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Early caregiving and physiological stress responses

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Abstract

Inadequate early caregiving has been associated with risks of stress-related psychological and physical illness over the life span. Dysregulated physiological stress responses may represent a mechanism linking early caregiving to health outcomes. This paper reviews evidence linking early caregiving to physiological responses that can increase vulnerability to stress-related illness. A number of high-risk family characteristics, including high conflict, divorce, abuse, and parental psychopathology, are considered in the development of stress vulnerability. Three theoretical pathways linking caregiving to physiological stress responses are outlined: genetic, psychosocial, and cognitive-affective. Exciting preliminary evidence suggests that early caregiving can impact long-term physiological stress responses. Directions for future research in this area are suggested.

Keywords: Caregiving; Health; Cortisol; Stress; Early experiences

1. Introduction

Accumulating evidence suggests that the characteristics of early family relationships, such as affection, expressiveness, and conflict, may contribute to physical health in adulthood (Repetti, Taylor, & Seeman, 2002; Streeck-Fischer & van der Kolk, 2000). A few longitudinal studies have reported that perceptions of parental caring and warmth during childhood are associated with adult physical health status (Russek & Schwartz, 1997; Thomas et al., 1979). Others have noted negative long-term (i.e., into adulthood) health effects of disrupted caregiving, as can occur following early parental loss and/or separation. Early parental loss, for example, has been associated, over the long term, with higher blood pressure (Luecken, 1998), greater risk of breast cancer (Jacobs & Bovasso, 2000), and health problems in older adulthood (Krause, 1998; Maier & Lachman, 2000).

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Recent research has begun to identify putative mechanisms linking early caregiving to health in adulthood. Previous reviews (e.g., Repetti et al., 2002) linking early caregiving experiences to long-term health outcomes have identified several potential mechanisms including the ability to regulate physiological responses to environmental challenges. Physiological stress responses prepare the body to survive physical threat by mobilizing stored energy, increasing cardiac output, and suppressing nonessential digestive, immune, and reproductive functions. Stress responses primarily involve the activation of two nervous system pathways: the hypothalamic–pituitary–adrenocortical (HPA) axis and the sympathetico–adrenomedullary (SAM) system. The HPA axis regulates the production and release of cortisol. Exaggerated or prolonged exposure to cortisol is associated with accelerated aging and increased risk of cognitive impairments, cardiovascular disease, infectious diseases, and other illnesses (McEwen, 1998), and may significantly impact the progression of chronic illness (Ironson et al., 2002; McEwen & Wingfield, 2003).

The SAM component of stress response results in increased cardiovascular arousal, secretion of norepinephrine and epinephrine into the blood stream, and the halting of nonessential parasympathetic functions. Heightened cardiovascular arousal has been associated with the development of hypertension and organ damage (Georgiades, Lemne, De Faire, Kindvall, & Fredrikson, 1997; Manuck, Kasprowicz, & Muldoon, 1990) and with the progression of cardiovascular disease (Lynch, Everson, Kaplan, Salonen, & Salonen, 1998).

Efficient and flexible physiological responses to stress are adaptive in the short run. However, pronounced or repeated, as well as delayed, recoveries of cardiovascular and neuroendocrine stress responses are thought to contribute, over time, to the etiology of hypertension, heart disease, infectious diseases, and other illnesses (Markovitz & Matthews, 1991). The allostatic load hypothesis suggests that stress responses can promote pathophysiology in the brain and body if prolonged, chronic, or not efficiently regulated (McEwen & Wingfield, 2003). Evidence of dysregulation is seen in response profiles that fail to habituate to recurring stress, fail to terminate in an efficient manner, or are of insufficient magnitude to mount an adaptive response. Biological measures that have been included in indices of allostatic load include cortisol and catecholamine excretion, blood pressure, waist–hip ratio, and cholesterol, although dysfunctions in other systems are also important (McEwen, 2002; Seeman et al., 1997). Health risk is increased through large dysregulation in a single system or through small dysregulations in multiple systems. Because differences in physiological responses to stress may partially account for the differential vulnerability to illness, it is important to expand our understanding of the impact of early experience on the development of stress responses.

The current article focuses on the viability of physiological stress responses as a mechanism underlying the long-term effects of early caregiving on health. In this review, the construct of ‘‘early caregiving’’ refers specifically to the characteristics of the immediate family environment and is broadly defined to include disruptions in parenting (e.g., as may occur with high family conflict or with parental death or divorce), along with characteristics related to the quality of parenting received by the child (e.g., caring, abusive). Because existing research has been inconsistent concerning critical periods for the impact of early caregiving on later-life health, this review considers the construct of early caregiving to include those received through infancy, childhood, and adolescence. Throughout the review, short-term effects are considered to be those that are seen during childhood, while long-term effects include those that last into adulthood. Thus, early caregiving may first impact short-term stress responses but, over time, may lead to long-term effects on physiological stress responses, which ultimately affect vulnerability to stress-related illness over the life span.

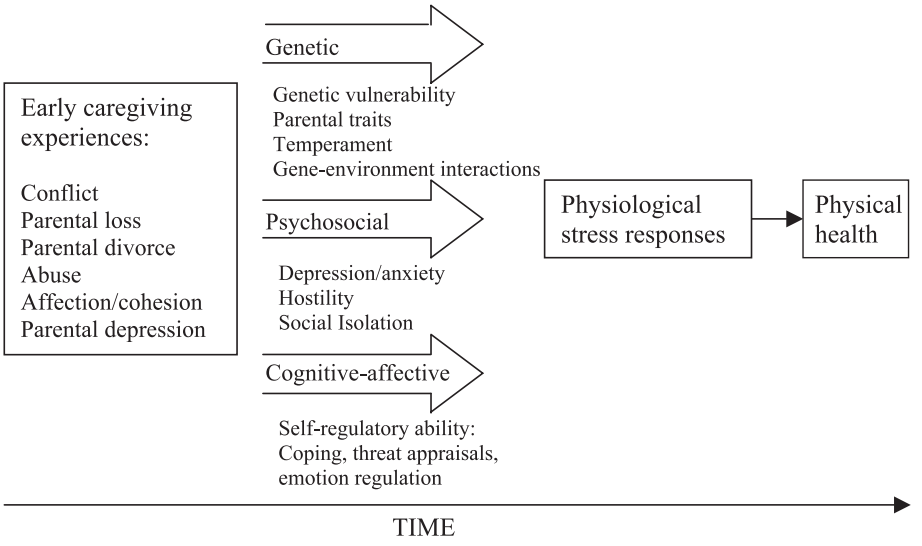

Fig. 1. Pathways to physiological stress vulnerability.

This review first considers evidence that early caregiving experiences are associated with the neurobiological development of physiological stress responses. Next, a number of family characteristics are considered which may increase the risk of the development of maladaptive stress responses. Finally, three theoretical pathways linking adverse early caregiving experiences to dysregulated physiological stress responses are proposed, including genetic, psychosocial, and cognitive-affective processes (see Fig. 1). The goal is to identify important early-family-related processes that operate over time to influence the course of health.

2. Early caregiving and the development of physiological stress responses

The brain undergoes rapid developmental changes during the early postnatal period, during which time it is susceptible to a variety of environmental influences. The plasticity of physiological stress response systems provides the opportunity for environmental factors to permanently alter set points or hardwire systems to respond in an optimal manner to an idiosyncratic environment (Welberg & Seckl, 2001). Animal studies provide strong evidence that behavior and neurohormonal functions are subject to environmental modification during early development. For most infants, the caregiver provides the most influential environmental exposure. Parental behavior can have direct, enduring effects on the development of neurobiological stress response systems in the young (DeBellis, 2002; Meaney, Brake, & Gratton, 2002).

Some of the earliest and strongest demonstrations of the long-term neurobiological impact of early caregiving have utilized animal models of maternal separation. Rat pups separated from their mothers show a series of short- and long-term physiological changes including decreased serum growth hormone secretion and stimulation of corticosterone and catecholamine secretion (Kuhn, Pauk, & Schanberg, 1990). Deprivation of the mother's regulatory influence may directly impact the pup's developing physiology, resulting in long-term changes in physiological stress responses

(Hofer, 1994). For nonhuman primates, maternal separation has been shown to result in long-term physiological changes including increases in heart rate (Reite, Kaemingk, & Boccia, 1989), plasma cortisol (Gunnar, Gonzalez, Goodlin, & Levine, 1981), cerebrospinal fluid monoamine concentrations (Higley, Suomi, & Linnoila, 1992), and cortisol reactivity during stress (Bayart, Hayashi, Raull, Barchas, & Levine, 1990).

Animal models also show that, independent of maternal separation, the quality of caregiving can also impact the development of physiological stress responses. Rosenblum and Andrews (1994) found that in nonhuman primate infants, erratic and dismissive parenting was associated with norepinephrine hyperreactivity. In contrast to the maladaptive consequences of poor caregiving, good-quality caregiving may promote the development of adaptive physiological responses to stress. Studies of early "handling" of rat pups have demonstrated that repeated, short maternal separations result in increased quality of maternal attention (Liu, Diorio, Day, Francis, & Meaney, 2000) and many beneficial long-term physiological alterations including lessened release and quicker return to baseline of glucocorticoids, in response to later novel stimuli (Meaney et al., 1993) and increased serotonin turnover in the rat frontal cortex and hippocampus (Mitchell, Iny, & Meaney, 1990). These same long-term benefits have been directly associated with higher quality maternal attention (Liu et al., 1997).

