

STRESS AND HEALTH: Psychological, Behavioral, and Biological Determinants

Neil Schneiderman, Gail Ironson, and Scott D. Siegel

*Department of Psychology, University of Miami, Coral Gables, Florida 33124-0751;
email: nschneid@miami.edu, gironson@aol.com, scottdsiegel@yahoo.com*

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■ **Abstract** Stressors have a major influence upon mood, our sense of well-being, behavior, and health. Acute stress responses in young, healthy individuals may be adaptive and typically do not impose a health burden. However, if the threat is unremitting, particularly in older or unhealthy individuals, the long-term effects of stressors can damage health. The relationship between psychosocial stressors and disease is affected by the nature, number, and persistence of the stressors as well as by the individual's biological vulnerability (i.e., genetics, constitutional factors), psychosocial resources, and learned patterns of coping. Psychosocial interventions have proven useful for treating stress-related disorders and may influence the course of chronic diseases.

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INTRODUCTION

Claude Bernard (1865/1961) noted that the maintenance of life is critically dependent on keeping our internal milieu constant in the face of a changing environment. Cannon (1929) called this "homeostasis." Selye (1956) used the term "stress" to represent the effects of anything that seriously threatens homeostasis. The actual or perceived threat to an organism is referred to as the "stressor" and the response to the stressor is called the "stress response." Although stress responses evolved as adaptive processes, Selye observed that severe, prolonged stress responses might lead to tissue damage and disease.

Based on the appraisal of perceived threat, humans and other animals invoke coping responses (Lazarus & Folkman 1984). Our central nervous system (CNS) tends to produce integrated coping responses rather than single, isolated response changes (Hilton 1975). Thus, when immediate fight-or-flight appears feasible, mammals tend to show increased autonomic and hormonal activities that maximize the possibilities for muscular exertion (Cannon 1929, Hess 1957). In contrast, during aversive situations in which an active coping response is not available, mammals may engage in a vigilance response that involves sympathetic nervous system (SNS) arousal accompanied by an active inhibition of movement and shunting of blood away from the periphery (Adams et al. 1968). The extent to which various situations elicit different patterns of biologic response is called "situational stereotypy" (Lacey 1967).

Although various situations tend to elicit different patterns of stress responses, there are also individual differences in stress responses to the same situation. This tendency to exhibit a particular pattern of stress responses across a variety of stressors is referred to as "response stereotypy" (Lacey & Lacey 1958). Across a variety of situations, some individuals tend to show stress responses associated with active coping, whereas others tend to show stress responses more associated with aversive vigilance (Kasprovicz et al. 1990, Llabre et al. 1998).

Although genetic inheritance undoubtedly plays a role in determining individual differences in response stereotypy, neonatal experiences in rats have been shown to produce long-term effects in cognitive-emotional responses (Levine 1957). For example, Meaney et al. (1993) showed that rats raised by nurturing mothers have increased levels of central serotonin activity compared with rats raised by less nurturing mothers. The increased serotonin activity leads to increased expression of a central glucocorticoid receptor gene. This, in turn, leads to higher numbers of glucocorticoid receptors in the limbic system and improved glucocorticoid feedback into the CNS throughout the rat's life. Interestingly, female rats who receive a high level of nurturing in turn become highly nurturing mothers whose offspring also have high levels of glucocorticoid receptors. This example of behaviorally induced gene expression shows how highly nurtured rats develop into low-anxiety adults, who in turn become nurturing mothers with reduced stress responses.

In contrast to highly nurtured rats, pups separated from their mothers for several hours per day during early life have a highly active hypothalamic-pituitary

adrenocortical axis and elevated SNS arousal (Ladd et al. 2000). These deprived rats tend to show larger and more frequent stress responses to the environment than do less deprived animals.

Because evolution has provided mammals with reasonably effective homeostatic mechanisms (e.g., baroreceptor reflex) for dealing with short-term stressors, acute stress responses in young, healthy individuals typically do not impose a health burden. However, if the threat is persistent, particularly in older or unhealthy individuals, the long-term effects of the response to stress may damage health (Schneiderman 1983). Adverse effects of chronic stressors are particularly common in humans, possibly because their high capacity for symbolic thought may elicit persistent stress responses to a broad range of adverse living and working conditions. The relationship between psychosocial stressors and chronic disease is complex. It is affected, for example, by the nature, number, and persistence of the stressors as well as by the individual's biological vulnerability (i.e., genetics, constitutional factors) and learned patterns of coping. In this review, we focus on some of the psychological, behavioral, and biological effects of specific stressors, the mediating psychophysiological pathways, and the variables known to mediate these relationships. We conclude with a consideration of treatment implications.

