The Role of Stress Factors during Aging of the Immune System

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This manuscript reviews current evidence suggesting that aging of the immune system (immunosenescence) may be closely related to chronic stress and stress factors. Healthy aging has been associated with emotional distress in parallel to increased cortisol to dehydroepiandrosterone (DHEA) ratio. The impaired DHEA secretion together with the increase of cortisol results in an enhanced exposure of lymphoid cells to deleterious glucocorticoid actions. The lack of appropriated growth hormone signaling during immunosenescence is also discussed. It follows that altered neuroendocrine functions could be underlying several immunosenescence features. Indeed, changes in both innate and adaptive immune responses during aging are also similarly reported during chronic glucocorticoid exposure. In addition, chronically stressed elderly subjects may be particularly at risk of stress-related pathology because of further alterations in both neuroendocrine and immune systems. The accelerated senescent features induced by chronic stress include higher oxidative stress, reduced telomere length, chronic glucocorticoid exposure, thymic involution, changes in cellular trafficking, reduced cell-mediated immunity, steroid resistance, and chronic low-grade inflammation. These senescent features are related to increased morbidity and mortality among chronically stressed elderly people. Overall, these data suggest that chronic stress leads to premature aging of key allostatic systems involved in the adaptation of the organisms to environmental changes. Stress management and psychosocial support may thus promote a better quality of life for elderly people and at the same time reduce hospitalization costs.

Key words: **aging; immunosenescence; glucocorticoids; lymphocytes**

Introduction

Aging is a continuous and slow process that compromises the normal functioning of various organs and systems in both qualitative and quantitative terms. Aging has been associated with several dynamic immunological alterations that are collectively called immunosenescence. The popular knowledge of immunosenescence is the decline of immune functions. The updated view is a remodeling of major immunological components involving multiple reorganization and developmentally regulated changes.[1] Immunosenescence could be the result of the adaptation of the body to the continuous challenge of bacterial and viral infections. These remodeling features can be demonstrated by significant decrements in adaptive immunity in parallel with overall maintenance or increased innate immune functions during aging. The remodeling immune system is particularly observed in centenarians,

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who present many intact adaptive or innate immune functions and are thus good examples of successful aging.

The clinical consequences of immunosenescence may include increased susceptibility to infectious diseases, neoplasias, and autoimmune disease.[2] This altered morbidity is not evenly distributed and should be influenced by other immune-modulating factors, including the genetic background and chronic stress exposure.[3] Indeed, several immunosenescence-related changes resemble those observed following chronic stress[4] or glucocorticoid (GC) treatment.[5] The present paper summarizes recent findings suggesting that stress factors may accelerate immunosenescence.

Changes in Adaptive Immunity

One of the major features of human immunosenescence is thymic involution, characterized by a progressive age-related reduction in size of the thymus and replacement of lymphoid by fat tissue and associated with the loss of thymic epithelial cells and impairment in thymopoiesis.[6] This thymic involution has been proposed to be a result of changes in the thymic microenvironment that result in its failure to support thymopoiesis.[7] The decline in the output of newly developed T cells results in a diminished number of circulating naive T cells (CD45RA+) and impaired cell-mediated immunity. In contrast, one of the major characteristics of immunosenescence is the accumulation of expanded clones of memory (CD45RO+) and effector T cells as a consequence of the continuous life-long exposure to a variety of antigens.[8] In particular, this phenomenon is faster and more marked in $CD8^+$ T cells.[9,10] The end result is a filling of the immunological space with memory and effector cells.[11]

In addition, a decrease of $CD28^+$ T cells in parallel with a progressive accumulation of $CD28^-$ T cells with aging has been observed.[10,12] These cells display several aspects of senescence, such as oligoclonal expansion, shortened telomeres, limited proliferative potential or replicative senescence, production of tumor necrosis factor (TNF)-α and interleukin (IL)-6, and resistance to apoptosis.[12–16] When diseased subjects are excluded, immunosenescence involves impaired humoral responses to new antigens, lower cytotoxicity, and blunted T cell proliferation. The latter is one of the most documented age-related changes observed during aging.[17,18] The effector phases adaptive immune responses are largely mediated by cytokines. Different subpopulations of $CD4^+$ T cells synthesize specific cytokines and have been designated Th1 [interferon (IFN)-γ, IL-2, lymphotoxin α] or Th2 (IL-4, IL-10) cells. Both human and mouse models have demonstrated that aging is associated with a Th1 to Th2 shift in cytokine production.[19,20] This altered cytokine profile could be further involved with reduced T cell functions, including lymphocyte proliferation and development of different T cell subsets.

