Abstract  All over the world people are surviving into their seventh and later decades of life more frequently today than ever before in human history. Some remain in good health, while others show chronic degenerative conditions (CDCs), frailty, and relatively rapid mortality. Thereafter, multiple factors promoting health and well-being become ever more complex as we age. After attainment of reproductive maturation, many physiological decrements occurring in concert with age reflect both senescent and disease processes, not simply the passage of time. Senescence is a process that begins with DNA, molecules and cells and ultimately terminates in cellular death, loss of organ function, and somatic frailty. These changes are different from benign changes with age that do not alter function. Both differ from the pathological processes represented by disease. Either disease or senescence may be age-related, but neither is age-determined. Disease results from pathological alterations and it affects all age groups. Diseases need not be related to senescence, which includes alterations due to inherent aspects of organismal biology. Distinctions among senescence, aging, and disease blur for the late-life CDCs because, in addition to disease processes, many CDCs are phenotypic manifestations of senescing DNA, organelles, cells, and organs. During earlier epochs of human evolution, greater environmental exposures and fewer cultural buffers likely lead to greater frailty and mortality before senescence progressed greatly, as they still do for most animals. In modern-day settings, culturally patterned behaviors have allowed human frailty to become disconnected somewhat from mortality, unlike non-human species. J Physiol Anthropol 26(3): 365–372, 2007 http://www.jstage.jst.go.jp/browse/jpa2 [DOI: 10.2114/jpa2.26.365]

Keywords: allostatic load, age-related disease, frailty, longevity

Introduction

The major demographic change affecting populations worldwide during the 21st century is unlike any previous demographic transition. This one is affecting most the 50% of people who survive past their 70th birthday in cosmopolitan settings, and the ever-increasing percent of such survivors in less privileged settings. That so many are surviving to their 8th decade represents the first half of the present demographic transition. The second part is that thereafter, these septuagenarians are surviving longer as mortality rates continue to decline at older ages (Carey and Papadopoulos, 2005; Crews, 2005a; Dobhammer and Kyttir, 2001). Currently, in most cosmopolitan settings, mortality rates are declining faster at ages over 70 than at younger ages. Among those aged 65+ years, population growth rates during the next decade are projected to be the largest ever recorded as the “baby boom” generation becomes order. Population pyramids for many cosmopolitan nations already more resemble modern-day skyscrapers (Fig. 1b) than they do ancient Egyptian tombs (Fig. 1a). Some populations with high fertility, high infant and childhood mortality, and low survival to age 65 still exist, such as India in 2000 (Fig. 2a). Others, such as Japan in 2000 PE, already are top heavy and showing an elderly and a middle-age bulge from the post-war generation and their offering (Fig. 2b). However, most nation states have transitioned to low fertility, low infant/child mortality, and high adult survival through the 6th and 7th decades. Those that have not yet done so or have regressed are found mainly in equatorial areas, regions of limited mineral, agricultural and industrial potential, and among those experiencing political, economic, and religious conflicts. A pattern of population growth among those aged 60+ and 80+ is consistent for the world population (Fig. 3). Although rates of change differ substantially across and within populations, over the 20th and into the 21st centuries, mortality continued to shift rapidly to older and older ages (Crews 2005a).

A Biocultural Perspective

A confluence of biological adaptations, environmental changes, and cultural developments over the past several thousand years have provided humankind with a bioculturally-constructed niche (see Oblying-Smee et al., 2003). This built environment promotes retention of reserve capacity (RC) through reduced exposures to environmental (e.g., heat, cold,
Fig. 1  Population distributions for a) American Samoa 1940 and b) Sweden 1981 (Redrawn from Smyer and Crews, 1985).

Fig. 2  Population distributions for a) India and b) Japan in 2000 (Redrawn from Lee and Mason, 2000).