As reviewed above, evidence from animal models strongly suggests that early caregiving experiences can directly impact neurobiological development, in a manner that affects long-term physiological stress response systems. Although less conclusive, growing evidence from studies with human infants and children is supportive of findings from animal models. For human infants, appropriate responses of the caregiver may promote the development of adaptive physiological responses to stress. The primary caregiver plays a critical role in the regulation of stress responses by modulating the physiological arousal of infants as they explore the environment, and by soothing a child who becomes overly stressed and aroused (Streeck-Fisher & van der Kolk, 2000). Wright et al. (1993) associated greater family cohesion and expressiveness with lower cardiovascular reactivity to stress in young children. Stress responses to brief parental separations can be diminished in children by providing a sensitive, responsive alternative caregiver (Gunnar, Larson, Hertsgaard, Harris, & Brodersen, 1992).

3. High-risk family structures and characteristics

3.1. High-conflict families

In children and adolescents, a number of studies have associated physical health outcomes with high levels of parental or family conflict (Katz & Gottman, 1997; Mechanic & Hansell, 1989). High-conflict family experiences have also been linked to slower growth (Montgomery, Bartley, & Wilkinson, 1997) and greater health care utilization (Riley et al., 1993). Luecken and Fabricius (2003) reported that higher levels of early family conflict were associated with increased somatic symptoms, illness reports, and health care visits in young adults from intact families. Physiological outcomes associated with family conflict are also apparent. Children from high-conflict homes display elevated urinary catecholamines and blood pressure (Ballard, Cummings, & Larkin, 1993; Gottman & Katz, 1989). A recent study utilizing rigorous methodology found that children from high-conflict homes exhibited elevated cardiovascular reactivity to audiotaped arguments, an effect that was moderated by self-blame and appraisals of threat (El-Sheikh & Harger, 2001). Similarly, Flinn and England (1995) reported that

children from high-conflict families showed elevated basal cortisol and unusually high cortisol spikes in response to punishment, quarreling, and fighting. Children from high-conflict homes have also been shown to exhibit patterns of parasympathetic withdrawal, suggestive of maladaptive interactions with their environment (Salomen, Matthews, & Allen, 2000). In children, the ability to regulate arousal in response to family conflict may attenuate the potential negative impact (El-Sheikh & Harger, 2001; Katz & Gottman, 1997). Despite growing evidence with children, existing studies have not evaluated long-term physiological responses as a function of early family conflict, and it is unclear if the effects carryover into adulthood. However, some evidence suggests that severe conflict is associated with greater long-term risk of self-reported physical illness and distress (Lundberg, 1993; Rahkonen, Lahelma, & Muuhka, 1997).

3.2. Parental loss

Studies of the effects of early parental loss have typically focused on psychosocial outcomes (e.g., depression, marital stability), with some consensus that negative long-term outcomes are more likely if the quality of the relationship with the surviving parent is poor (Saler & Skolnick, 1992). Some studies have also found links between the experience of parental loss and long-term physical health outcomes. For example, Jacobs and Bovasso (2000) reported that maternal death (but not paternal death) during childhood was associated with greater risk of hospitalization for breast cancer, although the number of women in their sample who developed breast cancer was unusually small, warranting caution in the interpretation of findings. Large-scale epidemiological studies have been somewhat inconclusive. Krause (1998) reported that declines in physical health in older adults were related to the combination of early parental loss and high current stress. In contrast, Maier and Lachman (2000) found no relationship between early parental loss and health problems in midlife.

Few studies have examined physiological stress vulnerability associated with childhood parental loss. Breier (1989) reported that participants who lost a parent and experienced a major psychiatric disorder during adulthood had significantly higher resting levels of cortisol and beta-endorphin; however, parental loss in the absence of psychiatric disorder was not associated with physiological outcomes. Nicolson (2003) found elevated daily cortisol in middle-aged men who experienced early parental loss. Meinlschmidt et al. (2003) reported preliminary findings that cortisol response to repeated exposure to a psychosocial stressor showed less habituation over time in subjects who experienced the early loss of a close relative than in those without such experiences. Luecken (1998) reported that in young adults, early parental loss was associated with higher blood pressure relative to those from intact families. For those experiencing early parental loss, a poor relationship with the surviving parent was associated with significantly greater cortisol reactivity to a speech task (Luecken, 2000). Similar with existing literature on psychological outcomes, it seems likely that while parental loss alone may increase the risk of negative physiological outcomes, the impact will be stronger in the presence of cooccurring risks such as poor caregiving from the surviving parent.

3.3. Parental divorce

Children of divorce may experience multiple disruptions in caregiving, potentially elevating their risk of negative health consequences. Children of divorce generally experience a decrease in contact with both parents and, particularly, with the noncustodial parent (Amato, 1993). Parental divorce has also

been associated with lower quality of parent–child relationships over the long-term (Amato & Booth, 1996). A final risk factor lies in greater exposure to marital conflict, both before and after the divorce (Amato, 1993).

Existing research is sparse on the long-term health consequences of parental divorce and tends to be erratic in terms of measured outcomes and conclusions. Parental divorce was related to decreased longevity in a long-term follow-up of the Terman Life Cycle Study (Schwartz et al., 1995). However, despite the methodological strengths of this study, the Terman study participants were raised in the 1920s, and it is unclear how relevant the findings are to current children of divorce. Increased somatic symptoms have been reported in adolescents from divorced, relative to intact, families (Aro, Hanninen, & Paronen, 1989; Borkhuis & Patalano, 1997). Goede and Spruijt (1996) reported poorer health only in young adult females from divorced families relative to intact families. Parental divorce was associated with higher levels of chest pain during treadmill exercises in adult noncardiac patients (Lumley, Torosian, Ketterer, & Pickard, 1997). Maier and Lachman (2000) reported significantly higher levels of acute and chronic health problems in middle-aged adults as a function of early parental divorce, an effect that was mediated by current income, education, drug use, and family support. In contrast, Luecken and Fabricius (2003) found that adult children of divorce were equivalent to those from intact families on hostility, somatic complaints, and illness reports. However, for children of divorce, the perceived negativity of the divorce (strongly associated with parental conflict) predicted somatic symptoms, hostility, and illness reports. Divorce may be a proximal variable for disrupted caregiving, such that the experience of divorce in itself does not increase children's long-term vulnerability to physical illness unless the divorce is experienced as highly negative or results in a loss of contact with one parent. Research is lacking on the impact of parental divorce on vulnerability to the physiological consequences of stress exposure. Given the high divorce rate, the potential long-term health and vulnerability correlates of parental divorce remain important questions to be explored.

3.4. Abusive families

Negative psychological sequelae of child abuse, including anxiety disorders, depression, attention deficit hyperactivity disorder, and posttraumatic stress disorder (PTSD), have been well documented in children and adults (Streeck-Fischer & van der Kolk, 2000). In addition, a strong and growing area of research demonstrates long-term physical health outcomes associated with abusive treatment during childhood. Physical and sexual abuses have been associated with a variety of health outcomes including gastrointestinal illnesses (Leserman et al., 1996), poor health behaviors (Felitti et al., 1998; Nagy, Adcock, & Nagy, 1994), alcohol and substance abuse disorders (DeBellis, 2002), greater health care utilization (Sansone, Wiederman, & Sansone, 1997), poorer self-rated health (Felitti et al., 1998), fibromyalgia (Walker et al., 1997), and greater incidence of chronic illnesses (Felitti et al., 1998).

Increased health problems may be related to alterations in physiological stress response systems. Several well-controlled studies have reported dysregulated neuroendocrine responses in abused children (DeBellis et al., 1994; Kaufman et al., 1997), with effects that may last into adulthood. Heim et al. (2000) reported exaggerated neuroendocrine reactivity to stress in adult women with a history of sexual and/or physical abuse. Recently, Seeman et al. (2002) reported evidence that uncaring and/or abusive early parenting, along with negative, current social relationship quality, is associated with higher allostatic load in older adults. Heim and Nemeroff (2002) suggests that alterations in neurobiological stress response systems resulting from early abuse may be implicated in the pathophysiology of affective

disorders. However, neuroendocrine alterations associated with abuse are complex. Severe abuse is a risk factor for PTSD, and several studies suggest abnormal neurohormonal profiles of individuals with PTSD. In severely maltreated children, diverse patterns of neurohormonal activity have been noted, including increased cortisol (e.g., DeBellis et al., 1999; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002), elevated morning cortisol, lower morning cortisol, smaller decreases over the day, and elevated afternoon cortisol (Cicchetti & Rogosch, 2002), and diminished cortisol responses to distressing situations (Hart, Gunnar, & Cicchetti, 1995). Studies with adults with PTSD have documented both abnormally elevated (Maes et al., 1998) and lowered cortisol (Yehuda, Giller, Levengood, Southwick, & Siever, 1995) profiles. In combination, evidence suggests that early maltreatment can result in long-term dysregulated biological stress responses that increase vulnerability to both psychopathological and physical disorders (DeBellis, 2002). Even less severe physical punishment may influence physiological indices of stress. Recently, Bugental, Martorell, and Barraza (2003) reported that frequent corporal punishment was associated with higher cortisol reactivity to stress in infants, and mothers' emotional withdrawal was associated with elevated baseline cortisol.

