

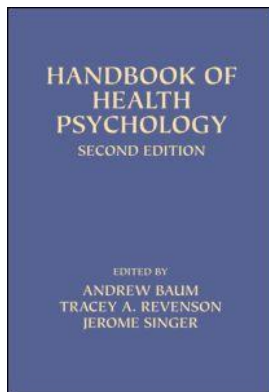
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### **Stress, Health, and Illness**

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# 3 Stress, Health, and Illness

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The customary introduction to stress suggests that it is still a matter of scientific debate, despite the fact that it is a common and influential state. It shares aspects of mind and body, representing a good instance of more holistic integration of these constructs. It is also a crosscutting process, influencing a wide array of illnesses, health behaviors, and aspects of health and well-being. Despite the general lack of a consensus on a precise definition of stress or the best approach to measuring it, there is considerable evidence to suggest that stress has important effects on physical and mental states, pathophysiology of disease, and performance (for reviews, see Baba, Jamal, & Tourigny, 1998; Juster, McEwen, & Lupien, 2010; Norris et al., 2002; Steptoe & Ayers, 2004). Major advances have been made during the last decade, particularly in our understanding of disease processes and the pathophysiological mechanisms that underlie the relationship between stress and health. This chapter considers conceptual models of stress, the broad array of behaviors and bodily systems involved in the stress response, and the impact of stress on chronic disease processes. Differences in the consequences of acute and chronic stress, as well as the implications of observed differences between them, are also explored.

## THE STRESS CONSTRUCT

Perhaps the most difficult aspect of studying stress is deriving a widely accepted definition of it. Most theorists agree that stress is (or can be) adaptive, that it is associated with threatening or harmful events, and that it is typically characterized by aversive or unpleasant feelings and mood. Beyond this, there are few areas of universal agreement. Some theorists have argued that stress can be positive, but others have insisted that it is a fundamentally aversive state (e.g., Baum, 1990; Selye, 1956/1984). Some have pointed out apparently simultaneous biological and psychological activation, suggesting that stress is an emotion; and some have described stress as a general state of arousal associated with taking strong action or dealing with a strong stimulus (e.g., Baum, 1990; Mason, 1971). Stress has been variously defined as a stimulus, as a response, and as a process involving both. It has been described as both specific and nonspecific responses to danger with little evidence to support one or another contention. However, it appears to be a fundamental component of adjustment and adaptation to environmental change, and as such it has assumed a critical role in theories of human evolution. From these many notions have come a few major theories of stress that reflect integration and synthesis of prior theories and that describe a pattern of responses to threat, harm, or loss.

## BIOLOGICAL THEORIES OF STRESS

A history of the stress concept could begin with early philosophers, but modern stress theory really began with Cannon's work early in the 20th century. Cannon (1914) was interested in the effects of stress on the sympathetic nervous system (SNS) and with application of the concept of homeostasis to interaction with the environment. Stressful events elicited negative emotions associated with SNS activation and disequilibrium in bodily systems. This activation was associated with the release of sympathetic adrenal hormones (i.e., epinephrine, norepinephrine), which prepared the organism

to respond to the danger posed, characteristically by fighting or fleeing. This early description of stress did not consider the measures of activation or persistence, focusing solely on SNS arousal and release of sympathetic hormones.

Selye (1956/1984) focused his attention solely on the activation of the hypothalamic-pituitary-adrenal cortical (HPA) axis. Initially interested in the effects of hormonal extracts, Selye (1956/1984) discovered a “universal” response to stressful events that included adrenal hypertrophy, lymphoid involution, and ulceration of the digestive tract. He characterized stress as a nonspecific physiological response to a variety of noxious events and argued that regardless of the stressor presented, the same response was seen, driven by activation of the HPA axis.

In contrast to these more focused approaches, Mason (1971) argued that stress affected many biological systems and that responses were based on the type of stressor presented. He concluded that stress was a unified catabolic response with the primary purpose of maintaining high levels of circulating blood glucose and providing the organism with energy to sustain resistance. Although he viewed emotional reactions as nonspecific, he maintained that responses in endocrine pathways followed response patterns that were specific to the stressor.

Whereas these early biological models of stress were typically narrow in focus and ignored or only hinted at important psychological aspects of stress, their importance can be illustrated in several ways. The systems that received most attention in these early theories were the SNS and the HPA axis. Both are arguably principal drivers of stress responding and persist today as focal points in studies of physiological responses during and after stress. Work by Cannon and Selye accurately identified these systems as integral parts of the stress response and focused attention on consequences of prolonged or excessive activation of these systems as primary consequences of stress. Mason recognized the integrated nature of these responses as well as the broad panoply of responses characterizing stress. Sympathetic arousal and activation of the HPA axis are hallmarks of the stress response and have been used as manipulation checks for stressors and explored as mechanisms underlying stress effects on the body.

These theories of biological activity offered some insights into psychological aspects of stress. Cannon’s (1914) notion of critical stress levels suggested that organisms had thresholds, or limits, on normal or nonpathogenic responses to threat, and his discussion of emotional stress suggested that emotional stimuli and responses were important in stress as well. In addition, stressors were stimuli that had to be recognized as a threat in order to elicit a response. Selye (1956/1984) argued that adaptive energy or the capacity to adapt to stressors is limited and depletion of adaptive reserves can have consequences, an idea consistent with notions of life change, stressful life events, and aftereffects of stress (e.g., Cohen, 1980; Holmes & Rahe, 1967; Rahe, 1987).

As critical as they are for understanding bodily responses to threat or challenge, these theories were also important because they introduced the notion that the nervous and endocrine systems jointly produced the arousal state characteristic of stress. Cannon incorporated emotional activation in his physiological model of stress, but Selye did not consider more psychologically relevant events or dynamics directly. Despite this, Selye was responsible for popularizing the construct and made stress theory more accessible and readily integrated into independent and parallel theories in the psychological literature on stress.

### PSYCHOLOGICAL THEORIES OF STRESS

Psychological theories of stress that developed largely independent of work on its biological bases, focused on variability of response to stressors. Lazarus (1966) emphasized the contribution of the individual to the interaction with an environmental stressor. Like Mason, Lazarus argued that people actively perceived and reacted to stressors and there was considerable individual variation in this experience. The occurrence of an event alone was not sufficient to induce stress. Instead, the notion of appraisal, or cognitive interpretation of the stressor, was introduced and integrated into a transactional model. For stress to be experienced, it was necessary for

an individual to appraise the event as threatening or harmful. Stress appraisals then elicited negative emotions; but unlike other models, it was the appraisal of the event, and not the emotional reaction, that determined subsequent physiological and behavioral responses. Additional appraisal processes were used by the individual to determine what available coping strategies could be used to deal with the situation and whether the problem should be attacked or accommodated.

The primary appraisals and perceived stress in this theory were important because they suggested that psychological variables or central nervous system (CNS) activity mediate the relation between stressful events and bodily reactions. Rather than envisioning a unidirectional process originating from the occurrence of a stressor, Lazarus conceptualized stress as a dynamic process in which an individual was constantly reappraising the situation as new information was obtained. Lazarus and Folkman (1984) later expanded on this model and defined stress as the “particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being” (p. 19). Central to this model were the processes of cognitive appraisals and coping, both of which mediated this relationship and determined stress-related outcomes. Sustained behavioral and physiological responding to stress that was not reduced or eliminated with directed coping efforts could lead to illness symptoms and disease.

