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Stress, Age, and Immune Function: Toward a Lifespan Approach

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Both aging processes and psychological stress affect the immune system: Each can dysregulate immune function with a potentially substantial impact on physical health. Worse, the effects of stress and age are interactive. Psychological stress can both mimic and exacerbate the effects of aging, with older adults often showing greater immunological impairment to stress than younger adults. In addition, stressful experiences very early in life can alter the responsiveness of the nervous system and immune system. We review the unique impact of aging and stress on immune function, followed by evidence of interactions between age and stress. Further, we suggest that prenatal or early life stress may increase the likelihood of maladaptive immune responses to stress in late life. An understanding of the interactive effects of stress and age is critical to efforts to determine underlying mechanisms, clarify the directionality of effects, and develop effective interventions in early and late life.

KEY WORDS: psychoneuroimmunology; aging; stress; immune function; behavioral immunology; caregiving.

It has become well accepted in recent decades that psychological stress can adversely affect many aspects of immune function (Glaser and Kiecolt-Glaser, 2005). The full health impact of stress, however, may not be fully revealed until the effects of aging are more widely appreciated. Chronic stress may speed the rate of normal age-related immune dysregulation (Kiecolt-Glaser and Glaser, 2001; Sapolsky *et al.*, 1986). Moreover, age-related disease and impairment may augment the effects of stress or result in more significant clinical impairment for older individuals (Hawkley and Cacioppo, 2004; Kiecolt-Glaser and Glaser, 2001). While it is thus important to examine the effects of stress in late life, it is also critical to look throughout the lifespan. Most notably, stress during early development can have lasting effects on the responsiveness of the nervous system and immune system. Following a review of the association between aging and immune function, we recount research on the association between stress and immune function, followed by evidence that age and stress interact to affect immune function. We then review evidence of the effects of prenatal and early life experiences and propose that the effects of stress in older adults may be influenced significantly by early developmental experiences. Understanding the interactive effects of stress and age will be critical as researchers and clinicians strive to develop interventions to mitigate the adverse immune impact of stress throughout the life span.

AGE AND IMMUNE FUNCTION

Of the many different ways to assess aspects of immune function, most if not all suggest that

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immune function declines with age. Aging is associated with a well-documented reduced efficiency ("immunosenescence") of both the innate immune system (which provides an immediate response to foreign invaders such as bacteria and certain viruses) and the adaptive immune system (a response which takes several days to engage but which is more efficient and effective once activated) (Gomez *et al.*, 2005; Lord *et al.*, 2001). Beginning soon after birth, there is a steady decrease in the ability of thymus gland to produce new ("naïve") white blood cells (T-lymphocytes, or "T cells"), with a substantial reduction by age 50 and almost complete incapacity by age 60 (Parham, 2005). One result is that older individuals have a greater percentage of memory T cells, which have been trained to respond to a particular pathogen, than naïve T cells, which can respond to a novel invader. As a result of these and other changes, cells of older individuals become less able to respond to both novel and previously encountered infectious agents (Lord *et al.*, 2001; Miller, 1996). As evidence of this, T cells from elderly individuals show a decreased ability to respond when "challenged" with a substance to which they would normally respond, with large differences seen at age 60 and increasingly thereafter (Murasko *et al.*, 1987). Studies like this are performed by observing white blood cells in an artificial medium outside the body (*in vitro*).

Although adaptive immunity is most notably affected, measures of innate immunity also show immunosenescence (Gomez *et al.*, 2005). For example, there is a decline in the functionality of natural killer (NK) cells with aging, although observable effects of this change are minimized by an increase in the number of NK cells in older individuals (Castle, 2000; Miller, 1996). An important component of the innate immune system, natural killer cells provide an early defense against viral infections and also have important implications for cancer progression and development (Heffner *et al.*, 2003; Keller *et al.*, 2000; Rabin, 1999). The most conclusive evidence of a decline in NK cell activity with aging comes from animals: Natural killer cells from the spleen and lymph nodes of older animals show *in vitro* decreases in their functionality compared to those from younger rats (Castle, 2000; Miller, 1996). Another change seemingly inherent in normal aging is that B-lymphocytes from elderly individuals show impaired functionality, with a corresponding decrease in the antibody production essential to both innate and adaptive immunity (Castle, 2000).