PSYCHOLOGICAL ASPECTS OF STRESS

Stressors During Childhood and Adolescence and Their Psychological Sequelae

The most widely studied stressors in children and adolescents are exposure to violence, abuse (sexual, physical, emotional, or neglect), and divorce/marital conflict (see Cicchetti 2005). McMahon et al. (2003) also provide an excellent review of the psychological consequences of such stressors. Psychological effects of maltreatment/abuse include the dysregulation of affect, provocative behaviors, the avoidance of intimacy, and disturbances in attachment (Haviland et al. 1995, Lowenthal 1998). Survivors of childhood sexual abuse have higher levels of both general distress and major psychological disturbances including personality disorders (Polusny & Follett 1995). Childhood abuse is also associated with negative views toward learning and poor school performance (Lowenthal 1998). Children of divorced parents have more reported antisocial behavior, anxiety, and depression than their peers (Short 2002). Adult offspring of divorced parents report more current life stress, family conflict, and lack of friend support compared with those whose parents did not divorce (Short 2002). Exposure to nonresponsive environments has also been described as a stressor leading to learned helplessness (Peterson & Seligman 1984).

Studies have also addressed the psychological consequences of exposure to war and terrorism during childhood (Shaw 2003). A majority of children exposed to war experience significant psychological morbidity, including both post-traumatic

stress disorder (PTSD) and depressive symptoms. For example, Nader et al. (1993) found that 70% of Kuwaiti children reported mild to severe PTSD symptoms after the Gulf War. Some effects are long lasting: Macksound & Aber (1996) found that 43% of Lebanese children continued to manifest post-traumatic stress symptoms 10 years after exposure to war-related trauma.

Exposure to intense and chronic stressors during the developmental years has long-lasting neurobiological effects and puts one at increased risk for anxiety and mood disorders, aggressive dyscontrol problems, hypo-immune dysfunction, medical morbidity, structural changes in the CNS, and early death (Shaw 2003).

Stressors During Adulthood and Their Psychological Sequelae

LIFE STRESS, ANXIETY, AND DEPRESSION It is well known that first depressive episodes often develop following the occurrence of a major negative life event (Paykel 2001). Furthermore, there is evidence that stressful life events are causal for the onset of depression (see Hammen 2005, Kendler et al. 1999). A study of 13,006 patients in Denmark, with first psychiatric admissions diagnosed with depression, found more recent divorces, unemployment, and suicides by relatives compared with age- and gender-matched controls (Kessing et al. 2003). The diagnosis of a major medical illness often has been considered a severe life stressor and often is accompanied by high rates of depression (Cassem 1995). For example, a meta-analysis found that 24% of cancer patients are diagnosed with major depression (McDaniel et al. 1995).

Stressful life events often precede anxiety disorders as well (Faravelli & Pallanti 1989, Finlay-Jones & Brown 1981). Interestingly, long-term follow-up studies have shown that anxiety occurs more commonly before depression (Angst & Vollrath 1991, Breslau et al. 1995). In fact, in prospective studies, patients with anxiety are most likely to develop major depression after stressful life events occur (Brown et al. 1986).

DISORDERS RELATED TO TRAUMA Lifetime exposure to traumatic events in the general population is high, with estimates ranging from 40% to 70% (Norris 1992). Of note, an estimated 13% of adult women in the United States have been exposed to sexual assault (Kilpatrick et al. 1992). The Diagnostic and Statistical Manual (DSM-IV-TR; American Psychiatric Association 2000) includes two primary diagnoses related to trauma: Acute Stress Disorder (ASD) and PTSD. Both these disorders have as prominent features a traumatic event involving actual or threatened death or serious injury and symptom clusters including re-experiencing of the traumatic event (e.g., intrusive thoughts), avoidance of reminders/numbing, and hyperarousal (e.g., difficulty falling or staying asleep). The time frame for ASD is shorter (lasting two days to four weeks), with diagnosis limited to within one month of the incident. ASD was introduced in 1994 to describe initial trauma reactions, but it has come under criticism (Harvey & Bryant 2002) for weak empirical and theoretical support. Most people who have symptoms of PTSD shortly

after a traumatic event recover and do not develop PTSD. In a comprehensive review, Green (1994) estimates that approximately 25% of those exposed to traumatic events develop PTSD. Surveys of the general population indicate that PTSD affects 1 in 12 adults at some time in their life (Kessler et al. 1995). Trauma and disasters are related not only to PTSD, but also to concurrent depression, other anxiety disorders, cognitive impairment, and substance abuse (David et al. 1996, Schnurr et al. 2002, Shalev 2001).