Fig. 3  Change in proportions of the world population by age group 1950–2150 (Redrawn from Mirkin and Weinberger, 2000).
exposure) and infectious and parasitic agents (Crews, 2003, 2005ab; Crimmins and Finch, 2005; Drenos et al., 2006). Alterations toward "cushy life styles" lived within built environmental niches have improved human health particularly during the earliest and latest phases of life history (LH). At older ages, health and illness are strongly determined by inherent biological stability (genetic and cellular propensities), life-long and ongoing biological modifications (wear-and-tear, senescence), environmental factors (stressors), history (age, period, cohort effects), and physiological function (allostatic load (AL), metabolic reserve capacity (RC), frailty) (Table 1).

Resulting from these are complex physiological states we define as health, illness/disease, senescence, aging and wellness. Individually, each state is difficult to define and measure empirically. Jointly, they form a complex web of causality that we assess through change and disease. Assessing senescence requires understanding genetic, protein, cellular, tissue, organ, and organ system levels and interactions across levels. Even examining manifestations of senescence at the individual level to understand human variation over the lifespan requires applications of multiple assessments of disease, wellness, ADLs/IADLs, stress, perceptions of health, stress responses, and frailty, along with assessments of physiological and genetic risk factors. To properly intervene on disease and senescent processes, practitioners and public health personnel need to differentiate between senescence, aging, and disease. A continuing question is whether differences between senescence, aging, and disease are conceptual or practical. The goal here is to examine differences between these states and to evaluate how well composite assessment scales, used to study human variation in physiological dysfunction during the last decades of life may measure the underlying senescent phenotype.

**Senescence, Aging, and Disease**

Senescence: Multiple definitions of senescence, aging, and disease litter the scientific literature (Arking, 2006; Crews, 2003; Cristofalo, 2000). Occasionally, there is limited agreement over definitions even in a single edited volume (Esser and Martin, 1995). Senescence mainly occurs during the LH phase from full maturity to death; it is characterized by an accumulation of metabolic byproducts and a decreased probability of reproduction and survival (Arking, 2006; Austad, 1992; Crews, 2003, 2005ab; Cristofalo, 2000; Finch and Rose, 1995; Kirkwood, 1981; Williams, 1957). Contrary to many historical definitions, senescence is now viewed as age-independent. In addition, senescent processes are individualized, progressive, multifactorial, and deleterious (Arking, 2006). Finally, senescence is an event-driven process affecting all organs and bodily systems, ultimately resulting from loss of reproductive potential, and leads to an increased probability of death (Arking, 2006; Austad, 1999; Crews, 2003). Although senescence is not time-dependent, senescent changes accumulate over an organism’s life span making it age-related (Arking, 2006; Crews, 2003). This is partly because early life history (LH) events pace the timing of senescence (Crews, 2003). And partly because, loss of function is dependent upon cellular processes of replication and differentiation that occur over biological time (Arking, 2006). Senescence is not a programmed process. Senescence follows a different pace across species and between individuals within species. Variable patterns and timing of senescence are its hallmarks (Crews, 2003). Senescent changes and longevity are poorly conserved phylogenetically. Rapid- and slow-senescing populations of wild mice, fruit flies, and mammals sharing the same family suggest that high variability in LH parameters is compatible with RS and population survival (Austad, 1997; Carey and Judge, 2001; Kirkwood and Austad, 2000; Rose et al., 2004). In general, senescence commences with cessation of growth and development and attainment of maximum reproductive potential (MRP); (see Crews 2003 for a complete definition). Growth and development represent a co-adaptive and allometrically related series of events that begin at conception and proceed through completion of the adult soma (Arking, 2006; Crews, 2003). Still, precursors of senescence may be observed as early as uterine development, infancy, and childhood (Barker, 1998; Cameron and Demerath, 2002). As organisms survive beyond their point of MRP, NS becomes weaker because the probability of mortality from extrinsic and intrinsic factors becomes greater with increasing survival time (Kirkwood, 1981; Medawar, 1952; Rose, 1995; Weismann, 1889; Williams, 1957). The force of natural selection (NS) declines with increasing time of survival after growth and development in most, but not all, sexually reproducing organisms. Senescent processes are cumulative, progressive, intrinsic, and deleterious (Arking, 2006).