The age-related immune changes described above put older adults at much greater risk of impairment and death from infection, such as from influenza or pneumonia (Castle, 2000; Yoshikawa, 1983). Relatedly, older adults do not respond as well to vaccines (Burns and Goodwin, 1997). Vaccine studies represent another technique for assessing immune function as they provide a window into how individuals typically respond to infection. Moreover, individuals who do not show an adequate response to a given vaccine may not be able to mount an effective immune defense if they encounter the virus: This is particularly true for individuals older than 65 years (Harper *et al.*, 2005).

Although direct causal relationships between age-related immune changes and the occurrence or severity of specific diseases are not always clear (Castle, 2000), immunosenescence plays a significant role in the increased incidence of shingles (herpes zoster) in late life, and is also relevant to the onset of other diseases such as tuberculosis, diabetes mellitus, and certain cancers (Kiecolt-Glaser and Glaser, 2001; Yoshikawa, 1983). In addition, wound infections increase with age and the elderly are at greater risk for surgical complications, including death from postsurgical infection (Kiecolt-Glaser *et al.*, 1998; Yoshikawa, 1983).

Dysregulation of inflammatory processes may further explain declines in physical function with age (Cesari *et al.*, 2004). Inflammatory processes are intimately intertwined with immune function: Under conditions of acute infection or tissue damage, elements of the immune system trigger inflammatory processes that play an adaptive role in wound healing and sickness response in the short-term even while they may cause temporary discomfort, such as swelling and fever. Proinflammatory cytokines, proteins that enable communication between cells, play a key role in this process. In fact, one likely mechanism underlying impaired wound healing in the elderly may be a diminished ability of macrophages (other key cells in the innate immune response) to produce proinflammatory cytokines in the local environment (Gomez *et al.*, 2005).

In contrast, chronic inflammation represents a dangerous disruption of homeostasis and confers an increased risk for development and severity of a range of diseases, including atherosclerosis and cardiovascular disease, certain cancers, osteoporosis, and rheumatoid arthritis (Harris *et al.*, 1999; Pradhan *et al.*, 2001; Ridker *et al.*, 2000). As compared to young adults, middle aged and particularly

elderly adults typically have higher levels of cytokines with proinflammatory functions circulating in their blood, such as interleukin-6 (IL-6) and tumor necrosis factor-a (TNF-a) (Ershler, 1993; Krabbe *et al.*, 2004). Peripheral blood mononuclear lymphocyte cells from aged people also produce more IL-6 than those from younger subjects when stimulated *in vitro* (Krabbe *et al.*, 2004; Roubenoff *et al.*, 1998). Another marker of inflammation is C-reactive protein (CRP), which is produced in the liver largely in response to elevations in IL-6. This general marker of inflammation is also elevated in older adults relative to young ones (Ballou *et al.*, 1996). All of these specific changes put older individuals at an increased risk for the diseases mentioned above, including but not limited to cardiovascular disease. Although pre-existing conditions or sub-acute illness may contribute to the presence of greater inflammation in older adults, IL-6 and CRP (in women) increase with age in samples with a wide age range even after controlling for cardiovascular risk factors and symptomotology (Ferrucci *et al.*, 2005).

There are also other immune-related changes common to aging, which are reviewed in detail elsewhere (e.g., Burns and Goodwin, 1997; Solomon and Morley, 2001). For example, aging is associated with endocrine, autoimmune, and cognitive changes, all of which are related to immune and inflammatory responses.