Other consequences of stress that could provide linkages to health have been identified, such as increases in smoking, substance use, accidents, sleep problems, and eating disorders. Populations that live in more stressful environments (communities with higher divorce rates, business failures, natural disasters, etc.) smoke more heavily and experience higher mortality from lung cancer and chronic obstructive pulmonary disorder (Colby et al. 1994). A longitudinal study following seamen in a naval training center found that more cigarette smoking occurred on high-stress days (Conway et al. 1981). Life events stress and chronically stressful conditions have also been linked to higher consumption of alcohol (Linsky et al. 1985). In addition, the possibility that alcohol may be used as self-medication for stress-related disorders such as anxiety has been proposed. For example, a prospective community study of 3021 adolescents and young adults (Zimmerman et al. 2003) found that those with certain anxiety disorders (social phobia and panic attacks) were more likely to develop substance abuse or dependence prospectively over four years of follow-up. Life in stressful environments has also been linked to fatal accidents (Linsky & Strauss 1986) and to the onset of bulimia (Welch et al. 1997). Another variable related to stress that could provide a link to health is the increased sleep problems that have been reported after psychological trauma (Harvey et al. 2003). New onset of sleep problems mediated the relationship between post-traumatic stress symptoms and decreased natural killer (NK) cell cytotoxicity in Hurricane Andrew victims (Ironson et al. 1997).

Variations in Stress Responses

Certain characteristics of a situation are associated with greater stress responses. These include the intensity or severity of the stressor and controllability of the stressor, as well as features that determine the nature of the cognitive responses or appraisals. Life event dimensions of loss, humiliation, and danger are related to the development of major depression and generalized anxiety (Kendler et al. 2003). Factors associated with the development of symptoms of PTSD and mental health disorders include injury, damage to property, loss of resources, bereavement, and perceived life threat (Freedy et al. 1992, Ironson et al. 1997, McNally 2003). Recovery from a stressor can also be affected by secondary traumatization (Pfefferbaum et al. 2003). Other studies have found that multiple facets of stress that may work synergistically are more potent than a single facet; for example, in the area of work stress, time pressure in combination with threat (Stanton et al. 2001), or high demand in combination with low control (Karasek & Theorell 1990).

Stress-related outcomes also vary according to personal and environmental factors. Personal risk factors for the development of depression, anxiety, or PTSD after a serious life event, disaster, or trauma include prior psychiatric history, neuroticism, female gender, and other sociodemographic variables (Green 1996, McNally 2003, Patton et al. 2003). There is also some evidence that the relationship between personality and environmental adversity may be bidirectional (Kendler et al. 2003). Levels of neuroticism, emotionality, and reactivity correlate with poor interpersonal relationships as well as "event proneness." Protective factors that have been identified include, but are not limited to, coping, resources (e.g., social support, self-esteem, optimism), and finding meaning. For example, those with social support fare better after a natural disaster (Madakaisira & O'Brien 1987) or after myocardial infarction (Frasure-Smith et al. 2000). Pruessner et al. (1999) found that people with higher self-esteem performed better and had lower cortisol responses to acute stressors (difficult math problems). Attaching meaning to the event is another protective factor against the development of PTSD, even when horrific torture has occurred. Left-wing political activists who were tortured by Turkey's military regime had lower rates of PTSD than did nonactivists who were arrested and tortured by the police (Basoğlu et al. 1994).

Finally, human beings are resilient and in general are able to cope with adverse situations. A recent illustration is provided by a study of a nationally representative sample of Israelis after 19 months of ongoing exposure to the Palestinian intifada. Despite considerable distress, most Israelis reported adapting to the situation without substantial mental health symptoms or impairment (Bleich et al. 2003).

BIOLOGICAL RESPONSES TO STRESSORS

Acute Stress Responses

Following the perception of an acute stressful event, there is a cascade of changes in the nervous, cardiovascular, endocrine, and immune systems. These changes constitute the stress response and are generally adaptive, at least in the short term (Selye 1956). Two features in particular make the stress response adaptive. First, stress hormones are released to make energy stores available for the body's immediate use. Second, a new pattern of energy distribution emerges. Energy is diverted to the tissues that become more active during stress, primarily the skeletal muscles and the brain. Cells of the immune system are also activated and migrate to "battle stations" (Dhabar & McEwen 1997). Less critical activities are suspended, such as digestion and the production of growth and gonadal hormones. Simply put, during times of acute crisis, eating, growth, and sexual activity may be a detriment to physical integrity and even survival.

Stress hormones are produced by the SNS and hypothalamic-pituitary adrenocortical axis. The SNS stimulates the adrenal medulla to produce catecholamines (e.g., epinephrine). In parallel, the paraventricular nucleus of the hypothalamus produces corticotropin releasing factor, which in turn stimulates the pituitary to

produce adrenocorticotropin. Adrenocorticotropin then stimulates the adrenal cortex to secrete cortisol. Together, catecholamines and cortisol increase available sources of energy by promoting lipolysis and the conversion of glycogen into glucose (i.e., blood sugar). Lipolysis is the process of breaking down fats into usable sources of energy (i.e., fatty acids and glycerol; Brindley & Rollan 1989).