Immunologists have recently characterized a new T cell subset ($CD4^+C25^+$ $FoxP3^+$) with an important regulatory role in suppressing excessive or misguided immune responses that can be harmful to the host. These lymphocytes are called regulatory T (Treg) cells and are responsible for turning off immune responses against self antigens in autoimmune disease, allergy, or commensal microbes in certain inflammatory diseases.[21,22] It is interesting that aging, GC, or chronic stress can increase peripheral Treg cell numbers.[23]

Also, there are some qualitative changes associated with remodeling adaptive immune responses. In particular, the T cell receptor (TCR) repertoire seems to be shortened during aging. Data on the variable segment β (Vβ) families of the TCR show a progressive shrinkage of the TCR repertoire in the $CD4^+$ and $CD8^+$ subsets and a concomitant marked clonal expansion of single Vβ families. This repertoire has been shaped by the selective action of specific T cell clones able to modulate the immune response to endogenous and exogenous antigens.[24,25]

Changes in Innate Immunity

The innate immunity constitutes the first line of defense against a broad range of infectious agents. The nonspecific identification of antigens requires binding to pathogen-associated molecular patterns via pattern recognition receptors [e.g., toll-like receptors (TLR)] expressed on various leukocytes, including macrophages, neutrophils, dendritic cells (DC), and natural killer (NK) cells. The mononuclear phagocyte lineage plays a pivotal role in innate immunity. Aged phagocytes, such as macrophages and neutrophils, showed an impaired respiratory burst and reactive nitrogen intermediate production with a decreased ability to destroy pathogens.[26,27]

The antigen-presenting cell function of DC is generally well retained in elderly people[28] but their numbers (and their precursors) are reduced with age.[29] Monocyte-derived DC from elderly individuals were not impaired in their ability to induce T cell responses[30] or proliferation of T cell lines.[31] Recently, a study measuring the induction of the costimulatory ligands CD80 and CD86 on monocytes found that TLR-mediated induction was compromised in elderly individuals and, importantly, that this correlated with decreased response to the influenza vaccination.[32]

NK cells are a population of heterogeneous lymphocytes that provide a critical role of the innate immune response against a broad variety of infections and tumors. Most studies report increased NK cell numbers in contrast to impaired cytotoxic function during aging.[33,34] This impaired function has been associated with reduced intracellular stores of cytotoxic molecules, such as perforin.[35] Moreover, the impaired NK cell cytotoxicity represents a high risk factor for the appearance of infections in advanced age.[36] An NK cell count in the lowest quartile was associated with a threefold increase in mortality of all causes in the subsequent 2 years.[37]

Chronic low-grade inflammation has repeatedly been observed during aging, as suggested by increased serum pro-inflammatory cytokines (TNF-α, IL-1, IL-6), acute phase proteins [C-reactive protein (CRP)], and soluble IL-2 receptors (sIL-2Rs).[38] It was postulated that inflammatory responses appear to be the prevalent triggering mechanism driving tissue damage associated with different age-related diseases, and the term *inflammaging* has been coined to explain the underlining inflammatory changes common to most age-associated diseases.[39] Inflammaging appears to be a universal phenomenon that accompanies the aging process and which is related to frailty, morbidity, and mortality in the elderly. Indeed, chronic inflammation is considered to be involved in the pathogenesis of major age-related diseases, including Alzheimer's disease, atherosclerosis, diabetes, major depression, sarcopenia, and cancer. In addition, low-grade increases in levels of circulating TNF-α, IL-6, sIL-2R, and CRP and low levels of albumin and cholesterol, which also act as inflammatory markers, are strong predictors of all-cause mortality risk in several longitudinal studies of elderly cohorts. However, low-grade inflammation could be observed in strictly healthy elderly individuals,[40] suggesting that inflammaging could be better associated with pathological aging or with common morbidities frequently observed during aging, including hypertension.