STRESS AND IMMUNE FUNCTION

Brief Naturalistic Stress

Even seemingly mild, fairly transient stress can result in immune dysregulation at all stages of life. For example, among diverse groups—including healthy medical students and both asthmatic and healthy high school students—academic examination periods provoke short-term changes in multiple facets of the immune response. Such studies indicate that examination periods elicit a decline in the ability of white blood cells (lymphocytes) to perform their key functions (Kiecolt-Glaser and Glaser, 1991). Natural killer cell activity is similarly diminished during examination periods (Kang *et al.*, 1997).

Transient psychological stressors, like academic examinations, can also slow wound healing (Kiecolt-Glaser *et al.*, 1998; Marucha *et al.*, 1998), an outcome with clear clinical relevance. The immune system plays an important role in the early stages of wound healing by helping to prepare tissue for repair and enhancing recruitment of certain key cells to the wounded area (Marucha *et al.*, 2001; Singer and Clark, 1999). Related to wound healing, examination stress can alter the production of certain cytokines (Deinzer *et al.*, 1999; Dobbin *et al.*, 1991; Maes *et al.*, 1998) that mediate inflammatory processes central to wound healing. That something as predictable and relatively mild as examination stress can affect wound healing and related cytokine production suggests that other common transient stressors may produce a similar deficiency in wound repair.

Acute pain is another form of stress that can lead to immune dysregulation. Although pain has many adaptive functions (Watkins and Maier, 2003), it can be conceptualized as both a physical and a psychological stressor, particularly when excessively strong or long-lasting. Like examination stress, acute pain can trigger changes in cytokines and both natural killer cell and lymphocyte activity (Lutgendorf *et al.*, 2004; Page, 2005a; Pezzone *et al.*, 1994; Shavit *et al.*, 1986). Acute pain also contributes to the development of cancerous tumors in laboratory animals, with preliminary research suggesting that the same may be true in humans (Page, 2005b; Page *et al.*, 2001). In humans it can sometimes be difficult to distinguish the effects of pain specifically from other effects of health problems. However, key evidence that pain itself plays a role in physical recovery and immune function is that pain medication and anesthetic techniques can protect against the immune suppressive effects of surgery (Cuschieri *et al.*, 1985; Page, 2005b; Page *et al.*, 2001; Pasqualucci *et al.*, 1994), but are themselves immune suppressive in the absence of pain (Page, 2005b; Page *et al.*, 2001). In addition, relatively healthy individuals experiencing greater postsurgical pain take longer to heal from a laboratory induced wound (McGuire *et al.*, in press), further demonstrating that the immune effects of acute pain can be clinically significant.

The adverse immune effects of acute stressors may be increased when state anxiety or perceived stress due to other events is elevated. For example, students undertaking examinations show greater immune dysregulation if they report stress due to daily hassles (Marshall *et al.*, 1998) or have high state anxiety (Maes *et al.*, 2002). In addition, more anxious participants report greater postsurgical pain (Johnston, 1988; Mathews and Ridgeway, 1981): The immune function of such individuals may thus be dysregulated by both presurgical stress and

postsurgical pain (Kiecolt-Glaser *et al.*, 1998), putting them at even greater risk of postsurgical complications. Perceived stress, negative affect, and reported life events are also associated with an increased risk of developing an infectious illness and objective measures of illness severity when exposed to a virus (e.g., a common cold virus) under controlled conditions (Cohen *et al.*, 1991). Risk increases in a dose-response fashion with increasing duration of the reported stress, suggesting that chronic, enduring stress is particularly problematic (Cohen, 2005).