Energy is then distributed to the organs that need it most by increasing blood pressure levels and contracting certain blood vessels while dilating others. Blood pressure is increased with one of two hemodynamic mechanisms (Llabre et al. 1998, Schneiderman & McCabe 1989). The myocardial mechanism increases blood pressure through enhanced cardiac output; that is, increases in heart rate and stroke volume (i.e., the amount of blood pumped with each heart beat). The vascular mechanism constricts the vasculature, thereby increasing blood pressure much like constricting a hose increases water pressure. Specific stressors tend to elicit either myocardial or vascular responses, providing evidence of situational stereotypy (Saab et al. 1992, 1993). Laboratory stressors that call for active coping strategies, such as giving a speech or performing mental arithmetic, require the participant to *do* something and are associated with myocardial responses. In contrast, laboratory stressors that call for more vigilant coping strategies in the absence of movement, such as viewing a distressing video or keeping one's foot in a bucket of ice water, are associated with vascular responses. From an evolutionary perspective, cardiac responses are believed to facilitate active coping by shunting blood to skeletal muscles, consistent with the fight-or-flight response. In situations where decisive action would not be appropriate, but instead skeletal muscle inhibition and vigilance are called for, a vascular hemodynamic response is adaptive. The vascular response shunts blood away from the periphery to the internal organs, thereby minimizing potential bleeding in the case of physical assault.

Finally, in addition to the increased availability and redistribution of energy, the acute stress response includes activation of the immune system. Cells of the innate immune system (e.g., macrophages and natural killer cells), the first line of defense, depart from lymphatic tissue and spleen and enter the bloodstream, temporarily raising the number of immune cells in circulation (i.e., leukocytosis). From there, the immune cells migrate into tissues that are most likely to suffer damage during physical confrontation (e.g., the skin). Once at "battle stations," these cells are in position to contain microbes that may enter the body through wounds and thereby facilitate healing (Dhabar & McEwen 1997).

Chronic Stress Responses

The acute stress response can become maladaptive if it is repeatedly or continuously activated (Selye 1956). For example, chronic SNS stimulation of the cardiovascular system due to stress leads to sustained increases in blood pressure and vascular hypertrophy (Henry et al. 1975). That is, the muscles that constrict the vasculature thicken, producing elevated resting blood pressure and response stereotypy, or a tendency to respond to all types of stressors with a vascular response. Chronically

elevated blood pressure forces the heart to work harder, which leads to hypertrophy of the left ventricle (Brownley et al. 2000). Over time, the chronically elevated and rapidly shifting levels of blood pressure can lead to damaged arteries and plaque formation.

The elevated basal levels of stress hormones associated with chronic stress also suppress immunity by directly affecting cytokine profiles. Cytokines are communicatory molecules produced primarily by immune cells (see Roitt et al. 1998). There are three classes of cytokines. Proinflammatory cytokines mediate acute inflammatory reactions. Th1 cytokines mediate cellular immunity by stimulating natural killer cells and cytotoxic T cells, immune cells that target intracellular pathogens (e.g., viruses). Finally, Th2 cytokines mediate humoral immunity by stimulating B cells to produce antibody, which “tags” extracellular pathogens (e.g., bacteria) for removal. In a meta-analysis of over 30 years of research, Segerstrom & Miller (2004) found that intermediate stressors, such as academic examinations, could promote a Th2 shift (i.e., an increase in Th2 cytokines relative to Th1 cytokines). A Th2 shift has the effect of suppressing cellular immunity in favor of humoral immunity. In response to more chronic stressors (e.g., long-term caregiving for a dementia patient), Segerstrom & Miller found that proinflammatory, Th1, and Th2 cytokines become dysregulated and lead both to suppressed humoral and cellular immunity. Intermediate and chronic stressors are associated with slower wound healing and recovery from surgery, poorer antibody responses to vaccination, and antiviral deficits that are believed to contribute to increased vulnerability to viral infections (e.g., reductions in natural killer cell cytotoxicity; see Kiecolt-Glaser et al. 2002).

Chronic stress is particularly problematic for elderly people in light of immunosenescence, the gradual loss of immune function associated with aging. Older adults are less able to produce antibody responses to vaccinations or combat viral infections (Ferguson et al. 1995), and there is also evidence of a Th2 shift (Glaser et al. 2001). Although research has yet to link poor vaccination responses to early mortality, influenza and other infectious illnesses are a major cause of mortality in the elderly, even among those who have received vaccinations (e.g., Voordouw et al. 2003).