3.5. Parental depression

The existence of parental depression increases the risk of poor quality caregiving, and as such may represent a proximal variable for disrupted caregiving. In general, the literature has been consistent in showing that parental depression is a significant risk factor for internalizing and externalizing disorders in children and adolescents (Anderson & Hammen, 1993; Goodman & Gotlib, 1999; Langrock, Compas, Keller, Merchant, & Copeland, 2002). Emotional and behavioral problems in children may be related to increased negative and inconsistent parenting behaviors, along with less supportive and affectionate behaviors from parents with depression (e.g., Gelfand & Teti, 1990; Lee & Gotlib, 1991). However, less is known about the potential influence of parental depression on children's physical health and physiological stress responses, much less any long-term effects. Several studies have found evidence of elevated cortisol in children with depressed mothers (Field et al., 1988, 1996) or mothers with high levels of stress or depression (Essex, Klein, Cho, & Kalin, 2002). Ashman, Dawson, Panagiotides, Yamada, and Wilkinson (2002) reported elevated cortisol responses to a stress challenge in children of depressed mothers who also exhibited internalizing symptoms.

3.6. Summary

Existing research with both animal and human participants provides intriguing evidence that physiological vulnerability to stress is influenced by characteristics of the early family environment. In particular, disruptions in early caregiving, as may occur following parental death or divorce, or inadequate caregiving, as can occur with parental conflict, abuse, or depression, can theoretically contribute to long-term dysregulated physiological stress responses. However, limited empirical research exists examining physiological responses following the family disruptions described above. Furthermore, the mechanisms behind the influence of early caregiving on long-term physiological responses have yet to be determined. There are multiple pathways by which early caregiving experiences might influence long-term physiological reactivity including genetic, psychosocial, and cognitive-affective. For example, early caregiving may interact with genetic predispositions, increase the risk of maladaptive psychosocial characteristics, or result in impaired self-regulatory abilities, each of which may impact the

regulation of physiological stress responses and ultimately affect physical health. Each potential pathway is briefly reviewed below.

4. Pathways to dysregulated physiological stress responses

4.1. Genetic pathway

Genetics and gene–environment interactions represent one plausible link among early caregiving and long-term physiological stress responses. Genetically informative studies can be used to tease apart genetic and environmental influences on individual differences and control for genetic links when considering the impact of the environment. Physiological functions relevant to stress responding may have a genetic component. For example, a meta-analysis of blood pressure data from twin pairs, full sibling pairs, and parent–offspring pairs indicated that heritability was around 40% (Iselius, Morton, & Rao, 1983). Results of studies on the heritability of cortisol secretion levels have been mixed. Wuest, Federenko, Hellhammer, and Kirschbaum (2000) reported a significant heritability of cortisol levels after awakening, but not on a profile of measures across the day. Bartels, de Geus, Sluyter, Kirschbaum, and Boomsma (2002) reported a significant genetic contribution to morning and afternoon basal cortisol levels. Molecular genetic studies are beginning to illustrate the causal impact that genotype has on HPA activity. Polymorphisms in the regulatory region of the corticotropin-releasing hormone (CRH) and the glucocorticoid-receptor genes have been identified, and their putative relationships to stress reactivity and disease susceptibility are being investigated. For example, Rosmond, Chagnon, Bouchard, and Bjorntorp (2001) reported significantly increased basal and reactive (during physiologic stress) cortisol levels in middle-aged Swedish men who were carriers of the rarer variants of both genes. Thus, incorporating gene–gene and gene–environment interactions into models will further elucidate the causal role of early environment on the stress response systems.

The development of psychosocial factors, such as depression or hostility, which may increase stress vulnerability in adulthood, also appears to contain a genetic component. From childhood to adolescence, heritability estimates for depression range from 30% to 80% and increase with age (Rice et al., 2002). In adults aged 70 years and older, estimates of heritability of depression range from 22% to 37% (McGue & Christensen, 2003). Thus, moderate genetic influences on individual differences in depression are maintained throughout the life span. Although relatively less studied, heritability estimates for hostility and associated aggressive behaviors have ranged from 28% to 47%, depending on the sample and method of measurement (Carmelli, Swan, & Rosenman, 1990; Coccaro, Bergeman, Kavoussi, & Seroczynski, 1997; Pedersen et al., 1989). Across all studies, the heritability of hostility and other Type A behaviors was significant, but moderate.

Perhaps less intuitive are findings that individual differences in caregiving contain a heritable component. Historically, parenting has been viewed as a strong environmental influence on development. However, genetically informative studies report that both subjective and objective measures of parenting contain genetic influence (Rende, Slomkowski, Stocker, Fulker, & Plomin, 1992). One mechanism of genetic influence on parenting is through parental traits. For example, genes influence parental personality and intelligence, which can influence parenting behaviors. High parent IQ is associated with an authoritative parenting style, which combines warmth with optimal levels of control, and has been associated with positive child outcomes (Losoya, Callor, Rowe, & Goldsmith, 1997).

Another means of genetic influence on parenting stems from the child. Genes influence child characteristics that, in turn, influence the parenting received. Inattentive, active children, for example, may elicit more monitoring and control from their parents. Children who are more genetically alike receive more similar parenting (Rowe, 1981, 1983). Retrospective reports from twins reared together or apart suggested that warmth/support and conflict were both heritable, with reared-apart identical twins rating their adoptive parents as more similar in treatment than reared-apart fraternal twins (Plomin, McLearn, Pedersen, Nesselroade, & Bergeman, 1989).

Similarly, the temperamental characteristics of children can influence both their physiological stress responses and the quality of caregiving they receive. Temperament is defined by Rothbart and Derryberry (1981) as constitutionally based individual differences that are influenced by heredity, experience, and maturation. Children with fearful or negative temperaments are more vulnerable to stress and demonstrate exaggerated physiological reactivity (Gunnar, Broderson, Krueger, & Rigatuso, 1996; Kagan, 2001). A temperamental style characterized by high levels of negativity also seems to attract more parental negativity and less warmth. Van den Boom (1989) found that more distress-prone infants had mothers that tended, over time, to play less with them and ignore them more. Children with difficult temperaments are also more adversely affected by family disruption (Hetherington & Stanley-Hagan, 1995). Easy children, on the other hand, elicit stronger relationships with adults and demonstrate increased resistance to stress (Werner, 1993). Temperament–environment interactions can either increase or buffer vulnerability to adverse outcomes (Bates, Pettit, Dodge, & Ridge, 1998). For example, children with difficult temperaments who receive sensitive, responsive caregiving, show decreased stress vulnerability (Gunnar, 1990). However, children with difficult temperaments may elicit harsher parenting, which may further increase vulnerability to negative health outcomes.

Genetic variations can render some individuals more vulnerable to long-term effects of early environmental experience than others. Particularly for vulnerable individuals, the early environment plays a critical role in gene expression, as documented by both animal and human studies. Monkeys with a short 5-HTT allele have impaired serotonergic function and are more severely affected by maternal deprivation (Bennett et al., 2000; Suomi, 2000). Those with the short allele, if peer reared, grew up to be socially anxious, easily emotionally aroused, fearful, aggressive, impulsive, and fell to the bottom of the dominance hierarchy. In contrast, these monkeys were behaviorally precocious and secure if reared by foster ‘‘super’’ mothers, demonstrating that early experience with caregivers can trigger gene expression in animals in ways that impact physiological stress responses. Aspects of the early environment have also been shown to modify gene expression in humans (Fonagy, 2001; Post, Weiss, & Leverich, 1994), although to our knowledge, no study has investigated how early caregiving can impact gene expression related to physiological stress responses.

4.2. Psychosocial pathway

Most studies of the neurobiological correlates of early caregiving have, by necessity, evaluated animal models. However, human children are likely to be affected on multiple levels by family relationships. A psychosocial pathway suggests that impaired early parent–child relationships can not only contribute to the development of negative psychological (e.g., depression, anxiety, hostility) and social characteristics (e.g., social isolation) which are in themselves significantly distressing, but also increase risk of the development of physical illness. Disturbances in attachment have been associated with a broad array of negative psychological outcomes, including low self-esteem, anxiety, poor social support networks,

increased aggression and hostility, depressive symptoms, and impaired coping (Houston and Vavak, 1991; Meyer, Chrousos, & Gold, 2001; Sandler et al., 1992). Several researchers have reported strong evidence from rigorous studies that trait hostility in children and young adults is associated with negative parental behaviors including rejection, low affection, conflict, and strict control (Houston & Vavak, 1991; Matthews, Woodall, Kenyon, & Jacob, 1996; Woodall & Matthews, 1993). Caring and affectionate parent–child relationships have been shown to be protective against the development of depression, while relationships characterized by rejection, strict control, conflict, and little affection are associated with depression in adulthood (Jacobsen, Fasman, & DiMascio, 1975; Oliver & Paull, 1995; Parker, 1983). The experience of interparental conflict can also negatively impact the development of protective family and social relationships (Brody, Stoneman, & Burke, 1987; Kerig, Cowan, & Cowan, 1993).