Aging: In contrast to senescence, aging measures the passage of time (Crews, 2003; 2005b). As existence through time, aging may be counted as years, days, or minutes. Aging is neither a process nor is it a LH phase. All things, whether living or non-living age, only the living senesces. Elsewhere, we have described this with the homily that rocks and socks weather and wear with age, wine mellows with age, and humans take on different social and biological roles with age (Crews, 2003; Harper and Crews, 2000). Many social, behavioral, cultural, life style, and biological changes affect people as they grow old in social settings. But, if these do not alter risks of death, then they are aging not senescence or

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measurable components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological stability</td>
<td>Genetic predispositions/Growth and Development</td>
</tr>
<tr>
<td>Biological Modifications</td>
<td>Senescent alterations/Illness/Slowlife responses</td>
</tr>
<tr>
<td>Environment</td>
<td>Stressors/Exposures/Climate</td>
</tr>
<tr>
<td>History</td>
<td>Age/Period/Cohort/Weather</td>
</tr>
<tr>
<td>Physiological function</td>
<td>Allostasis/Frailty/Homeostasis/Reserve capacity</td>
</tr>
</tbody>
</table>

Table 1 Determinants of health and illness during older ages
Many of the major risk factors for CDCs, such as obesity, hypertension, high serum cholesterol/lipids, hyperglycemia that predispose to life shortening CDCs may occur secondary to the breakdown of physiological defensive processes, loss of cells, and/or loss of organ reserves. Senescent processes contribute to many known risk factors for CDCs. Such findings suggest that CDCs may be visible signs of senescence (Crews, 2003; Cristofalo et al., 1999; Johnson et al., 1995). In many ways, CDCs are secondary to cellular senescence processes that increase the probability of death (Crews, 2003; Cristofalo et al., 1999; Johnson et al., 1995). Such interactions indicate that senescent-related changes at the cellular level produce changes at the whole soma level (Crews, 2003). Methods to measure senescence of individuals reflecting changes at the cellular level are needed. Several methods have been proposed, and some have received broad support for partly accomplishing this goal. Activities of Daily Living/Instrumental Activities of Daily Living (ADLs/IADLs) allostatic load, and frailty are the most widely used in current research and practice.

**Human Variation Over the Life Span**

Both prospective and retrospective data show that multiple physiological changes over the human life span are related to senescent alterations. Multiple attempts to identify “normal aging” and “biological age” have been made (Borkan and Norris, 1980). Unfortunately, for the first, little seems to be normal with regard to human variability at older ages, although variation for multiple physiological traits seems to be reduced at increasing ages over about age 65 years (Crews, 2003). Variation in many traits (e.g., blood pressure, height, serum cholesterol) increases with increasing age in the general population after attainment of MRP through about the 6th decade of life. However, coefficients of variation for most physiological and morphological traits tend to decrease with increasing age there after, particularly after the 8th decade of life. Biological age (BA) estimates were based upon concepts of deviations from average or normal values in population samples (Borkan et al., 1982). Given their dependence on age, estimates of BA are little different for predicting longevity and disease than is age itself (Borkan and Norris, 1980). For any aggregate measure to be a better predictor of senescent change than age, it should not be standardized on age. Indeed good biomarkers and composite estimates of senescence should be relatively poorly correlated with chronological age (Crews, 2003, 2005a). Genetological research does not need another proxy for chronological age. What are needed are biomarkers and scales that assess aspects of senescence that are not time dependant (Arking, 2006). A scale to assess senescence should not be correlated with chronological age nor should it be based on age. Cellular and physiological biomarkers should change independent of age, and scales should change with time in both positive and negative directions.