PSYCHOSOCIAL STRESSORS AND HEALTH

Cardiovascular Disease

Both epidemiological and controlled studies have demonstrated relationships between psychosocial stressors and disease. The underlying mediators, however, are unclear in most cases, although possible mechanisms have been explored in some experimental studies. An occupational gradient in coronary heart disease (CHD) risk has been documented in which men with relatively low socioeconomic status have the poorest health outcomes (Marmot 2003). Much of the risk gradient in CHD can be eliminated, however, by taking into account lack of perceived job

control, which is a potent stressor (Marmot et al. 1997). Other factors include risky behaviors such as smoking, alcohol use, and sedentary lifestyle (Lantz et al. 1998), which may be facilitated by stress. Among men (Schnall et al. 1994) and women (Eaker 1998), work stress has been reported to be a predictor of incident CHD and hypertension (Ironson 1992). However, in women with existing CHD, marital stress is a better predictor of poor prognosis than is work stress (Orth-Gomer et al. 2000).

Although the observational studies cited thus far reveal provocative associations between psychosocial stressors and disease, they are limited in what they can tell us about the exact contribution of these stressors or about how stress mediates disease processes. Animal models provide an important tool for helping to understand the specific influences of stressors on disease processes. This is especially true of atherosclerotic CHD, which takes multiple decades to develop in humans and is influenced by a great many constitutional, demographic, and environmental factors. It would also be unethical to induce disease in humans by experimental means.

Perhaps the best-known animal model relating stress to atherosclerosis was developed by Kaplan et al. (1982). Their study was carried out on male cynomolgus monkeys, who normally live in social groups. The investigators stressed half the animals by reorganizing five-member social groups at one- to three-month intervals on a schedule that ensured that each monkey would be housed with several new animals during each reorganization. The other half of the animals lived in stable social groups. All animals were maintained on a moderately atherogenic diet for 22 months. Animals were also assessed for their social status (i.e., relative dominance) within each group. The major findings were that (a) socially dominant animals living in unstable groups had significantly more atherosclerosis than did less dominant animals living in unstable groups; and (b) socially dominant male animals living in unstable groups had significantly more atherosclerosis than did socially dominant animals living in stable groups. Other important findings based upon this model have been that heart-rate reactivity to the threat of capture predicts severity of atherosclerosis (Manuck et al. 1983) and that administration of the SNS-blocking agent propranolol decreases the progression of atherosclerosis (Kaplan et al. 1987). In contrast to the findings in males, subordinate premenstrual females develop greater atherosclerosis than do dominant females (Kaplan et al. 1984) because they are relatively estrogen deficient, tending to miss ovulatory cycles (Adams et al. 1985).

Whereas the studies in cynomolgus monkeys indicate that emotionally stressful behavior can accelerate the progression of atherosclerosis, McCabe et al. (2002) have provided evidence that affiliative social behavior can slow the progression of atherosclerosis in the Watanabe heritable hyperlipidemic rabbit. This rabbit model has a genetic defect in lipoprotein clearance such that it exhibits hypercholesterolemia and severe atherosclerosis. The rabbits were assigned to one of three social or behavioral groups: (a) an unstable group in which unfamiliar rabbits were paired daily, with the pairing switched each week; (b) a stable group, in which littermates were paired daily for the entire study; and (c) an individually

caged group. The stable group exhibited more affiliative behavior and less agonistic behavior than the unstable group and significantly less atherosclerosis than each of the other two groups. The study emphasizes the importance of behavioral factors in atherogenesis, even in a model of disease with extremely strong genetic determinants.

Upper Respiratory Diseases

The hypothesis that stress predicts susceptibility to the common cold received support from observational studies (Graham et al. 1986, Meyer & Haggerty 1962). One problem with such studies is that they do not control for exposure. Stressed people, for instance, might seek more outside contact and thus be exposed to more viruses. Therefore, in a more controlled study, people were exposed to a rhinovirus and then quarantined to control for exposure to other viruses (Cohen et al. 1991). Those individuals with the most stressful life events and highest levels of perceived stress and negative affect had the greatest probability of developing cold symptoms. In a subsequent study of volunteers inoculated with a cold virus, it was found that people enduring chronic, stressful life events (i.e., events lasting a month or longer including unemployment, chronic underemployment, or continued interpersonal difficulties) had a high likelihood of catching cold, whereas people subjected to stressful events lasting less than a month did not (Cohen et al. 1998).

Human Immunodeficiency Virus

The impact of life stressors has also been studied within the context of human immunodeficiency virus (HIV) spectrum disease. Leserman et al. (2000) followed men with HIV for up to 7.5 years and found that faster progression to AIDS was associated with higher cumulative stressful life events, use of denial as a coping mechanism, lower satisfaction with social support, and elevated serum cortisol.