More recently, McEwen and colleagues (McEwen, 1998; Juster, McEwen, & Lupien, 2010) have proposed a model of allostasis and allostatic load that encompasses most of the preceding theories and literature. Like Lazarus and Folkman (1984), they propose that psychosocial, demographic, background, and environmental characteristics contribute to the perception of an event as a stressor and threaten an individual’s homeostasis. Allostatic physiological responses include activation of the sympathetic-adrenal-medullary axis and release of catecholamines and activation of the HPA axis and release of glucocorticoids. Whereas this physiological arousal can be adaptive in the immediate context of dealing with a stressor, long-term activation can have negative effects on many other physiological response systems (e.g., immune, metabolic, and neurological alterations) and lead to such outcomes as behavioral changes, cognitive deficits, and vulnerability to disease. This concept of allostatic load, or chronic wear and tear on the body, has provided a useful framework for organizing research on stress-related diseases. Although it can be challenging to design projects to measure allostatic load adequately, recent research has successfully used allostatic load algorithms to identify risk and protective factors that can be identified across the lifespan (Juster et al., 2010).

## DEFINING STRESS

A unifying theme in many of these theories is adaptation and adjustment to changes in a person’s environment. Selye (1956/1984) argued that life involves constant change and adaptation. Much of this is minor and hardly noticed, not unlike the continual adjustments a person makes to the steering wheel of a car while driving it. The grooves and bumps in the road represent an uneven environment that requires small changes in steering to maintain a straight path, not unlike minor or routine stressors that one encounters every day. Major stressors present dangers more similar to oncoming cars; they may require dramatic and memorable efforts to avoid collision or driving off the road. Each adjustment involves a specific response (e.g., the minor adjustment of the wheel or more effortful maneuvering to avoid other cars). Each also appears to have a nonspecific component, composed largely of SNS and HPA arousal and bodily “support” for cognitive or behavioral adjustments. When these adjustments are more substantial or sudden, they may also affect mood and behavior. Regardless, this nonspecific arousal both motivates and supports coping, making it faster, “stronger,” and more effective in accomplishing the adjustments needed to adapt. Collectively, the specific coping directed at threatening, harmful, or otherwise upsetting situations and the nonspecific activation supporting these responses may be considered “stress.”

There remains considerable variability in the way stress is defined or conceptualized. Consistent with the previous emphasis on adjustment and adaptation, stress can be described as “a negative emotional experience accompanied by predictable biochemical, physiological, and behavioral changes that are directed toward adaptation either by manipulating the situation to alter the stressor or by accommodating its effects” (Baum, 1990, p. 653). When challenged or threatened, both specific adjustments and supportive nonspecific activation are likely and both continue until the source of stress is eliminated or the individual has successfully accommodated its effects. In this context, stress is an adaptive process with the goal of either altering a stressful situation or adjusting to and minimizing its negative effects. When confronted with a stressor, the body responds in ways consistent with a catabolic fight-or-flight reaction. Negative health effects occur when these emergency responses are extreme or prolonged. In addition, variability in the stress process occurs through the influence of factors that affect appraisal of stressors and coping efforts.

### METHODOLOGICAL APPROACHES

Although these general and more specific models of stress have guided many studies, individual researchers' operational definitions of stress have varied. Historically, there has been an emphasis on the stimulus or stressor end of the model, often either measuring outcomes after an organism confronts a particular stressor or counting the number of accumulating life events. Other researchers focus on the emotional, physiological, or behavioral responses to stressors and use these responses to predict physical and mental health. More researchers are beginning to integrate these two elements and incorporate measures of such personal characteristics as appraisal and coping to more accurately predict who is more resilient or more vulnerable to stress.

Stimulus-based approaches often compare groups of organisms either exposed or not exposed to a particular stressor. Acute stress is often manipulated in the laboratory using such administered stimuli as noise, immobilization, and electric shock (in animals) and challenging mental tasks or threatening situations (in humans). Naturally occurring events are also examined, among them residential crowding, ambient noise, natural disasters, or life-threatening accidents. Differences across levels of exposure allow researchers to determine the impact of the stressor on physical and mental health outcomes. Another common approach is to ask participants to indicate which of a list of events occurred within a given time frame (e.g., 6–12 months). Participants can also rate each event on the amount of adjustment required to adapt to the stressor. The relations observed between life event measures and outcomes were consistent but usually modest, with life events generally accounting for less than 9% of the variance in outcome measures (for reviews, see Rahe, 1972; Sarason, de Monchaux, & Hunt, 1975; Zimmerman, 1983).

Substantial improvements have been made in the prediction of outcomes through the use of such personal interviews as those conducted through the Life Events and Difficulties Schedule (LEDS; G. W. Brown & Harris, 1989). Through the use of interview techniques, specific information regarding the actual event and its context can be gathered and rated by objective reviewers. Therefore, many of the response errors and sources of bias inherent in self-report measures can be minimized. Unfortunately, the extensive training of interviewers and raters, as well as the costs associated with lengthy individual visits with study participants, limits the feasibility of this approach. However, the incorporation of the contextual meaning of the events rather than just the occurrence of the event has increased the magnitude of the relationships found between life stress and outcomes. Using this method, researchers have demonstrated that life events and chronic difficulties contribute to the risk of developing many such mental and physical conditions as depression, schizophrenia, anxiety, myocardial infarction, multiple sclerosis, abdominal hip pain, and menstrual disorders (for a review, see G. W. Brown & Harris, 1989). More recently, chronic stress measured in this way has been linked to susceptibility to viral infection (Cohen, 2005). Clearly, identification of objective predictors of mental and physical health outcomes is valuable for the

prediction of stress consequences. However, such an approach reveals little about the way stress works or why it has these effects.

Other theories and measures of stress focus more intently on responses, arguing that it is the response that is most closely linked to outcomes or consequences and that the extent to which the event is experienced as stressful is a better metric than is the event itself. In controlled laboratory settings or in naturalistic environments, researchers can measure cognitive, behavioral, and physiological changes before, during, and/or after a stressor. Changes in these response systems can then be correlated with physical and mental health outcomes. Individual difference variables or other factors affecting how stressful events are experienced are also important predictors of both responses and outcomes. Situational factors affecting appraisals of stressors and a person's ability to resist them, as well as individual differences in appraisal or response, are critical determinants of outcomes.

There are many important intervening variables that affect interactions of the perceiver and the situation and affect appraisals of severity or the likelihood of successful adaptation. Among the more frequently studied stress mediators are perceptions of control, predictability, coping, and the availability of social support (Cohen, Gottlieb, & Underwood, 2000; Lazarus & Folkman, 1984; Revenson & Lepore, Chapter 9, this volume; Thompson, 2009; Wills & Ainette, Chapter 20, this volume). Individuals with greater perceptions of control and more social support, as well as situations characterized by appraisals of greater predictability, typically produce less stress and better outcomes. One reason for these differential effects may be the availability of and the types of coping strategies used to deal with the event. When individuals perceive that they can control the event, their perception may promote their use of more problem-focused techniques or greater acceptance, thereby alleviating much of the distress experienced. In addition, greater predictability of the event allows individuals to prepare in the time before the event to deal effectively with the situation. Similarly, perceptions of available social support may serve to enhance the coping resources of individuals through offers of tangible aid or advice (Wills & Ainette, Chapter 20, this volume).

