leonard, Thom McDade, Jared Bragg, Lee Gettler, Ben Campbell, Aryeh Jacobsohn, Aaron Miller, Zaneta Thayer, Emma Adam, Jim DeVona, Obed Garcia, and two anonymous reviewers also provided valuable feedback on earlier iterations of this manuscript. Shripad Tuljapurkar and Cedric Puleston generously shared data on the force of selection for Figure 2.

LITERATURE CITED

Achi MV, Ravindranath N, Dym M. 2000. Telomere length in male germ cells is inversely correlated with telomerase activity. Biol Reprod 63:591–598.

Adaikalakoteswari A, Balasubramanyam M, Mohan V. 2005. Telomere shortening occurs in Asian Indian type 2 diabetic patients. Diabet Med 22:1151–1156.

Aida J, Izumo T, Shimomura N, Nakamura K-I, Ishikawa N, Matsuura M, Poon SS, Fujiwara M, Sawabe M, Arai T, Takubo K. 2010. Telomere lengths in the oral epithelia with and without carcinoma. Eur J Cancer 46:430–438.

Akbar AN, Beverley PC, Salmon M. 2004. Will telomere erosion lead to a loss of T-cell memory? Nat Rev Immunol 4:737–743.

Akkad A, Hastings R, Konje JC, Bell SC, Thurston H, Williams B. 2006. Telomere length in small-for-gestational-age babies. BJOG 113:318–323.

Alaux C, Ducloz F, Crauser D, Le Conte Y. 2010. Diet effects on honeybee immunocompetence. Biol Lett 6:562–565.

Allsopp RC, Harley CB. 1995. Evidence for a critical telomere length in senescent human fibroblasts. Exp Cell Res 219:130–136.

Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, Greider CW, Harley CB. 1992. Telomere length predicts replicative capacity of human fibroblasts. Proc Natl Acad Sci USA 89:10114–10118.

Andrew T, Aviv A, Falchi M, Surdulescu GL, Gardner JP, Lu X, Kimura M, Kato BS, Valdes AM, Spector TD. 2006. Mapping genetic loci that determine leukocyte telomere length in a large sample of unselected female sibling pairs. Am J Hum Genet 78:480–486.

Ardia DR, Pérez JH, Clotfelter ED. 2010. Experimental cooling during incubation leads to reduced innate immunity and body condition in nestling tree swallows. Proc R Soc B Biol Sci 277:1881–1888.

Armanios M, Chen JL, Chang YP, Brodsky RA, Hawkins A, Griffin CA, Eshleman JR, Cohen AR, Chakravarti A, Hamosh A, Greider CW. 2005. Haploinsufficiency of telomerase reverse transcriptase leads to anticipation in autosomal dominant dyskeratosis congenita. Proc Natl Acad Sci USA 102:15960–15964.

Asquith B, Zhang Y, Mosley AJ, de Lara CM, Wallace DL, Worth A, Kaftantzi L, Meekings K, Griffin GE, Tanaka Y, Tough DF, Beverley PC, Taylor GP, Macallan DC, Bangham CR. 2007. In vivo T lymphocyte dynamics in humans and the impact of human T-lymphotropic virus 1 infection. Proc Natl Acad Sci USA 104:8035–8040.

