

# Stress, Aging, and Resilience: Can Accrued Wear and Tear Be Slowed?

LOUISE C. HAWKLEY<sup>1,2</sup>  
GARY G. BERNTSON<sup>3</sup>  
CHRISTOPHER G. ENGELAND<sup>4</sup>  
PHILLIP T. MARUCHA<sup>4</sup>  
CHRISTOPHER M. MASI<sup>1,5</sup>  
JOHN T. CACIOPPO<sup>1,2</sup>

## Abstract

The impact of stress on age-related physiological capacities (i.e., resilience) is influenced not only by endowed genetic substrate, but also by individual differences, including the frequency of exposure to stress, the nature and intensity of psychological and physiological reactions to stress, and the efficacy of restorative processes that replenish physiological reserves and fortify against future stress (Cacioppo, Hawkley, & Berntson, 2003). This paper outlines a conceptualization of stress that acknowledges human susceptibility and resistance to the stresses of life and considers the net impact of human frailties and strengths on physiological resilience and health during the aging process.

Aging is inevitable. Indeed, one could say it is written into our genes. Cellular biological age is reflected in the gradual shortening of telomeres, the protective caps at the ends of chromosomes that normally prevent cell senescence (Frenck, Blackburn, & Shannon, 1998). Although the relationship between cellular and organismic age is not well understood (Chan & Blackburn, 2003), chronological age is inversely correlated with telomere length in adults across all age groups (Brouillette, Singh, Thompson, Goodall, & Samani, 2003; Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003; Epel et al., 2004). Moreover, stress

appears to contribute to cellular aging. For instance, among 20- to 50-year-old mothers who had been caring for a chronically ill child, telomere length in peripheral blood mononuclear cells was inversely related to the duration of caregiving (Epel et al.), even after controlling for mother's age. This finding lends credence to the notion that stress is bad for the organism, and that it contributes to the wear-and-tear on the organism that marks the aging process.

The thesis here is that aging is not simply equivalent to accrued exposure to stress, however. In the study referred to above, telomere length did not differ between the group of caregiving mothers and the group of control mothers not subjected to this chronic stress. However, telomere length was inversely related to *perceived* stress in both groups (Epel et al., 2004). Using established age-related means of telomere length, and controlling for chronological age and body mass index, the authors estimated that the lymphocytes of those in the highest perceived stress quartile were 9-17 years older than those in the lowest stress quartile (Epel et al.).

Importantly, however, telomere length is insufficient to index cellular age. Telomere length is regulated by the telomere-protective and lengthening actions of telomerase, a cellular enzyme (Chan & Blackburn, 2003) whose activity decreases under conditions of repeated exposure to antigenic stimuli and with the approach of cellular senescence (Weng et al., 1997). Notably, then, caregiving and control mothers whose perceived stress scores were in the highest quartile not only had shorter telomeres, but also had significantly lower telomerase activity than those in the lowest stress quartile (Epel et al., 2004).

These data suggest that, across the spectrum of stressful experiences, the impact of stress on age-related physiological capacities (i.e., resilience) is influenced not only by individual differences in exposure to stress, but also by individual differences in response to and recovery from stressful experiences. In addition, we maintain that stress effects are influenced by the efficacy of restorative (e.g., anabolic) processes that serve to replenish physiological reserves. Our goal in this paper is to outline a conceptualization of stress that acknowledges not only human susceptibility but also human resistance to the stresses of life, and to consider the net impact of these frailties and strengths

1 Chicago Center for Cognitive and Social Neuroscience, University of Chicago

2 Department of Psychology, University of Chicago

3 Department of Psychology, Ohio State University

4 Department of Periodontics, University of Illinois at Chicago

5 Department of Medicine, University of Chicago

on physiological resilience and health during the aging process.

#### *Stress is Neither Good Nor Bad*

The central dogma of stress research has long been that stress is “bad.” Numerous studies have shown that stress is associated with acute responses that mimic pathophysiological states (e.g., elevated blood pressure, diminished lymphocyte proliferation), and with higher rates of morbidity and mortality. Stressors and stress responses are neither inherently good nor inherently bad, however. The normalizing forces that constitute physiological responses to acute stress (i.e., discrete stress of relatively short duration) evolved because there were reproductive benefits to being able to respond to disturbing environmental forces (i.e., stressors). These homeostatic processes can have long-term costs. The short-term benefits and long-term costs of stress are perhaps best illustrated by examining the effects of acute and chronic stress on physiological functioning (see also, Cacioppo & Berntson, in press; Hawkley, Bosch, Engeland, Marucha, & Cacioppo, in press). Importantly, homeostatic processes can also promote growth, adaptation, and resilience – especially if the resources that can be marshaled are sufficient to meet adaptive demands and the associated restorative processes promote adaptive responding to future similar demands. For instance, stress in the form of exercise is encouraged precisely because exercise exposes the myocardium to a brief period of ischemia that elicits compensatory cardioprotective actions and decreases the risk of coronary artery disease and subsequent cardiac ischemia or infarction (Eisen et al., 2004; Taylor & Starnes, 2003).