Major Endocrine Changes

In addition to immunosenescence, the endocrine system also undergoes important changes during aging (endocrinosenescence). A decline in growth hormone (GH), sex hormones, and dehydroepiandrosterone (DHEA) with aging has been demonstrated.[41] DHEA is the major secretory product of the human adrenal and is synthesized from cholesterol stores. The hormone is uniquely sulfated (DHEAS) before entering the plasma, and this prohormone is converted to DHEA and its metabolites in various peripheral tissues.[42] Following secretion, total DHEA in the circulation consists mainly of DHEAS—the serum concentration of free DHEA is less than

1%. Serum DHEA levels decrease by the second decade of life, reaching about 5% of the original level in elderly people.[43] It has been suggested that DHEAS/DHEA may antagonize many physiological changes of endogenous GCs, including enhancing immunomodulatory properties.[3]

There is also evidence suggesting that aging is associated with significant activation of the hypothalamic–pituitary–adrenal (HPA) axis in increased production of cortisol in humans.[40,44] The HPA axis is pivotal for the homeostasis of the immune system and its dysregulation has been associated with several immune-mediated diseases. For instance, HPA axis overactivation, as occurs during chronic stress, can affect susceptibility to or severity of infectious disease through the immunosuppressive effect of the GCs.[45,46] In contrast, blunted HPA axis responses are associated with enhanced susceptibility to autoimmune inflammatory disease.[47] It is noteworthy to mention that elderly subjects are particularly at risk for both infectious and chronic inflammatory diseases. Furthermore, chronic inflammatory diseases may be associated with premature aging of the immune system and present several similarities of immunosenescence, including shortening of cellular telomeres, decreased TCR specificities, loss of naive T cells, and increased production of pro-inflammatory cytokines.[48] Dysregulation of the HPA axis may contribute to—but it is not solely responsible for—immunosenescence. Chronically stressed elderly subjects may be at risk of stress-related pathology because of further alterations in GC immunoregulation (immune signaling).

Interplay between Cytokines and Hormones during Aging

Recent work suggests that cytokines and hormones could be considered as possible links between endocrinosenescence and immunosenescence.[49] Indeed, it has long been known that pro-inflammatory cytokines can readily activate the HPA axis during infection in animals[50] or after administration in humans.[51] Other studies have linked the age-related decline in DHEA production to increased serum levels of IL-6.[52,53] In addition, increased plasma TNF-α levels were correlated to major depression in the elderly.[54] However, we do not know exactly to what extent these changes may be related to altered psychological and HPA axis functions in elderly people.

We have investigated whether the psychoneuroendocrine status of healthy elderly individuals was associated with changes in lipopolysaccharide-induced monocyte production of pro-inflammatory cytokines (TNF-α and IL-6) and sIL-2Rα production by T cells *in vitro*.[40] Cells of healthy elderly individuals produced equivalent pro-inflammatory cytokines and sIL-2Rα when compared to cells of young adults. These data are in disagreement with previous work showing that human aging was associated with increased serum[53] or monocyte pro-inflammatory cytokines.[55,56] However, these data should be interpreted with caution because cellular sources other than monocytes can produce cytokines and thus increase serum levels. Considering that our cohort of elderly subjects was significantly distressed, we hypothesize this could have normalized the cytokines investigated in this study as a result of anti-inflammatory GC actions. On the other hand, there is also some evidence of increased pro-inflammatory cytokines during major depression.[54,57,58] Therefore, it becomes difficult to dissociate the cytokine changes observed in elderly subjects with those induced by psychological stimuli.