After, the limitations of BA and normal aging studies were revealed, the search for biomarkers of senescence began. Not age-determined, biomarkers were seen as aspects of cellular and physiological function whose alteration, appearance, or disappearance coincided with specific aspects of senescent biology (Arking, 2006). Biomarkers are thought to scale with senescent change. An obvious biomarker of senescence in women is menopause. This alteration in ovarian function is...
associated with multiple phenotypic changes that conform to senescence change models. Lowering of serum estrogen at menopause increases rates of bone loss, ends reproductive capability, and enhances a number of disease processes (Austad, 1997; Peccei, 2001; Snowdon, 1990). Biomarkers have been identified for a number of diseases and conditions (Arking, 2006). If the concept is extended to genes, then specific predisposing alleles, such as those for Huntington's disease or coronary artery disease are clear biomarkers of senescence. Most biomarkers are not so clear cut. A number of biomarkers of senescence have been identified (Arking, 2006). These range from hearing loss to slowed nerve conduction velocity. Many have been known for decades, while new ones are constantly being identified, c-reactive protein (CRP) and the interlukins (IL). Hopefully, continued study of biomarkers will lead to the development of interventions for senescent processes.

Assessing Somatic Declines

Stress responses: Allostatic load (AL) is a method of assessing physiological stress generated by both mentally and physically perceived stressors (Crews, 2007 in press; McEwen, 1997; Stewart, 2006). AL is a composite assessment that cuts across multiple physiological domains that show responses to events occurring in the world outside one's soma. Stress inducing factors may be environmental (cold, heat, hypoxia). They also may include mental stress from anxiety, work performance, or public speaking. Variability in morbidity, mortality, and physical and cognitive function are highly correlated with estimates of AL (McEwen, 1998, 2000, 2003; McEwen and Seeman, 1999). That AL may assess senescent somatic alterations is implicit in its design and applications (Crews, 2003, 2005b, 2007 in press; Stewart, 2006; McEwen, 1998, 2000, 2003; McEwen and Seeman, 1999). Assessments of AL rely on various combinations of physiological measures scored as 1 in the highest quartile of risk and 0 in all others (McEwen, 2003; Stewart, 2006). As originally constructed (McEwen, 1997, 1998), AL included 10 factors (Table 2). Since then, dozens of physiological, metabolic, hormonal and biological measures have been examined as components of AL (reviewed by Stewart, 2006). One suggestion is that AL may reflect variability in senescent decline among individuals within samples (McEwen and Seeman, 1999; Crews, 2007). Although useful within populations, AL is difficult to interpret in cross-cultural comparisons (Crews, 2007 in press).

Population-specific distributions of component risk factors reveal the broad range of human physiological variation compatible with reproductive success and long life. Combining samples from different populations into a hyper-population sample places all members of some populations at extremely low (Yanomami, Japanese) or high AL (American Samoans, African Americans). Among populations such as the Yanomami, Haazda, or Mieka few individuals may survive sufficiently long or have changes in risk factors sufficiently large to show senescence-related changes based upon such factors. While, in other populations such as Samoans or African Americans some individuals may show large changes very early in life. When multiple population samples are combined, their joint distribution shows how these latter groups all are at higher AL compared to more traditional-living populations (Crews 2003, 2007 in press).

Frailty: In nursing homes and community settings abilities to complete activities of daily living (Katz et al., 1963) are frequently used to assess disability and the need for assistance in living or nursing home placement (Crews and Zavotka, 2006). ADLs also are used as a proxy for frailty and senescence when more appropriate measurements are not available. This has lead to an intensified search for ways to assess frailty in living humans. Frailty is a complex biological phenomenon that is closely associated with pathology and disease (Fried et al., 2004; Hogan et al., 2003; Morley et al., 2002; Walston, 2005), making it difficult to quantify physiologically. Frailty may be a better measure of senescent alterations in humans than in other animals. Given humankind's abilities to care for members of their families and groups, frailty in humans has to a large extent been disconnected from mortality, but not morbidity and dependence (Crews, 2005b). Loss of ability to complete ADLs provides a measure of dependence on others, thereby indirectly assessing the ability of human social systems to alter the strong association of frailty with mortality observed in other species (Carey et al., 2005).