#### *Short-Term Benefits of Acute Stress*

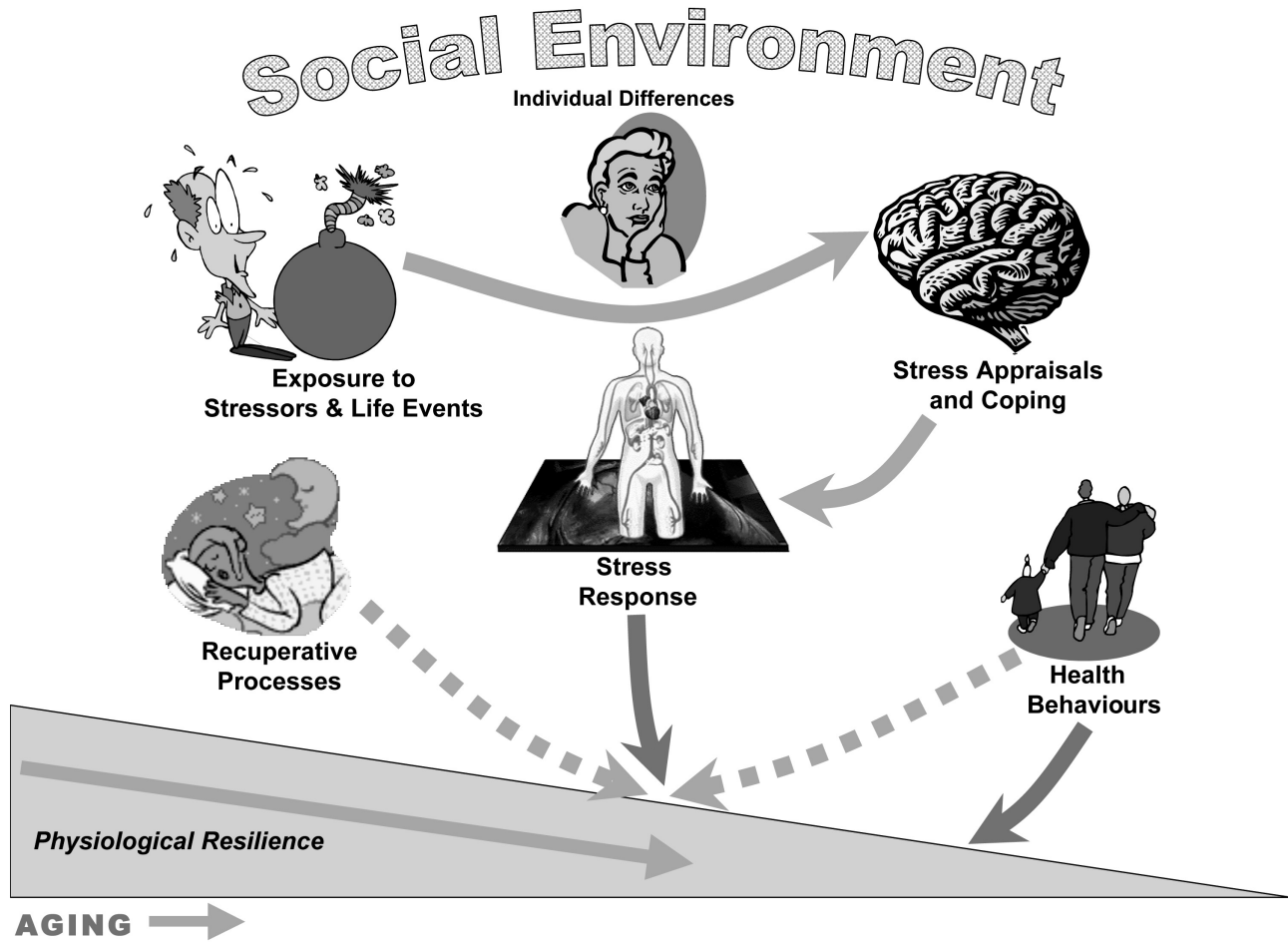
In general, exposure to acute stress elicits central, autonomic, neuroendocrine, immune, and motor responses that support the behaviours necessary to survive a threat (i.e., a fight or flight situation). For example, having a bear wander into your campsite will result in activation of the sympathetic nervous system and the release of the neurotransmitter norepinephrine; its actions at the heart and in the vasculature support the demand for increased blood supply (i.e., heart rate and blood pressure increase). Sympathetic activation of the adrenal medulla prompts the release of hormonal epinephrine to further support demand for increased heart rate, and activation of the hypothalamic pituitary adrenocortical (HPA) axis results in the release of cortisol to support increased metabolic needs. The immune system also becomes involved in responses to acute stress, with some types of immunity

being suppressed and other types enhanced. We turn to the immune system to illustrate how the acute stress response is adaptive and promotes resilience.

In animal models, acute stress elicits immune changes consistent with sickness. For instance, placing a rodent in an unfamiliar open-field causes a rise in both core body temperature and circulating levels of IL-6 (LeMay, Vander, & Kluger, 1990). Other acute stressors (e.g., foot shock, restraint) have been shown to cause fever and to increase quantities of circulating leukocytes, acute phase proteins (APPs), and IL-6, and these effects may last for days (reviewed by Maier, 2003). Very intense acute stressors (e.g., inescapable tail shock) are sufficient to produce a full complement of prototypical sickness behaviours (i.e., increases in sleep; decreases in food/water intake, activity, and social interactions).

Importantly, however, activation of these immune components alone does not signify that sickness or inflammation will occur. Instead, when induced by acute stress, these changes serve largely to limit pathogen growth, buffer inflammation, and minimize damage to the organism in the event of infection. For instance, the functions of APPs include removal of cellular debris, inhibition of pathogen growth, and promotion of bacterial destruction by the activation of complement (Barton, 1996; Tilg, Dinarello, & Mier, 1997). Protease inhibitors are one class of APPs with helpful actions, of which C-reactive protein is an exemplar. C-reactive protein is frequently used as a marker of heightened inflammation, but its function, like that of other protease inhibitors, is to limit the tissue damage that excessive inflammation typically incurs (Barton). In addition, IL-6, a cytokine that plays a prominent role in mediating the effects of the acute phase response, is elevated in response to inflammation and appears to have largely anti-inflammatory systemic actions (reviewed in Hawkley et al., in press). Acute stress also shifts enzymatic activity in blood to a state that is less conducive for bacterial growth/replication (Hart, 1988). Thus, acute stress appears to have beneficial effects over the short-term by priming the immune system and placing it into a state of readiness to combat potential injury and infection. This makes sense from an evolutionary perspective because an organism with a primed immune system would mount a more efficacious response to, and be more likely to survive, infection and tissue damage in the event of injury suffered in a fight or flight situation.

Consistent with the priming hypothesis of acute stress, an oral wound-healing study in humans showed that individuals with higher anticipatory stress (of the wounding procedure) healed significantly faster than individuals who were less stressed at the time of



*Figure 1.* Stress, aging, and resilience: The impact of stress on age-related physiological capacities (i.e., resilience) is influenced by individual differences, reflecting genetic and environmental influences, which contribute to differential exposure and differential reactivity to stressors. The stress response, in turn, is influenced by stress appraisals (e.g., controllable versus uncontrollable) and coping responses (e.g., active versus passive coping). Salubrious health behaviours (e.g., exercise) not only reduce the impact of stress on resilience, but also fortify the body against future stress. Poor health behaviours (e.g., smoking), on the other hand, weaken physiological resistance to stress and further diminish resilience. Recuperative processes are also important for resilience. The efficacy of sleep, for example, influences the maintenance and enhancement of physiological reserves that are needed to withstand stress demands. In addition, feedback mechanisms (not illustrated) link peripheral physiological processes to the central nervous system to further modulate physiological resilience and aging.

wounding. This appeared related to higher circulating levels of glucocorticoids (GCs) at the time of wounding and decreased inflammation in the wound tissue 24h postwounding (Engeland, Cacioppo, & Marucha, in preparation). Other studies have shown that animals, previously stressed with inescapable tail shock and then challenged with lipopolysaccharide (LPS), displayed an enhanced induction of proinflammatory cytokines (Johnson et al., 2002), and an augmentation of both fever and sickness behaviours (Johnson, O'Connor, Hansen, Watkins, & Maier, 2003). Similar stressors also activate the acute phase response (Deak et al., 1997) and enhance recovery from bacterial

challenge (Deak, Nguyen, Fleshner, Watkins, & Maier, 1999). Taken together, these findings indicate that, over the short-term, acute stress can both prime and increase the effectiveness of the immune response against antigenic challenge and injury.