Aubert G, Lansdorp PM. 2008. Telomeres and aging. Physiol Rev 88:557–579.
Austad SN, Kristan DM. 2003. Are mice calorically restricted in nature? Aging Cell 2:201–217.
Aviv A, Chen W, Gardner JP, Kimura M, Brimacombe M, Cao X, Srinivasan SR, Berenson GS. 2009. Leukocyte telomere dynamics: Longitudinal findings among young adults in the Bogalusa Heart Study. Am J Epidemiol 169:323–329.
Baird DM, Britt-Compton B, Rowson J, Amso NN, Gregory L, Kipling D. 2006. Telomere instability in the male germline. Hum Mol Genet 15:45–51.
Bakaysa SL, Mucci LA, Slagboom PE, Boomsma DI, McClearn GE, Johansson B, Pedersen NL. 2007. Telomere length predicts survival independent of genetic influences. Aging Cell 6:769–774.
Barrandon Y, Green H. 1985. Cell size as a determinant of the clone-forming ability of human keratinocytes. Proc Natl Acad Sci USA 82:5390–5394.
Bateson P. 2001. Fetal experience and good adult design. Int J Epidemiol 30:928–934.
Bechter OE, Eisterer W, Pall G, Hilbe W, Kuhr T, Thaler J. 1998. Telomere length and telomerase activity predict survival in patients with B cell chronic lymphocytic leukemia. Cancer Res 58:4918–4922.
Bekaert S, Derradji H, Baatout S. 2004. Telomere biology in mammalian germ cells and during development. Dev Biol 274:15–30.
Benetos A, Okuda K, Lajemi M, Kimura M, Thomas F, Skurnick J, Labat C, Bean K, Aviv A. 2001. Telomere length as an indicator of biological aging : The gender effect and relation with pulse pressure and pulse wave velocity. Hypertension 37:381–385.
Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabe-Heider F, Walsh S, Zupicich J, Alkass K, Buchholz BA, Druid H, Jovinge S, Frisen J. 2009. Evidence for cardiomyocyte renewal in humans. Science 324:98–102.
Berry RJ, Bronson FH. 1992. Life history and bioeconomy of the house mouse. Biol Rev Camb Philos Soc 67:519–550.
Bhardwaj RD, Curtis MA, Spalding KL, Buchholz BA, Fink D, Björk-Eriksson T, Nordborg C, Gage FH, Druid H, Eriksson PS, Frisén J. 2006. Neocortical neurogenesis in humans is restricted to development. Proc Natl Acad Sci USA 103:12564–12568.
Bickle CA, Cantrell MA, Austad SN, Wichman HA. 1998. Effects of domestication on telomere length in *Mus musculus* and *Peromyscus maniculatus*. FASEB J 12:1845.
Bischoff C, Graakjaer J, Petersen HC, Hjelmborg JV, Vaupel JW, Bohr V, Koelvraa S, Christensen K. 2005. The heritability of telomere length among the elderly and oldest-old. Twin Res Hum Genet 8:433–439.
Bischoff C, Petersen H, Graakjaer J, Andersen-Ranberg K, Vaupel JW, Bohr VA, Kølvraa S, Christensen K. 2006. No association between telomere length and survival among the elderly and oldest old. Epidemiology 17:190–194.
Bize P, Criscuolo F, Metcalfe NB, Nasir L, Monaghan P. 2009. Telomere dynamics rather than age predict life expectancy in the wild. Proc R Soc B Biol Sci 276:1679–1683.
Bize P, Roulin A, Tella JL, Richner H. 2005. Female-biased mortality in experimentally parasitized Alpine Swift *Apus melba* nestlings. Funct Ecol 19:405–413.
Blackburn EH, Gall JG. 1978. A tandemly repeated sequence at the termini of the extrachromosomal ribosomal RNA genes in *Tetrahymena*. J Mol Biol 120:33–53.
Blackburn EH, Greider CW, Szostak JW. 2006. Telomeres and telomerase: The path from maize, *Tetrahymena* and yeast to human cancer and aging. Nat Med 12:1133–1138.
Bleyer WA. 1993. What can be learned about childhood cancer from ldquocancer statistics review 1973-1988rdquo. Cancer 71:3229–3236.
Borgerhoff Mulder M, Bowles S, Hertz T, Bell A, Beise J, Clark G, Fazzio I, Gurven M, Hill K, Hooper PL, Irons W, Kaplan H, Leonetti D, Low B, Marlowe F, McElreath R, Naidu S, Nolin D, Piraino P, Quinlan R, Schniter E, Sear R, Shenk M, Smith EA, von Rueden C, Wiessner P. 2009. Intergenerational wealth transmission and the dynamics of inequality in small-scale societies. Science 326:682–688.
Boutin S. 1990. Food supplementation experiments with terrestrial vertebrates: Patterns, problems, and the future. Can J Zool 68:203–220.
Bribiescas RG. 2001. Reproductive ecology and life history of the human male. Am J Phys Anthropol 116:148–176.
Bribiescas RG. 2006. On the evolution, life history, and proximate mechanisms of human male reproductive senescence. Evol Anthropol 15:132–141.
Broggi J, Hohtola E, Koivula K, Orell M, Nilsson JA. 2010. Idle slow as you grow old: Longitudinal age-related metabolic decline in a wild passerine. Evol Ecol 24:177–184.
Brooks R, Kemp DJ. 2001. Can older males deliver the good genes? Trends Ecol Evol 16:308–313.
Brouilette SW, Moore JS, McMahon AD, Thompson JR, Ford I, Shepherd J, Packard CJ, Samani NJ. 2007. Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: A nested case-control study. Lancet 369:107–114.
Brouilette SW, Whittaker A, Stevens SE, van der Harst P, Goodall AH, Samani NJ. 2008. Telomere length is shorter in healthy offspring of subjects with coronary artery disease: Support for the telomere hypothesis. Heart 94:422–425.
Bruderlein S, Muller K, Melzner J, Hogel J, Wiegand P, Moller P. 2008. Different rates of telomere attrition in peripheral lymphocytes in a pair of dizygotic twins with hematopoietic chimerism. Aging Cell 7:663–666.
Bryan TM, Englezou A, Dalla-Pozza L, Dunham MA, Reddel RR. 1997. Evidence for an alternative mechanism for maintaining telomere length in human tumors and tumor-derived cell lines. Nat Med 3:1271–1274.
Cameron N, Demerath EW. 2002. Critical periods in human growth and their relationship to diseases of aging. Am J Phys Anthropol 119:159–184.
Campbell BC, Gray PB, Ellison PT. 2006. Age-related changes in body composition and salivary testosterone among Ariaal Males. Aging Clin Exp Res 18:470–476.
Campisi J. 2005a. Aging, tumor suppression and cancer: High wire-act! Mech Ageing Dev 126:51–58.
Campisi J. 2005b. Senescent cells, tumor suppression, and organismal aging: Good citizens, bad neighbors. Cell 120:513–522.
Campisi J, Kim S-h, Lim C-S, Rubio M. 2001. Cellular senescence, cancer and aging: The telomere connection. Exp Gerontol 36:1619–1637.
Cancer Research UK. UK cancer mortality statistics by age. Available at: http://info.cancerresearchuk.org/cancerstats/mortality/age/. Accessed on April 12, 2009.
Careau V, Thomas DW, Humphries MM. 2010. Energetic cost of bot fly parasitism in free-ranging eastern chipmunks. Oecologia 162:303–312.
Casjens SR, Huang WM. 2008. Prokaryotic telomeres: Replication mechanisms and evolution. In: Nosek J, Tomáska L, editors. Origin and evolution of telomeres. Austin, TX: Landes Bioscience. p 154–162.
Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. 2003. Association between telomere length in blood and mortality in people aged 60 years or older. Lancet 361:393–395.
Cecil RL, Goldman L, Ausiello DA. 2008. Cecil medicine. Philadelphia, PA: Saunders Elsevier. p xxxiii, 3078.
Cherif H, Tarry JL, Ozanne SE, Hales CN. 2003. Ageing and telomeres: A study into organ- and gender-specific telomere shortening. Nucleic Acids Res 31:1576–1583.
Chiang YJ, Calado RT, Hathcock KS, Lansdorp PM, Young NS, Hodes RJ. 2010. Telomere length is inherited with resetting of the telomere setpoint. Proc Natl Acad Sci USA 107:10148–10153.
Choi J, Fauce SR, Effros RB. 2008. Reduced telomerase activity in human T lymphocytes exposed to cortisol. Brain Behav Immun 22:600–605.
Choi YD, Park JA, Mah SY, Lee MS, Choi HK. 1999. Effects of androgen on telomerase activity in the adult rat penis. Korean J Urol 40:925–932.
Codd V, Mangino M, van der Harst P, Braund PS, Kaiser M, Beveridge AJ, Rafelt S, Moore J, Nelson C, Soranzo N, Zhai G, Valdes AM, Blackburn H, Leach IM, de Boer RA, Goodall AH, Ouwehand W, van Veldhuisen DJ, van Gilst WH, Navis G, Burton PR, Tobin MD, Hall AS, Thompson JR, Spector T, Samani NJ. 2010. Common variants near TERC are associated with mean telomere length. Nat Genet 42:197–1999.
Cong Y-S, Wright WE, Shay JW. 2002. Human telomerase and its regulation. Microbiol Mol Biol Rev 66:407–425.
Constantino BT, Cogionis B. 2000. Nucleated RBCs—Significance in the peripheral blood film. Lab Med 31:223–229.
Cooke H, Smith B. 1986. Variability at the telomeres of the human X/Y pseudoautosomal region. Woodbury NY, USA: Cold Spring Harbor Laboratory Press. p 213–219.
Coors M, Suttmann U, Trimborn P, Ockenga J, Muller MJ, Selberg O. 2001. Acute phase response and energy balance in stable human immunodeficiency virus-infected patients: A doubly labeled water study. J Lab Clin Med 138:94–100.
Counter CM, Avilion AA, Lefeuvre CE, Stewart NG, Greider CW, Harley CB, Bacchetti S. 1992. Telomere shortening associated with chromosome instability is arrested in immortal cells which express telomerase activity. EMBO J 11:1921–1929.
Coviello-McLaughlin GM, Prowse KR. 1997. Telomere length regulation during postnatal development and ageing in Mus spretus. Nucleic Acids Res 25:3051–3058.
Cox AV, Bennett ST, Parokonny AS, Kenton A, Callimassia MA, Bennett MD. 1993. Comparison of plant telomere locations using a PCR-generated synthetic probe. Ann Bot 72:239–247.
Crews DE. 2003. Human senescence: Evolutionary and biocultural perspectives. Cambridge, UK: Cambridge University Press. 291 p.
Crick FH. 1958. On protein synthesis. Symp Soc Exp Biol 12:138–163.
Cuthbert JA, Lipsky PE. 1987. Provision of cholesterol to lymphocytes by high-density and low-density lipoproteins—Requirement for low-density-lipoprotein receptors. J Biol Chem 262:7808–7818.
Cutrera AP, Zenuto RR, Luna F, Antenucci CD. 2010. Mounting a specific immune response increases energy expenditure of the subterranean rodent *Ctenomys talarum* (tuco-tuco): Implications for intraspecific and interspecific variation in immunological traits. J Exp Biol 213: 715–724.

d'Adda di Fagagna F, Reaper PM, Clay-Farrace L, Fiegler H, Carr P, Von Zglinicki T, Saretzki G, Carter NP, Jackson SP. 2003. A DNA damage checkpoint response in telomere-initiated senescence. Nature 426:194–198.

Dale DC, Liles WC, Llewellyn C, Price TH. 1998. Effects of granulocyte-macrophage colony-stimulating factor (GM-CSF) on neutrophil kinetics and function in normal human volunteers. Am J Hematol 57:7–15.

Damjanovic AK, Yang Y, Glaser R, Kiecolt-Glaser JK, Nguyen H, Laskowski B, Zou Y, Beversdorf DQ, Weng N. 2007. Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. J Immunol 179:4249–4254.

Damm K, Hemmann U, Garin-Chesa P, Hauel N, Kauffmann I, Priepke H, Niestroj C, Daiber C, Enenkel B, Guilliard B, Lauritsch I, Muller E, Pascolo E, Sauter G, Pantic M, Martens UM, Wenz C, Lingner J, Kraut N, Rettig WJ, Schnapp A. 2001. A highly selective telomerase inhibitor limiting human cancer cell proliferation. EMBO J 20:6958–6968.

Davis T, Kipling D. 2005. Telomeres and telomerase biology in vertebrates: Progress towards a non-human model for replicative senescence and ageing. Biogerontology 6:371–385.

de La Roche Saint-Andre C. 2008. Alternative ends: Telomeres and meiosis. Biochimie 90:181–189.