As with AL, a number of composite assessment scales of frailty have been developed and tested. One problem is that frailty scales should not assess disease pathology. For example, the Clinical Global Impression of Change in Physical Frailty (CGIC-PF) is a consensus-based scale. It was developed by a team of clinicians, patients, caregivers, and other “experts” (Studenski et al., 2004). CGIC-PF includes assessments of mobility, endurance, balance, nutrition, strength, and neuromotor performance, along with 7 medical complexity variables - health care use, appearance, ADLs, self-perceived health, and emotional and health status (Studenski et al., 2004). This is a complex scale, and may not be useful for field assessments. The CGIC-PF scale is expected to change as an individual’s innate disability alters over time and this is incorporated as a sliding scale from 1–7, with 1 indicating marked worsening of health and 7 marked improvements in

<table>
<thead>
<tr>
<th>Table 2 The components of allostatic load after McEwen (1999)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary Mediators of Stress:</strong></td>
</tr>
<tr>
<td>Systolic and diastolic blood pressure</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
</tr>
<tr>
<td>HDL-cholesterol and total-cholesterol</td>
</tr>
<tr>
<td>Glycated hemoglobin</td>
</tr>
<tr>
<td><strong>Primary Mediators of Stress:</strong></td>
</tr>
<tr>
<td>Serum dihydroyandosterone—sulfate</td>
</tr>
<tr>
<td>Overnight urinary cortisol, adrenaline, noradrenaline</td>
</tr>
</tbody>
</table>

health (Studenski et al., 2004). Therefore change may be used to
gauge an individual's personal trajectory of disability over
time. Walston (2004, 2005) and colleagues (Fried et al., 2001;
Walston et al., 2002) developed a frailty-screening exam based
on muscle weakness, slow walking speed, fatigue, weight loss,
and low activity levels that may be used in field research. This
simple index shows positive associations with future
hospitalization and death (Walston, 2005). It also is associated
with multiple metabolic markers indicative of poor function in
older adults. Several specific metabolic markers, increases in
IL-6, C-reactive protein and white blood cells, are associated
with senescent changes in cells. These also are indicators of
inflammation (Walston, 2005). Elsewhere inflammation has
been labeled the fire of senescence (Fried et al., 2001). One
model of frailty is that it starts with sarcopenia and reduced
expenditure of energy; this leads to weight loss, weakness,
exhaustion, and low levels of physical ability, i.e. frailty (Fried
et al., 2001; Walston, 2005). Frailty predicts falls, and is
associated with declining mobility, loss of ADLs, and death
(Fried et al., 2001; Walston, 2005). Both DHEA-S and CRP
are included in frailty composites, suggesting that the
neuroendocrine and inflammatory/immune systems are
intimately involved in senescent alterations at the cellular level.

Discussion

Unraveling senescence, aging, and disease will be a difficult
process. However it may be necessary in order to progress in
our understanding of senescence. This starts with developing
ways to measure and assess the senescent phenotype. Multiple
avenues of research are leading to a decomposition of
senescence, aging, and disease. Senescence arises as the
probability of reproduction decreases. This leads to a declining
force of natural selection with increasing time of survival.
Unfortunately, natural selection can not prevent the increasing
probability of mortality that occurs secondary to senescence.
To untangle disease from senescence we must acknowledge
that many age-related CDCs reflect cellular senescence. There
is synergism between the 2 domains, emphasizing the need to
develop age and disease-independent assessments of senescent
change at the cellular level that may be used to disentangle
senescence and disease in the whole organism. Measures of
AL, ADLs/IADLs, and frailty need to be correlated with
assessments of DNA expression and protein profiles, because
the latter are the markers of cellular senescence. To fully
integrate these processes it will be necessary to add DNA
profiles, and high-risk and longevity-enhancing alleles to
studies of disease and senescence. Then we may start to
untangle the threads of senesence and disease processes.