## ACUTE AND CHRONIC STRESS

Not all exposures to stressors are equal, and it can probably be assumed that more or worse exposures have more impact than fewer or less severe exposures. Stressor intensity and duration likely interact to produce a range of potential effects. The most common distinction between acute and chronic stress is based on the duration of the stressor. However, as already noted, there is inter- and intraindividual variability in stress responding even to the same stressor. Therefore, acute and chronic stress may best be conceptualized by examining the interactions among the duration of the event itself (acute or chronic), the duration of threat perception (acute or chronic), and the duration of psychological, physiological, or behavioral responses (acute or chronic; Baum, O'Keeffe, & Davidson, 1990).

A "perfect acute" stress situation would refer to a situation characterized by an acute stressor duration, short-lived threat perception, and an acute response, typical of most laboratory stress situations. A subject in a laboratory study of stress is normally exposed to a brief (5–30-minute) stressor (or combination of stressors), views it as stressful for as long as it is present, and recovers rapidly after termination of the stressor. Chronic stress, however, is more complex. A "perfect chronic" situation would refer to a chronic event, chronic threat, and chronic responding. In reality, most stressful experiences consist of combinations of acute and chronic durations of the event, threat, and response, and this characterization may not be stable. For example, following a hurricane (an acute event), an individual may continue to experience perceived threat or harm and may exhibit such chronic responding as elevations in norepinephrine (NE), epinephrine (EPI), cortisol, heart rate (HR), and blood pressure (BP) and reductions in immune system functions. Over time, however, the individual may start to habituate to the chronic threat and show decreased stress responding

(i.e., chronic threat with short-lived responding). The goal for stress reduction is for the individual to adapt to the stress situation and no longer perceive the chronic threat or respond to it. Unfortunately, not all individuals habituate or adapt to a stressor, and chronic stress persists or can even sensitize people to new stressors.

The alterations seen in the physiological, cognitive, and behavioral response systems are generally the same in both acute and chronic stress situations; but where acute stress occurs continuously, chronic stress does not appear to be a steady-state phenomenon. Rather, responding appears to be episodic, occurring repeatedly throughout the day as reminders or unwanted intrusions accost an individual. This appears to be the case whether the stressor is still present or long past. It is unlikely that an individual is conscious of a stressor 24 hours a day, 7 days a week, 365 days a year. Instead, it seems more likely that people experience good and bad days and good and bad moments within each day. Episodes of stress may be triggered by exposures to the event, reminders of the event, or anticipation of the event. Most models of stress fail to consider the impact of this repetitive activation of stress response systems or the possibility that the experience of chronic stress may be best characterized as acute episodes of stress related to an overarching stressor.

The episodic nature of chronic stress is supported by evidence that although certain populations report higher levels of distress than comparison groups, there is considerable day-to-day and within-day variations among individuals within the group (Dougall, Baum, & Jenkins, 1998; Stone, Reed, & Neale, 1987). These variations average to consistent high levels over longer time frames. In addition to experiencing these daily fluctuations, the response systems themselves do not always covary. Each system has its own circadian or activity-based pattern of ups and downs, as well as different reactivity and recovery times (e.g., Mason, 1968; Nesse et al., 1985). For example, EPI and NE show immediate increases in response to an acute stressor, whereas cortisol responses are delayed and last much longer. Therefore, single assessments limit an individual's view of the stress process.

It is not difficult to understand why an individual faced with daily stressors (e.g., hectic commutes to work or longtime care giving to a sick relative) experiences stress or excessive demand when dealing with them. Persistence of chronic stress responding after an event is long over is more difficult to explain and is an important question for stress researchers to tackle. It has been suggested that one important element in understanding chronic stress is the occurrence of stressor-related intrusive thoughts, especially in the absence of an ongoing stressor (Baum, Cohen, & Hall, 1993; Baum, Schooler, & Dougall, 1998; Craig, Heisler, & Baum, 1996). Plenty of evidence suggests that stressor-related intrusive thoughts are a common symptom following threatening events (e.g., Holmes & Bourne, 2008; Kangas, Henry, & Bryant, 2005). Intrusive thoughts are thought to be part of ongoing cognitive processing of the event (Creamer, Burgess, & Pattison, 1992; Greenberg, 1995; Horowitz, 1986). They help an individual work through the situation. Indeed, as individuals recover, they report fewer stressor-related intrusions (e.g., Delahanty, Dougall, Craig, Jenkins, & Baum, 1997). However, intrusive thoughts tend to be unwanted, unbidden, and uncontrollable, which are characteristics common to many other types of stressors. In at least some cases, these characteristics of intrusive thoughts may make them more stressful and are related to greater chronic stress (e.g., Dougall, Craig, & Baum, 1999). Rather than being exclusively adaptive, these thoughts may serve as stressors in their own right, possibly sensitizing individuals to other reminiscent stimuli. Intrusions combined with other environmental event-related stimuli may serve to perpetuate chronic stress by eliciting the acute episodes described earlier.

## TRAUMA AND CHRONIC STRESS

Intrusive thoughts are most prevalent following extreme stressors. However, they do occur following less severe events and even after benign and positive events that occur in everyday life (Berntsen, 1996). Although positive and neutral intrusions also occur, intrusive thoughts with

negative valences are implicated in chronic stress and are probably one of the most salient hallmark symptoms of posttraumatic stress disorder (PTSD; American Psychiatric Association, 2000). Posttraumatic stress disorder is a special case of extreme stress responding following life threatening or extreme stressors. It has broad-base effects across all domains of functioning, impairing an individual's ability to function normally. Victims experience the persistent recurrence of three categories of symptoms: reexperiencing or reliving the event, emotional numbing and avoidance of trauma-related stimuli, and heightened physiological arousal (APA, 2000). In addition to intrusive thoughts, victims experience such other common symptoms as recurrent and disruptive dreams, sleep disturbances, emotional withdrawal, anxiety, dissociation, aggressiveness, hyperarousal, and an exaggerated startle response (APA, 2000).

Posttraumatic stress disorder is also characterized by unusual physiological response profiles. When victims are reminded of the trauma, cardiovascular, respiratory, and negative emotional responses are typically more exaggerated compared with reactivity to unrelated stimuli. As in chronic stress situations, circulating levels of EPI, NE, and their metabolites are elevated (Southwick et al., 2007). This chronic sympathetic-adrenal-medullary (SAM) activation is accompanied by down regulation of adrenergic receptors, thereby helping to sustain the increased output. Dysregulation of serotonin is also evident with PTSD, and use of selective serotonin reuptake inhibitors has proven effective in treating all three of the key symptom criteria (Friedman & Davidson, 2007; Southwick et al., 2007). In contrast, abnormalities in the functioning of the HPA axis are also associated with PTSD, but the nature of these findings is mixed. One body of research has found consistent suppression of cortisol related to an enhanced negative feedback and reduced adrenal capacity (e.g., Yehuda, 2002). However, these findings appear to be limited to male combat veterans and male and postmenopausal female Holocaust survivors (Southwick et al., 2007). Research with other populations, including premenopausal women and children who have comorbid symptoms of depression, has found increased cortisol levels that are associated with an increased pituitary adrenocorticotropic hormone (ACTH) response to corticotrophin-releasing factor (CRF) from the hypothalamus (Rasmusson et al., 2004; Southwick et al., 2007). ACTH travels to the adrenal cortex, where it stimulates release of cortisol; the adrenal cortex then increases its capacity to release cortisol to meet these demands. Taken together, these complex neuroendocrine alterations associated with PTSD have important implications for physical health outcomes. Research indicates that PTSD not only is a mechanism through which exposure to traumatic events may impact physical health but also serves as an independent risk factor (Schnurr, Green, & Kaltman, 2007).