De Meyer T, Rietzschel ER, De Buyzere ML, De Bacquer D, Van Criekinge W, De Backer GG, Gillebert TC, Van Oostveldt P, Bekaert S, Asklepios I. 2007. Paternal age at birth is an important determinant of offspring telomere length. Hum Mol Genet 16:3097–3102.

De Vivo I, Prescott J, Wong JY, Kraft P, Hankinson SE, Hunter DJ. 2009. A prospective study of relative telomere length and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 18: 1152–1156.

Demerath EW, Cameron N, Gillman MW, Towne B, Siervogel RM. 2004. Telomeres and telomerase in the fetal origins of cardiovascular disease: A review. Hum Biol 76:127–146.

DePinho RA, Kwok-Kin W. 2003. The age of cancer: Telomeres, checkpoints, and longevity. J Clin Invest 111:S9–S14.

Di Donna S, Mamchaoui K, Cooper R, Seigneurin-Venin S, Tremblay J, Butler-Browne G, Mouly V. 2003. Telomerase can extend the proliferative capacity of human myoblasts, but does not lead to their immortalization. Mol Cancer Res 1:643.

Diez Roux AV, Ranjit N, Jenny NS, Shea S, Cushman M, Fitzpatrick A, Seeman T. 2009. Race/ethnicity and telomere length in the multi-ethnic study of atherosclerosis. Aging Cell 8:251–257.

Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O, Peacocke M, Campisi J. 1995. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. Proc Natl Acad Sci USA 92:9363–9367.

Dorshkind K, Swain S. 2009. Age-associated declines in immune system development and function: Causes, consequences, and reversal. Curr Opin Immunol 21:404–407.

Drummond MW, Balabanov S, Holyoake TL, Brummendorf TH. 2007. Concise review: Telomere biology in normal and leukemic hematopoietic stem cells. Stem Cells 25:1853–1861.

Edwards RG, Tarkowski AK, McLaren A, Peters H. 1970. Are oocytes formed and used sequentially in the mammalian ovary? [and discussion]. Philos Trans R Soc Lond B Biol Sci 259:103–106.

Effros RB. 2004. Replicative senescence of CD8 T cells: Potential effects on cancer immune surveillance and immunotherapy. Cancer Immunol Immunother 53:925–933.

Ehrlenbach S, Willeit P, Kiechl S, Willeit J, Reindl M, Schanda K, Kronenberg F, Brandstatter A. 2009. Influences on the reduction of relative telomere length over 10 years in the population-based Bruneck Study: Introduction of a well-controlled high-throughput assay. Int J Epidemiol 38:1725–1734.

Eickbush T. 1997. Molecular biology: Telomerase and retrotransposons: Which came first? Science 277:911–912.

Eisenberg DTA, Kuzawa CW, Hayes MG, Salpea KD, Humphries SE; EARS II group. Substantial variation in qPCR measured mean blood telomere lengths in young men from eleven European countries. Am J Hum Biol (in press).

Ellison PT. 1999. Chapter 6: Reproductive ecology and reproductive cancers. In: Panter-Brick C, Worthman CM, editors. Hormones, health, and behavior: A socio-ecological and lifespan perspective. Cambridge, NY: Cambridge University Press. p 184–209.

Ellison PT, Bribiescas RG, Bentley GR, Campbell BC, Lipson SF, Panter-Brick C, Hill K. 2002. Population variation in age-related decline in male salivary testosterone. Hum Reprod 17:3251–3253.

Enomoto S, Glowczewski L, Berman J. 2002. MEC3, MEC1, and DDC2 are essential components of a telomere checkpoint pathway required for cell cycle arrest during senescence in *Saccharomyces cerevisiae*. Mol Biol Cell 13:2626–2638.

Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. 2004. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci USA 101:17312–17315.

Eskenazi B, Wyrobek AJ, Sloter E, Kidd SA, Moore L, Young S, Moore D. 2003. The association of age and semen quality in healthy men. Hum Reprod 18:447–454.

Farzaneh-Far R, Lin J, Epel E, Lapham K, Blackburn E, Whooley MA. 2010. Telomere length trajectory and its determinants in persons with coronary artery disease: Longitudinal findings from the heart and soul study. PLoS One 5:e8612.

Fenner JN. 2005. Cross-cultural estimation of the human generation interval for use in genetics-based population divergence studies. Am J Phys Anthropol 128:415–423.

Finch CE. 2007. The biology of human longevity: Inflammation, nutrition, and aging in the evolution of life spans. Burlington, MA: Academic Press. 626 p.

Fisher RA. 1930. The genetical theory of natural selection. Oxford: The Clarendon press. 272 p.

Fitzpatrick AL, Kronmal RA, Gardner JP, Psaty BM, Jenny NS, Tracy RP, Walston J, Kimura M, Aviv A. 2007. Leukocyte telomere length and cardiovascular disease in the cardiovascular health study. Am J Epidemiol 165:14–21.

Flores I, Cayuela ML, Blasco MA. 2005. Effects of telomerase and telomere length on epidermal stem cell behavior. Science 309:1253–1256.

Forsyth NR, Evans AP, Shay JW, Wright WE. 2003. Developmental differences in the immortalization of lung fibroblasts by telomerase. Aging Cell 2:235–243.

Fox JG. 2007. The mouse in biomedical research. Amsterdam: Elsevier, AP.

Fradiani PA, Ascenzioni F, Lavitrano M, Donini P. 2004. Telomeres and telomerase activity in pig tissues. Biochimie 86:7–12.

Friedrich U, Griese E-U, Schwab M, Fritz P, Thon K-P, Klotz U. 2000. Telomere length in different tissues of elderly patients. Mech Ageing Dev 119:89–99.

Friedrich U, Schwab M, Griese EU, Fritz P, Klotz U. 2001. Telomeres in neonates: New insights in fetal hematopoiesis. Pediatr Res 49:252–256.

Frisancho AR. 1993. Human adaptation and accommodation. Ann Arbor: University of Michigan Press. 532 p.

Furumoto K, Inoue E, Nagao N, Hiyama E, Miwa N. 1998. Age-dependent telomere shortening is slowed down by enrichment of intracellular vitamin C via suppression of oxidative stress. Life Sci 63:935–948.

Gadgil M, Bossert WH. 1970. Life historical consequences of natural selection. Am Nat 104:1–24.

Garcia NW, Greives TJ, Zysling DA, French SS, Chester EM, Demas GE. 2010. Exogenous insulin enhances humoural immune responses in short-day, but not long-day, Siberian hamsters (*Phodopus sungorus*). Proc R Soc B Biol Sci 277:2211–2218.

Gardner JP, Kimura M, Chai W, Durrani JF, Tchakmakjian L, Cao X, Lu X, Li G, Peppas AP, Skurnick J, Wright WE, Shay JW, Aviv A. 2007. Telomere dynamics in macaques and humans. J Gerontol A Biol Sci Med Sci 62:367–374.

Gluckman PD, Hanson MA, Beedle AS. 2007. Non-genomic transgenerational inheritance of disease risk. Bioessays 29:145–154.

Goncalves I, Stenstrom K, Skog G, Mattsson S, Nitulescu M, Nilsson J. 2010. Short communication: Dating components of human atherosclerotic plaques. Circ Res 106:1174–1177.

Goronzy JJ, Fujii H, Weyand CM. 2006. Telomeres, immune aging and autoimmunity. Exp Gerontol 41:246–251.

Graakjaer J, Bischoff C, Korsholm L, Holstebroe S, Vach W, Bohr VA, Christensen K, Kølvraa S. 2003. The pattern of chromosome-specific variations in telomere length in humans is determined by inherited, telomere-near factors and is maintained throughout life. Mech Ageing Dev 124:629–640.

Greaves M. 2007. Darwinian medicine: A case for cancer. Nat Rev Cancer 7:213–221.