A diverse body of research has supported the role of psychosocial characteristics in heightened risk for cardiovascular and other physical illnesses. Hostility has been linked to increased sympathetic reactivity to stress, which may represent the biological mechanism by which hostility increases coronary heart disease (CHD) risk (Davis, Matthews, & McGrath, 2000; Engebretson & Matthews, 1992). Depression has been associated with increased risk of developing CHD (Anda, Williamson, & Jones, 1989), increased mortality in patients with CHD (Frasure-Smith, 2000), and increased sympathetic reactivity to stress (Heim & Nemeroff, 2002; Vieth, Lewis, & Linares, 1994). High levels of anxiety are also associated with increased risk of cardiovascular and other physical illnesses, potentially through increased sympathetic arousal and reactivity (Suin, 2001). In contrast, high-quality social relationships and a secure attachment style have both been implicated in lowering disease risk and may alter cardiovascular responses to stress (Christenfeld & Gerin, 2000; Uchino, Cacioppo, & Kiecolt-Glaser, 1996).

4.3. Cognitive-affective pathway

Cognitive and emotional self-regulatory abilities have been linked to vulnerability to psychological illness, although less is known about their impact on physiological processes. Human beings actively make attempts to self-regulate their responses to potential threat in their environments. Self-regulatory processes involve the regulation of sensory input, information processing, emotions, physiological arousal, and behavior (Compas, Connor, Osoweicki, & Welch, 1997; Eisenberg & Fabes, 1992; Eisenberg, Fabes, & Guthrie, 1997; Losoya, Eisenberg, & Fabes, 1998). Effective self-regulation has been linked to better coping with daily stressors (Davies & Cummings, 1994), lower levels of aggression and hostility (Taylor, Repetti, & Seeman, 1997), and better health behaviors (McCubbin, Needle, & Wilson, 1985).

Coping is recognized as a subset of the broader category of self-regulation. Although specific definitions of coping have varied, most include the effortful control of internal and external demands that tax an individual's resources (Lazarus & Launier, 1978). Definitions also emphasize the role of cognitive appraisals, such that situations that are uniquely appraised as threatening will elicit self-regulatory responses (Lazarus & Folkman, 1984). The ways in which individuals make sense of situations will influence both their behavioral and physiological responses. Biases in cognitive interpretation of experiences have been widely reported in depressed adults (Abramson, Seligman, & Teasdale, 1978), and aggressive youths (Dodge, Bates, & Pettit, 1990).

The emergence of adaptive coping and self-regulatory skills is a central task of development (Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001). Infants rely heavily on their

caregivers to assist them in regulating their emotions (reviewed in Bornstein, 2002). A number of studies have suggested that family experiences influence the development of self-regulatory ability in children (e.g., Eisenberg et al., 2001). In particular, limited parental affection and elevated family conflict have been associated with poor emotion regulation and maladaptive coping styles (Davies & Cummings, 1994). Fox (1989), in studies of infants and toddlers, associated vagal tone (indicating parasympathetic influence) with greater maternal affection, infant sociability, and better ability to regulate responses to the environment. In contrast, children who have been victims of chronic abuse exhibit severe deficiencies in the ability to effectively self-regulate emotion (Streeck-Fischer & van der Kolk, 2000). Abusive or harsh parenting is also associated with cognitive biases in the interpretation of others' behavior, which can then lead to future problems (Dodge & Schwartz, 1997). The cognitive-contextual model of Grych and Fincham (1990) theorizes that the impact of family conflict on children is mediated by cognitive appraisals and coping behaviors.

The tendency to make negative appraisals in ambiguous or neutral situations may result in maladaptive coping and exaggerated reactivity. It has been proposed that the effectiveness of coping responses can moderate physiological reactivity to stress (Taylor, Repetti, & Seeman, 1997), although surprisingly few empirical studies have specifically reported on the role of coping in physiological stress responses. Several researchers have reported that children who demonstrate negative appraisals in ambiguous social situations respond with greater aggression and increased cardiovascular reactivity (Chen & Matthews, 2001; Flory, Matthews, & Owen, 1998). However, these studies did not directly correlate coping with a specific situation with resulting reactivity. Children who have been exposed to chronic abuse may lack the ability to accurately appraise stimuli, resulting in inappropriate perceptions of threat and exaggerated fight-or-flight responses. Chen and Matthews (2003) hypothesize that children raised in unpredictable and stressful environments are more likely to view the world as a threatening place, leading to hypervigilance and the tendency to make threat appraisals in ambiguous situations. This tendency may lead to greater physiological reactivity and higher risk of stress-related illnesses.

Little is known about the long-term impact of early family experiences on self-regulatory ability. Cummings et al. (1994) suggest that repeated exposure to marital conflict leaves children primed to respond with increasingly negative emotion to later conflict situations. The emotional security hypothesis of Davies and Cummings (1994) suggests that past caregiving and conflict experiences exert a primary influence on future emotional and cognitive self-regulatory ability. It has been theorized that a stressful early family environment, resulting in impaired self-regulatory abilities, can lead to physiological hyperreactivity and vulnerability to poor psychological and physical health throughout the life span (Repetti et al., 2002; Streeck-Fisher & van der Kolk, 2000; Taylor, Repetti, & Seeman, 1997), although currently, little long-term empirical data are available to support or negate this theory. However, Larkin, Semenchuk, Frazer, Suchday, and Taylor (1998) provide preliminary evidence that an early family environment characterized by low cohesion and adaptability is associated with greater negative verbal behavior and elevated diastolic blood pressure during a stressful role-play task.

4.4. Summary

Existing research provides intriguing evidence that characteristics of the early family environment may be associated in the long term with dysregulated physiological stress responses and, ultimately, disease outcomes. Evidence to support three theoretical pathways linking early caregiving to physiological stress responses was reviewed. A *genetic* pathway is implicated because the expression of genetic

predispositions to stress vulnerability can be influenced by environmental experiences, because psychosocial risk factors contain a heritable component, and because genetic characteristics of the child and the parent can influence the quality of parenting provided. A *psychosocial* pathway is probable because early caregiving can impact the development of individual psychosocial characteristics such as depression or anxiety, which may increase or decrease vulnerability to stress. A *cognitive-affective* pathway suggests that early caregiving experiences influence the development of cognitive and emotional self-regulatory abilities and threat appraisals, which can then alter subsequent responses to stress.

5. Limitations in existing literature and directions for future research

There are a number of limitations to existing knowledge, which will be important to address in future studies. The pathways reviewed and illustrated in Fig. 1 provide the framework for understanding the long-term physiological outcomes associated with early caregiving experiences, yet it is highly unlikely that these pathways represent independent processes. Rather, each undoubtedly interacts and influences the others. For example, adverse early family relationships may affect the neurobiological organization of the brain, resulting in direct effects on physiological stress responses, but may also impair cognitive and emotional abilities to organize and understand information, resulting in dysfunctional cognitions and coping abilities, which may further affect stress responses. Furthermore, overlap may exist between the constructs in each pathway (e.g., genetic–temperamental factors may be associated with psychosocial traits). Although the purpose of the current review was to examine the plausibility of physiological stress responses as a mediator of the link between early caregiving and long-term physical health, it should be recognized that there may also be direct effects of each of the constructs in the pathways on physical health outcomes. The current review did not attempt to illustrate all links between early caregiving and long-term physical health; however, existing data strongly support the plausibility of physiological stress responses as one potential link. This field of study is in its early stages, and future research will need to take on the difficult task of examining an interactive model of the long-term consequences of early caregiving experiences.

We have illuminated a number of areas in which gaps exist in the knowledge of long-term physiological outcomes of early caregiving experiences. For example, although considerable research has demonstrated the potential impact of parental depression on children's psychological health, evidence of effects on physiological vulnerability and physical health is in its earliest stages. Similarly, although coping is recognized as an important aspect of self-regulatory ability, future research is needed examining the impact of coping styles on physiological responses to stress. More comprehensive studies that examine several concurrent aspects of self-regulation (i.e., cognitive, affective, behavioral, and physiological) are necessary to advance the understanding of the long-term health consequences of early caregiving. Further research into gene–environment interactions and the long-term impact on health is also needed. What remains to be answered is the extent to which genetic influences mediate the observed associations between early environment and long-time physiological stress vulnerability. Despite some evidence of heritability for caregiving, physiological indices, and health, genetically informed literature on the relations among these variables is scarce, and more studies are needed.

The correlational nature of most studies limits the conclusions that can be drawn. In particular, the processes involved in the relationships are as yet unknown, as are individual protective or vulnerability

factors. For example, beyond simple correlational studies linking parental death or divorce to long-term health outcomes, it is important to begin to understand the complex pre- and postloss factors (such as parental depression, changes in SES, or changes in family routines; e.g., Sandler et al., 1992) that may influence long-term vulnerability. It is also unknown which aspects of early care (e.g., affection, control) are most important in the development of physiological outcomes, and it is likely that the beneficial components of parental care will depend on a child's developmental level. The concept of "good enough" parenting (Scarr, 1992) suggests that the relationship of parenting to long-term outcomes may not be a linear one; yet, few studies go beyond a linear approach to consider the nonlinear influences of parenting on long-term physical health. Furthermore, potential mediators and moderators of these relationships have yet to be identified. Longitudinal and intervention studies will be necessary to tease apart the effects of variables that typically covary and to better understand the mediators and moderators of the impact of early caregiving on long-term health.

A common question that arises concerns the existence of critical periods in the developmental impact of early caregiving on physiological stress response systems. The evidence reviewed previously suggests that there may be permanent neurobiological alterations associated with early caregiving, which may have limited plasticity in response to later-life environments. However, few studies have found evidence for age differences in the impact of inadequate caregiving, and findings have been inconsistent. Recently, Essex et al. (2002) reported that elevated cortisol in children with highly stressed/depressed mothers was only evident in children exposed to maternal stress/depression in infancy, suggesting that early-life adversity was more strongly associated with neurobiological alterations than that occurring later in childhood. It is also unclear how later environment and social relationships can ameliorate or exacerbate the consequences of negative early environments. Some studies have noted profound improvements following adoption in children exposed to extremely deprived early environments (Croft et al., 2001; Rutter, 1998), suggesting that interventions later in life may be able to reverse at least some of the health consequences of inadequate early caregiving.