Chronic Stress

Unsurprisingly, chronic stress is strongly and consistently linked with immune dysregulation that is greater in magnitude and longer in duration than that seen in response to acute stress. Conflict within close relationships, for example, is a powerful predictor of immune dysregulation. While the support provided by close relationships confers considerable health benefits, relationships can nonetheless be a powerful source of ongoing stress (Graham *et al.*, in press-b). Both older and newlywed couples whose interactions in a laboratory setting are negative and hostile show greater hormonal and less adaptive immunological responses subsequent to those interactions than those with less negative interactions (Kiecolt-Glaser *et al.*, 1997; Kiecolt-Glaser *et al.*, 1993; Malarkey *et al.*, 1994). Such dysregulation may reflect chronic patterns of conflictive interactions between couples, who tend to argue more intensely outside of a laboratory setting (Margolin *et al.*, 1989). Several lines of work suggest that immune changes due to relationship stress are clinically significant. For example, individuals who report relationship conflict lasting one month or more (or long-term work-related strain) are at particularly strong risk of developing illness when exposed to an infectious agent (Cohen, 2005). Slower wound healing can also result from relationship stress: Blister wounds induced on the forearms of married couples healed more slowly following conflictive as opposed to supportive discussions and even more slowly for individuals who evidenced more hostile and negative interactions during both types of discussions (Kiecolt-Glaser *et al.*, 2005). These studies were conducted with relatively well-functioning and healthy couples and may thus underestimate the risk of relationship conflict. In addition, some interesting gender differences have emerged in this literature (Kiecolt-Glaser and Newton, 2001), with women often showing greater immune dysregulation than men following conflictive marital interactions (e.g., Mayne *et al.*, 1997).

The death of a spouse, parent, or child is also associated with dysregulation of several measures of immune functioning (Graham *et al.*, in press-a). For example, healthy individuals who recently experienced unexpected bereavement show lower natural killer cell and lymphocyte activity compared to non-bereaved matched controls; this deficit was observed 40 days after the death and in some cases persisted for 6 months (Gerra *et al.*, 2003). Bereavement following the death of a spouse specifically is also associated with these functional measures of immunity (Hall and Irwin, 2001; Irwin *et al.*, 1987; Schleifer *et al.*, 1983). It is not clear, however, the degree to which perceived stress plays a role in these responses, as opposed to other sequelae of bereavement such as depression and dysregulated sleep (Hall and Irwin, 2001). For example, men with wives diagnosed with breast cancer show significant immune dysregulation subsequent to spousal death, but not during the period immediately following the diagnosis, even though they reported significant stress during that time (Schleifer *et al.*, 1983). Unlike the findings with marital conflict, men appear to be at a greater risk of mortality following spousal bereavement (Kiecolt-Glaser and Newton, 2001).

Another form of chronic stress consistently associated with immune dysregulation is caregiving, such as providing care for a spouse with dementia. Caregivers are often socially isolated (Ell, 1996), experience overwhelming demands on their time and emotional, financial, and physical resources, and experience high levels of depression and anxiety (Bodnar and Kiecolt-Glaser, 1994). Compared to well-matched controls, spousal caregivers show poorer immune function, including responses to virus and vaccine challenges (Glaser *et al.*, 2000; Vedhara *et al.*, 1999), dysregulation of natural killer cell activity (Esterling *et al.*, 1994; Esterling *et al.*, 1996), and slower wound healing (Kiecolt-Glaser *et al.*, 1995). Moreover, several studies indicate that spousal caregivers are more likely to have elevated levels of inflammatory markers in their blood (Kiecolt-Glaser *et al.*, 2003; Lutgendorf *et al.*, 1999; von Kanel *et al.*, 2005), putting them at greater risk for cardiovascular and other age-related diseases (Harris *et al.*, 1999; Pradhan *et al.*, 2001). The immune dysregulation of this intense chronic stressor can continue at detectable levels even several years after the spouse dies and caregiving activities have ended

(Kiecolt-Glaser, 1999). The persistence of these maladaptive changes may be at least in part a function of the longer-lasting distress typically reported by bereaved caregivers as compared to bereaved noncaregivers. As will be discussed further, other studies suggest that caregiving status and age interact to predict immune dysregulation (e.g., Kiecolt-Glaser *et al.*, 2003), putting older caregivers at particularly high risk.

Chronic stress has also been related to important immunologically-relevant health outcomes among caregivers of chronically ill children. Among healthy mothers, a subset of whom were providing care to a chronically ill child, perceived stress and chronicity of stress were associated with lower telomerase activity and shorter telomere length (Epel *et al.*, 2004); these outcomes decrease with age and are, in fact, widely considered important markers of aging at the cellular level. In conjunction with immune dysregulation found among caregivers of spouses, these results suggest that chronic stress may cause premature aging (Glaser and Kiecolt-Glaser, 2005).