Greenberg SB, Grove GL, Cristofalo VJ. 1977. Cell size in aging monolayer cultures. In Vitro 13:297–300.

Gregory TR. 2002. A bird's-eye view of the c-value enigma: Genome size, cell size, and metabolic rate in the class aves. Evolution 56:121–130.

Gregory TR, editor. 2005a. Chapter 1. Genome size evolution in animals. In: The evolution of the genome. Burlington, MA: Elsevier Academic. p 4–89.

Gregory TR, editor. 2005b. Chapter 11. Macroevolution and the genome. In: The evolution of the genome. Burlington, MA: Elsevier Academic. p 679–729.

Gregory TR. 2006. Animal genome size database. Available at: http://www.genomesize.com. Accessed on July 2010.

Greider CW, Blackburn EH. 1985. Identification of a specific telomere terminal transferase activity in *Tetrahymena* extracts. Cell 43:405–413.

Guo C, Armbruster BN, Price DT, Counter CM. 2003. In vivo regulation of hTERT expression and telomerase activity by androgen. J Urol 170:615–618.

Gurney JG, Severson RK, Davis S, Robison LL. 1995. Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. Cancer 75:2186–2195.

Gurven M, Kaplan H, Gutierrez M. 2006. How long does it take to become a proficient hunter? Implications for the evolution of extended development and long life span. J Hum Evol 51:454–470.

Gurven M, Kaplan H, Supa AZ. 2007. Mortality experience of *Tsimane amerindians* of Bolivia: Regional variation and temporal trends. Am J Hum Biol 19:376–398.

Hall ME, Nasir L, Daunt F, Gault EA, Croxall JP, Wanless S, Monaghan P. 2004. Telomere loss in relation to age and early environment in long-lived birds. Proc Biol Sci 271:1571–1576.

Hao LY, Armanios M, Strong MA, Karim B, Feldser DM, Huso D, Greider CW. 2005. Short telomeres, even in the presence of telomerase, limit tissue renewal capacity. Cell 2005; 123:1121–1131.

Hapangama DK, Turner MA, Drury JA, Quenby S, Saretzki G, Martin-Ruiz C, Von Zglinicki T. 2008. Endometriosis is associated with aberrant endometrial expression of telomerase and increased telomere length. Hum Reprod 23:1511–1519.

Harley CB, Futcher AB, Greider CW. 1990. Telomeres shorten during ageing of human fibroblasts. Nature 345:458–460.

Harris SE, Deary IJ, Maclntyre A, Lamb KJ, Radhakrishnan K, Starr JM, Whalley LJ, Shiels PG. 2006. The association between telomere length, physical health, cognitive ageing, and mortality in non-demented older people. Neurosci Lett 406:260–264.

Hastie ND, Dempster M, Dunlop MG, Thompson AM, Green DK, Allshire RC. 1990. Telomere reduction in human colorectal carcinoma and with ageing. Nature 346:866–868.

Haussmann MF, Winkler DW, O'Reilly KM, Huntington CE, Nisbet ICT, Vleck CM. 2003. Telomeres shorten more slowly in long-lived birds and mammals than in short-lived ones. Proc R Soc Lond B Biol Sci 270:1387–1392.

Haussmann MF, Winkler DW, Vleck CM. 2005. Longer telomeres associated with higher survival in birds. Biol Lett 1:212–214.

Hecht S. 2006. Cigarette smoking: Cancer risks, carcinogens, and mechanisms. Langenbecks Arch Surg 391:603–613.

Hedrich HJ, Bullock GR. 2004. The laboratory mouse. Amsterdam: Elsevier Academic Press. 600 p.

Hemann MT, Greider CW. 2000. Wild-derived inbred mouse strains have short telomeres. Nucleic Acids Res 28:4474–4478.

Hemann MT, Strong MA, Hao L-Y, Greider CW. 2001. The shortest telomere, not average telomere length, is critical for cell viability and chromosome stability. Cell 107:67–77.

Herbig U, Ferreira M, Condel L, Carey D, Sedivy JM. 2006. Cellular senescence in aging primates. Science 311:1257–1257.

Hermansen MC. 2001. Nucleated red blood cells in the fetus and newborn. Arch Dis Child Fetal Neonatal Ed 84:F211–F215.

Heron M. 2007. Deaths: Leading causes for 2004. Natl Vital Stat Rep 56:1–96.

Herrera LA, Benitez-Bribiesca L, Mohar A, Ostrosky-Wegman P. 2005. Role of infectious diseases in human carcinogenesis. Environ Mol Mutagen 45:284–303.

Hill K, Hurtado AM. 1996. Aché life history: The ecology and demography of a foraging people. New York: Aldine de Gruyter. 561 p.

Hill K, Hurtado AM, Walker RS. 2007. High adult mortality among Hiwi hunter-gatherers: Implications for human evolution. J Hum Evol 52:443–454.

Hiyama E, Hiyama K. 2007. Telomere and telomerase in stem cells. Br J Cancer 96:1020–1024.

Hodgson ME, Newman B, Millikan R. 2004. Birthweight, parental age, birth order and breast cancer risk in African-American and white women: A population-based case-control study. Breast Cancer Res 6:R656–R667.

Holmes DK, Bellantuono I, Walkinshaw SA, Alfirevic Z, Johnston TA, Subhedar NV, Chittick R, Swindell R, Wynn RF. 2009. Telomere length dynamics differ in foetal and early post-natal human leukocytes in a longitudinal study. Biogerontology 10:279–284.

Hommes MJ, Romijn JA, Godfried MH, Schattenkerk JK, Buurman WA, Endert E, Sauerwein HP. 1990. Increased resting energy expenditure in human immunodeficiency virus-infected men. Metabolism 39:1186–1190.

Honig LS, Flores I, Schupf N, Lee JH, Mayeux R. 2004. Biological aging: Does telomere length predict dementia and mortality? Neurobiol Aging 25:S435–S435.

Hornsby PJ. 2006. Short telomeres: Cause or consequence of aging? Aging Cell 5:577–578.

Hug N, Lingner J. 2006. Telomere length homeostasis. Chromosoma 115:413–425.

Hulbert AJ, Else PL. 2005. Membranes and the setting of energy demand. J Exp Biol 208:1593–1599.

Hunt SC, Chen W, Gardner JP, Kimura M, Srinivasan SR, Eckfeldt JH, Berenson GS, Aviv A. 2008. Leukocyte telomeres are longer in African Americans than in whites: The National Heart, Lung, and Blood Institute Family Heart Study and the Bogalusa Heart Study. Aging Cell 7:451–458.

Iczkowski KA, Huang W, Mazzucchelli R, Pantazis CG, Stevens GR, Montironi R. 2004. Androgen ablation therapy for prostate carcinoma suppresses the immunoreactive telomerase subunit hTERT. Cancer 100:294–299.

Ilmonen P, Kotrschal A, Penn DJ. 2008. Telomere attrition due to infection. PLoS One 3:e2143.

Ishii A, Nakamura K, Kishimoto H, Honma N, Aida J, Sawabe M, Arai T, Fujiwara M, Takeuchi F, Kato M, Oshimura M, Izumiyama N, Takubo K. 2006. Telomere shortening with aging in the human pancreas. Exp Gerontol 41:882–886.

Iwama H, Ohyashiki K, Ohyashiki JH, Hayashi S, Yahata N, Ando K, Toyama K, Hoshika A, Takasaki M, Mori M, Shay JW. 1998. Telomeric length and telomerase activity vary with age in peripheral blood cells obtained from normal individuals. Hum Genet 102:397–402.

Jablonka E, Lamb MJ. 2005. Evolution in four dimensions: Genetic, epigenetic, behavioral, and symbolic variation in the history of life. Cambridge, MA: MIT Press. x, 462 p.

Jablonka E, Raz G. 2009. Transgenerational epigenetic inheritance: Prevalence, mechanisms, and implications for the study of heredity and evolution. Q Rev Biol 84:131–176.