The experience of trauma is not limited by the physical presence of the precipitating event. Despite the often acute nature of traumatic events, responding may last for months or years. In addition, time of onset is not limited to the time of exposure, and episodes of acute and chronic PTSD have been defined based on whether or not symptoms last less than or more than 3 months (APA, 2000). Although individual symptoms of PTSD predict subsequent diagnosis, not all the symptoms need to be present for a diagnosis to occur. Also, many of these same symptoms are exaggerations of normal stress reactions to an overwhelming event and may, in fact, serve to promote adaptation to such a situation. This observation is consistent with the pervasive finding that a majority of trauma victims do not develop PTSD, but there are still a significant number of victims (approximately 10%–25%) who are affected (Breslau, 2009; Green, 1994).

These considerations suggest that it is important to identify factors in the environment or in the individual that affect whether or not an individual experiences symptoms of posttraumatic stress or ultimately develops PTSD. Several vulnerability factors have been identified, among them a history of psychopathology and gene by environment interactions (e.g., Kilpatrick et al., 2007; Parslow, Jorm, & Christensen, 2006; Segman et al., 2005), as well as such factors that influence normal stress responses as gender, social class, social support, perceived control, and coping (e.g., Norris et al., 2002; Breslau, 2009; Kilpatrick et al., 2007; Olf, Langeland, & Gersons, 2005; Thompson, 2009).



## STRESS RESPONSES AND CONSEQUENCES

Emerging models of stress consider a range of responses and consequences of stress that bear on productivity, health, and well-being. Stress affects mood, behavior, and problem solving, changes individuals' motivation to achieve goals or engage in self-protective behavior, and appears to lessen restraints against harmful behaviors. Stress affects the whole body. The effects of stress on the SAM and the HPA axis were documented in the seminal work of Selye (1956/1984) and Cannon (1914). These systems contribute to stimulation of others and exert direct and indirect effects on metabolism and arousal. Changes in these response systems are thought to account for some of the effects of stress on health but are consistent with a mobilization of energy and as such are inherently adaptive. Increases in heart rate and blood pressure, as well as increases in the release of such neuroendocrine factors as EPI, NE, ACTH, glucocorticoids, and prolactin prepare an individual to face a stressor and fight or flee from the scene. In addition, stress-related decreases in several markers of immune system functioning have been observed (for reviews, see Segerstrom, 2010; Segerstrom & Miller, 2004). These changes could be adaptive in that when an organism is injured in battle, the swelling, fever, and other characteristics of an immune response are delayed and therefore do not interfere with the actions of the organism. However, prolonged suppression of a variety of functions could open windows of heightened vulnerability to infection or progression of neoplastic disease.

In addition to bringing about physiological changes, stress can increase such negative emotions as depression, anxiety, anger, fear, and overall symptom reporting. Unwanted or uncontrollable thoughts and memories about a stressor may also be experienced (Holmes & Bourne, 2008; Kangas et al., 2005). These stressor-related intrusions are both a symptom of stress and a stressor in their own right. Painful event-related images and thoughts may elicit their own stress response and may help to perpetuate chronic stress responding by repeatedly exposing an individual to the stressor.

Stress also affects performance. Because attention is typically focused on dealing with stressors when they are present, people may have problems attending to such more mundane tasks as balancing a checking account, monitoring computer screens, or assembling a product (e.g., Baba et al., 1998; Gilboa, Shirom, Fried, & Cooper, 2008; Kompier & DiMartino, 1995; Krueger, 1989). Unfortunately, many of these tasks may be work or safety related (e.g., writing a report or driving an automobile) and could have severe consequences if done improperly. Further, exposure to even a brief laboratory stressor has been shown to induce transient performance deficits in tasks given during the stressor or after it (Glass & Singer, 1972). These negative aftereffects occur even though physiological and emotional responding has decreased and the individual appears to have adapted to the acute stressor. Other consequences of stress include deterioration of sleep quality and quantity, increases in aggressive behaviors, and changes in such appetitive behaviors as eating, drinking, and smoking (e.g., Brunello et al., 2001; Field, Claassen, & O'Keefe, 2001; Mellman, 1997; Smith, Christiansen, Vincent, & Hann, 1999). These wide-reaching effects of stress illustrate the importance of examining the effects of stress on the whole organism rather than focusing on one system such as the SNS, reports of depression, or alcohol use. Responses across all systems work in concert to help the individual adapt by either altering the situation or accommodating its effects. Whereas these biological, cognitive, and behavioral alterations may be adaptive in the short term, chronic activation of these response systems results in wear and tear on the organism and may make the organism more susceptible to negative mental and physical health outcomes.

## STRESS AND HEALTH

Stress can affect health as well as intervene at any point in the disease process—in disease etiology, progression, treatment, recovery, or recurrence. Stress exerts these effects in three basic ways: as direct physiological changes resulting from stress-related arousal (e.g., immunosuppression, damage to blood vessels), as cognitive and behavioral changes that convey physiological changes

(e.g., intrusive thoughts, smoking, drug use), and as physiological, cognitive, and behavioral changes associated with an individual's illness that affect exposure or treatment (e.g., viral exposure, drug metabolism, treatment adherence, seeking medical help). As discussed later, stress has important implications for the onset, progression, and treatment of almost every known major disease.

Although often difficult to measure, stress appears to affect pathogenic processes that contribute to the onset of disease. One of the most salient mechanisms through which stress can promote disease is through chronic, sustained, and/or exaggerated responses, making them pathological. Prolonged feelings of depression or anxiety can interrupt normal functioning and result in the development of clinical disorders, whereas transient alterations in mood are considerably less harmful (e.g., Kendler et al., 1995; Terrazas, Gutierrez, & Lopez, 1987). Continued self-medication or use of licit or illicit drugs may lead to addiction, and eating disorders may develop from extreme alterations in eating behaviors (e.g., Meyer, 1997; Sharpe, Ryst, Hinshaw, & Steiner, 1997; Vlahov et al., 2004). Prolonged or often-repeated elevations in blood pressure may result in permanent changes contributing to hypertension, and elevated circulating levels of stress hormones may contribute to atherosclerosis and heart disease (Markovitz & Matthews, 1991). Chronic immune system suppression appears to interfere with the ability to ward off pathogens, making individuals more susceptible to such infectious diseases as colds, flu, and HIV disease (Segerstrom, 2010; Segerstrom & Miller, 2004). Stress also appears to affect tumor suppression and progression of cancer (Baum, Trevino, & Dougall, 2011; Kemeny & Schedlowski, 2007). Although exhaustive evaluations of the direct role of stress in disease etiology are difficult to conduct, recent evidence from studies of controlled viral challenges (Cohen, 2005) and wound healing (Christian, Graham, Padgett, Glaser, & Kiecolt-Glaser, 2006; Marucha & Engeland, 2007) confirm the clinically relevant impact of stress on health and disease.

Behavioral and cognitive deficits seen during stress can also affect disease by increasing an individual's chance of exposure to pathogenic agents. Individuals under stress are more likely to engage in high-risk behaviors like unprotected sex and intravenous drug use (Chiasson et al., 2005; Evans-Campbell, Lindhorst, Huang, & Walters, 2006; Wagner et al., 2009). These activities increase the likelihood that an individual will be exposed to an infectious disease or experience such unplanned consequences as pregnancy. As already discussed, decrements in performance can result in dismissal from work or injury and death as a result of inattention and lack of concentration while engaging in such important activities as driving a car or operating machinery (Baba et al., 1998; Gilboa et al., 2008; Kompier & DiMartino, 1995; Krueger, 1989). Such stress-related behaviors as smoking, alcohol use, and sedentary lifestyles may also contribute to etiology of serious health problems (Kiviniemi & Rothman, 2010).