#### *Long-Term Costs of Chronic Stress*

The adaptivity of responses to acute stress does not extend to chronic forms of stress, however. Instead, chronic stress affects the very homeostatic structures, setpoints, and processes whose functions are to support resilience (Berntson & Cacioppo, 2000). These influences are evident across the central nervous (e.g.,

hippocampus; McEwen, 2000), autonomic nervous (e.g., sympathetic system; Cacioppo et al., 1998, 2000), and immune systems (Maier & Watkins, 1998). We again focus on the immune system, this time to illustrate the detrimental effects of chronic stress.

The research reviewed above (Engeland et al., in preparation) indicates that proper HPA functioning largely prevents overactivation of the inflammatory cascade following acute stress (Nguyen et al., 2000). Chronic (i.e., protracted) stress involves a lasting dysregulation of the HPA axis, and the consequences include suppressed cellular immunity (Lupien & McEwen, 1997; Sheridan, 1998), reduced response to vaccination (Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996), and slowed healing of experimental cutaneous and mucosal wounds (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995; Marucha, Kiecolt-Glaser, & Favagehi, 1998; Padgett, Marucha, & Sheridan, 1998). Recent studies have revealed that HPA dysregulation may also be marked by cellular resistance to the immunosuppressant effects of GCs on proinflammatory cytokine release (Avitsur, Stark, & Sheridan, 2001; O'Connor et al., 2003). This phenomenon has been well-demonstrated in animal studies that employ social disruption (SDR) as a stress model. In this experimental model, male mice are housed in groups of five until a stable hierarchy develops. Next, an aggressive intruder is introduced, at which time, excessive fighting re-establishes the social hierarchy. In a series of studies, it was found that SDR stress induces a strong HPA activation in the defeated animals (Padgett et al., 1998; Stark et al., 2001), and simultaneously leads to glucocorticoid resistance in splenocytes that have been activated with LPS (Stark et al.). Consistent with the glucocorticoid sensitivity hypothesis, the SDR-induced reduction in glucocorticoid sensitivity results in greater likelihood of hyperinflammation, leading to increased mortality from experimental influenza infection and septic shock in mice (Padgett, Sheridan, et al., 1998; Quan et al., 2001).

Studies in humans confirm and extend the results of animal experiments. In human studies, glucocorticoid sensitivity is measured *ex vivo*, whereby immune cells are incubated with bacterial endotoxin (e.g., LPS) or a mitogen (e.g., PHA) in combination with varying concentrations of GCs (e.g., dexamethasone). Using this approach, studies have found a reduced glucocorticoid sensitivity of immune cells in spousal caregivers of dementia patients (Bauer et al., 2000), in parents of children undergoing cancer treatment (Miller, Cohen, & Ritchey, 2002), and in stress-related syndromes such as vital exhaustion and depression (Bauer et al., 2003; Miller, Pariante, & Pearce, 1999;

Wirtz et al., 2003). Thus, animal and human research each suggest that chronic stress has long-term costs evident in down-regulated glucocorticoid sensitivity of immune cells that leave the organism at risk for inflammatory disease (e.g., metabolic syndrome; Das, 2004) and other chronic diseases.

#### *Summary*

The differential effects of short- and long-term stress outlined above illustrate the principle that stress is not inherently bad. Although acute stress tends to elicit an adaptive physiological response, repeated and/or intense bouts of acute stress can push the organism beyond its ability to meet the challenges. In addition, the pervasive and ongoing demands of chronic stress change the character of the physiological response in ways that contribute to diminished physiological resilience and poor health. This distinction between acute and chronic stress is insufficient, however, to explain diverse outcomes among individuals confronting comparable stressors. How can these outcome differences be explained? Certainly, genetic endowment contributes, but individuals also differ in their social systems, stress appraisals, and coping responses. We turn to coping as a factor contributing to individual differences in physiological stress responses that influence resilience and health.

#### *Stress is Neither Good Nor Bad, But Coping Can Make It So*

One of the helpful distinctions in research on coping is that of active versus passive coping. Active coping refers to the individual's efforts to achieve actual or perceived control over the outcome of a stressful situation or task (e.g., mental arithmetic), whereas passive coping requires only that the individual endure the stress (e.g., cold pressor). Light, and colleagues have demonstrated that active coping tasks tend to elicit beta-adrenergic (e.g., cardiac) activation and increased blood pressure, whereas passive coping tasks tend to elicit alpha-adrenergic (e.g., vasomotor) activation (Light, Girdler, & Hinderliter, in press) and increased blood pressure. However, cardiovascular response differences have been found, with some individuals showing greater cardiac reactivity and others greater vasomotor reactivity to the same stressor (Kasprowicz, Manuck, Malkoff, & Krantz, 1990; Light, Turner, Hinderliter, Girdler, & Sherwood, 1994; Llabre, Klein, Saab, McCalla, & Schneiderman, 1998; Sherwood, Dolan, & Light, 1990).

These differences could have implications for physiological resilience and health. Beta-adrenergically mediated increases in blood pressure that characterize an active coping response are adaptive in the sense that task-related demands are most efficiently achieved

by increasing cardiac output and blood flow, but these physiological changes can have long-term consequences in risk for disease (Cacioppo et al., 1995). On the other hand, passive coping can be adaptive in situations in which the stressor must be endured and cannot be actively controlled, but the alpha-adrenergically mediated increases in blood pressure that characterize a passive coping response can have damage potential because increased vascular resistance and the structural vascular changes that ensue contribute to the development of essential hypertension (Staessen, Wang, Bianchi, & Birkenhaeger, 2003).