Acknowledgements The author thanks J Wantsala, T
Thomas, and C Mcfadden for aid in typing this manuscript and
James Stewart for aid with graphics.

References

Austad S (1997) Comparative aging and life histories in
mammals. Experimental Gerontol 32: 23–38
2nd ed., Churchill Livingston, New York
Borkan GA, Norris AH (1980) Assessment of age using a
profile of physical parameters. Gerontol 35: 177–184
anthropological approaches to aging. Year of Phys
Anthropol 25: 181–202
growth and their relationship to diseases of aging. Yearb
Physical Anthropol 45: 159–184
Carey JR, Judge DS (2001) Life span extension in humans is
self-reinforcing: a general theory of longevity. Popul Dev
Rev 27: 411–436
model: implications for biodemographic research. In Carey
R, Robine JM, Michel JP, Christen Y eds. Longevity and
Frailty, Springer-Verlag, New York, 1–16
Longevity and Frailty. Springer-Verlag, New York
Crews DE (2003) Human Senescence: Evolutionary and
Biocultural Perspectives. Cambridge University Press, New
York
Crews DE (2005a) Artificial environments and an aging
population: designing for age-related functional loss. J
Crews DE (2005b) Evolutionary perspectives on human
longevity and frailty. In Carey R, Robine JM, Michel JP,
Christen Y eds. Longevity and Frailty. Springer-Verlag, New
York, 57–65
implications for universal design. J Physiol Anthropol
25: 113–118
Crews DE (2007) Assessing composite estimates of stress in
Crews DE, Gerber LM (1994) Chronic degenerative diseases,
aging. In DE Crews and RM Garruto (eds) Biological
Anthropology and Aging: Perspectives on Human Variation
Crimmins EM, Finch CE (2005) Early life conditions affect
historical change in old-age mortality. In Carey R, Robine
JM, Michel JP, Christen Y eds. Longevity and Frailty.
Springer-Verlag, New York, 99–106
Cristofalo VG, Tresini M, Francis MK, Volker C (1999)
Biological theories of senescence. In VL Bengston, KW
Shaie ed. Handbook of Theories of Aging, Springer
Publishing Company, New York, 98–112
Doblhammer G, Kyrit J (2001) Compression or expansion of
morbidity? Trend in healthy-life expectancy in the elderly
McEwen BS, Seeman T (1999b) Protective and damaging effects of mediators of stress- Elaborating and testing the concepts of allostasis and allostatic load: Socioeconomic Status and Health in Industrial Nations, 30–47
Medawar PB (1952) An Unsolved Problem of Biology. Lewis HK, London
Walston J, McBurnie MA, Newman A, Tracy R, Kop WJ,
Hirsch CH, Gottdiener J, Fried LP, Cardiovascular Health Study (2002) Frailty and activation of the inflammation and coagulation systems with and without clinical morbidities: Results from the Cardiovascular Health Study. Arch Intern Med 162: 2333–2341


Williams GC (1957) Pleiotrophy, natural selection and the evolution of senescence. Evolution 11: 393–411

---

This article was presented at the 8th International Congress of Physiological Anthropology, 2006 (ICPA 2006), in Kamakura, Japan.

Received: September 30, 2006
Accepted: November 16, 2006

Correspondence to: Douglas E. Crews, Department Anthropology, 244 Lord Hall, The Ohio State University, 124 West 17th Avenue, Columbus, OH 43210–1364, USA
Phone: +1–614–292–1329
Fax: +1–614–292–4155
e-mail: Crews.8@osu.edu