STRESS, AGE AND IMMUNE FUNCTION

Stress and Immune Function in Late Life

Although there are significant changes in immune function with age, there is considerable variability in these age-related changes (Solomon and Morley, 2001). Individual differences in exposure and physiological, emotional, and behavioral responses to stress contribute to this variance. Indeed, chronic psychosocial stress may "age" the immune system in a number of ways.

Stress and aging have similar effects on the immune system: Many of the specific changes in immune function observed among psychologically stressed individuals parallel changes seen with aging (Burns and Goodwin, 1997; Hawkley and Cacioppo, 2004). For example, changes in the functionality of cells involved in innate immunity (e.g., natural killer cells) and lymphocytes (e.g., white blood cells) are associated with both acute and chronic stress (Gerra *et al.*, 2003; Kiecolt-Glaser and Glaser, 1991) as well as age (Murasko *et al.*, 1987). Similarly, cellular changes seemingly inherent to normal aging, such as a decrease in telomere length and function, have also been observed in chronically stressed individuals as compared to less stressed individuals of the same age (Epel *et al.*, 2004). Transient increases in inflammatory markers increase with acute stress (Lutgendorf *et al.*, 2004) and chronically elevated levels of similar markers are seen both among those encountering unremitting psychological stress over a long-term (Kiecolt-Glaser *et al.*, 2003; Lutgendorf *et al.*, 1999) and in older individuals (Franceschi *et al.*, 2000). Deficits in vaccine response, surgical and wound healing recovery, and increases in infectious illness risk are also similarly observed among the aged (Castle, 2000; Kiecolt-Glaser *et al.*, 1998) as well as in psychologically stressed but otherwise healthy and young or middle-aged individuals (Cohen, 2005; Kiecolt-Glaser *et al.*, 1998). Thus, one useful perspective is that psychological stress, particularly chronic and unremitting stress, can mimic, and at least in some situations accelerate, the effects of aging.

The decrement in functioning of the thymus that occurs with normal aging (Parham, 2005) may also be mimicked by psychological stress. Experiments with laboratory animals consistently show that both acute and chronic psychological stress leads to thymic involution (e.g., Engler and Stefanski, 2003). Moreover, work following from classic experiments by Hans Seyle has consistently shown that stress hormones, such as glucocorticoids, are an important mechanism in such stress-associated thymus changes (Berczi, 1998). Thus, there is the distinct but as yet unstudied possibility that changes in the thymus may represent one mechanism by which age and stress interact (Rabin, 1999).

Indeed, a perspective for which there is accumulating evidence is that the effects of stress and age are truly interactive, with stress exacerbating the effects of aging (Hawkley and Cacioppo, 2004; Kiecolt-Glaser and Glaser, 2001; Sapolsky *et al.*, 1986). In support of this, a recent meta-analysis showed that maladaptive responses to brief naturalistic stressors, including decreases in natural killer cell and lymphocyte activity, are more often observed in studies of older individuals (Segerstrom and Miller, 2004).

Comparisons between chronically stressed individuals and age-matched controls provide key data on the interactive effects of stress and age. For example, chronic stress interacts with age to predict responses to influenza vaccine. In a study of caregivers and well-matched controls, a main effect of stress was observed, such that caregivers exhibited a deficit in their response to influenza vaccine compared to controls (Kiecolt-Glaser *et al.*, 1996). However, these differences were magnified in older subjects:

Among those older than 70, only 23.3% of caregivers responded, compared with 60% of the control subjects (Kiecolt-Glaser *et al.*, 1996). In comparison, among subjects younger than 70, 53.8% of the caregivers responded adequately to the vaccine, compared with 75% of the control subjects. This study indicates that elderly individuals experiencing chronic stress may be less able to mount a successful immune response in general and may be less protected by specific vaccinations.