Healthy Aging Is Associated with Significant Distress

Psychological distress may be an important risk factor for immunosenescence. Human aging has been associated with several psychological and behavioral changes, including difficulty in concentrating, progressive cognitive impairments, and sleep disturbances.[59,60] Although individually identified, these alterations may

be associated with major depression. Indeed, depression is highly prevalent in several age-related chronic degenerative diseases, including cardiovascular diseases, Parkinson's disease, Alzheimer's dementia, cancer, and rheumatoid arthritis.[61] In addition, both aging[55] and major depression[57,58] have been associated with increased levels of pro-inflammatory cytokines and could thus contribute to further immunological diseases in frail elderly individuals.

We have recently demonstrated that healthy aging was associated with significant psychological distress. In particular, it was found that strictly healthy (SENIEUR) elderly individuals were significantly more stressed, anxious, and depressed than young adults.[40,62] The literature regarding age-related psychological changes is controversial, and other researchers did not find these changes.[63] This could be a result of methodological issues because specific clinical interviews are required to assess depression in elderly people.

In parallel with psychological distress, we have also observed that SENIEUR elderly individuals have significantly higher (approximately 45%) salivary cortisol production throughout the day compared to young adults.[40] Cortisol peaked in the morning and presented a nadir at night, with a regular circadian pattern for both groups. These data further suggest that healthy aging is associated with significant activation of the HPA axis.[44,64–66] Increased cortisol levels are also seen in demented patients,[67] major depression,[68] or during chronic stress.[69,70]

In addition, it was observed that healthy elderly individuals had lower DHEA levels (a reduction of 54%) throughout the day compared to young adults.[71] Furthermore, elderly individuals also displayed a flat circadian pattern for DHEA secretion. The morphological correlates of the age-related changes of DHEAS/DHEA secretion are progressive atrophy of the zona reticularis of adrenal glands.[72] The lack of appropriate DHEA levels could be another detrimental factor during immunosenescence because this hormone has immune-enhancing properties (as further discussed in this chapter).

Higher cortisol levels in parallel with lower DHEA levels will consequently lead to higher C/D ratios throughout the day. The assessment of molar concentrations constitutes another way to evaluate the adrenal function in the organism.[49,72,73] The measurement of isolated hormonal samples may be an oversimplification, and the C/D ratio may contribute to the effective determination of functional hypercortisolemia. The impaired DHEA secretion, together with the increase of cortisol, results in enhanced exposure of various bodily systems (including brain and immune system) to the cytotoxic and modulatory effects of GCs and thus more allostatic load. Some brain cells (hypocampus) and lymphocytes are specially targeted by the cortisol because they express higher densities of mineralo-receptors and GC receptors.[4] The peripheral tissues of elderly people may thus be more vulnerable to the GC actions in a milieu of low-protective DHEA levels. The antagonist action of DHEA to cortisol in the brain suggests that measurement of cortisol alone may provide an incomplete estimate of hypercortisolemia.

In our previous study, psychological distress was positively related to salivary cortisol levels and negatively correlated to DHEA levels during aging.[40] Therefore, it becomes difficult to dissociate these neuroendocrine changes observed in elderly individuals with those produced by psychological stimuli. It should also be pointed out that endocrinosenescence includes a substantial decline in several hormones, including GH, testosterone, progesterone, and aldosterone—all of which with reported immunomodulatory properties. Thus endocrinosenescence may be considered as an important risk factor for immunosenescence.

Similarities between Aging, Stress, and Glucocorticoid Treatment

All leukocytes exhibit receptors for the neuroendocrine products of the HPA and

sympathetic-adrenal medullary axes. It seems reasonable to speculate that increased cortisol and lower DHEA may thus contribute to immunological changes observed during aging. This section provides evidence that the age-related immunological changes are not exclusively observed during aging. In fact, they are also similarly found during chronic GC exposure, as observed during psychological stress or GC treatments *in vitro* or *in vivo*.