Inflammation, the Immune System, and Physical Health

Despite the stress-mediated immunosuppressive effects reviewed above, stress has also been associated with exacerbations of autoimmune disease (Harbuz et al. 2003) and other conditions in which excessive inflammation is a central feature, such as CHD (Appels et al. 2000). Evidence suggests that a chronically activated, dysregulated acute stress response is responsible for these associations. Recall that the acute stress response includes the activation and migration of cells of the innate immune system. This effect is mediated by proinflammatory cytokines. During periods of chronic stress, in the otherwise healthy individual, cortisol eventually suppresses proinflammatory cytokine production. But in individuals with autoimmune disease or CHD, prolonged stress can cause proinflammatory cytokine production to remain chronically activated, leading to an exacerbation of pathophysiology and symptomatology.

Miller et al. (2002) proposed the glucocorticoid-resistance model to account for this deficit in proinflammatory cytokine regulation. They argue that immune cells become "resistant" to the effects of cortisol (i.e., a type of glucocorticoid), primarily through a reduction, or downregulation, in the number of expressed cortisol receptors. With cortisol unable to suppress inflammation, stress continues to promote proinflammatory cytokine production indefinitely. Although there is only preliminary empirical support for this model, it could have implications for diseases of inflammation. For example, in rheumatoid arthritis, excessive inflammation is responsible for joint damage, swelling, pain, and reduced mobility. Stress is associated with more swelling and reduced mobility in rheumatoid arthritis patients (Affleck et al. 1997). Similarly, in multiple sclerosis (MS), an overactive immune system targets and destroys the myelin surrounding nerves, contributing to a host of symptoms that include paralysis and blindness. Again, stress is associated with an exacerbation of disease (Mohr et al. 2004). Even in CHD, inflammation plays a role. The immune system responds to vascular injury just as it would any other wound: Immune cells migrate to and infiltrate the arterial wall, setting off a cascade of biochemical processes that can ultimately lead to a thrombosis (i.e., clot; Ross 1999). Elevated levels of inflammatory markers, such as C-reactive protein (CRP), are predictive of heart attacks, even when controlling for other traditional risk factors (e.g., cholesterol, blood pressure, and smoking; Morrow & Ridker 2000). Interestingly, a history of major depressive episodes has been associated with elevated levels of CRP in men (Danner et al. 2003).

Inflammation, Cytokine Production, and Mental Health

In addition to its effects on physical health, prolonged proinflammatory cytokine production may also adversely affect mental health in vulnerable individuals. During times of illness (e.g., the flu), proinflammatory cytokines feed back to the CNS and produce symptoms of fatigue, malaise, diminished appetite, and listlessness, which are symptoms usually associated with depression. It was once thought that these symptoms were directly caused by infectious pathogens, but more recently, it has become clear that proinflammatory cytokines are both sufficient and necessary (i.e., even absent infection or fever) to generate sickness behavior (Dantzer 2001, Larson & Dunn 2001).

Sickness behavior has been suggested to be a highly organized strategy that mammals use to combat infection (Dantzer 2001). Symptoms of illness, as previously thought, are not inconsequential or even maladaptive. On the contrary, sickness behavior is thought to promote resistance and facilitate recovery. For example, an overall decrease in activity allows the sick individual to preserve energy resources that can be redirected toward enhancing immune activity. Similarly, limiting exploration, mating, and foraging further preserves energy resources and reduces the likelihood of risky encounters (e.g., fighting over a mate). Furthermore, decreasing food intake also decreases the level of iron in the blood, thereby decreasing bacterial replication. Thus, for a limited period, sickness behavior may be looked upon as an adaptive response to the stress of illness.

Much like other aspects of the acute stress response, however, sickness behavior can become maladaptive when repeatedly or continuously activated. Many features of the sickness behavior response overlap with major depression. Indeed, compared with healthy controls, elevated rates of depression are reported in patients with inflammatory diseases such as MS (Mohr et al. 2004) or CHD (Carney et al. 1987). Granted, MS patients face a number of stressors and reports of depression are not surprising. However, when compared with individuals facing similar disability who do not have MS (e.g., car accident victims), MS patients still report higher levels of depression (Ron & Logsdail 1989). In both MS (Fassbender et al. 1998) and CHD (Danner et al. 2003), indicators of inflammation have been found to be correlated with depressive symptomatology. Thus, there is evidence to suggest that stress contributes to both physical and mental disease through the mediating effects of proinflammatory cytokines.