A major limitation of the existing literature is the lack of studies on cultural influences on parenting styles, family structures, and social norms of families and parents, and their unique associations with health outcomes. Few, if any, studies have closely examined ethnic group differences in the relations of early caregiving and long-term physiological stress responses or long-term physical health. It is not clear if conclusions formed about health outcomes associated with parental loss, for example, can be generalized to diverse ethnic groups. Cultural differences in extended-family housing and caregiving styles may vastly impact long-term outcomes. For example, the ready availability of alternative attachment figures may moderate the potential negative impact of a number of high-risk family situations.

A number of limitations in the current literature extend to measurement issues. Existing research on long-term health outcomes has largely relied on retrospective reports of early family environment. The validity of retrospective reports is often called into question, leading many researchers and clinicians to ignore early experience as a causative factor in psychological and physical illness (Brewin, Andrews, & Gotlib, 1993). A common concern is that current negative affectivity might bias participants towards reporting more difficult early family experiences. Measurement limitations are also apparent in the classification of health outcomes. Again, retrospective reports are often relied upon in the form of checklists of current or past health problems. Brewin et al. (1993) conducted a review of literature addressing retrospective reports, with the conclusion that there is little evidence that retrospective reports are inherently inaccurate, even among those experiencing current psychopathological symptoms.

Nonetheless, lingering doubts remain, and it will be important to clarify the reliability of retrospective reports and to conduct prospective studies of early caregiving and long-term health consequences. Ultimately, longitudinal designs will be necessary to understand the complex mix of risk and protective factors associated with long-term health outcomes.

A further limitation is in the measurement of physiological stress responses. For many reasons, the existing literature has largely focused on easily accessible measures of physiological stress responses, primarily salivary cortisol and noninvasive blood pressure monitoring. A large number of physiological changes occur in response to threat, including interactions between systems to either enhance or suppress activity in other systems. However, invasive techniques (e.g., blood draws) are required to measure most aspects of the body's stress response. It is clear that while they are important aspects of physiological stress vulnerability, to focus exclusively on cortisol or blood pressures as mechanisms is an oversimplification. It will be important to expand this model as measurement techniques advance.

An early focus in the stress-response literature has been on the magnitude of reactivity as a risk factor. However, as Gunnar and Donzella (2002) note, complex alterations in neuroendocrine function, including flattened diurnal rhythms, may result from inadequate early caregiving. The allostatic load hypothesis emphasizes that it is dysregulation in stress responses, rather than simply elevated reactivity, that increases long-term health risk. Studies that fail to find greater cortisol reactivity may wrongly conclude a lack of association with early-life stress (Gunnar & Vazquez, 2001), making it imperative to advance the measurement techniques and understanding of the complicated relations between early caregiving and physiology.

6. Conclusions

Early caregiving clearly exerts influences that can last a lifetime. The evidence reviewed demonstrates that the impact of caregiving experiences extends beyond psychological outcomes, as have traditionally been studied, to neurobiological and physiological outcomes that can impact long-term physical health. This is an exciting time for the field of research on early experience. Accumulating evidence demonstrates relations between disrupted or inadequate parenting and a host of cognitive, affective, behavioral, and physiological outcomes. Long-term studies provide intriguing preliminary evidence that these relations may last long into adulthood. Alterations in physiological stress responses may represent a mechanism linking early experiences to long-term health outcomes. Multiple pathways exist by which early caregiving may affect physiological responses and long-term health. These pathways include genetic mediation and gene–environment interactions, such as the ability of caregiving experiences to influence the expression of genes that may render a child, more or less, vulnerable to stress. A psychosocial pathway suggests that early parenting contributes to the development of psychosocial characteristics that may alter stress vulnerability. Finally, a cognitive-affective pathway suggests that parenting experiences influence cognitive or emotional responses to stress, which then influence physiological responses. We have illustrated a number of areas in need of further empirical data, with the hope of inspiring future research to help fill in the gaps and further understanding of how early experiences impact long-term physiological processes. The implications for at-risk children are enormous. For example, knowledge of the influence of caregiving on the development of self-regulatory stress responses will assist in defining specific targets and techniques for intervention with those whose early life experiences render them vulnerable to stress-related illness. The evidence reviewed above

suggests that early intervention with vulnerable children may have beneficial effects on physiological stress responses and, ultimately, on physical health throughout the life span.

References

Abramson, L. Y., Seligman, M. E., & Teasdale, J. D. (1978). Learned helplessness in humans: Critique and reformulation. *Journal of Abnormal Psychology*, *87*, 49–74.

Amato, P. (1993). Children's adjustment to divorce: Theories, hypotheses, and empirical support. *Journal of Marriage and Family*, *55*, 23–28.

Amato, P. R., & Booth, A. (1996). A prospective study of divorce and parent–child relationships. *Journal of Marriage and Family*, *58*, 356–365.

Anda, R. F., Williamson, D. F., & Jones, D. (1989). Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. *Epidemiology*, *4*, 285–294.

Anderson, C. A., & Hammen, C. (1993). Psychosocial outcomes of children of unipolar depressed, bipolar, medically ill, and normal women: A longitudinal study. *Journal of Consulting and Clinical Psychology*, *61*, 448–454.

Aro, H., Hanninen, V., & Paronen, O. (1989). Social support, life events, and psychosomatic symptoms among 14–16 year-old adolescents. *Social Science and Medicine*, *29*, 1051–1056.

Ashman, S. B., Dawson, G., Panagiotides, H., Yamada, E., & Wilkinson, C. W. (2002). Stress hormone levels of children of depressed mothers. *Development and Psychopathology*, *14*, 333–349.

Ballard, M. E., Cummings, E. M., & Larkin, K. (1993). Emotional and cardiovascular responses to adult's angry behavior and challenging tasks in children of hypertensive and normotensive parents. *Child Development*, *64*, 500–515.

Bartels, M., de Geus, E. J. C., Sluyter, F., Kirschbaum, C., & Boomsma, D. I. (2003). Heritability of daytime cortisol in children. *Behavior Genetics*, *33*, 421–433.

Bates, J. E., Pettit, G. S., Dodge, K. A., & Ridge, B. (1998). Interaction of temperamental resistance to control and restrictive parenting in the development of externalizing behavior. *Developmental Psychology*, *34*, 982–995.

Bayart, F., Hayashi, K. T., Raull, K. F., Barchas, J. D., & Levine, S. (1990). Influence of maternal proximity on behavioral and physiological responses to separation in infant rhesus monkeys. *Behavioral Neuroscience*, *104*, 98–107.

Bennett, A. J., Lesch, K. P., Heils, A., Long, J., Lorenz, J., Shoaf, S. E., Suomi, S. J., Linnoila, M., Higley, J. D. (2000). *Serotonin transporter gene variation, strain and early rearing environment affect CSF 5-HIAA concentrations in rhesus monkeys (Macaca mulatta)*. Unpublished manuscript.

Borkhuis, G. W., & Patalano, F. (1997). MMPI personality differences between adolescents from divorced and non-divorced families. *Psychology: A Journal of Human Behavior*, *34*, 37–41.

Bornstein, M. H. (Ed.) (2002). *Parenting and the development of children's self-regulation. Handbook of parenting* (2nd ed.). *Practical issues in parenting vol. 5* (pp. 89–110). NJ: Lawrence Erlbaum Associates.

Breier, A. (1989). Experimental approaches to human stress research: Assessment of neurobiological mechanisms of stress in volunteers and psychiatric patients. *Biological Psychiatry*, *26*, 438–462.

Brewin, C. R., Andrews, B., & Gotlib, I. H. (1993). Psychopathology and early experience: A reappraisal of retrospective reports. *Psychological Bulletin*, *113*, 82–98.

Brody, G. H., Stoneman, Z., & Burke, M. (1987). Child temperaments, maternal differential behavior, and sibling relationships. *Developmental Psychology*, *23*, 354–362.

Bugental, D. B., Martorell, G. A., & Barraza, V. (2003). The hormonal costs of subtle forms of infant maltreatment. *Hormones and Behavior*, *43*, 237–344.

Carmelli, D., Swan, G. E., & Rosenman, R. H. (1990). The heritability of the cook and medley hostility scale revisited. *Journal of Social Behavior and Personality*, *5*, 107–116.

Coccaro, E. F., Bergeman, C. S., Kavoussi, R. J., & Seroczynski, A. D. (1997). Heritability of aggression and irritability: A twin study of the Buss–Durkee aggression scales in adult male subjects. *Biological Psychiatry*, *41*, 273–284.

Chen, E., & Matthews, K. A. (2001). Cognitive appraisal biases: An approach to understanding the relation between socioeconomic status and cardiovascular reactivity in children. *Annals of Behavioral Medicine*, *23*, 101–111.

Chen, E., & Matthews, K. A. (2003). Development of the cognitive appraisal and understanding of social events (CAUSE) videos. *Health Psychology*, *22*, 106–110.