Most, if not all, immunological changes are similarly observed during aging or chronic GC exposure. Changes in cellular trafficking are the major changes produced during chronic GC exposure. Trafficking or redistribution of peripheral immune cells in the body is of pivotal importance for effective cell-mediated immune responses. Stress-related increase in GC[74] or GC treatment[5] also atrophy the thymus and, to a lesser extent, other lymphoid tissues, triggering apoptotic death in immature T and B cell precursors and mature T cells.[75] Therefore, thymic involution is not an exclusive phenomenon of aging. In addition, both naive or memory T cell subsets decline during chronic stress or treatment with GC.[4,76,77] Interestingly, GC or chronic stress can also increase peripheral Treg cell numbers.[78,79] In spite of the several similarities among age- and stress-related immunological alterations, only a few studies have addressed the role of stress factors on human immunosenescence. Overall, these results indicate that there are complex psychoneuroendocrine interactions involved with the regulation of the peripheral pool of lymphocytes. In particular, both psychological stress and GCs may synergize during aging to produce alterations in T cell trafficking.

Changes in cell-mediated immunity are also similarly described in aging, chronic stress, or GC exposure. For instance, blunted T cell proliferation is one of the most documented age-related changes observed during aging.[17,18] Yet, these changes are not exclusive of aging, and stress or GC treatment are also associated with decrements of T cell proliferation.[75,76] Indeed, we have observed that healthy SENIEUR elderly individuals were significantly more distressed, had activated HPA axis, and had significant lower (a reduction of 53.6%) T cell proliferation compared to young adults.[71] Interestingly, the HPA axis may be implicated with this change because salivary cortisol levels were found negatively correlated to T cell proliferation. Similarly to aging, psychological stress[76,80] or GC treatment[81,82] is also associated with a Th1 to Th2 shift in cytokine production.

Role of DHEA during Immunosenescence

The lack of appropriate DHEAS levels during aging could be another detrimental factor for immunosenescence. This androgen and its metabolites have reported immune-enhancing properties in contrast to the immunosuppressive action of GCs. Indeed, this hormone may be considered a natural antagonist of GCs, and the impaired DHEA secretion, together with the increase of cortisol, results in enhanced exposure of lymphoid cells to deleterious GC actions. Therefore, previous studies have evaluated the immunomodulatory DHEA(S) effects *in vitro* as well as DHEA(S) properties during *in vivo* supplementation. The immunomodulatory *in vitro* effects include increased mitogen-stimulated IL-2 production,[83,84] increased rodent or human lymphocyte proliferation,[85] stimulated monocyte-mediated cytotoxicity,[86] diminished TNF-α or IL-6 production,[53,87] and enhanced NK cell activity.[88]

DHEA(S) replacement therapy has yielded significant beneficial effects for healthy elderly individuals, including increased well-being, memory performance, bone mineral density, and altered immune function.[89] It has been shown that DHEA supplementation significantly increased NK cell counts and activity and decreased IL-6 production and T cell proliferation in elderly subjects.[90] These data highlight the potential use of DHEA as an anti-aging hormone and suggest that DHEA supplementation would attenuate chronic low-grade

inflammation and age-related frailty by inhibiting production of pro-inflammatory cytokines.

Because of its enhanced immunomodulatory properties, several studies investigated the potential of DHEA(S) as adjuvants in vaccine preparations. Initial studies reported increased adjuvant effects on the immunization of aged mice with recombinant hepatitis B surface antigen[91] or influenza.[92] These studies reported increased antibody titers to vaccines or even effective protection against challenge with the influenza infection.[92] More recently we studied the adjuvant effects of DHEAS during immunization to *Mycobaterium tuberculosis* in mice.[93] Only young mice co-immunized with *M. tuberculosis* heat shock protein 70 (HSP70) and DHEAS showed an early increase in specific IgG levels compared to old mice. However, splenocytes of both young and old mice that received DHEAS showed increased IFN-γ production following priming *in vitro* with HSP70. These data further highlight the importance of DHEAS as a hormonal adjuvant as a result of the role of this cytokine in the cellular response against mycobacteria. However, these animal data are in contrast to previous studies reporting DHEA(S) with minor[94] or no adjuvant effects[95–97] during immunization to influenza or tetanus in human elderly populations. Therefore, extrapolation from studies on murine models to humans should be regarded with caution—especially because of lower circulating DHEA(S) levels in rodents.