HOST VULNERABILITY-STRESSOR INTERACTIONS AND DISEASE

The changes in biological set points that occur across the life span as a function of chronic stressors are referred to as allostasis, and the biological cost of these adjustments is known as allostatic load (McEwen 1998). McEwen has also suggested that cumulative increases in allostatic load are related to chronic illness. These are intriguing hypotheses that emphasize the role that stressors may play in disease. The challenge, however, is to show the exact interactions that occur among stressors, pathogens, host vulnerability (both constitutional and genetic), and such poor health behaviors as smoking, alcohol abuse, and excessive caloric consumption. Evidence of a lifetime trajectory of comorbidities does not necessarily imply that allostatic load is involved since immunosenescence, genetic predisposition, pathogen exposure, and poor health behaviors may act as culprits.

It is not clear, for example, that changes in set point for variables such as blood pressure are related to cumulative stressors per se, at least in healthy young individuals. Thus, for example, British soldiers subjected to battlefield conditions for more than a year in World War II showed chronic elevations in blood pressure, which returned to normal after a couple of months away from the front (Graham 1945). In contrast, individuals with chronic illnesses such as chronic fatigue syndrome may show a high rate of relapse after a relatively acute stressor such as a hurricane (Lutgendorf et al. 1995). Nevertheless, by emphasizing the role that chronic stressors may play in multiple disease outcomes, McEwen has helped to emphasize an important area of study.

TREATMENT FOR STRESS-RELATED DISORDERS

For PTSD, useful treatments include cognitive-behavioral therapy (CBT), along with exposure and the more controversial Eye Movement Desensitization and Reprocessing (Foa & Meadows 1997, Ironson et al. 2002, Shapiro 1995).

Psychopharmacological approaches have also been suggested (Berlant 2001). In addition, writing about trauma has been helpful both for affective recovery and for potential health benefit (Pennebaker 1997). For outpatients with major depression, Beck's CBT (Beck 1976) and interpersonal therapy (Klerman et al. 1984) are as effective as psychopharmacotherapy (Clinical Practice Guidelines 1993). However, the presence of sleep problems or hypercortisolemia is associated with poorer response to psychotherapy (Thase 2000). The combination of psychotherapy and pharmacotherapy seems to offer a substantial advantage over psychotherapy alone for the subset of patients who are more severely depressed or have recurrent depression (Thase et al. 1997). For the treatment of anxiety, it depends partly on the specific disorder [e.g., generalized anxiety disorder (GAD), panic disorder, social phobia], although CBT including relaxation training has demonstrated efficacy in several subtypes of anxiety (Borkovec & Ruscio 2001). Antidepressants such as selective serotonin reuptake inhibitors also show efficacy in anxiety (Ballenger et al. 2001), especially when GAD is comorbid with major depression, which is the case in 39% of subjects with current GAD (Judd et al. 1998).

BEHAVIORAL INTERVENTIONS IN CHRONIC DISEASE

Patients dealing with chronic, life-threatening diseases must often confront daily stressors that can threaten to undermine even the most resilient coping strategies and overwhelm the most abundant interpersonal resources. Psychosocial interventions, such as cognitive-behavioral stress management (CBSM), have a positive effect on the quality of life of patients with chronic disease (Schneiderman et al. 2001). Such interventions decrease perceived stress and negative mood (e.g., depression), improve perceived social support, facilitate problem-focused coping, and change cognitive appraisals, as well as decrease SNS arousal and the release of cortisol from the adrenal cortex. Psychosocial interventions also appear to help chronic pain patients reduce their distress and perceived pain as well as increase their physical activity and ability to return to work (Morley et al. 1999). These psychosocial interventions can also decrease patients' overuse of medications and utilization of the health care system. There is also some evidence that psychosocial interventions may have a favorable influence on disease progression (Schneiderman et al. 2001).

Morbidity, Mortality, and Markers of Disease Progression

Psychosocial intervention trials conducted upon patients following acute myocardial infarction (MI) have reported both positive and null results. Two meta-analyses have reported a reduction in both mortality and morbidity of approximately 20% to 40% (Dusseldorp et al. 1999, Linden et al. 1996). Most of these studies were carried out in men. The major study reporting positive results was the Recurrent Coronary Prevention Project (RCPP), which employed group-based CBT, and decreased hostility and depressed affect (Mendes de Leon et al. 1991), as well as the composite medical end point of cardiac death and nonfatal MI (Friedman et al. 1986).