The foregoing evidence suggests that neither active nor passive coping is necessarily optimal, in that coping strategies appear to interact with the nature of the stressor to influence outcomes.<sup>6</sup> If an individual has no potential for control over the outcome of a stressful situation (e.g., being caught by police for speeding), then active coping (arguing with the police about the validity of the charge) may elicit more physiological activation than is warranted by the type of situation. Physiological activation in response to stressors is beneficial up to a point, but excessive autonomic, neuroendocrine, and immune activation can diminish health across time. On the other hand, if the individual faces a stressful situation over which he or she has some control (e.g., facing a deadline for a manuscript), then active coping (setting aside time and actually writing the manuscript) is desirable because it increases the likelihood that the stress will be resolved. Passive coping in these circumstances would be less than optimal because the stressful situation would persist and fester, and the accompanying physiological activity could work to the detriment of physiological resilience and health.

Controllability has for some time been recognized as an important stress dimension to predict consequences of stress exposure (e.g., Lundberg & Frankenhaeuser, 1978; Maier & Watkins, 1998). Recent research has identified critical components of the central circuitry underlying responses to controllable versus uncontrollable stress (Amat et al., 2005). The two areas of the brain studied by Amat et al. were the ventral medial prefrontal cortex (mPFCv), an area of the brain implicated in executive function and affective processing, and the dorsal raphe nucleus (DRN), a brainstem nucleus that provides most of the serotonin input to cortical and limbic structures that play a role in regulating autonomic and neuroen-

docrine functioning. Serotonin also plays a prominent role in depression and anxiety (Graeff, Guimarães, De Andrade, & Deakin, 1996), and in social behaviour (Insel & Winslow, 1998). Amat et al. found that uncontrollability defines the default stress circuitry in the brain: A stressful circumstance elicits activation of the DRN neurons, and a flood of serotonin is released that contributes to autonomic activation and failure to learn to escape in a new situation. On the other hand, during controllable stressors, the mPFCv inhibits activation of the DRN, thereby reducing autonomic activation and preserving escape learning. This elegant study raises an interesting possibility for human research on stress and coping, namely, that seeing a stressful situation as controllable, and coping actively in response, produces its physiological benefits, at least in part, from diminished autonomic and neuroendocrine activity subsequent to inhibition of the DRN. Of course, if the stressor is perceived as controllable but is actually uncontrollable, the consequences could be maladaptive if the reduced autonomic activation is inadequate to endure and survive the uncontrollable stressor.

#### *Stress: Take a Bad Thing and Make It Better*

Although stress is not necessarily bad, there is empirical support for its adverse effects on physiological functioning, particularly in the context of chronic stress. For instance, when individuals inoculated with rhinovirus were subsequently monitored for development of a cold, those who had experienced severe chronic stressors (mostly involving employment problems or interpersonal difficulties) were at significantly greater risk of developing the disease (Cohen et al., 1998). Similarly, the chronic stress of caring for a spouse with dementia resulted in a significantly smaller antibody response to pneumococcal bacterial vaccine in caregivers than in controls or former caregivers (Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000).

The metabolic requirements posed by psychological stressors in today's society (e.g., personal affronts, traffic congestion, pressing deadlines, public-speaking engagements, unreasonable bosses, perceived injustices) are often minimal, and physiological reactions in response to these events can substantially exceed metabolic requirements. The accrued wear-and-tear on the organism takes its physiological toll on resilience. Add to that the adverse physiological consequences of chronic stress, and it seems inevitable that health should decline over the years. Given that humans continually confront daily stressors and, in some cases, unrelenting stressful situations, how is it that humans survive as long and, in some cases, as well

<sup>6</sup> Endler (1997) outlined a similar multidimensional model in which coping strategies interact with the type of stress to predict outcomes, although his focus was on task-oriented versus emotion- and avoidance-oriented coping.

as they do?

The answer to this question lies not only in the human body's innate restorative processes, but also in individual differences in the efficacy of these processes. Some of these differences may be determined by inherited physiological competencies, others by behaviours that enhance the organism's capacity to engage in, and benefit from, innate restorative processes. Indeed, stress can activate maladaptive behaviours that reflect attempts to cope with negative emotional responses. Persons experiencing psychological stress, for example, may engage in unhealthy practices such as smoking, not eating or sleeping properly, and not exercising, and these behaviours may foster accidents, cardiovascular disease, and suppressed immune function (Baum, 1994; Cohen, 1991). On the other hand, a balanced diet, moderate exercise, sleep, and rich social connections can have beneficial and rejuvenating effects.

Learning, muscular development, and humoral immunity are illustrative of the empowering aspects of the restorative powers of the body in response to stress. A student pianist who makes the transition from graduate school to the realm of professional performances may initially be overwhelmed and fatigued by the amount of practice needed to accommodate scheduled performance events. The same performance expectations, however, become less and less demanding as the pianist's back, arm, and hand muscles have time to repair and grow following each practice. Thus, at least some long-term costs of stress may be minimized, or in some cases reversed, if appropriate repair and maintenance processes also unfold. Indeed, vaccinations work in this way. A weakened antigen is inserted to immunologically challenge the body to produce the antibodies needed to eradicate the pathogen and repair the body. An individual who is vaccinated may suffer a brief, mild bout of the illness, but subsequently have an effective immune response in the event of exposure to a strong dose of the antigen.

Conversely, if deprived of adequate opportunities to rebuild physiological resources, resilience diminishes and risk of disease increases.<sup>7</sup> Sleep has taken on increasing importance as a mechanism by which some of the detrimental effects of stress are undone, and deficits in sleep quantity or quality have stunning consequences for learning, physiological functioning, health, and well-being. In an illustrative study, Spiegel,

Leproult, and Van Cauter (1999) found that a sample of 11 young men restricted to four hours sleep per night for six nights exhibited lowered glucose tolerance, elevated evening cortisol concentrations, and increased sympathetic tonus. These effects mirror what is seen in normal aging, leading the authors to conclude that sleep debt may increase the severity of age-related chronic health disorders.

There is no question that adequate sleep is necessary to optimize physiological functioning, but given the same amount of sleep, some individuals do not appear to derive equivalent benefits. In our study of young adults differing in degree of loneliness, quantity of sleep did not differ, but the quality of sleep did, as indicated by reports of greater daytime dysfunction (Cacioppo, Hawkey, Crawford, et al., 2002) and more frequent micro-awakenings (Cacioppo, Hawkey, Bernstson, et al., 2002) among lonely compared to nonlonely individuals. In a small convenience sample of older adults ( $n = 25$ ; 53-78 yrs.), too, greater daytime dysfunction was reported by lonely than by nonlonely individuals, despite equivalent hours of nightly sleep (Cacioppo et al., 2002a). These results have been replicated in a population-based sample of 229 urban adults enrolled in the Chicago Loneliness Study (Hawkey & Cacioppo, 2005). To the extent differences in sleep quality contribute to differences in physiological functioning, these findings support the notion that sleep may contribute to poorer health among lonely than nonlonely individuals. Whether stress contributes to poor sleep quality or vice versa (or both) remains an important question for future research examining the health consequences of loneliness.