Role of Growth Hormone during Aging

Previous studies have demonstrated that serum GH levels are significantly reduced during aging[98] (somatosenescence). The lack of peripheral GH-immune signaling may be detrimental for immunosenescence. In particular, in GH-deficient rodents, there is significant immune dysfunction, which is reversed after GH replacement.[99] In addition, treatment with recombinant human GH or insulin-like growth factor (IGF)-1 enhances immune function in monkeys.[100] The GH, directly or through GH induction of IGF-1, has been implicated in lymphocyte development and function. It has been shown to maintain competence of macrophages, T cells, and B cells, and stimulate antibody production and NK-cell activity.[101]

However, GH is not exclusively produced by pituitary gland, and human immune cells are also capable of secreting several neuropeptides, including GH.[102,103] The role of lymphocyte-derived hormones in immune responses is not well understood, although they might have a role in modulating cell function within the microenvironment of lymphoid organs. The immunoreactive GH has shown several immunoenhancing proprieties and may be important in modulating both humoral and cellular immune function.[102,104]

In a recent study we investigated whether somatosenescence could be correlated with respective reduced immunoreactive GH levels. We also analyzed the role of psychological distress of healthy SENIEUR elderly subjects on GH levels.[71] We found that elderly individuals had significantly lower (a reduction of 77%) serum GH levels compared to young adults. In contrast, no changes in GH production by activated monocytes or lymphocytes were observed between elderly and young adult subjects.[71] Interestingly, psychological distress (stress, anxiety, and depression) was found negatively correlated to serum GH levels only. No differences in serum GH levels were observed between groups when controlling for psychological variables. Chronic psychological stress may produce severe effects on the production of GH by lymphoid cells. Indeed, a significantly reduced expression (a reduction of 60%) of GH mRNA has been observed in peripheral lymphocytes in stressed elderly individuals (caregivers of patients with Alzheimer's disease) compared to controls.[105] These data suggest that age-related psychological distress may be implicated with impaired GH production and that immunoreactive GH is probably dissociated from pituitary GH levels.

Ghrelin, an endogenous ligand of the GH secretagogue receptor, has recently been demonstrated to inhibit the expression and production of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6).[106] This effect was mediated via binding on ghrelin receptors expressed on peripheral T cells and monocytes. There is some evidence for increased stomach ghrelin production in the aged rat.[107] Increased peripheral ghrelin levels may thus attenuate cytokine levels during aging. It remains to be investigated, however, whether psychological stress is capable of producing significant effects on stomach or immunoreactive ghrelin levels.

Chronic Stress and Aging Are Associated with Resistance to Glucocorticoids

The functional effect of a stress hormone will depend on the sensitivity of the target tissue for that particular hormone. It has been shown that GC sensitivity changes dramatically during ontogeny. Kavelaars and colleagues have shown that cord blood T cells of human newborns appear to be extremely sensitive to inhibition of the proliferative response.[108] At 1 year of age, the adult response pattern has been acquired. It is interesting that the increased sensitivity of the immune system to GC inhibition occurs at a period in life when the endogenous levels of GC are low.[109]

Recent evidence suggests that aging, chronic stress, or chronic GC levels are associated with significant resistance to GC effects. We have assessed the effects of GC in suppressing T cell proliferation *in vitro* and so examined whether aging was associated with alterations in neuroendocrine immunoregulation.[71] It was found that strictly healthy elderly subjects had a reduced (a reduction of 19%) *in vitro* lymphocyte sensitivity to dexamethasone when compared to young adults. This phenomenon has previously been described during chronic stress,[70,110] major depression,[77,111,112] or in clinical situations where GCs are administered, including treatment of autoimmune diseases, organ transplantation, and allergies. It has also been shown that aging is associated with changes in GC sensitivity of pro-inflammatory cytokine (TNF-α and IL-6) production following psychosocial stress testing.[113] These data suggest that psychological factors may be implicated in regulating peripheral GC sensitivity during healthy aging. The acquired resistance to GC may have an important physiological significance of protecting cells from the dangerous effects of prolonged GC-related immunosuppression. Additionally, altered steroid immunoregulation may have important therapeutic implications in clinical situations where GCs are administered, including treatment of autoimmune diseases, organ transplantation, and allergies.