In contrast, the major study reporting null results for medical end points was the Enhancing Recovery in Coronary Heart Disease (ENRICHD) clinical trial (Writing Committee for ENRICHD Investigators 2003), which found that the intervention modestly decreased depression and increased perceived social support, but did not affect the composite medical end point of death and nonfatal MI. However, a secondary analysis, which examined the effects of the psychosocial intervention within gender by ethnicity subgroups, found significant decreases approaching 40% in both cardiac death and nonfatal MI for white men but not for other subgroups such as minority women (Schneiderman et al. 2004). Although there were important differences between the RCPP and ENRICHD in terms of the objectives of psychosocial intervention and the duration and timing of treatment, it should also be noted that more than 90% of the patients in the RCPP were white men. Thus, because primarily white men, but not other subgroups, may have benefited from the ENRICHD intervention, future studies need to attend to variables that may have prevented morbidity and mortality benefits among gender and ethnic subgroups other than white men.

Psychosocial intervention trials conducted upon patients with cancer have reported both positive and null results with regard to survival (Classen 1998). A number of factors that generally characterized intervention trials that observed significant positive effects on survival were relatively absent in trials that failed to show improved survival. These included: (a) having only patients with the same type and severity of cancer within each group, (b) creation of a supportive environment, (c) having an educational component, and (d) provision of stress-management and coping-skills training. In one study that reported positive results, Fawzy et al. (1993) found that patients with early stage melanoma assigned to a six-week cognitive-behavioral stress management (CBSM) group showed significantly longer survival and longer time to recurrence over a six-year follow-up period compared with those receiving surgery and standard care alone. The intervention also significantly reduced distress, enhanced active coping, and increased NK cell cytotoxicity compared with controls.

Although published studies have not yet shown that psychosocial interventions can decrease disease progression in HIV/AIDS, several studies have significantly influenced factors that have been associated with HIV/AIDS disease progression (Schneiderman & Antoni 2003). These variables associated with disease progression include distress, depressed affect, denial coping, low perceived social support, and elevated serum cortisol (Ickovics et al. 2001, Leserman et al. 2000). Antoni et al. have used group-based CBSM (i.e., CBT plus relaxation training) to decrease the stress-related effects of HIV+ serostatus notification. Those in the intervention condition showed lower distress, anxiety, and depressed mood than did those in the control condition as well as lower antibody titers of herpesviruses and higher levels of T-helper (CD4) cells, NK cells, and lymphocyte proliferation (Antoni et al. 1991, Esterling et al. 1992). In subsequent studies conducted upon symptomatic HIV+ men who were not attempting to determine their HIV serostatus, CBSM decreased distress, dysphoria, anxiety,

herpesvirus antibody titers, cortisol, and epinephrine (Antoni et al. 2000a,b; Lutgendorf et al. 1997). Improvement in perceived social support and adaptive coping skills mediated the decreases in distress (Lutgendorf et al. 1998). In summary, it appears that CBSM can positively influence stress-related variables that have been associated with HIV/AIDS progression. Only a randomized clinical trial, however, could document that CBSM can specifically decrease HIV/AIDS disease progression.

CONCLUSION

Stress is a central concept for understanding both life and evolution. All creatures face threats to homeostasis, which must be met with adaptive responses. Our future as individuals and as a species depends on our ability to adapt to potent stressors. At a societal level, we face a lack of institutional resources (e.g., inadequate health insurance), pestilence (e.g., HIV/AIDS), war, and international terrorism that has reached our shores. At an individual level, we live with the insecurities of our daily existence including job stress, marital stress, and unsafe schools and neighborhoods. These are not an entirely new condition as, in the last century alone, the world suffered from instances of mass starvation, genocide, revolutions, civil wars, major infectious disease epidemics, two world wars, and a pernicious cold war that threatened the world order. Although we have chosen not to focus on these global threats in this paper, they do provide the backdrop for our consideration of the relationship between stress and health.

A widely used definition of stressful situations is one in which the demands of the situation threaten to exceed the resources of the individual (Lazarus & Folkman 1984). It is clear that all of us are exposed to stressful situations at the societal, community, and interpersonal level. How we meet these challenges will tell us about the health of our society and ourselves. Acute stress responses in young, healthy individuals may be adaptive and typically do not impose a health burden. Indeed, individuals who are optimistic and have good coping responses may benefit from such experiences and do well dealing with chronic stressors (Garmezy 1991, Glanz & Johnson 1999). In contrast, if stressors are too strong and too persistent in individuals who are biologically vulnerable because of age, genetic, or constitutional factors, stressors may lead to disease. This is particularly the case if the person has few psychosocial resources and poor coping skills. In this chapter, we have documented associations between stressors and disease and have described how endocrine-immune interactions appear to mediate the relationship. We have also described how psychosocial stressors influence mental health and how psychosocial treatments may ameliorate both mental and physical disorders. There is much we do not yet know about the relationship between stress and health, but scientific findings being made in the areas of cognitive-emotional psychology, molecular biology, neuroscience, clinical psychology, and medicine will undoubtedly lead to improved health outcomes.

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