Stress and anxiety may also interact with age to heighten surgical risks for older adults. Surgery and surgery-related stress are immune dysgregulating for all individuals (Kiecolt-Glaser *et al.*, 1998; Linn *et al.*, 1988). However, older individuals are at even greater risk of immune dysregulation following surgery. In one study, for example, older participants had poorer responses compared to younger individuals on two immune measures 5 days after surgery for hernia repair, even though they were equivalent on these measures prior to the operation (Linn and Jensen, 1983). Preoperative anxiety was also predictive of more surgical complications in this study, suggesting that older adults experiencing presurgical stress may be at a particularly high risk.

Prospective studies with older adults further indicate that stress may accelerate the effects of aging on inflammatory dysregulation. The average caregiver experiences a 4-fold faster increase in IL-6 levels over a span of 6 years compared to non-caregiving control participants (Kiecolt-Glaser *et al.*, 2003). Thus, the average caregiver at age 75 has levels of IL-6 that put him or her at high risk for disease and death based on large epidemiological studies (Harris *et al.*, 1999; Ridker *et al.*, 2000), whereas the average non-caregiver would not approach that high-risk category until age 90 (Kiecolt-Glaser *et al.*, 2003). The cytokine IL-6 also stimulates the liver to produce CRP (Black, 2003), a marker of general inflammation also associated with morbidity and mortality from a range of diseases, particularly cardiovascular disease (Pearson *et al.*, 2003; Ridker, 2003). Adult caregivers with CRP levels indicative of high risk of cardiovascular disease reported significantly lower health-related quality of life than caregivers with low risk CRP levels (Robles *et al.*, under review): Their quality-of-life was equivalent to that typically seen in individuals 10–20 years older. In this and other research, CRP was strongly related to pain and other quality of life markers among caregivers but not among age-matched non-caregivers (Graham *et al.*, in press-c; Robles *et al.*, under review), suggesting that chronic stress may exacerbate age-related increases in inflammation and their effects on health.

In some situations, the number of years of intense chronic stress (e.g., the number of years of caregiving) may help explain the interactive effects of age and stress. That is, older individuals may show the most dramatic immune responses to stress because they have experienced a given stressor for a longer amount of time. This possibility was supported by Epel *et al.* (2004) who found that those who had provided care for an ill or disabled child for a greater number of years had shorter telomere length and less telomerase activity, cellular markers that decline with age. However, other studies of adult caregivers have failed to support the so-called "wear and tear" hypothesis (Kiecolt-Glaser *et al.*, 1996). It is possible that the effects of stressor duration may be obscured in age-restricted or older populations. Moreover, to date, studies of stress and immune function have focused primarily on healthy individuals: Research with ill populations may reveal stronger interactive effects of stress and age or more evidence for wear-and-tear effects.

Overall, the existing evidence strongly suggests that chronic psychological stress exacerbates the effects of aging on immune function. Specific interactive effects with age and stress have emerged (e.g., Kiecolt-Glaser *et al.*, 1996) that can not be accounted for by number of years of stress or age alone. The strong effects of stress on immune function in older adults are particularly troubling given that older adults are at greater risk of health complications and mortality from dysregulated immune function (Burns and Goodwin, 1990). Differences in sympathetic nervous system activity, social support, and depression among the aged have all been posed as factors related to interactive aging and stress effects on immune function (Herbert and Cohen, 1993; Kiecolt-Glaser *et al.*, 1996), at least some of which may be related to stress experiences earlier and perhaps very early in life, as reviewed below.

Effects of Early Life Experience

Although the effects of stress on health outcomes are especially observable in older adults due to the effects of aging, early developmental experiences may "set the stage" for vulnerability in later life. Most thoroughly studied in relation to the environmental insult of prenatal malnutrition (Lucas *et al.*, 1996; Lucas *et al.*, 1999; McCance, 1962), the

fetal-programming hypothesis proposes that exposure to stimuli or insults at critical developmental periods can have lifelong effects (Barker, 1998; Lucas, 1991). Increasingly, research has focused on the extent to which psychosocial stressors during fetal development and early life cause lasting effects on physiology. As reviewed below, data from animal and human studies suggest that this is a promising avenue of investigation.