Christenfeld, N., & Gerin, W. (2000). Social support and cardiovascular reactivity. *Biomedicine and Pharmacotherapy*, *54*(5), 251–257.

Cicchetti, D., & Rogosch, F. A. (2002). Diverse patterns of neuroendocrine activity in maltreated children. *Developmental Psychopathology*, *13*(3), 677–693.

Compas, B. E., Connor, J. K., Osowiechi, D. N., & Welch, A. (1997). Effortful and involuntary responses to stress: Implications for coping with chronic stress. In B. Gottlieb (Ed.), *Coping with chronic stress* (pp. 105–132). New York: Plenum.

Compas, B. E., Connor-Smith, J. K., Saltzman, H., Thomsen, A. H., & Wadsworth, M. E. (2001). Coping with stress during childhood and adolescence: Progress, problems, and potential in theory and research. *Psychological Bulletin*, *127*, 87–127.

Croft, C., O'Connor, T. G., Keaveney, L., Groothues, C., Rutter, M., and the English and Romanian Adoption Study Team (2001). Longitudinal change in parenting associated with developmental delay and catch-up. *Journal of Child Psychology and Psychiatry*, *42*(5), 649–659.

Cummings, E. M., Davies, P. T., & Simpson, K. S. (1994). Marital conflict, gender, and children's appraisals and coping efficacy as mediators of child adjustment. *Journal of Family Psychology*, *8*, 141–149.

Davies, P. T., & Cummings, E. M. (1994). Marital conflict and child adjustment: An emotional security hypothesis. *Psychological Bulletin*, *116*, 387–411.

Davis, M. C., Matthews, K. A., & McGrath, C. E. (2000). Hostile attitudes predict elevated vascular resistance during interpersonal stress in men and women. *Psychosomatic Medicine*, *62*, 17–25.

DeBellis, M. D. (2002). Developmental traumatology: A contributory mechanism for alcohol and substance use disorders. *Psychoneuroendocrinology*, *27*, 155–170.

DeBellis, M. D., Baum, A. S., Birmaher, B., Keshavan, M. S., Eccard, C. H., Boring, A. M., Jenkins, F. J., & Ryan, N. D. (1999). Developmental traumatology: Part 1. Biological stress systems. *Biological Psychiatry*, *9*, 1259–1270.

DeBellis, M. D., Chrousos, G. P., Dorn, L. D., Burke, L., Helmers, K., Kling, M. A., Trickett, P. K., & Putman, F. W. (1994). Hypothalamic–pituitary–adrenal axis dysregulation in sexually abused girls. *Journal of Clinical Endocrinology and Metabolism*, *78*, 249–255.

Dodge, K. A., Bates, J. E., & Pettit, G. S. (1990). Mechanisms in the cycle of violence. *Science*, *250*, 1678–1683.

Dodge, K. A., & Schwartz, D. (1997). Social information processing mechanisms in aggressive behavior. In D. M. Stoff, & J. Breiling's (Eds.), *Handbook of antisocial behavior* (pp. 171–180). New York, NY: Wiley.

Eisenberg, N., & Fabes, R.A. (1992). Emotion, regulation, and the development of social competence. In M. S. Clark (Ed.), *Review of personality and social psychology: Emotion and social behavior* (pp. 119–150). Newbury Park, CA: Sage Publications.

Eisenberg, N., Fabes, R. A., & Guthrie, I. (1997). Coping with stress: The roles of regulation and development. In J. N. Sandler, & S. A. Wolchik (Eds.), *Handbook of children's coping with common stressors: Linking theory, research, and intervention* (pp. 41–70). New York: Plenum.

Eisenberg, N., Losoya, S., Fabes, R. A., Guthrie, I. K., Reiser, M., Murphy, B., Shepard, S. A., Poulin, R., & Padgett, S. J. (2001). Parental socialization of children's dysregulated expression of emotion and externalizing problems. *Journal of Family-Psychology*, *15*(2), 183–205.

El-Sheikh, M., & Harger, J. (2001). Appraisals of marital conflict and children's adjustment, health, and physiological reactivity. *Developmental Psychology*, *37*, 875–885.

Engebretson, T. O., & Matthews, K. A. (1992). Dimensions of hostility in men, women, and boys: Relationships to personality and cardiovascular responses to stress. *Psychosomatic Medicine*, *54*, 311–323.

Essex, M. J., Klein, M. H., Cho, E., & Kalin, N. H. (2002). Maternal stress beginning in infancy may sensitize children to later stress exposure: Effects on cortisol and behavior. *Biological Psychiatry*, *52*, 776–784.

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., Koss, M. P., & Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. *American Journal of Preventive Medicine*, *14*, 245–258.

Field, T., Grizzle, N., Scafidi, F., Abrams, S., Richardson, S., Kuhn, C., & Schanberg, S. (1996). Massage therapy for infants of depressed mothers. *Infant Behavior and Development*, *19*, 107–112.

Field, T., Healy, B., Goldstein, S., Perry, S., Bendell, D., Schanberg, S., Zimmerman, E. A., & Kuhn, C. (1988). Infants of depressed mothers show 'depressed' behavior even with nondepressed adults. *Child Development*, *59*, 1569–1579.

Flinn, M. V., & England, B. G. (1995). Childhood stress and family environment. *Current Anthropology*, *5*, 854–866.

Flory, J. D., Matthews, K. A., & Owens, J. F. (1998). A social information processing approach to dispositional hostility:

Relationships with negative mood and blood pressure elevations at work. *Journal of Social and Clinical Psychology*, *17*, 491–504.

Fonagy, P. (2001). The human genome and the representational world: The role of early mother–infant interaction in creating an interpersonal interpretive mechanism. *Bulletin of the Menninger Clinic*, *65*, 427–448.

Fox, N. A. (1989). Psychophysiological correlates of emotional reactivity during the first year of life. *Developmental Psychology*, *25*, 364–372.

Frasure-Smith, N. (2000). Social support, depression, and mortality during the first year after myocardial infarction. *Circulation*, *101*, 1919–1924.

Gelfand, D. M., & Teti, D. M. (1990). The effects of maternal depression on children. *Clinical Psychology Review*, *10*, 329–353.

Georgiades, A., Lemne, C., De Faire, U., Kindvall, K., & Fredrikson, M. (1997). Stress-induced blood pressure measurements predict left ventricular mass over three years among borderline hypertensive men. *European Journal of Clinical Investigations*, *27*, 733–739.

Goede, M., & Spruijt, E. (1996). Effects of parental divorce and youth unemployment on adolescent health. *Patient Education and Counseling*, *29*, 269–276.

Goodman, S. H., & Gotlib, I. H. (1999). Risk for psychopathology in the children of depressed mothers: A developmental model for understanding mechanisms of transmission. *Psychological Review*, *106*, 458–490.

Gottman, J. M., & Katz, L. F. (1989). Effects of marital discord on young children's peer interaction and health. *Developmental Psychology*, *25*, 373–381.

Grych, J. H., & Fincham, F. D. (1990). Marital conflict and children's adjustment: A cognitive-contextual framework. *Psychological Bulletin*, *108*, 267–290.

Gunnar, M. R. (1990). *The psychobiology of infant temperament*. Hillsdale, NJ: Erlbaum.

Gunnar, M. R., Broderson, L., Krueger, K., & Rigatuso, J. (1996). Dampening of adrenocortical responses during infancy: Normative changes and individual differences. *Child Development*, *67*, 877–889.

Gunnar, M. R., & Donzella, B. (2002). Social regulation of the cortisol levels in early human development. *Psychoneuroendocrinology*, *27*, 199–220.

Gunnar, M. R., Gonzalez, C. A., Goodlin, B. L., & Levine, S. (1981). Behavioral and pituitary–adrenal responses during a prolonged separation period in infant rhesus macaques. *Psychoneuroendocrinology*, *6*, 65–75.

Gunnar, M. R., Larson, M., Hertsgaard, L., Harris, M., & Brodersen, L. (1992). The stressfulness of separation among 9-month infants: Effects of social context variables and infant temperament. *Child Development*, *63*, 290–303.

Gunnar, M. R., & Vazquez, D. M. (2001). Low cortisol and a flattening of expected daytime rhythm: Potential indices of risk in human development. *Developmental Psychopathology*, *13*(3), 515–538.

Hart, J., Gunnar, M. R., & Cicchetti, D. (1995). Salivary cortisol in maltreated children: Evidence of relations between neuroendocrine activity and social competence. *Developmental Psychopathology*, *7*, 11–26.

Heim, C., & Nemeroff, C. B. (2002). Neurobiology of early life stress. *Seminars in Clinical Neuropsychiatry*, *7*, 147–159.

Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., Miller, A. H., & Nemeroff, C. B. (2000). Pituitary–adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *Journal of the American Medical Association*, *284*, 592–597.

Hetherington, E. M., & Stanley-Hagan, M. M. (1995). Parenting in divorced and remarried families. In M. H. Bornstein (Ed.), *Handbook of parenting. Status and social conditions of parenting, vol. 3* (pp. 233–54). Hillsdale, NJ, England: Lawrence Earlbaum Associates.

Higley, J. D., Suomi, S. J., & Linnoila, M. (1992). A longitudinal assessment of CSF monoamine metabolite and plasma cortisol concentrations in young rhesus monkeys. *Society of Biological Psychiatry*, *32*, 127–145.

Hofer, M. A. (1994). Early relationships as regulators of infant physiology and behavior. *Acta Pediatrica Supplement*, *397*, 9–18.