As noted above, sleep, although potent in its salubrious effects if sufficient in quantity and quality, is not the only means to undo the ravages of daily life. Health behaviours are known to influence physiological robustness, with dietary choices (e.g., fats, fruits, and vegetables), physical activity, and substance use (e.g., alcohol, tobacco) being examples of lifestyle factors currently being addressed by national health oversight committees in Canada (Minister of Public Works and Government Services Canada, 2002, 2003) and the United States (e.g., Office of Disease Prevention and Health Promotion, 2000, 2005). Moreover, just as individual differences in sleep can be distinguished along the orthogonal dimensions of quantity and quality, the salubrious consequences afforded by health behaviours may also be distinguished along these dimensions. For instance, although a certain minimal quantity of each nutrient category is required, individuals differ in the nutritional complexes in which these nutrients are consumed, and in

<sup>7</sup> If the pianist noted above overtrains - that is, if he/she is not getting sufficient nutrition and rest to allow her body to repair as a result of the catabolic costs of the practice - then the practice will not provide the same physiological growth or resilience.

their responses to these nutrients (e.g., the study of nutrigenomics; Allison, Barnes, & Garvey, 2004). In sum, the human organism has an innate capacity to heal itself, and individual differences in the efficacy of these restorative processes are important to understanding the conditions under which physiological resilience is maintained or enhanced.

#### *Relevance for Aging*

Across the lifespan, individuals encounter numerous daily stressors as well as chronic stressors and life-altering events. The cumulative load of these stressors differs across individuals, however, because individuals differ not only in their endowed genetic substrate, but also in the frequency with which they are exposed to stress, the nature and intensity of their psychological and physiological reactions to stress, and the efficacy of restorative processes that replenish physiological reserves and fortify against future stress (Cacioppo, Hawkley, & Berntson, 2003). As such, age is an imperfect measure of total wear-and-tear on the organism. Correspondingly, the typical age-related decline in physiological resilience is not uniform across individuals but is influenced by individual differences in any or all of these dimensions of stress (i.e., exposure, reactivity, restoration).

Not only does stress have a number of dimensions by which resilience is affected, but stress dimensions may be differentially affected over the life course. For instance, in our study of college undergraduates, lonely and nonlonely college students did not differ in the number of major life events or traumas they reported. Nevertheless, psychological surveys indicated that lonely individuals perceived higher levels of stress, more serious hassles, and less potent “uplifts” than nonlonely individuals (Cacioppo et al., 2000). In addition, an experience sampling component of the study showed that lonely and nonlonely young adults did not differ in the frequency or type of daily activities in which they engaged during everyday life, yet lonely individuals rated their daily circumstances as more stressful, threatening, and demanding, and themselves as less capable of meeting those demands than did nonlonely individuals (Hawkley, Burleson, Berntson, & Cacioppo, 2003). Notably, stress perceptions were unrelated to measures of physiological functioning in these young adults.

In our Chicago Loneliness Study, general and life event-related perceptions of stress were higher among lonely than nonlonely individuals, as they were in young adults. In contrast to the young adults, however, lonely older adults also reported a greater number of major life events in the past year than did their nonlonely counterparts (Hawkley, Cao, Schumm, &

Cacioppo, under preparation). An important follow-up question to these cross-sectional results is whether loneliness is causal or consequential relative to increased stress exposure and (hyper)reactivity. To the extent loneliness adds to the total stress load by one or more stress mechanisms, lonely individuals are vulnerable to a more rapid age-related decrease in physiological resilience.

Indeed, consistent with the notion that stress contributes to diminished resilience, in older adults we found that perceived stress was associated with higher levels of systolic blood pressure (SBP), independently of demographic characteristics (age, gender, ethnicity, income, education) (Hawkley, Masi, Berry, & Cacioppo, under review). However, perceived stress was insufficient to explain loneliness differences in measures of health and physiology. Specifically, associations between loneliness and SBP (Hawkley et al., under review), and between loneliness and number of chronic health conditions and self-rated health (Cacioppo, Hughes, Waite, & Hawkley, under review), were independent of perceived stress, hostility, depressed affect, social support, and demographic characteristics. Moreover, loneliness interacted with age such that SBP was higher by 0.85 mm Hg per standard deviation of loneliness for each additional year of age, suggesting that loneliness accelerates typical age-related reductions in physiological resilience (Hawkley et al.). Social support has also been found to slow age-related SBP increases in chronically stressed individuals (Uchino, Kiecolt-Glaser, & Cacioppo, 1992), but as noted above, we found that the effects of loneliness on SBP increases were independent of social support (Hawkley et al.). Whether increased exposure and/or reactivity to stress contribute prospectively to diminished resilience and increased health risk among lonely individuals is a topic of study in longitudinal research currently underway.

#### *Concluding Remarks*

Over four decades ago, the journal *Science* published a “General Theory of Mortality and Aging” by Strehler and Mildvan (1960), in which the authors presented a stochastic model to explain associations between aging, physiologic decline, and mortality. According to their theory, an organism dies when stress magnitude exceeds capacity to compensate physiologically. Ability to compensate, in turn, was postulated to be determined by initial physiologic reserves and by a linear decrease in physiologic reserves (i.e., resilience) of 0.9 to 1.4% per year. Mathematical models and observational data showed that, at the population level, this rate of decline is con-

stant across the decades after age 30. At the individual level, however, Strehler and Mildvan (1960) acknowledged that there is considerable variability in initial physiologic reserves and in rate of physiologic decline. The authors proposed that these differences can be attributed to, and modeled as, a function of the interaction of genetic and environmental factors. It has been the goal of the current paper to present stress-related factors that contribute to these individual differences.

The multifaceted conceptualization of stress we have described above clearly has implications for the aging process. Although limited by genetically endowed physiology, humans have sometimes astonishing capacities to minimize or contain the long-term costs of stress, thereby maintaining a resilient physiology and helping to ensure a long and healthful life. These capacities are attributable in part to lifestyle choices that limit exposure to stress, in part to adaptive appraisal and coping strategies that reduce the impact of stress exposure, and in part to efficient restorative processes that rebuild physiological reserves. Improvement in any of these domains would be expected to have an impact on health and resilience. Thus, although aging is inevitable, engaging human strengths in the face of contemporary stressors can considerably slow the accrual of bodily wear and tear.