Disease progression and treatment are also affected by stress. New feelings of depression or anxiety may interfere with treatment of preexisting disorders and can increase the likelihood of such acute disease events as heart attacks (e.g., Frasure-Smith, Lesperance, & Talajic, 1995; Mizrahi, 2010; Steptoe & Brydon, 2009; Zautra et al., 1997). Individuals in treatment for psychiatric disorders (e.g., schizophrenia, depression, substance use, or eating disorders) may relapse and experience a return of their symptoms or return to their abusive behaviors (e.g., Grilo, Pagano, & Stout, 2009; Mizrahi, 2010; Monroe & Harkness, 2005; Park et al., 2009; Sinha, 2007). Physiological changes may also interfere with the metabolism of prescription drugs (Grunberg, Berger, & Hamilton, 2011), and behavioral and cognitive stress effects may impair treatment, reducing the likelihood that patients comply with instructions, prescriptions, and recommendations given by their medical teams (e.g., Brickman & Yount, 1996; Perez, Cruess, & Kalichman, 2011). In addition, transient stressors, especially those producing such strong emotions as depression, anxiety, or outward expressions of anger, can promote platelet aggregation, contributing to the underlying cardiovascular disease state, or can trigger such acute cardiac events as myocardial infarction and sudden cardiac death (Steptoe & Brydon, 2009).

Stress can also retard the speed of recovery, make adjustment to diseases and injuries more difficult, and increase the rates of disease recurrence. Patients who report more stress have a more

difficult time recovering from and adjusting to illnesses or injuries than do individuals who report less stress (e.g., Grassi & Rosti, 1996; Kiecolt-Glaser, Stephens, Lipetz, Speicher, & Glaser, 1995; Marucha, Kiecolt-Glaser, & Favagehi, 1998; Mullins, Chaney, Pace, & Hartman, 1997). Stress management interventions given prior to surgery or other medical procedures have improved subsequent healing and rehabilitation, however, and stress management interventions have been incorporated into multidisciplinary cardiac rehabilitation programs to improve cardiovascular risk factors and promote recovery (e.g., Blumenthal et al., 2005; Enqvist & Fischer, 1997; Ross & Berger, 1996; Schneiderman & Orth-Gomér, Chapter 29, this volume). Stress may also make patients in remission more vulnerable to recurrence of their disease; among people with latent viruses (e.g., HSV, EBV, HIV), stress has been linked to reactivation of the viruses and disease symptoms (Aiello, Simanek, & Galea, 2010; Glaser, 2005). Stress has also been linked with recurrence of cancer, which is possibly a result of stress's immunosuppressive effects (Baltrusch, Stangel, & Titze, 1991).

Most of these health effects are linked with episodes of long-term or chronic stress. However, acute stressors may also affect health by making an individual more vulnerable during a time of exposure to an infectious agent or by triggering such acute events as heart attacks, as discussed earlier. The difference between acute and chronic stress is not always clearly defined, and most of the models already discussed fail to make a distinction between the two. Closer examination of the meaning and implications of short- and long-term stress needs to be addressed before examining the relationship between stress and disease more closely.

## STRESS AND DISEASE

Although stress affects everyday functioning and well-being, its more profound consequences are manifest as influences on disease processes. Whereas the effects of stress on the immune system are one putative mechanism for explaining the relationship between stress and disease, other stress response systems affect disease processes as well. Further, these effects are apparent at several levels and stages of ill health. By examining the effects of stress on some major diseases, the importance of stress in the disease process as well as the integration of whole body responses are highlighted.

In addition to the effects of stress on the onset, management, and recovery from disease, there is evidence to suggest that people with chronic diseases experience more stress, that is, that these illnesses (or aspects of their management) can cause stress. Patients tend to report more social problems and psychological symptoms than do people in the general population, and more psychiatric morbidity has been associated with poorer disease management (e.g., R. F. Brown, Tennant, Dunn, & Pollard, 2005; Dougall et al., 1998; Irvine, Brown, Crooks, Roberts, & Browne, 1991; Mayou, Peveler, Davies, Mann, & Fairburn, 1991; Mullins et al., 1997). This bidirectional relationship between stress and disease has led researchers to propose that in some cases a vicious cycle develops, in which chronic diseases predispose individuals to psychiatric symptoms and social problems that then impair self-care and result in poor disease management. Disease flare-ups, recurrence, or increases in symptoms then further exacerbate psychiatric symptoms and social problems (e.g., Mayou et al., 1991). In the next sections of this chapter we review the evidence for the association of stress with several disease conditions.

## STRESS AND IMMUNE-MEDIATED DISEASE

One of the most salient mechanisms through which stress can make an individual more vulnerable to disease is the link between stress and immune functioning. Both acute and chronic stress have been linked to alterations in immune system activity (Segerstrom, 2010; Segerstrom & Miller, 2004). In response to acute stressors, there is a redistribution of immune cells, especially increases in numbers of circulating natural killer cells and large granular lymphocytes that are important components of the immune system's first line of defense against pathogens (natural immunity; e.g., Dhabhar & McEwen, 1997). However, there is a concomitant down regulation of such specific

immune responses as the ability of B and T lymphocytes to proliferate, which is also evidenced during chronic stress exposure (e.g., Bachen et al., 1992; Delahanty et al., 1996; Zakowski, Cohen, Hall, Wollman, & Baum, 1994). Further evidence of immunosuppression during chronic stress is seen in decreased activity of natural killer cells that are important for destroying viral and cancer cells (e.g., Esterling, Kiecolt-Glaser, Bodnar, & Glaser, 1994; Ironson et al., 1997). Furthermore, stress can interfere with seroconversion following vaccination, decreasing the amount of protection normally afforded (e.g., Pedersen, Zachariae, & Bovbjerg, 2009; Phillips, 2008). Therefore, stress-induced immunosuppression could render the body less able to fight off pathogens or recover from injuries.

Immune system alterations are related to SAM and HPA activation (i.e., increases in catecholamines and glucocorticoids). Lymphatic tissue and immune cells express adrenergic and noradrenergic receptors and stress-related elevations in catecholamines trigger redistribution of immune cells and alter immune cell function, including production of cytokines and development of inflammation (Glaser & Kiecolt-Glaser, 2005; Kemeny & Schedlowski, 2007). Activation of the HPA axis and release of glucocorticoids work in conjunction with SAM activation to produce suppression of specific immune system activity and further elevate inflammatory markers (Glaser & Kiecolt-Glaser, 2005; Kemeny & Schedlowski, 2007). Chronic inflammation has been implicated in such chronic disease processes as the development and progression of cardiovascular disease, metabolic syndrome, diabetes, and such inflammatory conditions as arthritis. Even acute bouts of stress have been associated with increases in inflammation, suggesting important implications for health outcomes (Steptoe, Hamer, & Chida, 2007). Such psychological variables as control, predictability, social support, and availability of a behavioral response have also been shown to mediate immune system alterations associated with stress. In general, uncontrollable or unpredictable stressors or situations affording little social support produce greater immunosuppression (e.g., Sieber, Rodin, Larson, Ortega, & Cummings, 1992; Uchino, Cacioppo, & Kiecolt-Glaser, 1996; Zakowski, 1995).