Houston, B. K., & Vavak, C. R. (1991). Cynical hostility: Developmental factors, psychosocial correlates, and health behaviors. *Health Psychology*, *10*, 9–17.

Ironson, G., Solomon, G. F., Balbin, E. G., O'Cleirigh, C., George, A., Kumar, M., Larson, D., & Woods, T. E. (2002). The Ironson–Woods Spirituality/Religiousness Index is associated with long survival, health behaviors, less distress, and low cortisol in people with HIV/AIDS. *Annals of Behavioral Medicine*, *24*(1), 34–48.

Iselius, L., Morton, N. E., & Rao, D. C. (1983). Family resemblance for blood pressure. *Human Heredity*, *33*, 277–286.

Jacobs, J. R., & Bovasso, G. B. (2000). Early and chronic stress and their relation to breast cancer. *Psychological*, 669–678.

Jacobson, S., Fasman, J., & DiMascio, A. (1975). Deprivation in the childhood of depressed women. *Journal of Nervous and Mental Disorders*, *160*, 5–14.

Kagan, J. (2001). Temperamental contributions to affective and behavioral profiles in childhood. In S. G. Hofmann, & P. M. DiBartolo (Eds.), *From social anxiety to social phobia: Multiple perspectives* (pp. 216–234). Needham Heights, MA, USA: Allyn and Baconm.

Kaufman, J., Birmaher, B., Perel, J., Dahl, R. E., Moreci, P., Nelson, B., Wells, W., & Ryan, N. D. (1997). The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. *Biological Psychiatry*, *42*, 669–679.

Katz, L. F., & Gottman, J. M. (1997). Buffering children from marital conflict and dissolution. *Journal of Clinical Child Psychology*, *26*, 157–171.

Kerig, P. K., Cowan, P. A., & Cowan, C. P. (1993). Marital quality and gender differences in parent–child interaction. *Developmental Psychology*, *29*, 931–939.

Krause, N. (1998). Early parental loss, recent life events, and changes in health among older adults. *Journal of Aging and Health*, *10*, 395–421.

Kuhn, C. M., Pauk, J., & Schanberg, S. (1990). Endocrine responses to mother–infant separation in developing rats. *Developmental Psychobiology*, *23*, 395–410.

Langrock, A. M., Compas, B. E., Keller, G., Merchant, M. J., & Copeland, M. E. (2002). Coping with the stress of parental depression: Parent reports of children's coping, emotional, and behavioral problems. *Journal of Clinical Child and Adolescent Psychology*, *31*, 312–324.

Larkin, K. T., Semenchuk, E. M., Frazer, N. L., Suchday, S., & Taylor, R. L. (1998). Cardiovascular and behavioral response to social confrontation: Measuring real-life stress in the laboratory. *Annals of Behavioral Medicine*, *20*, 294–301.

Lazarus, R. S., & Launier, R. (1978). Stress-related transactions between person and environment. In L. A. Pervin, & M. Lewis (Eds.), *Perspectives in international psychology* (pp. 287–327). New York: Plenum.

Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal, and coping*. New York: Springer.

Lee, C., & Gotlib, I. H. (1991). Adjustment of children of depressed mothers: A 10-month follow-up. *Journal of Abnormal Psychology*, *100*, 473–477.

Leserman, J., Drossman, D. A., Li, Z., Toomey, T. C., Nachman, G., & Glogau, L. (1996). Sexual and physical abuse history in gastroenterology practice: How types of abuse impact health status. *Psychosomatic Medicine*, *58*(1), 4–15.

Liu, D., Diorio, J., Day, J. C., Francis, D. D., & Meaney, M. J. (2000). Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature Neuroscience*, *3*, 799–806.

Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., Sharma, S., Pearson, D., Plotsky, P. M., & Meaney, M. J. (1997). Maternal care, hippocampal glucocorticoid receptors, and hypothalamic–pituitary–adrenal responses to stress. *Science*, *12*, 1659–1662.

Losoya, S. H., Callor, S., Rowe, D. C., & Goldsmith, H. H. (1997). Origins of familial similarity in parenting: A study of twins and adoptive siblings. *Developmental Psychology*, *33*, 1012–1023.

Losoya, S., Eisenberg, N., & Fabes, R. A. (1998). Developmental issues in the study of coping. *International Journal of Behavioral Development*, *22*, 287–313.

Luecken, L. J. (1998). Childhood attachment and loss experiences affect adult cardiovascular and cortisol function. *Psychosomatic Medicine*, *60*, 765–772.

Luecken, L. J. (2000). Parental caring and loss during childhood and adult cortisol responses to stress. *Psychology and Health*, *15*, 841–851.

Luecken, L. J., & Fabricius, B. (2003). Physical health vulnerability in adult children from divorced and intact families. *Journal of Psychosomatic Research*, *55*, 221–228.

Lumley, M. A., Torosian, T., Ketterer, M. W., & Pickard, S. D. (1997). Psychosocial factors related to noncardiac chest pain during treadmill exercise. *Psychosomatics*, *38*, 230–238.

Lundberg, O. (1993). The impact of childhood living conditions on illness and mortality in adulthood. *Social Science and Medicine*, *36*, 1047–1052.

Lynch, J. W., Everson, S. A., Kaplan, G. A., Salonen, R., & Salonen, J. T. (1998). Does low socioeconomic status potentiate the effects of heightened cardiovascular responses to stress on the progression of carotid atherosclerosis? *American Journal of Public Health*, *88*, 389–394.

Maier, E. H., & Lachman, M. E. (2000). Consequences of early parental loss and separation for health and well-being in midlife. *International Journal of Behavioral Development*, *24*, 183–189.

Maes, M., Lin, A., Bonaccorso, S., van Hunsel, F., Van Gastel, A., Delmeire, L., Biondi, M., Bosmans, E., Kenis, G., & Scharpe, S. (1998). Increased 24-hour urinary cortisol excretion in patients with post-traumatic stress disorder

and patients with major depression, but not in patients with fibromyalgia. *Acta Psychiatrica Scandinavica*, *98*(4), 328–335.

Manuck, S. B., Kasprowicz, A. L., & Muldoon, M. F. (1990). Behaviorally-evoked cardiovascular reactivity and hypertension: Conceptual issues and potential associations. *Annals of Behavioral Medicine*, *12*, 17–29.

Markovitz, J. H., & Matthews, K. A. (1991). Platelets and coronary heart disease: Potential physiologic reaction. *Psychosomatic Medicine*, *53*(6), 643–668.

Matthews, K. A., Woodall, K. L., Kenyon, K., & Jacob, T. (1996). Negative family environment as a predictor of boys' future status on measures of hostile attitudes, interview behavior, and anger expression. *Health Psychology*, *15*, 30–37.

McCubbin, H. I., Needle, R. H., & Wilson, M. (1985). Adolescent health risk behaviors: Family stress and adolescent coping as critical factors. *Family Relations*, *34*, 51–62.

McGue, M., & Christensen, K. (2003). The heritability of depression symptoms in elderly Danish twins: Occasion-specific versus general effects. *Behavior Genetics*, *33*, 83–93.

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences*, *840*, 33–44.

McEwen, B. S. (2002). Sex, stress, and the hippocampus: Allostasis, allostatic load, and the aging process. *Neurobiology of Aging*, *23*, 921–939.

McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostatis in biology and biomedicine. *Hormones and Behavior*, *42*, 2–15.

Meaney, M. J., Bhatnagar, S., Diorio, J., Larocque, S., Francis, D., O'Donnell, D., Shanks, N., Sharma, S., Smythe, J., & Viau, V. (1993). Molecular basis for the development of individual differences in the hypothalamic–pituitary–adrenal stress response. *Cellular and Molecular Neurobiology*, *13*, 321–346.

Meaney, M. J., Brake, W., & Gratton, A. (2002). Environmental regulation of mesolimbic dopamine systems: A neurobiological mechanism for vulnerability to drug abuse? *Psychoneuroendocrinology*, *27*, 127–138.

Mechanic, D., & Hansell, S. (1989). Divorce, family conflict, and adolescent's well-being. *Journal of Health and Social Behavior*, *30*, 106–116.

Meinlschmidt, G., Federenko, I., Hellhammer, D. H., Wüst, S., & Heim, C. (2003). Early loss experiences influence habituation of the hypothalamus–pituitary–adrenal (HPA)-axis responses to repeated psychosocial stress in adulthood. Poster presented at the XXXIV ISPNE Meeting, New York City.

Meyer, S. E., Chrousos, G. P., & Gold, P. W. (2001). Major depression and the stress system: A life-span perspective. *Development and Psychopathology*, *13*, 565–580.

Mitchell, J. B., Iny, L. J., & Meaney, M. J. (1990). The role of serotonin in the development and environmental regulation of hippocampal Type II corticosteroid receptors. *Developmental Brain Research*, *55*, 231–235.

Montgomery, S. M., Bartley, M. J., & Wilkinson, R. G. (1997). Family conflict and slow growth. *Archives of Disease in Children*, *77*, 326–330.

Nagy, S., Adcock, A. G., & Nagy, M. C. (1994). A comparison of risky health behaviors of sexually active, sexually abused, and abstaining adolescents. *Pediatrics*, *93*(4), 570–575.

Nicolson, N. (2003). *Childhood parental loss and adult cortisol levels* (submitted manuscript).