The Impact of Chronic Stress on Strictly Healthy Aging—Damaging and Protecting Effects

The caregiving to demented patients is a recognized model to study the impact of chronic stress in elderly populations.[45,70,114] Care of the chronically ill is a demanding task that is associated with increased stress, depression, and poorer immune function.[115] Furthermore, providing care for a relative with dementia typically falls on the partners who are themselves elderly and often ill prepared for the physical and emotional demands placed upon them.

The daily stress experienced by the caregivers of Alzheimer's disease patients may accelerate many age-related changes, particularly on neuroendocrine and immune systems. We have previously demonstrated that caregivers of demented patients had a blunted T cell proliferation in association with increased cortisol levels compared to nonstressed elderly adults.[70] Furthermore, lymphocytes of elderly caregivers were more resistant to GC treatment *in vitro* compared to elderly non-caregivers. When stressed elderly individuals are compared to healthy elderly and young adults, these immunological changes are found in similar

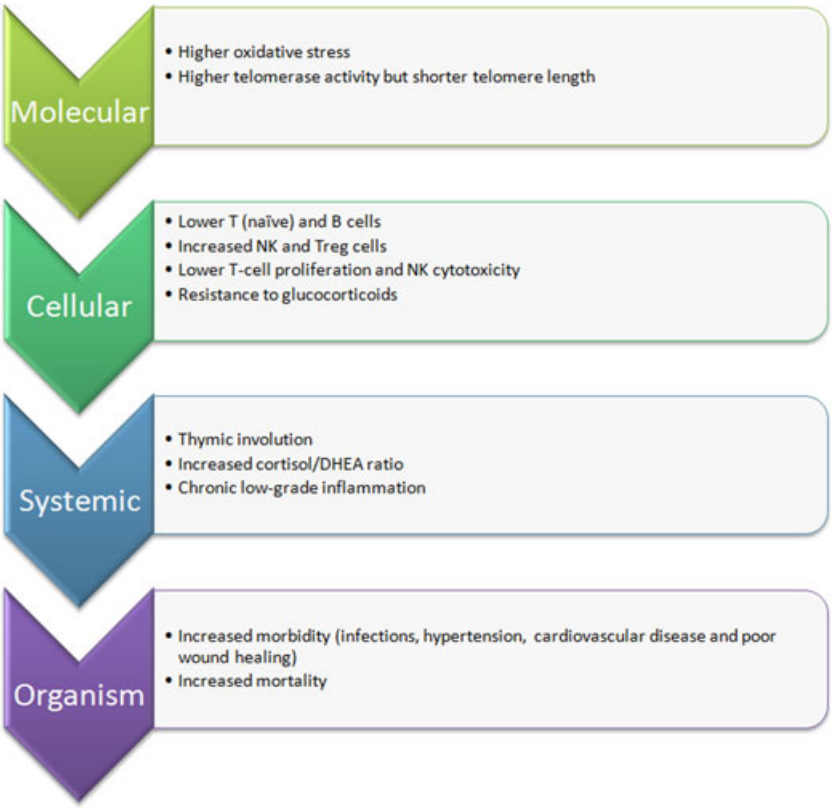

Figure 1. Psychological stress accelerates aging at various levels. Abbreviations: DHEA, dehydroepiandrosterone; NK, natural killer. (In color in *Annals* online.)

magnitude to increased cortisol levels.[3] These data suggest that chronic stress and cortisol would thus accelerate human senescence. Indeed, it has recently been observed that psychological stress (both perceived stress and chronicity of stress) was significantly associated with higher oxidative stress, lower telomerase activity, and shorter telomere length, which are known determinants of cell senescence and longevity.[116] Therefore, chronic stress may accelerate key allostatic systems and senescent features can be described at various levels (Fig. 1).