Jackson S, Diamond J. 1996. Metabolic and digestive responses to artificial selection in chickens. Evolution 50:1638–1650.

Jemielity S, Kimura M, Parker KM, Parker JD, Cao XJ, Aviv A, Keller L. 2007. Short telomeres in short-lived males: What are the molecular and evolutionary causes? Aging Cell 6:225–233.

Jennings BJ, Ozanne SE, Dorling MW, Hales CN. 1999. Early growth determines longevity in male rats and may be related to telomere shortening in the kidney. FEBS Lett 448:4–8.

Jeyapalan JC, Ferreira M, Sedivy JM, Herbig U. 2007. Accumulation of senescent cells in mitotic tissue of aging primates. Mech Ageing Dev 128:36–44.

Kaplan H. 1996. A theory of fertility and parental investment in traditional and modern human societies. Yearb Phys Anthropol 1996; 39:91–135.

Kaplan HS, Robson AJ. 2002. The emergence of humans: The coevolution of intelligence and longevity with intergenerational transfers. Proc Natl Acad Sci USA 99:10221–10226.

Kappei D, Londono-Vallejo JA. 2008. Telomere length inheritance and aging. Mech Ageing Dev 129:17–26.

Kaszubowska L. 2008. Telomere shortening and ageing of the immune system. J Physiol Pharmacol 9:169–186.

Katepalli MP, Adams AA, Lear TL, Horohov DW. 2008. The effect of age and telomere length on immune function in the horse. Dev Comp Immunol 2008; 32:1409–1415.

Keefe DL, Liu L, Marquard K. 2007. Telomeres and aging-related meiotic dysfunction in women. Cell Mol Life Sci 64:139–143.

Kim NW, Piatyszek MA, Prowse KR, Harley CB, West MD, Ho PLC, Coviello GM, Wright WE, Weinrich SL, Shay JW. 1994. Specific association of human telomerase activity with immortal cells and cancer. Science 266:2011–2015.

Kimura M, Cherkas LF, Kato BS, Demissie S, Hjelmborg JB, Brimacombe M, Cupples A, Hunkin JL, Gardner JP, Lu X, Cao X, Sastrasinh M, Province MA, Hunt SC, Christensen K, Levy D, Spector TD, Aviv A. 2008a. Offspring's leukocyte telomere length, paternal age, and telomere elongation in sperm. PLoS Genet 4:e37.

Kimura M, Hjelmborg JVB, Gardner JP, Bathum L, Brimacombe M, Lu XB, Christiansen L, Vaupel JW, Aviv A, Christensen K. 2008b. Telomere length and mortality: A study of leukocytes in elderly Danish twins. Am J Epidemiol 167:799–806.

Kirkwood TBL. 2005. Understanding the odd science of aging. Cell 120:437–447.

Kirkwood TBL, Holliday R. 1979. The evolution of ageing and longevity. Proc R Soc Lond B Biol Sci 205:531–546.

Kliegman R, Nelson WE. 2007. Nelson textbook of pediatrics. Philadelphia: Saunders. lii, 3147 p.

Koteja P, Carter PA, Swallow JG, Garland T Jr. 2003. Food wasting by house mice: Variation among individuals, families, and genetic lines. Physiol Behav 80:375–383.

Kotrschal A, Ilmonen P, Penn DJ. 2007. Stress impacts telomere dynamics. Biol Lett 3:128–130.

Kruger D, Nesse R. 2004. Sexual selection and the male:female mortality ratio. Evol Psychol 2:66–77.

Kruger DJ. 2008. Human life history variation and sex differences in mortality rates. J Soc Evol Cult Psychol 2:281–288.

Krunic D, Moshir S, Greulich-Bode KM, Figueroa R, Cerezo A, Stammer H, Stark HJ, Gray SG, Nielsen KV, Hartschuh W, Boukamp P. 2009. Tissue context-activated telomerase in human epidermis correlates with little age-dependent telomere loss. Biochim Biophys Acta 1792: 297–308.

Kuningas M, May L, Tamm R, van Bodegom D, van den Biggelaar AHJ, Meij JJ, Frölich M, Ziem JB, Suchiman HED, Metspalu A, Slagboom PE, Westendorp RGJ. 2009. Selection for genetic variation inducing pro-inflammatory responses under adverse environmental conditions in a ghanaian population. PLoS One 4:e7795.

Kuzawa CW. 2005. Fetal origins of developmental plasticity: Are fetal cues reliable predictors of future nutritional environments? Am J Hum Biol 17:5–21.

Kuzawa CW. 2008. The developmental origins of adult health: Intergenerational inertia in adaptation and disease. In: Trevathan W, Smith EO, McKenna JJ, editors. Evolutionary medicine and health: New perspectives. New York: Oxford University Press. p 325–349.

Kuzawa CW, Quinn EA. 2009. Developmental origins of adult function and health: Evolutionary hypotheses. Ann Rev Anthropol 38:131–147.

Laland KN, Odling-Smee J, Feldman MW. 2001. Cultural niche construction and human evolution. J Evol Biol 14:22–33.

Lee D-C, Im J-A, Kim J-H, Lee H-R, Shim J-Y. 2005. Effect of long-term hormone therapy on telomere length in postmenopausal women. Yonsei Med J 46:471–479.

Lee HW, Blasco MA, Gottlieb GJ, Horner JW II, Greider CW, DePinho RA. 1998. Essential role of mouse telomerase in highly proliferative organs. Nature 392:569–574.

Lee KA. 2006. Linking immune defenses and life history at the levels of the individual and the species. Integr Comp Biol 46:1000–1015.

Levy D, Neuhausen SL, Hunt SC, Kimura M, Hwang S-J, Chen W, Bis JC, Fitzpatrick AL, Smith E, Johnson AD, Gardner JP, Srinivasan SR, Schork N, Rotter JI, Herbig U, Psaty BM, Sastrasinh M, Murray SS, Vasan RS, Province MA, Glazer NL, Lu X, Cao X, Kronmal R, Mangino M, Soranzo N, Spector TD, Berenson GS, Aviv A. 2010. Genome-wide association identifies OBFC1 as a locus involved in human leukocyte telomere biology. Proc Natl Acad Sci USA 107:9293–9298.

Lin J, Epel E, Cheon J, Kroenke C, Sinclair E, Bigos M, Wolkowitz O, Mellon S, Blackburn E. 2010. Analyses and comparisons of telomerase activity and telomere length in human T and B cells: Insights for epidemiology of telomere maintenance. J Immunol Methods 352:71–80.

Long CL, Schaffel N, Geiger JW, Schiller WR, Blakemore WS. 1979. Metabolic response to injury and illness: Estimation of energy and protein needs from indirect calorimetry and nitrogen balance. JPEN J Parenter Enteral Nutr 3:452–456.

Lukens JN, Van Deerlin V, Clark CM, Xie SX, Johnson FB. 2009. Comparisons of telomere lengths in peripheral blood and cerebellum in Alzheimer's disease. Alzheimers Dement 5:463–469.

Macallan DC, Wallace DL, Zhang Y, Ghattas H, Asquith B, de Lara C, Worth A, Panayiotakopoulos G, Griffin GE, Tough DF, Beverley PC. 2005. B-cell kinetics in humans: Rapid turnover of peripheral blood memory cells. Blood 105:3633–3640.

Mangino M, Richards JB, Soranzo N, Zhai G, Aviv A, Valdes AM, Samani NJ, Deloukas P, Spector TD. 2009. A genome-wide association study identifies a novel locus on chromosome 18q12.2 influencing white cell telomere length. J Med Genet 46:451–454.

Manning EL, Crossland J, Dewey MJ, Van Zant G. 2002. Influences of inbreeding and genetics on telomere length in mice. Mamm Genome 13:234–238.

Mariani E, Meneghetti A, Formentini I, Neri S, Cattini L, Ravaglia G, Forti P, Facchini A. 2003. Different rates of telomere shortening and telomerase activity reduction in CD8 T and CD16 NK lymphocytes with ageing. Exp Gerontol 38:653–659.