Oliver, J. M., & Paull, J. C. (1995). Self-esteem and self-efficacy: Perceived parenting and family climate and depression in university students. *Journal of Clinical Psychology*, *51*, 467–481.

Parker, G. (1983). Parental "affectionless control" as an antecedent to adult depression. *Archives of General Psychiatry*, *134*, 138–147.

Pedersen, N. L., Lichtenstein, P., Plomin, R., DeFaire, U., McClearn, G. E., & Matthews, K. A. (1989). Genetic and environmental influences for type A-like measures and related traits: A study of twins reared apart and twins reared together. *Psychosomatic Medicine*, *51*, 428–440.

Plomin, R., McClearn, G., Pedersen, N. L., Nesselroade, J. R., & Bergeman, C. S. (1989). Genetic influences on adults' ratings of their current family environment. *Journal of Marriage and the Family*, *51*, 791–803.

Post, R. M., Weiss, S. R. B., & Leverich, G. S. (1994). Recurrent affective disorder: Roots in developmental neurobiology and illness progression based on changes in gene expression. *Development and Psychopathology*, *6*, 781–813.

Rahkonen, O., Lahelma, E., & Huuhka, M. (1997). Past or present? Childhood living conditions and current socioeconomic status as determinants of adult health. *Social Science and Medicine*, *44*, 327–336.

Reite, M., Kaemingk, K., & Boccia, M. L. (1989). Maternal separation in bonnet monkey infants: Altered attachment and social support. *Child Development*, *60*, 473–480.

Rende, R. D., Slomkowski, C. L., Stocker, C., Fulker, D. W., & Plomin, R. (1992). Genetic and environmental influences on maternal and sibling interaction in middle childhood: A sibling adoption study. *Developmental Psychology*, *28*, 484–490.

Repetti, R. L., Taylor, S. E., & Seeman, T. E. (2002). Risky families: Family social environments and the mental and physical health of offspring. *Psychological Bulletin*, *128*(2), 330–366.

Rice, F., Harold, G., & Thapar, A. (2002). The genetic aetiology of childhood depression: A review. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *43*, 65–79.

Riley, A. W., Finney, E., Mellits, D., Starfield, B., Kidwell, S., Quaskey, S., Cataldo, M. F., Filipp, L., & Shematek, J. P. (1993). Determinants of children's health care use: An investigation of psychosocial factors. *Medical Care*, *31*, 767–783.

Rosenblum, L. A., & Andrews, M. W. (1994). Influences of environmental demand on maternal behavior and infant development. *Acta Paediatrica Supplement*, *397*, 57–63.

Rosmond, R., Chagnon, M., Bouchard, C., & Bjorntorp, P. (2001). A polymorphism in the regulatory region of the corticotrophin-releasing hormone gene in relation to cortisol secretion, obesity, and gene–gene interaction. *Metabolism*, *50*, 1059–1062.

Rothbart, M. K., & Derryberry, D. (1981). Development of individual differences in temperament. In M. E. Lamb, & A. L. Brown (Eds.), *Advances in developmental psychology, vol. 1* (pp. 37–86). Hillsdale, NJ: Erlbaum.

Rowe, D. C. (1981). Environmental and genetic influences on dimensions of perceived parenting: A twin study. *Developmental Psychology*, *17*, 203–208.

Rowe, D. C. (1983). A biometric analysis of perceptions of family environment: A study of twins and singleton sibling kinships. *Child Development*, *54*, 416–423.

Russek, L. G., & Schwartz, G. E. (1997). Perceptions of parental caring predict health status in midlife: A 35-year follow-up of the Harvard Mastery of Stress Study. *Psychosomatic Medicine*, *59*, 144–149.

Rutter, M. (1998). Developmental catch-up and deficit following adoption after severe global early privation. *Journal of Child Psychology and Psychiatry*, *39*(4), 465–476.

Saler, L., & Skolnick, N. (1992). Childhood parental death and depression in adulthood: Roles of surviving parent and family environment. *American Journal of Orthopsychiatry*, *62*, 504–516.

Salomen, K., Matthews, K. A., & Allen, M. T. (2000). Patterns of sympathetic and parasympathetic reactivity in a sample of children and adolescents. *Psychophysiology*, *37*, 842–849.

Sandler, I. N., West, S. G., Baca, L., Pillow, D. R., Gerstein, J. C., Rogosch, F., Virdin, L., Beals, J., Reynolds, K. D., Kallgren, C., Tein, J. Y., Kriege, G., Cole, E., & Ramirez, R. (1992). Linking empirically based theory and evaluation: The Family Bereavement Program. *American Journal of Community Psychology*, *20*, 491–521.

Sansone, R. A., Wiederman, M. W., & Sansone, L. A. (1997). Health care utilization and history of trauma among women in a primary care setting. *Violence and Victims*, *12*(2), 165–172.

Scarr, S. (1992). Presidential address: Developmental theories of the 1990s: Development and individual differences. *Child Development*, *63*, 1–19.

Schwartz, J. E., Friedman, H. S., Tucker, J. S., Tomlinson-Keasey, C., Wingard, D. L., & Criqui, M. H. (1995). Sociodemographic and psychosocial factors in childhood as predictors of adult mortality. *American Journal of Public Health*, *85*, 1237–1245.

Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997). Price of adaptation: Allostatic load and its health consequences. *Archives of Internal Medicine*, *157*, 2259–2268.

Seeman, T. E., Singer, B. H., Ryff, C. D., Love, G. D., & Levy-Storms, L. (2002). Social relationships, gender, and allostatic load across two age cohorts. *Psychosomatic Medicine*, *64*, 395–406.

Solomon, G. S., Kay, N., & Morley, J. E. (1986). Endorphins: A link between personality, stress, emotions, immunity, and disease? In N. P. Plotnikoff, R. E. Faith, A. J. Murgo, & R. A. Good (Eds.), *Enkephalins and endorphins: Stress and the immune system*. New York: Plenum Press.

Streeck-Fisher, A., & van der Kolk, B. A. (2000). Down will come baby, cradle and all: Diagnostic and therapeutic implications of chronic trauma on child development. *Australian and New Zealand Journal of Psychiatry*, *34*, 903–918.

Suin, R. M. (2001). The terrible twos: Anger and anxiety. *American Psychologist*, *56*(1), 27–36.

Suomi, S. J. (2000). A biobehavioral perspective on developmental psychopathology: Excessive aggression and serotonergic dysfunction in monkeys. In A. J. Samaroff, M. Lewis, & S. Miller (Eds.), *Handbook of developmental psychopathology* (pp. 237–256). New York: Plenum.

Taylor, S. E., Repetti, R. L., & Seeman, T. (1997). Health psychology: What is an unhealthy environment and how does it get under the skin? *Annual Review of Psychology*, *48*, 411–447.

Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., & Navalta, C. P. (2002). Developmental neurobiology of childhood stress and trauma. *The Psychiatric Clinics of North America*, *25*(2), 397–426.

Thomas, C. B., Duszynski, K. R., & Shaffer, J. W. (1979). Family attitudes reported in youth as potential predictors of cancer. *Psychosomatic Medicine*, *41*, 287–302.

Uchino, B. N., Cacioppo, J. T., & Kiecolt-Glaser, J. K. (1996). The relationship between social support and physiological processes: A review with emphasis on underlying mechanisms and implications for health. *Psychology Bulletin*, *119*, 488–531.

Van den Boom, D. C. (1989). Neonatal irritability and the development of attachment. In G. A. Kohnstamm, & J. E. Bates (Eds.), *Temperament in childhood* (pp. 299–318). Oxford, England: Wiley.

Vieth, R. C., Lewis, N., & Linares, O. A. (1994). Sympathetic nervous system activity in major depression: Basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Archives of General Psychiatry*, *51*, 411–422.

Walker, E. A., Keegan, D., Gardner, G., Sullivan, M., Bernstein, D., & Katon, W. J. (1997). Psychosocial factors in fibromyalgia compared with rheumatoid arthritis: II. Sexual, physical, and emotional abuse and neglect. *Psychosomatic Medicine*, *59*(6), 572–577.

Welberg, L. A. M., & Seckl, J. R. (2001). Prenatal stress, glucocorticoids and the programming of the brain. *Journal of Neuroendocrinology*, *13*, 113–128.

Werner, E. E. (1993). Risk, resilience, and recovery: Perspectives from the Kauai Longitudinal Study. *Development and Psychopathology*, *5*, 503–575.

Woodall, K. L., & Matthews, K. A. (1993). Changes in and stability of hostile characteristics from a 4-year longitudinal study of children. *Journal of Personality and Social Psychology*, *64*, 491–499.

Wright, L. B., Treiber, F. A., Davis, H., Strong, W. B., Levy, M., Van Huss, E., & Batchelor, C. (1993). Relationship between family environment and children's hemodynamic responses to stress: A longitudinal evaluation. *Behavioral Medicine*, *19*(3), 115–121.

Wuest, S., Federenko, I., Hellhammer, D. H., & Kirschbaum, C. (2000). Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology*, *25*, 707–720.

Yehuda, R., Giller, E. L, Levengood, R. A., Southwick, S. M., & Siever, L. J. (1995). Hypothalamic–pituitary–adrenal functioning in post-traumatic stress disorder. In M. J. Friedman, D. S. Charney, & A. Y. Deutch (Eds.), *Neurobiological and clinical consequences of stress: From normal adaptation to PTSD* (pp. 351–366). Philadelphia: Lippincott-Raven Publishers.