The adage that it is better to have loved and lost than never to have loved at all reminds us that there are worse things in life than encountering stressors. It is perhaps appropriate to recall a Greek myth to illustrate this point. When Selene, the Moon, fell in love with a handsome shepherd boy, Endymion, she pleaded with Zeus to grant Endymion eternal life, and then, to make sure he would not succumb to eternal aging, she also asked Zeus to grant him eternal youth. Reluctantly, Zeus granted Selene's request. Much to Selene's dismay, however, Zeus combined these gifts with the "blessing" of perpetual sleep. Endymion never died, never aged, and in truth, never lived either. In his recounting of this myth, William Thomas (2004) concludes, "Aging is part of what makes us human. To live is to age. To live long is to age much" (p. 33). To live is also to experience difficult, painful, and discouraging events and situations. To live well, indeed, to age well, is to be able to derive rewards from these stressful experiences. Personal growth and mastery, meaningful close relationships, and opportunities to nurture the next generation are just some of the rewards experienced by individuals with a capacity to put their stressful experiences to good use. The model outlined here suggests that human biology has evolved accordingly.

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Address correspondence to Louise C. Hawley or John T. Cacioppo, Department of Psychology, University of Chicago, 940 E. 57th St., Chicago, IL 60637, USA (E-mail: hawley@uchicago.edu or cacioppo@uchicago.edu).

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### Résumé

L'incidence du stress sur les capacités physiologiques liées à l'âge (p. ex. la résilience) est influencée non seulement par le substrat génétique légué, mais aussi par les différences individuelles. Ces différences comprennent notamment la fréquence d'exposition au stress, la nature et l'intensité des réactions psychologiques et physiologiques au stress et l'efficacité des processus réparateurs qui refont les réserves physiologiques et fortifient contre le stress futur (Cacioppo, Hawley, & Berntson, 2003). Le présent article décrit une conceptualisation du stress qui reconnaît la susceptibilité et la résistance de l'humain aux stress de la vie et examine l'incidence des fragilités et des forces de l'humain sur la résilience physiologique et la santé au cours du processus de vieillissement.

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### References

- Allison, D. B., Barnes, S., & Garvey, W. T. (2004). Foreword from the editors. *Nutrition*, 20, 1.
- Amat, J., Baratta, M. V., Paul, E., Bland, S. T., Watkins, L. R., & Maier, S. F. (2005). Medial prefrontal cortex determines how stressor controllability affects behaviour and dorsal raphe nucleus. *Nature Neuroscience, Advance Online Publication*, 6 February 2005, 1-7.
- Avitsur, R., Stark, J. L., & Sheridan, J. F. (2001). Social stress induces glucocorticoid resistance in subordinate animals. *Hormones & Behaviour*, 39, 247-257.
- Barton, B. (1996). The biological effects of interleukin 6. *Medicinal Research Reviews*, 16, 87-109.
- Bauer, M. E., Papadopoulos, A., Poon, L., Perks, P., Lightman, S. L., Checkley, S., et al. (2003). Altered glucocorticoid immunoregulation in treatment resistant depression. *Psychoneuroendocrinology*, 28, 49-65.
- Bauer, M. E., Vedhara, K., Perks, P., Wilcock, G. K., Lightman, S. L., & Shanks, N. (2000). Chronic stress in caregivers of dementia patients is associated with reduced lymphocyte sensitivity to glucocorticoids. *Journal of Neuroimmunology*, 103, 84-92.
- Baum, A. (1994). Behavioural, biological, and environmental interactions in disease processes. In S. Blumenthal, K. Matthews, & S. Weiss (Eds.), *New research frontiers in behavioural medicine: Proceedings of the national conference*. Washington, DC: NIH Publications.
- Berntson, G. G., & Cacioppo, J. T. (2000). From homeosta-