The strongest evidence for the role of prenatal and early life experiences on immune function comes from animal models (Coe *et al.*, 2002; Coe and Lubach, 2005; Weinstock, 2005). In monkeys as well as rats, offspring of mothers who are repeatedly stressed during their pregnancies show decrements in immune function compared to offspring of undisturbed pregnancies: Their immune cells show less robust responses when exposed to an antigen *in vitro* (Coe *et al.*, 2002; Kay *et al.*, 1998; Reyes and Coe, 1997). Maternal stress also affects placental transfer of antibodies from the mother to the neonate (Coe and Crispen, 2000), although this effect may depend on the sex of the offspring (Coe and Crispen, 2000). Decreased maternal transfer of antibodies may affect the neonate's ability to fight infection.

Demonstrating the effects of disruption in early rearing conditions, monkeys raised by humans show decreased natural killer cell activity and less robust antibody responses to vaccination compared to monkeys reared by their mothers (Coe *et al.*, 1992; Lubach *et al.*, 1995), suggesting that such animals would be less able to mount an effective immune response when needed. These differences persisted through a two-year evaluation period, even though the human-reared monkeys were placed in the care of an older female monkey after the first year of evaluation (Lubach *et al.*, 1995), suggesting that early life stress may lead to the readjustment of an immune "set-point" that is resistant to later alteration. The degree to which such effects translate into disease or mortality in later life is unknown. However, retrospective data indicate that a history of early maternal separation is associated with faster pathogenesis of simian immunodeficiency virus (SIV) in adult monkeys (Capitanio and Lerche, 1991), suggesting that early life experiences are meaningful in immune-compromised populations.

Data addressing early life stress in humans parallel findings from animal studies. In humans, however, limited research on the effects of early life stress has utilized measures of immune function, with a greater focus on the related nervous and endocrine systems. For children, exposure to frequent family conflict and aggression may disrupt functioning of the two primary hormonal systems governing the stress response, the sympathetic-adrenomedullary (SAM) and hypothalamic-pituitary-adrenocortical (HPA) axes, increasing sensitivity to stress throughout the lifespan (Repetti *et al.*, 2002). Indeed, young children who experience abuse or neglect show abnormal cortisol levels (Gunnar *et al.*, 2001), indicative of a dysregulated stress response. Paralleling findings in monkeys, these changes often remain after the child has been moved to a safe, caring environment (Gunnar *et al.*, 2001) and are particularly persistent in children who show clinical or subclinical symptoms of post-traumatic stress disorder (Carrion *et al.*, 2002). Because it is not experimental in design, research with humans does not allow definitive statements about direction of causality. However, similar experimental findings with animals strengthen an argument for a causal path from early life stress to immune dysregulation.

In prospective studies of early life stress, subjects are typically assessed for 1 to 5 years. However, retrospective data indicate that early life difficulties have health implications that may persist through adult life. Individuals who experience childhood trauma or abuse show greater stress hormone responses to acute stress in adulthood (Heim *et al.*, 2000; Otte *et al.*, 2005). These data have great relevance to immune function because of the bidirectional connections between the nervous, endocrine, and immune system (Glaser and Kiecolt-Glaser, 2005; Lutgendorf and Costanzo, 2003) and suggest that a greater focus on the effects of early life experience on immune outcomes is warranted.