### INFECTIOUS ILLNESS

Infectious illness refers to diseases caused by pathogens (e.g., viruses, bacteria) that is communicable between two or more individuals. Primary defenses against these illnesses are immune system activity that seeks to control and destroy infectious agents. Because stress is associated with periods of lowered immune activity, it should also be associated with less resistance to infectious illnesses. Research in both controlled and natural settings provides support for the contention that stress is associated with vulnerability to infectious illness (Glaser & Kiecolt-Glaser, 2005; Kemeny & Schedlowski, 2007). In natural environments, increases in stress often precede the onset of illnesses (Kasl, Evans, & Niederman, 1979; Rahe, 1972; Stone et al., 1987). In addition, physiological reactivity moderates the effects of stress on illness, with high reactors developing more respiratory infections than low reactors (Boyce et al., 1995).

Clinical markers of immune system functioning have also been examined as indicators of the effects of stress on immunity. Chronic stress can interfere with the body's ability to heal following an injury. In addition to indicating delays in wound healing, there is evidence for stress-induced alterations in the wound milieu, including changes in proinflammatory cytokines and enzymes (Christian, Graham, Padgett, Glaser, & Kiecolt-Glaser, 2006; Marucha & Engeland, 2007). Reactivations of such latent viral infections as herpes simplex virus (HSV) and Epstein-Barr virus (EBV) also appear more likely when individuals are experiencing ongoing stress (Aiello et al., 2010; Glaser, 2005).

In addition to these, correlational studies are studies in controlled environments. Recent advances in measurement procedures have made it possible to conduct studies in controlled environments, confirming that individuals with high levels of life stress are more likely to become infected and display symptoms, for example, when exposed to cold viruses (Cohen, 2005). In these studies, healthy participants are typically exposed to known amounts of a cold virus and then quarantined

in a hotel room for 5 or more days. Two major disease outcomes are examined. One outcome is the rate of viral infection, typically ranging from 69% to 100% of the sample exposed to the virus; and the other is the actual incidence of cold symptoms, ranging from 19% to 71% of the sample (Cohen et al., 1998; Cohen, Tyrrell, & Smith, 1991; Stone et al., 1992). Although individuals cannot have cold symptoms without being infected, they can be infected without showing signs of a cold. Rates of both viral infection and cold symptoms increase in a dose-response fashion with the amount of life stress the participants report (Cohen et al., 1991, 1998; Stone et al., 1992). More severe and chronic stressors tend to have a greater impact on disease development than do less severe or acute stressors (Cohen et al., 1998).

## HIV DISEASE

A chronic illness that affects more than one million Americans (CDC, 2008a), HIV is a retrovirus that preferentially attacks the CD4<sup>+</sup> T lymphocytes, ultimately causing depletion of these cells (Westergaard & Gupta, 2009). After an acute infection phase, the virus can remain latent for years in the form of a provirus. Reactivation of the virus leads to viral replication, destruction of the CD4<sup>+</sup> T-cells, and progression of the disease to AIDS, the acquired immunodeficiency syndrome, which is characterized by a compromised immune system and development of such symptoms as opportunistic infections and cancers.

Perhaps the most salient effects of stress on vulnerability to HIV infection are the behavioral changes associated with high-risk status, especially greater use of such substances as IV drugs and increases in high-risk sexual encounters (Chiasson et al., 2005; Evans-Campbell et al., 2006; Wagner et al., 2009). HIV disease is an infectious illness. Therefore, reductions in immunocompetence associated with stress, as described earlier, also place an individual at greater risk for contracting HIV if exposed (Solomon, Kemeny, & Temoshok, 1991). In addition, reactivation of latent herpes viruses that can be triggered by chronic stress (e.g., herpes simplex virus Type 2 and Epstein-Barr virus) has been identified as a risk factor for HIV acquisition (Aiello et al., 2010).

Considerable more research has examined the effects of stress on HIV disease progression. Living with HIV disease can be stressful for numerous reasons. For example, the disease can have an unpredictable time course, and patients may experience distrust in the medical system and stigma related to their disease (Whetten, Reif, Whetten, & Murphy-McMillan, 2008). Chronic stress either from living with HIV or from experiencing other stressful events has been associated with greater progression of HIV disease as evidenced by decreases in CD4<sup>+</sup> cell numbers and increases in viral load, disability, and mortality (Chida & Vedhara, 2009; Leserman, 2008). Also, patients who are experiencing stress are less likely to adhere to the rigorous highly active antiretroviral therapy (HAART), for which strict adherence is necessary to keep HIV replication suppressed (Whetten et al., 2008). In contrast, there is emerging evidence that such positive psychosocial factors as optimism, spirituality, and active coping are associated with slower disease progression (Ironson & Hayward, 2008). Not surprisingly, interventions designed to reduce stress among patients with HIV disease have substantial effects on decreasing symptoms of stress and depression and improving quality of life (J. L. Brown & Vanable, 2008; Crepaz et al., 2008; Scott-Sheldon, Kalichman, Carey, & Fielder, 2008). A few cognitive behavioral interventions have also demonstrated improvements in such disease-related outcomes as CD4<sup>+</sup> cell counts and viral load, especially if combined with a medication adherence intervention (Antoni, Carrico, et al., 2006; Antoni et al., 2005; Crepaz et al., 2008). Therefore, stress management interventions have become a common component of tertiary interventions for patients with HIV disease and AIDS.

## CANCER

The relationships among stress, immunity, and cancer appear to be more complex than those underlying the pathophysiology of infectious diseases. In part, this is a consequence of the chronic nature

of cancer and the more acute time frames of most infections. In addition, immune activity has an unknown role in controlling initial mutations in the process from benign to malignant neoplastic growth and a suspected, but underexplored, role in resistance to tumor growth and metastatic spread. There is better general evidence that stress is associated with cancer progression and may be linked to survival and quality of life. Again, problems related to the chronic nature of cancer development and treatment have made studies of stress and cancer incidence difficult; and research on disease course, recurrence, and survival share similar problems.

These problems have often left the literature linking stress and cancer weak and open to alternative explanations. Inconsistent findings are also an issue, with few studies finding relationships between major stressors or depression and the development of cancer (Chida Hamer, Wardle, & Steptoe, 2008; Kemeny & Schedlowski, 2007; Lutgendorf, Costanzo, & Siegel, 2007; Reiche, Nunes, & Morimoto, 2004). A recent meta-analysis (Chida et al., 2008) demonstrated that higher levels of distress were associated with higher cancer incidence rates, especially among studies that had large sample sizes and long time frames. However, findings varied based on the quality of the study design, the psychosocial risk factor, and the type of cancer examined. Again, problems of timing and tracking of disease-related events makes this research difficult and uncontrolled. Tumors develop over years or decades and grow irregularly. Furthermore, several different mutagenic events are needed to produce malignancy, suggesting several points at which stress could affect initial development. Such mechanisms as cellular DNA repair have been proposed, and some studies have linked stress and its neuroendocrine changes to poorer DNA-repair capabilities (e.g., Flint, Baum, Chambers, & Jenkins, 2007; Gidron, Russ, Tissarchondou, & Warner, 2006). In addition, chronic stress has been associated with shortening of the telomere length and alterations in telomerase activity that may promote accelerated cell aging and make the cell more vulnerable to DNA damage (Epel et al., 2004; Epel et al., 2006).