- sis to allodynamic regulation. In G. G. Berntson & J. T. Cacioppo, (Eds.), *Handbook of psychophysiology* (pp. 459-481).
- Brouillette, S., Singh, R. K., Thompson, J. R., Goodall, A. H., & Samani, N. J. (2003). White cell telomere length and risk of premature myocardial infarction. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 23, 842-846.
- Cacioppo, J. T., & Berntson, G. G. (in press). The brain, homeostasis, and health: Balancing demands of the internal and external milieu. In H. S. Friedman & R. Cohen Silver (Eds.), *Oxford handbook of health psychology*. New York: Oxford University Press.
- Cacioppo, J. T., Berntson, G. G., Malarkey, W. B., Kiecolt-Glaser, J. K., Sheridan, J. F., Poehlmann, K. M., Burleson, M. H., Ernst, J. M., Hawley, L. C., & Glaser, R. (1998). Autonomic, neuroendocrine, and immune responses to psychological stress: The reactivity hypothesis. *Annals of the New York Academy of Sciences*, 840, 664-673.
- Cacioppo, J. T., Burleson, M. H., Poehlmann, K. M., Malarkey, W. B., Kiecolt-Glaser, J. K., Berntson, G. G. et al. (2000). Autonomic and neuroendocrine responses to mild psychological stressors: Effects of chronic stress on older women. *Annals of Behavioural Medicine*, 22, 140-148.
- Cacioppo, J. T., Hawley, L. C., & Berntson, G. G. (2003). The anatomy of loneliness. *Current Directions in Psychological Science*, 12, 71-74.
- Cacioppo, J. T., Hawley, L. C., Berntson, G. G., Ernst, J. M., Gibbs, A. C., Stickgold, R., et al. (2002). Lonely days invade the nights: Potential social modulation of sleep efficiency. *Psychological Science*, 13, 38-387.
- Cacioppo, J. T., Hawley, L. C., Crawford, L. E., Ernst, J. M., Burleson, J. M., Kowalewski, R. B., et al. (2002). Loneliness and health: Potential mechanisms. *Psychosomatic Medicine*, 64, 407-417.
- Cacioppo, J. T., Hughes, M. E., Waite, L. J., & Hawley, L. C. (year). *Loneliness and depressive symptoms, self-rated health, and chronic health conditions: Evidence from two population-based studies*. (Manuscript under review)
- Cacioppo, J. T., Malarkey, W. B., Kiecolt-Glaser, J. K., Uchino, B. N., Sgoutas-Emch, S. A., Sheridan, J. F., et al. (1995). Heterogeneity in neuroendocrine and immune responses to brief psychological stressors as a function of autonomic cardiac activation. *Psychosomatic Medicine*, 57, 154-164.
- Cawthon, R. M., Smith, K. R., O'Brien, E., Sivatchenko, A., & Kerber, R. A. (2003). Association between telomere length in blood and mortality in people aged 60 years or older. *The Lancet*, 361, 393-395.
- Chan, S. R. W. L., & Blackburn, E. H. (2003). Telomeres and telomerase. *Philosophical Transactions of the Royal Society of London, B*, 359, 109-121.
- Cohen, S. (1991). Social supports and physical health: Symptoms, health behaviours and infectious disease. In A. L. Greene, M. Cummings, & K. H. Karraker (Eds.), *Life-span developmental psychology: Perspectives on stress and coping*. Hillsdale, NJ: Erlbaum.
- Cohen, S., Frank, E., Doyle, W. J., Skoner, D. P., Rabin, B. S., & Gwaltney, J. M. Jr. (1998). Types of stressors that increase susceptibility to the common cold in healthy adults. *Health Psychology*, 17, 214-23.
- Das, U. N. (2004). Metabolic syndrome X: An inflammatory condition? *Current Hypertension Reports*, 6, 66-73.
- Deak, T., Meriwether, J. L., Fleshner, M., Spencer, R. L., Abouhamze, A., Moldawer, L. L., et al. (1997). Evidence that brief stress may induce the acute phase response in rats. *American Journal of Physiology*, 273, R1998-R2004.
- Deak, T., Nguyen, K. T., Fleshner, M., Watkins, L. R., & Maier, S. F. (1999). Acute stress may facilitate recovery from a subcutaneous bacterial challenge. *Neuroimmunomodulation*, 6, 344-354.
- Eisen, A., Fisman, E. Z., Rubenfire, M., Freimark, D., McKechnie, R., Tenenbaum, A., et al. (2004). Ischemic preconditioning: Nearly two decades of research. A comprehensive review. *Atherosclerosis*, 172, 201-210.
- Endler, N. S. (1997). Stress, anxiety and coping: The multidimensional interaction model. *Canadian Psychology*, 38, 136-153.
- Engeland, C. G., Cacioppo, J. T., & Marucha, P.T. (year). Stress hormones modulate the healing rates of oral wounds. Manuscript in preparation.
- Epel, E. S., Blackburn, E. H., Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D., et al. (2004). Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences*, 101, 17312-17315.
- Frenck, R. W., Blackburn, E. H., & Shannon, K. M. (1998). The rate of telomere sequence loss in human leukocytes varies with age. *Proceedings of the National Academy of Sciences*, 95, 5607-5610.
- Glaser, R., Sheridan, J., Malarkey, W. B., MacCallum, R. C., & Kiecolt-Glaser, J. K. (2000). Chronic stress modulates the immune response to a pneumococcal pneumonia vaccine. *Psychosomatic Medicine*, 62, 804-807.
- Graeff, F. G., Guimarçes, F. S., De Andrade, T. G. C., & Deakin, J. F. W. (1996). Role of 5-HT in stress, anxiety, and depression. *Pharmacology, Biochemistry, and Behaviour*, 54, 129-141.
- Hart, B. L. (1988). Biological basis of the behaviour of sick animals. *Neuroscience & Biobehavioural Reviews*, 12, 123-137.
- Hawley, L. C., Bosch, J. A., Engeland, C. G., Marucha, P. T., & Cacioppo, J. T. (in press). Loneliness, dysphoria, stress and immunity: A role for cytokines. In N. Plotnikoff et al., (Eds.), *Cytokines: Stress and immunity* (2nd ed). Boca Raton, FL: CRC Press.