Martin-Ruiz C, Dickinson HO, Keys B, Rowan E, Kenny RA, von Zglinicki T. 2006. Telomere length predicts poststroke mortality, dementia, and cognitive decline. Ann Neurol 60:174–180.

Martin-Ruiz CM, Gussekloo J, Heemst D, Zglinicki T, Westendorp RGJ. 2005. Telomere length in white blood cells is not associated with morbidity or mortality in the oldest old: A population-based study. Aging Cell 4:287–290.

Martin LB, Hasselquist D, Wikelski M. 2006. Investment in immune defense is linked to pace of life in house sparrows. Oecologia 147:565–575.

Mayer S, Bruderlein S, Perner S, Waibel I, Holdenried A, Ciloglu N, Hasel C, Mattfeldt T, Nielsen KV, Moller P. 2006. Sex-specific telomere length profiles and age-dependent erosion dynamics of individual chromosome arms in humans. Cytogenet Genome Res 112:194–201.

McDade TW. 2003. Life history theory and the immune system: Steps toward a human ecological immunology. Yearbook of physical anthropology, Vol. 46. New York: Wiley-Liss, Inc. p 100–125.

McDade TW, Reyes-Garcia V, Tanner S, Huanca T, Leonard WR. 2008. Maintenance versus growth: Investigating the costs of immune activation among children in lowland Bolivia. Am J Phys Anthropol 136:478–484.

McEachern MJ, Blackburn EH. 1995. Runaway telomere elongation caused by telomerase RNA gene mutations. Nature 376:403–409.

McNab BK. 1988. Complications inherent in scaling the basal rate of metabolism in mammals. Q Rev Biol 63:25–54.

Meier A, Fiegler H, Munoz P, Ellis P, Rigler D, Langford C, Blasco MA, Carter N, Jackson SP. 2007. Spreading of mammalian DNA-damage response factors studied by ChIP-chip at damaged telomeres. EMBO J 26:2707–2718.

Meyne J, Ratliff RL, Moyzis RK. 1989. Conservation of the human telomere sequence (TTAGGG)n among vertebrates. Proc Natl Acad Sci USA 86:7049–7053.

Miller RA, Harper JM, Dysko RC, Durkee SJ, Austad SN. 2002. Longer life spans and delayed maturation in wild-derived mice. Exp Biol Med 227:500–508.

Monaghan P. 2010. Telomeres and life histories: the long and the short of it. Ann N Y Acad Sci 1206(1):130-142.

Muehlenbein MP, Bribiescas RG. 2005. Testosterone-mediated immune functions and male life histories. Am J Hum Biol 17:527–558.

Muehlenbein MP, Hirschtick JL, Bonner JZ, Swartz AM. 2010. Toward quantifying the usage costs of human immunity: Altered metabolic rates and hormone levels during acute immune activation in men. Am J Hum Biol 22:546–556.

Mueller P, Diamond J. 2001. Metabolic rate and environmental productivity: Well-provisioned animals evolved to run and idle fast. Proc Natl Acad Sci USA 98:12550–12554.

Muller M, Wrangham R. 2004. Dominance, aggression and testosterone in wild chimpanzees: A test of the 'challenge hypothesis'. Anim Behav 67:113–123.

Nakamura K-I, Izumiyama-Shimomura N, Sawabe M, Arai T, Aoyagi Y, Fujiwara M, Tsuchiya E, Kobayashi Y, Kato M, Oshimura M, Sasajima K, Nakachi K, Takubo K. 2002. Comparative analysis of telomere lengths and erosion with age in human epidermis and lingual epithelium. J Invest Dermatol 119:1014–1019.

Nawrot TS, Staessen JA, Gardner JP, Aviv PA. 2004. Telomere length and possible link to X chromosome. Lancet 363:507–510.

Njajou O, Hsueh W, Blackburn E, Newman A, Wu S, Li R, Simonsick E, Harris T, Cummings S, Cawthon R. 2009. Association between telomere length, specific causes of death, and years of healthy life in health, aging, and body composition, a population-based cohort study. J Gerontol A Biol Sci Med Sci 64:860–864.

Njajou OT, Cawthon RM, Damcott CM, Wu SH, Ott S, Garant MJ, Blackburn EH, Mitchell BD, Shuldiner AR, Hsueh WC. 2007. Telornere length is paternally inherited and is associated with parental lifespan. Proc Natl Acad Sci USA 104:12135–12139.

Nordfjäll K, Larefalk A, Lindgren P, Holmberg D, Roos G. 2005. Telomere length and heredity: Indications of paternal inheritance. Proc Natl Acad Sci 102:16374–16378.

Nordfjäll K, Svenson U, Norrback K-F, Adolfsson R, Lenner P, Roos G. 2009. The individual blood cell telomere attrition rate is telomere length dependent. PLoS Genet 5:e1000375.

Nordfjäll K, Svenson U, Norrback K-F, Adolfsson R, Roos G. 2010. Large-scale parent-child comparison confirms a strong paternal influence on telomere length. Eur J Hum Genet 18:385–389.

Nunn CL, Barton RA. 2001. Comparative methods for studying primate adaptation and allometry. Evol Anthropol 10:81–98.

O'Callaghan N, Clifton P, Noakes M, Fenech M. 2009. Weight loss in obese men is associated with increased telomere length and decreased abasic sites in rectal mucosa. Rejuvenation Res 12:169–176.

O'Meally D, Miller H, Patel H. 2010. The first cytogenetic map of the Tuatara, *Sphenodon punctatus*. Cytogenet Genome Res 127:213–223.

Oikawa S, Kawanishi S. 1999. Site-specific DNA damage at GGG sequence by oxidative stress may accelerate telomere shortening. FEBS Lett 453:365–368.

Okuda K, Bardeguez A, Gardner JP, Rodriguez P, Ganesh V, Kimura M, Skurnick J, Awad G, Aviv A. 2002. Telomere length in the newborn. Pediatr Res 52:377.

Olovnikov AM. 1971. Principle of marginotomy in template synthesis of polynucleotides. Dokl Akad Nauk SSSR 201:1496–1499.

Ornish D, Lin J, Daubenmier J, Weidner G, Epel E, Kemp C, Magbanua MJM, Marlin R, Yglecias L, Carroll PR, Blackburn EH. 2008. Increased telomerase activity and comprehensive lifestyle changes: A pilot study. Lancet Oncol 9:1048–1057.

Ouellette MM, Liao M, Herbert BS, Johnson M, Holt SE, Liss HS, Shay JW, Wright WE. 2000. Subsenescent telomere lengths in fibroblasts immortalized by limiting amounts of telomerase. J Biol Chem 275:10072–10076.

Paiva CSD, Pflugfelder SC, Li D-Q. 2006. Cell size correlates with phenotype and proliferative capacity in human corneal epithelial cells. Stem Cells 24:368–375.

Parks CG, Miller DB, McCanlies EC, Cawthon RM, Andrew ME, DeRoo LA, Sandler DP. 2009. Telomere length, current perceived stress, and urinary stress hormones in women. Cancer Epidemiol Biomarkers Prev 18:551–560.

Pendergrass WR, Lane MA, Bodkin NL, Hansen BC, Ingram DK, Roth GS, Yi L, Bin H, Wolf NS. 1999. Cellular proliferation potential during aging and caloric restriction in rhesus monkeys (*Macaca mulatta*). J Cell Physiol 180:123–130.

Plunkett FJ, Soares MV, Annels N, Hislop A, Ivory K, Lowdell M, Salmon M, Rickinson A, Akbar AN. 2001. The flow cytometric analysis of telomere length in antigen-specific CD8+ T cells during acute Epstein-Barr virus infection. Blood 97:700–707.

Potten CS, Kellett M, Rew DA, Roberts SA. 1992. Proliferation in human gastrointestinal epithelium using bromodeoxyuridine in vivo: Data for different sites, proximity to a tumour, and polyposis coli. Gut 33:524–529.