There is some evidence of stress-related modulation of cancer course and of immune system involvement. Studies of life stress and cancer have suggested that higher levels of stress are associated with poorer quality of life, cancer recurrence, and shorter survival (e.g., Chida et al., 2008; Golden-Kreutz et al., 2005; Palesh et al., 2007). However, some investigators have not found evidence of life-stress associations with cancer course (Eil, Nishimoto, Mediansky, Mantell, & Hamovitch, 1992; Jamison, Burish, & Wallston, 1987). Nevertheless, stress has been associated with alterations in biological and behavioral responses that have also been implicated in cancer progression: inflammation, hormone levels, immune markers, lack of physical activity, and nonadherence to treatment regimens (Antoni, Lutgendorf, et al., 2006). For example, there is some evidence that coping, social support, and other stress mediators are associated with cancer recurrence and length of survival (Chida, Hamer, Wardle, & Steptoe, 2008; Helgeson & Cohen, 1996; Petticrew, Bell, & Hunter, 2002). The presence of conflicting findings may be because studies have not consistently examined the impact of cancer-related stress on disease course; nor has systematic consideration of stressor timing issues, coping, or social assets been characteristic of this work.

Cancer diagnosis and treatment can be a stressful event in its own right, further complicating the stress and cancer-course relationship. Many patients with cancer do not report psychosocial problems, but a significant group can report symptoms of stress, depression, and even posttraumatic stress disorder (Kangas et al., 2005; Snyderman & Wynn, 2009; Spiegel & Giese-Davis, 2003). These symptoms appear to be more pronounced among patients diagnosed with cancers that have poorer prognoses (Kadan-Lottick, Vanderwerker, Block, Zhang, & Prigerson, 2005).

A multitude of interventions have been developed and disseminated to cancer patients aimed at decreasing stress, improving quality of life, and altering disease outcomes. Many of these interventions are targeted for a particular type of cancer, focusing on the needs and obstacles specific to that disease. For example, interventions with breast cancer patients may have components on body image and sexual functioning, whereas smoking cessation may be a major component of interventions that target patients with head and neck cancers. These interventions appear to improve quality

of life, but whether or not they affect disease outcomes and survival are equivocal (Coyne, 2009; Coyne, Stefanek, & Palmer, 2007; McGregor & Antoni, 2009). Therefore, the evidence that stress affects cancer course is suggestive and encouraging but far from definitive or complete.

### RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a debilitating chronic disease that afflicted approximately 1.5 million adults in the United States during 2007 (Myasoedova, Crowson, Kremers, Therneau, & Gabriel, 2010). It is characterized by abnormal autoimmune responses that result in joint inflammation and destruction (Firestein et al., 2008). Some cases also involve the production of autoantibodies called rheumatoid factor. As with other chronic diseases, people with RA experience many limitations and disease-related stressors. The most frequent stressors patients report are taking care of their disease, their lack of control over the disease, and the resultant fatigue, pain, and functional impairment (Katz, 1998; Melanson & Down-Wamboldt, 1995).

In addition to the inherent stressfulness of RA is that disease activity and symptoms are exacerbated by the occurrence of daily stressors (Herrmann, Scholmerich, & Straub, 2000). Similar to the stress and disease relationship observed in diabetes and other chronic diseases, a cyclic pattern can develop in which RA leads to increases in stress, which in turn exacerbates RA symptoms. However, the relationship between stress and disease activity is not clear-cut. The type of stressful event as well as such important psychosocial factors as spousal support, optimism, and coping can alter the relationship between stress and RA (Treharne, Lyons, Booth, & Kitas, 2007; Zautra et al., 1998). For example, pain flares and increases in disease activity in rheumatoid disease tend to be preceded by interpersonal stress (Zautra & Smith, 2001). In addition, symptoms of pain and fatigue may be moderated by such psychosocial factors as depressive symptoms or the interaction of positive and negative interpersonal events (Finan et al., 2010; Smith & Zautra, 2008; Zautra et al., 2007). Minor types of stressors appear to affect RA disease activity and symptoms differently than do such major life events as the death of a loved one. Although daily stress has been linked to exacerbation of RA, major life events have actually been associated with decreases in disease activity (Potter & Zautra, 1997).

This finding is supported by differences in immunological responses in RA patients to minor and major stressors. Some researchers have suggested that acute, minor stressors are generally associated with increases in immune system activity, whereas major stressors are generally associated with decreases in the same immune parameters (Huyser & Parker, 1998; Zautra et al., 1989). Several components of the immune system are responsible for the joint inflammation and destruction seen in RA, especially T-cells, autoantibodies from B-cells, and release of inflammatory cytokines. Therefore, increases in the activity of these cells in response to minor stress should be associated with increases in disease activity. Likewise, the decreases in immune system activity following major stressors should be associated with less disease activity (Herrmann et al., 2000; Huyser & Parker, 1998; Potter & Zautra, 1997).

These differential effects appear to be mediated by the release of catecholamines and cortisol (Herrmann et al., 2000; Huyser & Parker, 1998). Rheumatoid arthritis is typically characterized by decreases in HPA axis activity (i.e., cortisol) and increases in SAM activity (i.e., epinephrine and norepinephrine). Each of these systems has opposing effects on RA management and symptoms. Cortisol has important anti-inflammatory actions that decrease RA activity by reducing the chemical activators of the inflammation process and by suppressing the immune system. Consequently, corticosteroids are often prescribed to RA patients to help manage their symptoms (O'Dell, 2007). In contrast, SAM activation has been associated with changes in immune activity and RA symptoms (Huyser & Parker, 1998). Also, RA patients have heightened SAM reactivity to minor stressors (Zautra et al., 1998). Although both catecholamine and cortisol levels increase in response to stress, it has been proposed that the heightened SAM reactivity to minor stressors counteracts any anti-inflammatory effects of HPA axis activation and cortisol release and results in exacerbations of

RA activity and symptoms (Huysen & Parker, 1998). In contrast, RA patients who report major life events may experience dramatic increases in HPA axis activation and cortisol release, which may in turn result in decreases in disease activity (Huysen & Parker, 1998; McFarlane & Brooks, 1990).

Although stress can have a profound impact on the etiology and course of RA, there is a subset of RA patients who appear to be immune to its effects. In these patients, genetic and etiological influences appear to be more influential in determining RA symptoms (Rimon & Laakso, 1985). Two subgroups of RA patients have been identified based on whether or not RA patients are seropositive for the autoantibody rheumatoid factor. In patients who are seronegative, the occurrence of negative life events is associated not only with increases in disease activity but also with the onset of the disease. In contrast, in people who are seropositive no such relations exist (Stewart, Knight, Palmer, & Highton, 1994), suggesting that vulnerability to stress is linked to the physiology of the disease process.

### **METABOLIC DISEASE**

Stress has been implicated in the development of metabolic disorders, especially the onset and progression of metabolic syndrome, cardiovascular disease, and diabetes. Metabolic syndrome is a constellation of metabolic symptoms that when present confer high risk of development or progression of such disorders as cardiovascular disease, hypertension, and diabetes. The key component of the syndrome is visceral obesity or the accumulation of fat around the middle. To be classified as meeting criteria for metabolic syndrome, a patient must also present with at least two of the four remaining features: high levels of fasting plasma glucose (or diabetes), elevated blood pressure, raised levels of triglycerides, and reduced levels of high-density lipoproteins (Alberti, Zimmet, Shaw, & IDF Epidemiology Task Force Consensus Group, 2005). Physiological arousal associated with stress, especially of the HPA axis, has been identified as a key pathway linking stress to the onset and progression of metabolic syndrome (Kyrou, Chrousos, & Tsigos, 2006; Rosmond, 2005). Chronic increases in cortisol, such as those exhibited during stress, can inhibit insulin excretion from the pancreas, promote insulin resistance, alter lipid metabolism, and change the distribution of adipose tissue to produce visceral obesity. Activation of both the HPA axis and the SAM axis promotes such cardiovascular disease processes as hypertension and atherosclerosis. Metabolic syndrome is also characterized by chronic inflammation in part attributable to increased release of proinflammatory cytokines from the visceral adipose tissue (Kyrou et al., 2006). Increases in inflammation feed back to the HPA axis, signaling further release of cortisol and thereby creating a harmful cycle. Fortunately, there is a greater awareness now of metabolic syndrome, and efforts are being made to develop interventions that will disrupt these physiological pathways through alterations in lifestyle: for example, better nutrition, increased physical activity, or decreased stress (e.g., Diabetes Prevention Program Research Group, 2002; Tuomilehto et al., 2001).