Evidence that prenatal stress affects physiology in humans is more limited than that provided by animal data. However, one important pathway by which maternal stress may alter offspring health is by affecting rates of preterm birth and fetal weight. A number of studies, including large epidemiological approaches, have found associations between psychosocial stress, preterm birth, and/or low birth weight (Copper *et al.*, 1996; Dole *et al.*, 2003; Lobel *et al.*, 2000; Nordentoft *et al.*, 1996; Wadhwa *et al.*, 1993). In part because maternal antibodies are transferred to the fetus primarily in the final weeks of pregnancy, infants born prematurely are likely to have significantly impaired immune function, putting them at greater risk for infection (Ballow *et al.*, 1986). Furthermore, low birth weight predicts poorer vaccine responses in adolescence (McDade *et al.*, 2001),

higher cortisol responses to acute psychosocial stress in adulthood (Wust *et al.*, 2005), and increased risk of cardiovascular and metabolic disorders including diabetes later in life (Lawlor *et al.*, 2005; Rich-Edwards *et al.*, 1999). The effects of low birth weight on these adult health outcomes have primarily been interpreted as demonstrating the lasting effects of prenatal malnutrition. However, given the evidence that maternal stress affects birth outcomes, we propose that maternal stress may contribute to such findings. Moreover, because a growing literature supports a link between glucocorticoid dysregulation, inflammatory immune responses, and cardiovascular outcomes, the exploration of a potential link between birth outcomes and adult immune function is warranted.

Because of the malleability of the developing physiology, early life is a period that may lend itself to intervention. Indeed, in animal studies, the negative effects of maternal stress are mitigated to a large extent if offspring are raised in enriched environments that offer opportunities for exploration and social contact (Francis *et al.*, 2002). If human toddlers are accompanied by a responsive and sensitive adult when exposed to a novel situation, they show less elevation in cortisol, indicating a reduced stress response (Nachmias *et al.*, 1996). These findings are promising. However, as described earlier, other studies have found immune and endocrine dyregulation to be resistant to alteration, even when intervention occurs at a relatively young age (Gunnar *et al.*, 2001; Lubach *et al.*, 1995). This raises important and largely unanswered questions regarding the window during which developing physiology remains most malleable, and the extent to which early life programming affects responses to stress-related interventions later in life.

In sum, research to date provides strongly suggestive evidence that prenatal and early life stress can have lasting effects on physiology and immune function. First, prenatal and early life stress have predicted altered immune function in animal studies, effects that are observable years later. Moreover, retrospective and correlational data from human studies link early life stress to functioning of the nervous and endocrine systems into adulthood. To address gaps in the current literature, research is needed to address the following: 1) the extent to which prenatal and early life stress in humans predict immune outcomes in addition to measures of endocrine and nervous system function, 2) whether these alterations persist throughout life in humans, and 3) the effect of these alterations on disease development and longevity. Addressing these issues will inform interventions targeting psychological and physiological development in early life.

CONCLUSIONS AND FUTURE DIRECTIONS

A developmental approach to understanding the effects of stress on immune function is warranted; as physiology changes throughout the lifespan, so do the effects of stress. In late life, when the immune system tends to show functional decline, the effects of stress are especially potent. Stress can not only mimic but also exacerbate the effects of aging. Moreover, because of other effects of age, immune dysregulation in older adults is associated more frequently and seriously with clinical impairment and death. Additional studies are needed with older adults and with adults spanning a range of ages to further establish and tease out interactive effects of psychological stress and aging.

During early life, animal and human data support the proposition that an "imprinting" process occurs while critical physiological systems are developing. Indeed, stressful experiences during fetal development and early life can alter the responsiveness of the endocrine, immune, and central nervous systems. Questions remain regarding the importance of types and timing of stressors, as well as the duration of effects. A greater understanding of the extent to which early life experiences affect risk of stress-related health outcomes in old age is also needed.

The interactive effects of stress and age highlighted in this review have important implications for intervention efforts as well as basic science. Strategies to reduce stress may be particularly important for pregnant populations. Further, early life experiences may affect which individuals are amenable to stress-reducing interventions in adulthood. Because late life is another critical period, it will also be critical to refine experimental trials designed to mitigate the impact of stress in older populations, particularly those already experiencing functional decline and disability (Ferrucci *et al.*, 2004).

In addition to intervention studies, future research is needed to clarify underlying mechanisms, directionality of effects, and the implications of stress and age for clinically ill patients. However, the effects of aging and psychological stress on immune function are now well established: They interact in ways that put oldest individuals at great risk.

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