Several studies have implicated caregiving as a risk factor for the health of elderly populations. Compared with non-caregivers, subjects who provide care to a spouse with a stroke or dementia report more infectious illness episodes,[114] they have poorer immune responses to influenza virus[45,46] and pneumococcal pneumonia vaccines,[117] they present a slow wound healing,[118] they are at greater risk for developing mild hypertension,[119] and they may be at greater risk for coronary heart disease.[120] In addition, a prospective longitudinal study found that the relative risk for mortality among caregivers was significantly higher (63%) than non-caregiving controls.[121] A recent study indicates that a pro-inflammatory cytokine (IL-6) may be involved with this increased morbidity in caregiving populations.[122]

Recent data produced by our laboratory have suggested that the maintenance of health status during aging may protect elderly people from chronic stress exposure. We have recruited strictly healthy (SENIEUR) elderly caregivers from a large population of primary caregivers of demented patients ($n = 342$). Only 12% of caregivers were considered "strictly healthy" according to this stringent protocol, and this

may further confirm that chronic stress exposure is associated with increased morbidity in elderly populations. Therefore, we investigated whether a stringent health status would protect caregivers from chronic stress exposure and compared psychoneuroendocrine and immunological changes to nonstressed controls. Although the SENIEUR elderly caregivers were significantly distressed, their salivary cortisol levels remained unchanged compared to nonstressed controls (C. M. Moriguchi Jeckel *et al.*, submitted for publication). This could be of beneficial value for the caregiver and may indicate that a stringent health status in elderly individuals can buffer the impact of chronic stress on neuroendocrine responses. Therefore, healthy caregivers would be protected from the deleterious effects of cortisol excess in the organism. The peripheral lymphoid cells could be spared from the increased and deleterious cortisol signaling normally observed during chronic stress exposure. Indeed, it was observed that healthy caregivers had increased T cell proliferation when compared to nonstressed healthy controls. Taken together, these results suggest that a strictly healthy (SENIEUR) aging may buffer or attenuate many deleterious neuroendocrine and immunological effects associated with chronic stress exposure.

Conclusions and Outlook

The studies reviewed here support the notion that immunological changes observed during healthy aging may be closely related to both psychological distress and stress hormones. Of note, changes in cellular trafficking as well as cell-mediated immunity observed during aging are similarly found following stress or chronic GC exposure. These changes are mainly produced via engagement of specific intracellular adrenal receptors expressed on peripheral lymphocytes. The impaired DHEAS secretion, together with increased cortisol levels, would result in an enhanced exposure of various bodily systems (including brain and immune system) to the cytotoxic/immunomodulatory effects of GCs.

Human aging is associated with changes in allostatic systems (endocrine and immune) that play major roles in the adaptation of organisms to outside forces that are threatening the homeostasis of the internal milieu. In particular, healthy aging is associated with significant psychological distress and activation of the HPA axis (increased cortisol and reduced DHEA). Over weeks, months, or years, exposure to increased secretion of stress hormones would result in allostatic load ("wear and tear") and its pathophysiologic consequences.[123] Given the findings that even discrete HPA axis activation may impair cognitive function[124] and induce sleep disturbances,[125] conditions frequently associated in the elderly, psychological or pharmacological strategies attenuating or preventing increased HPA function during aging might be of considerable benefit for the elderly population.

Chronic stressed elderly subjects may be particularly at risk of stress-related pathology because of further increases in tissue exposure to cortisol. Elderly individuals who experience chronic stress exhibit poorer immune functions, and thus increased disease vulnerability, than nonstressed controls. Overall, these data suggest that chronic stress leads to premature aging of key allostatic systems involved in the adaptation of the organisms to environmental changes. Stress management and psychosocial support may thus promote a better quality of life for the elderly individual as well as reducing hospitalization costs.

Conflicts of Interest

The authors declare no conflicts of interest.

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