- Hawley, L. C., Burleson, M. H., Berntson, G. G., & Cacioppo, J. T. (2003). Loneliness in everyday life: Cardiovascular activity, psychosocial context, and health behaviours. *Journal of Personality & Social Psychology, 85*, 105-120.
- Hawley, L. C., & Cacioppo, J. T. (2005, March). *Sleep quality as a function of psychosocial risk factors in a population-based sample of older adults: Loneliness as a proximal and distal predictor*. Poster presented at the annual meeting of the American Psychosomatic Society, Vancouver, BC.
- Hawley, L. C., Cao, D., Schumm, P., & Cacioppo, J. T. (in press). *The multifarious nature of ubiquitous stress: Chicago Health, Aging and Social Relations Study (CHASRS)*. Manuscript in preparation.
- Hawley, L. C., Masi, C. M., Berry, J. D., & Cacioppo, J. T. (in press). *Cardiovascular and endocrine functioning in an aging population: The effects of loneliness, depressed affect, perceived stress, social support, and hostility*. Manuscript under review.
- Insel, T. R., & Winslow, J. T. (1998). Serotonin and neuropeptides in affiliative behaviour. *Biological Psychiatry, 44*, 207-219.
- Johnson, J. D., O'Connor, K. A., Deak, T., Stark, M., Watkins, L. R., & Maier, S. F. (2002). Prior stressor exposure sensitizes LPS-induced cytokine production. *Brain, Behaviour & Immunity, 16*, 461-476.
- Johnson, J. D., O'Connor, K. A., Hansen, M. K., Watkins, L. R., & Maier, S. F. (2003). Effects of prior stress on LPS-induced cytokine and sickness responses. *American Journal of Physiology, 284*, R422-R432.
- Kasprowicz, A. L., Manuck, S. B., Malkoff, S. B., & Krantz, D. S. (1990). Individual differences in behaviourally evoked cardiovascular response: Temporal stability and hemodynamic patterning. *Psychophysiology, 27*, 605-619.
- Kiecolt-Glaser, J. K., Glaser, R., Gravenstein, S., Malarkey, W. B., & Sheridan, J. (1996). Chronic stress alters the immune response to influenza virus vaccine in older adults. *Proceedings of the National Academy of Sciences: United States of America, 93*, 3043-3047.
- Kiecolt-Glaser, J. K., Marucha, P. T., Malarkey, W. B., Mercado, A. M., & Glaser, R. (1995). Slowing of wound healing by psychological stress. *The Lancet, 346*, 1194-1196.
- LeMay, L. G., Vander, A. J., & Kluger, M. J. (1990). The effects of psychological stress on plasma interleukin-6 activity in rats. *Physiology & Behaviour, 47*, 957-961.
- Light, K. C., Girdler, S. S., & Hinderliter, A. L. (in press). Genetic and behavioural factors in combination influence risk of hypertensive heart disease. In N. Anderson, F. Kessel, & P. Rosenfield (Eds.), *Expanding the boundaries of health: Bio-behavioural-social perspectives*. New York: Oxford University Press.
- Light, K. C., Turner, J. R., Hinderliter, A. L., Girdler, S. S., & Sherwood, A. (1994). Comparison of cardiac versus vascular reactors and ethnic groups in plasma epinephrine and norepinephrine responses to stress. *International Journal of Behavioural Medicine, 3*, 229-246.
- Llabre, M. M., Klein, B. R., Saab, P. G., McCalla, J. B., & Schneiderman, N. (1998). Classification of individual differences in cardiovascular responsiveness: The contribution of reactor type controlling for race and gender. *International Journal of Behavioural Medicine, 5*, 213-229.
- Lundberg, U., & Frankenhaeuser, M. (1978). Psychophysiological reactions to noise as modified by personal control over noise intensity. *Biological Psychology, 6*, 51-59.
- Lupien, S. J., & McEwen, B. S. (1997). The acute effects of corticosteroids on cognition: Integration of animal and human model studies. *Brain Research Reviews, 24*, 1-27.
- Maier, S. F. (2003). Bi-directional immune-brain communication: Implications for understanding stress, pain, and cognition. *Brain, Behaviour, & Immunity, 17*, 69-85.
- Maier, S. F., & Watkins, L. R. (1998). Cytokines for psychologists: Implications of bidirectional immune-to-brain communication for understanding behaviour, mood, and cognition. *Psychological Review, 105*, 83-107.
- Marucha, P. T., Kiecolt-Glaser, J. K., & Favagehi, M. (1998). Mucosal wound healing is impaired by examination stress. *Psychosomatic Medicine, 60*, 362-365.
- McEwen, B. S. (2000). The neurobiology of stress: From serendipity to clinical relevance. *Brain Research, 886*, 172-189.
- Miller, A. H., Pariante, C. M., & Pearce, B. D. (1999). Effects of cytokines on glucocorticoid receptor expression and function. Glucocorticoid resistance and relevance to depression. *Advances in Experimental Medicine & Biology, 461*, 107-116.
- Miller, G. E., Cohen, S., & Ritchey, A. K. (2002). Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. *Health Psychology, 21*, 531-41.
- Minister of Public Works and Government Services Canada (2002). *Canada's food guide to healthy eating* (Cat. No. H39-252/1992E). Ottawa, ON: Public Health Canada.
- Minister of Public Works and Government Services Canada (2003). *Canada's physical activity guide to healthy active living* (Cat. No. H39-429/1998-1E). Ottawa, ON: Health Canada.
- Nguyen, K. T., Deak, T., Will, M. J., Hansen, M. K., Hunsaker, B. N., Fleshner, M., et al. (2000). Timecourse and corticosterone sensitivity of the brain, pituitary, and serum interleukin-1beta protein response to acute stress. *Brain Research, 859*, 193-201.
- O'Connor, K. A., Johnson, J. D., Hammack, S. E., Brooks, L. M., Spencer, R. L., Watkins, L. R., et al. (2003). Inescapable shock induces resistance to the effects of dexamethasone. *Psychoneuroendocrinology, 28*, 481-500.

- Office of Disease Prevention and Health Promotion (2000). *Healthy people 2010* (Stock No. 017-001-00550-9). Washington, DC: U.S. Government Printing Office.
- Office of Disease Prevention and Health Promotion (2005). *Dietary guidelines for americans, 2005* (Stock No. 001-000-04719-1). Washington, DC: U.S. Government Printing Office.
- Padgett, D. A., Marucha, P. T., & Sheridan, J. F. (1998). Restraint stress slows cutaneous wound healing in mice. *Brain, Behaviour and Immunity, 12*, 64-73.
- Padgett, D. A., Sheridan, J. F., Dorne, J., Berntson, G. G., Candelora, J., & Glaser, R. (1998). Social stress and the reactivation of latent herpes simplex virus type 1. *Proceedings of the National Academy of Sciences of the United States of America, 95*, 7231-7235.
- Quan, N., Avitsur, R., Stark, J. L., He, L., Shah, M., Caligiuri, M., et al. (2001). Social stress increases the susceptibility to endotoxic shock. *Journal of Neuroimmunology, 115*, 36-45.
- Sheridan, J. F. (1998). Stress-induced modulation of antiviral immunity. *Brain, Behaviour and Immunity, 12*, 1-6.
- Sherwood, A., Dolan, C. A., & Light, K. C. (1990). Hemodynamics of blood pressure responses during active and passive coping. *Psychophysiology, 27*, 656-668.
- Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of a sleep debt on metabolic and endocrine function. *Lancet, 354*, 1435-1439.
- Staessen, J. A., Wang, J., Bianchi, G., & Birkenhaefer, W. H. (2003). Essential hypertension. *Lancet, 361*, 1629-1641.
- Stark, J. L., Avitsur, R., Padgett, D. A., Campbell, K. A., Beck, F. M., & Sheridan, J. F. (2001). Social stress induces glucocorticoid resistance in macrophages. *American Journal of Physiology - Regulatory Integrative & Comparative Physiology, 280*, R1799-R1805.
- Strehler, B. L., & Mildvan, A. S. (1960). General theory of mortality and aging. *Science, 132*, 14-21.
- Taylor, R. P., & Starnes, J. W. (2003). Age, cell signaling and cardioprotection. *Acta Physiologica Scandinavica, 178*, 107-116.
- Thomas, W. H. (2004). *What are old people for? How elders will save the world*. Acton, MA: VanderWyk & Burnham.
- Tilg, H., Dinarello, C., & Mier, J. (1997). IL-6 and APPs: Anti-inflammatory and immunosuppressive mediators. *Immunology Today, 18*, 428-432.
- Uchino, B. N., Kiecolt-Glaser, J. K., & Cacioppo, J. T. (1992). Age-related changes in cardiovascular response as a function of a chronic stressor and social support. *Journal of Personality and Social Psychology, 63*, 839-846.
- Weng, N. P., Palmer, L. D., Levine, B. L., Lane, H. C., June, C. H., & Hodes, R. J. (1997). Tales of tails: Regulation of telomere length and telomerase activity during lymphocyte development, differentiation, activation, and aging. *Immunological Reviews, 160*, 43-54.
- Wirtz, P. H., von Kanel, R., Schnorpfel, P., Ehlert, U., Frey, K., & Fischer, J. E. (2003). Reduced glucocorticoid sensitivity of monocyte interleukin-6 production in male industrial employees who are vitally exhausted. *Psychosomatic Medicine, 65*, 672-8.