Potter AJ, Wener MH. 2005. Flow cytometric analysis of fluorescence in situ hybridization with dye dilution and DNA staining (flow-FISH-DDD) to determine telomere length dynamics in proliferating cells. Cytometry A 68:53–58.

Prowse KR, Greider CW. 1995. Developmental and tissue-specific regulation of mouse telomerase and telomere length. Proc Natl Acad Sci USA 92:4818–4822.

Rampazzo E, Bertorelle R, Serra L, Terrin L, Candiotto C, Pucciarelli S, Del Bianco P, Nitti D, De Rossi A. 2010. Relationship between telomere shortening, genetic instability, and site of tumour origin in colorectal cancers. Br J Cancer 102:1300–1305.

Richter T, Zglinicki T. 2007. A continuous correlation between oxidative stress and telomere shortening in fibroblasts. Exp Gerontol 42:1039–1042.

Riha K, McKnight TD, Griffing LR, Shippen DE. 2001. Living with genome instability: Plant responses to telomere dysfunction. Science 291:1797–1800.

Roberts SB, Rosenberg I. 2006. Nutrition and aging: Changes in the regulation of energy metabolism with aging. Physiol Rev 86:651–667.

Roelofs H, de Pauw ES, Zwinderman AH, Opdam SM, Willemze R, Tanke HJ, Fibbe WE. 2003. Homeostasis of telomere length rather than telomere shortening after allogeneic peripheral blood stem cell transplantation. Blood 101:358–362.

Rudolph KL, Chang y, Lee H-W, Blasco M, Gottlieb GJ, Greider C, DePinho RA. 1999. Longevity, stress response, and cancer in aging telomerase-deficient mice. Cell 96:701–712.

Salomons HM, Mulder GA, van de Zande L, Haussmann MF, Linskens MH, Verhulst S. 2009. Telomere shortening and survival in free-living corvids. Proc Biol Sci 276:3157–3165.

Salpea KD, Nicaud V, Tiret L, Talmud PJ, Humphries SE, on behalf of the EARS II group. 2008. The association of telomere length with paternal history of premature myocardial infarction in the European Atherosclerosis Research Study II. J Mol Med 86:815–824.

Salpea KD, Talmud PJ, Cooper JA, Maubaret CG, Stephens JW, Abelak K, Humphries SE. 2010. Association of telomere length with type 2 diabetes, oxidative stress and UCP2 gene variation. Atherosclerosis 209:42–50.

Samper E, Flores JM, Blasco MA. 2001. Restoration of telomerase activity rescues chromosomal instability and premature aging in Terc-/- mice with short telomeres. EMBO Rep 2:800–807.

Schaetzlein S, Lucas-Hahn A, Lemme E, Kues WA, Dorsch M, Manns MP, Niemann H, Rudolph KL. 2004. Telomere length is reset during early mammalian embryogenesis. Proc Natl Acad Sci USA 101:8034–8038.

Schoknecht PA, Ebner S, Pond WG, Zhang SD, McWhinney V, Wong WW, Klein PD, Dudley M, Goddardfinegold J, Mersmann HJ. 1994. Dietary-cholesterol supplementation improves growth and behavioral-response of pigs selected for genetically high and low serum-cholesterol. J Nutr 124:305–314.

Schwartz D, Mayaux M, Spira A, Moscato M, Jouannet P, Czyglik F, David G. 1983. Semen characteristics as a function of age in 833 fertile men. Fertil Steril 39:530–535.

Schwartz SO, Stansbury F. 1954. Significance of nucleated red blood cells in peripheral blood: Analysis of 1,496 cases. J Am Med Assoc 154:1339–1340.

Seluanov A, Chen Z, Hine C, Sasahara T, Ribeiro A, Catania K, Presgraves D, Gorbunova V. 2007. Telomerase activity coevolves with body mass not lifespan. Aging Cell 6:45–52.

Seluanov A, Hine C, Bozzella M, Hall A, Sasahara TH, Ribeiro AA, Catania KC, Presgraves DC, Gorbunova V. 2008. Distinct tumor suppressor mechanisms evolve in rodent species that differ in size and lifespan. Aging Cell 7:813–823.

Shanley DP, Aw D, Manley NR, Palmer DB. 2009. An evolutionary perspective on the mechanisms of immunosenescence. Trends Immunol 30:374–381.

Shay JW, Wright WE. 2005. Senescence and immortalization: Role of telomeres and telomerase. Carcinogenesis 26:867–874.

Shay JW, Wright WE. 2007. Hallmarks of telomeres in ageing research. J Pathol 211:114–123.

Shore D, Bianchi A. 2009. Telomere length regulation: Coupling DNA end processing to feedback regulation of telomerase. EMBO J 28:2309–2322.

Sidorov I, Kimura M, Yashin A, Aviv A. 2009. Leukocyte telomere dynamics and human hematopoietic stem cell kinetics during somatic growth. Exp Hematol 37:514–524.

Sitte N, Saretzki G, von Zglinicki T. 1998. Accelerated telomere shortening in fibroblasts after extended periods of confluency. Free Radic Biol Med 24:885–893.

Slagboom PE, Droog S, Boomsma DI. 1994. Genetic determination of telomere size in humans: A twin study of three age groups. Am J Hum Genet 55:876–876.

Slijepcevic P, Hande MP. 1999. Chinese hamster telomeres are comparable in size to mouse telomeres. Cytogenet Genome Res 85:196–199.

Smogorzewska A, de Lange T. 2004. Regulation of telomerase by telomeric proteins. Annu Rev Biochem 73:177–208.

Soda H, Raymond E, Sharma S, Lawrence R, Davidson K, Oka M, Kohno S, Izbicka E, Hoff DDV. 2000. Effects of androgens on telomerase activity in normal and malignant prostate cells in vitro. Prostate 43:161–168.

Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, Blomqvist L, Hoffstedt J, Naslund E, Britton T, Concha H, Hassan M, Ryden M, Frisen J, Arner P. 2008. Dynamics of fat cell turnover in humans. Nature 453:783–787.

Spalding KL, Bhardwaj RD, Buchholz BA, Druid H, Frisen J. 2005. Retrospective birth dating of cells in humans. Cell 122:133–143.

Spaulding C, Guo W, Effros RB. 1999. Resistance to apoptosis in human CD8+ T cells that reach replicative senescence after multiple rounds of antigen-specific proliferation. Exp Gerontol 34:633–644.

Speakman J, Król E. 2005. Limits to sustained energy intake IX: A review of hypotheses. J Comp Physiol B 175:375–394.

Spyridopoulos I, Hoffmann J, Aicher A, Brummendorf TH, Doerr HW, Zeiher AM, Dimmeler S. 2009. Accelerated telomere shortening in leukocyte subpopulations of patients with coronary heart disease: Role of cytomegalovirus seropositivity. Circulation 120:1364–1372.

Sridevi V, Uma KD, Sivaramakrishnan S, Isola NR. 2002. Telomere length as related to chromosome length in the genus pennisetum. Cytologia 67:185–190.

Stachon A, Holland-Letz T, Krieg M. 2004. High in-hospital mortality of intensive care patients with nucleated red blood cells in blood. Clin Chem Lab Med 42:933–938.

Starostová Z, Kubicka L, Konarzewski M, Kozlowski J, Kratochvil L. 2009. Cell size but not genome size affects scaling of metabolic rate in eyelid geckos. Am Nat 174:E100–E105.

Stearns SC. 1992. The evolution of life histories. Oxford, NY: Oxford University Press. xii, 249 p.

Steinert S, Shay JW, Wright WE. 2000. Transient expression of human telomerase extends the life span of normal human fibroblasts. Biochem Biophys Res Commun 273:1095–1098.

Steinman L, Conlon P, Maki R, Foster A. 2003 The intricate interplay among body weight, stress, and the immune response to friend or foe. J Clin Invest 111:183–185.

Steuber JG. 2007. The cost of an emerging disease: *Mycobacterium leprae* infection alters metabolic rate of the nine-banded armadillo (*Dasypus novemcinctus*). Akron, OH: The Graduate Faculty of The University of Akron, Masters of Science.

Svenson U, Nordfjall K, Stegmayr B, Manjer J, Nilsson P, Tavelin B, Henriksson R, Lenner P, Roos G. 2008. Breast cancer survival is associated with telomere length in peripheral blood cells. Cancer Res 68:3618–3623.

Tabori U, Nanda S, Druker H, Lees J, Malkin D. 2007. Younger age of cancer initiation is associated with shorter telomere length in Li-Fraumeni syndrome. Cancer Res 67:1415–1418.

Takubo K, Izumiyama-Shimomura N, Honma N, Sawabe M, Arai T, Kato M, Oshimura M, Nakamura KI. 2002. Telomere lengths are characteristic in each human individual. Exp Gerontol 37:523–531.

Tarry-Adkins JL, Chen JH, Smith NS, Jones RH, Cherif H, Ozanne SE. 2009. Poor maternal nutrition followed by accelerated postnatal growth leads to telomere shortening and increased markers of cell senescence in rat islets. FASEB J 23:1521–1528.

Tchirkov A, Lansdorp PM. 2003. Role of oxidative stress in telomere shortening in cultured fibroblasts from normal individuals and patients with ataxia-telangiectasia. Hum Mol Genet 12:227–232.

Teixeira MT, Arneric M, Sperisen P, Lingner J. 2004. Telomere length homeostasis is achieved via a switch between telomerase- extendible and -nonextendible states. Cell 117:323–335.

Thibeault S, Glade R, Li W. 2006. Comparison of telomere length of vocal folds with different tissues: A physiological measurement of vocal senescence. J Voice 20:165–170.

Tilly JL, Niikura Y, Rueda BR. 2009. The current status of evidence for and against postnatal oogenesis in mammals: A case of ovarian optimism versus pessimism? Biol Reprod 80:2–12.

Tremblay M, Vézina H. 2000. New estimates of intergenerational time intervals for the calculation of age and origins of mutations. Am J Hum Genet 66:651–658.

Trevathan W. 2007. Evolutionary medicine. Annu Rev Anthropol 36:139–154.

Trkova M, Prochazkova K, Krutilkova V, Sumerauer D, Sedlacek Z. 2007. Telomere length in peripheral blood cells of germline *TP53* mutation carriers is shorter than that of normal individuals of corresponding age. Cancer 110:694–702.

Tuljapurkar SD, Puleston CO, Gurven MD. 2007. Why men matter: Mating patterns drive evolution of human lifespan. PLoS One 2:e785.

Tyrka AR, Price LH, Kao H-T, Porton B, Marsella SA, Carpenter LL. 2010. Childhood maltreatment and telomere shortening: Preliminary support for an effect of early stress on cellular aging. Biol Psychiatry 67:531–534.

Ujvari B, Madsen T. 2009. Short telomeres in hatchling snakes: Erythrocyte telomere dynamics and longevity in tropical pythons. PLoS One 4:e7493.

Ulaner GA, Giudice LC. 1997. Developmental regulation of telomerase activity in human fetal tissues during gestation. Mol Hum Reprod 3:769–773.

Unryn BM, Cook LS, Riabowol KT. 2005. Paternal age is positively linked to telomere length of children. Aging Cell 4:97–101.

Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, Aviv A, Spector TD. 2005. Obesity, cigarette smoking, and telomere length in women. Lancet 366:662–664.

Vasa-Nicotera M, Brouilette S, Mangino M, Thompson JR, Braund P, Clemitson J-R, Mason A, Bodycote CL, Raleigh SM, Louis E, Samani NJ. 2005. Mapping of a major locus that determines telomere length in humans. Am J Hum Genet 76:147–151.

Vaziri H, Schachter F, Uchida I, Wei L, Zhu X, Effros R, Cohen D, Harley CB. 1993. Loss of telomeric DNA during aging of normal and trisomy 21 human lymphocytes. Am J Hum Genet 52:661–667.

von Zglinicki T, Martin-Ruiz CM, Saretzki G. 2005. Telomeres, cell senescence and human ageing. Signal Transduct 5:103–114.

von Zglinicki T, Serra V, Lorenz M, Saretzki G, Lenzen-Groimlighaus R, Gener R, Risch A, Steinhagen-Thiessen E. 2000. Short telomeres in patients with vascular dementia: An indicator of low antioxidative capacity and a possible risk factor? Lab Invest 80:1739–1747.

Wagner W, Bork S, Horn P, Krunic D, Walenda T, Diehlmann A, Benes V, Blake J, Huber F, Eckstein V. 2009. Aging and replicative senescence have related effects on human stem and progenitor cells. PLoS One 4:e5846.

Wagner W, Horn P, Castoldi M, Diehlmann A, Bork S, Saffrich R, Benes V, Blake J, Pfister S, Eckstein V, Ho AD. 2008. Replicative senescence of mesenchymal stem cells: A continuous and organized process. PLoS One 3:e2213.

Watson JD. 1972. Origin of concatemeric T7 DNA. Nat New Biol 239:197–201.

Watts G. 2009. Nobel medicine prize is won by scientists for work on chromosomal telomeres. BMJ 339:b4120.

Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. 2004. Epigenetic programming by maternal behavior. Nat Neurosci 7:847–854.

Weinstein BS, Ciszek D. 2002. The reserve-capacity hypothesis: Evolutionary origins and modern implications of the trade-off between tumor-suppression and tissue-repair. Exp Gerontol 37:615–627.

Weinstein GD, McCullough JL, Ross P. 1984. Cell proliferation in normal epidermis. J Invest Dermatol 82:623–628.

Weise JM, Gunes C. 2009. Differential regulation of human and mouse telomerase reverse transcriptase (TERT) promoter activity during testis development. Mol Reprod Dev 76:309–317.

Weismann A. 1889. Essays upon heredity. Oxford: Clarendon Press. Available at: http://www.esp.org/books/weismann/essays/facsimile/.

West-Eberhard MJ. 2003. Developmental plasticity and evolution. Oxford, NY: Oxford University Press. xx, 794 p.

Wilson WR, Herbert KE, Mistry Y, Stevens SE, Patel HR, Hastings RA, Thompson MM, Williams B. 2008. Blood leucocyte telomere DNA content predicts vascular telomere DNA content in humans with and without vascular disease. Eur Heart J 29:2689–2694.

Woo J, Suen EWC, Leung JCS, Tang NLS, Ebrahim S. 2009. Older men with higher self-rated socioeconomic status have shorter telomeres. Age Ageing 38:553–558.

Wright WE, Piatyszek MA, Rainey WE, Byrd W, Shay JW. 1996. Telomerase activity in human germline and embryonic tissues and cells. Dev Genet 18:173–179.

Wright WE, Shay JW. 1995. Time, telomeres and tumors—Is cellular senescence more than an anticancer mechanism. Trends Cell Biol 5:293–297.

Yashima K, Maitra A, Rogers BB, Timmons CF, Rathi A, Pinar H, Wright WE, Shay JW, Gazdar AF. 1998. Expression of the RNA component of telomerase during human development and differentiation. Cell Growth Differ 9:805–813.

Zeichner SL, Palumbo P, Feng Y, Xiao X, Gee D, Sleasman J, Goodenow M, Biggar R, Dimitrov D. 1999. Rapid telomere shortening in children. Blood 93:2824–2830.

Zijlmans JMJM, Martens UM, Poon SSS, Raap AK, Tanke HJ, Ward RK, Lansdorp PM. 1997. Telomeres in the mouse have large inter-chromosomal variations in the number of T2AG3 repeats. Proc Natl Acad Sci USA 94:7423–7428.

Zou Y, Sfeir A, Gryaznov SM, Shay JW, Wright WE. 2004. Does a sentinel or a subset of short telomeres determine replicative senescence? Mol Biol Cell 15:3709–3718.