### **CARDIOVASCULAR DISEASE**

Stress can be implicated throughout the natural history of cardiovascular disease (CVD), in its formation, its progression, and its triggering of a cardiac event. Stress affects CVD mainly through its influences on behavioral factors and activation of the SAM and HPA axes. In particular, elevations in epinephrine and norepinephrine lead to increased beta and alpha receptor activity (Kamarck & Jennings, 1991; Markovitz & Matthews, 1991). Briefly, beta activation increases heart rate and heart contractility, therefore increasing cardiac output and blood pressure (Guyton & Hall, 2006). Alpha activation causes vasoconstriction of the arteries and veins and causes increases in total peripheral resistance and venous return, both of which increase blood pressure (Guyton & Hall, 2006). Dysregulation of the HPA axis contributes to elevated lipids and chronic inflammation that promote development and progression of cardiovascular disease processes, among them atherosclerotic plaque development (Kyrou et al., 2006). All these physiological events may contribute to



CVD. For example, with an increase in blood flow, shear stress on the arteries is increased, causing endothelium damage, inflammation, and plaque formation and/or rupture (Traub & Berk, 1998). This, along with sharp increases in epinephrine, stimulates platelet activation and the sequelae that follow (Markovitz & Matthews, 1991; Wenneberg et al., 1997). Activation of the parasympathetic nervous system (PNS) can have opposite effects on the heart and blood vessels, and extensive PNS activation can also lead to cardiac events (Lane, Adcock, & Burnett, 1992; Podrid, 1984).

Stress can contribute to atherosclerosis and other underlying CVD processes by increasing heart rate and decreasing diastolic and washout periods in recirculation zones, leading to increased contact of the blood constituents and vessel walls (Markovitz & Matthews, 1991; Traub & Berk, 1998). Platelet aggregation, along with coronary vasoconstriction and plaque rupture, can lead to such other priming processes as thrombosis, ischemia, and acute myocardial infarction. As discussed earlier, stress and its related emotional indices (e.g., hostility) increase platelet aggregation through induction of the autonomic nervous system (ANS) (Kamarck & Jennings, 1991; Markovitz & Matthews, 1991; Wenneberg et al., 1997).

Psychological stress is also associated with transient changes in coronary circulation and metabolism, along with the other coronary changes discussed earlier. Stress elicits such physiological changes as autonomic activation and inflammation that can trigger arrhythmias, myocardial ischemia, and plaque formation or eruption that can, in turn, ultimately lead to such clinical events as angina, ventricular tachycardia, myocardial infarction, or even sudden cardiac death (Steptoe & Brydon, 2009). For example, stress may reduce oxygen delivery to the heart and thereby lower the threshold for myocardial ischemia or may trigger acute arrhythmic events through activation of the ANS, making myocardial infarction more likely. Recent evidence has also suggested that mental stress-induced ischemic episodes are good indicators of 5-year rates of cardiac events (Jiang et al., 1996). In addition, stress-induced silent ischemia (ischemia without angina) occurs much more frequently than is detectable by some clinical measures (Deanfield et al., 1984; Modena, Corghi, Fantini, & Mattioli, 1989). There is also evidence that such acute stress events as public speaking and anger-provoking situations can disrupt cardiac electrical potential and lead to arrhythmias and other acute cardiac events, including myocardial infarction (Steptoe & Brydon, 2009). Cardiac events may also be linked to an individual's prevailing psychological state. For example, markers of CVD are associated with anxiety and depressive disorders, anger, and coping styles (Dedert, Calhoun, Watkins, Sherwood, & Beckham, 2010; Grippo & Johnson, 2009; Hamer & Malan, 2010; Steptoe & Brydon, 2009). Therefore, intervention efforts are aimed at preventing cardiac events by targeting multiple lifestyle risk factors, among them physical activity, nutrition, and stress management. These multifactorial lifestyle interventions have demonstrated some success at decreasing the incidence of cardiac events and death and may offer promise for CVD patients (Angermayr, Melchart, & Linde, 2010).

## DIABETES

Just about every neuroendocrine system responds to stress. Hormonal control is essential for individuals with endocrine disorders; if this control is upset by stress, the hormonal balance is lost and disease symptoms worsen. In addition to having direct effects on hormonal levels, stress affects many of the risk factors associated with disease onset and flare-ups, among them diet, licit and illicit drug intake, and compliance with treatment regimens.

One of the most common neuroendocrine disorders is diabetes mellitus, affecting approximately 8% of the U.S. population (Centers for Disease Control and Prevention, 2008b). There are two primary types of diabetes mellitus, insulin-dependent or Type 1 and insulin independent or Type 2 (Amorosa & Swee, 2007). Both disorders are the result of high blood glucose levels and are characterized by such symptoms as blurred vision, unexplained fatigue, and increases in thirst and urination. A primary fuel for all body cells, circulating glucose enters cells to be used through the action of another hormone called insulin. In Type 1 diabetes, the immune system attacks the

insulin-producing cells in the pancreas, slowing insulin production and decreasing the amount of glucose that can be used by cells. The onset of Type 1 diabetes usually occurs during childhood, with 15,000 youths diagnosed a year, and is more common among whites than among other racial groups (CDC, 2008b).

In contrast, Type 2 diabetes typically occurs later in life, but there are still 5.3 new diagnoses per 100,000 youths each year, increasing concerns over such behavioral factors as poor diet and lack of physical activity that contribute to diabetes onset (CDC, 2008b). In addition, Type 2 diabetes is more commonly diagnosed among such minority ethnic groups as American Indian, Hispanic American, and African American populations. Type 2 diabetes develops gradually over time as the cells in the body become resistant to the effects of insulin, thereby decreasing the amount of glucose that can enter the cells to be used. Although both Type 1 and Type 2 diabetes are more prevalent when there is a family history of the disease and appear to have genetic links (Amorosa & Swee, 2007), Type 2 diabetes is also associated with several other behavioral and physiological risk factors. The most common Type 2 risk factors are older age, ethnicity, being overweight, being a smoker, having high blood pressure, having high levels of fat in the blood, and being a woman who has had gestational diabetes (Amorosa & Swee, 2007).

Stress does not directly cause diabetes but may be a risk factor for the onset and progression of both types of the disease (Boyer, 2007; Fisher, Thorpe, DeVellis, & DeVellis, 2007; Ionescu-Tirgoviste, Simion, Mariana, Dan, & Iulian, 1987). For example, part of the stress response is oriented toward liberation of large quantities of glucose for cells to use for energy. In Type 1 diabetes, stress may overwhelm the pancreas's ability to produce insulin and, as a result, unmask the diabetes sooner than the onset would normally occur. Similarly, in Type 2 diabetes, stress hormones interfere with insulin use in an already compromised system, resulting in earlier detection of diabetic symptoms. Furthermore, stress plays a role in the risk factors associated with diabetes onset (e.g., obesity and high blood pressure) and can impact treatment by interfering with glycemic control (Boyer, 2007). Stress-related behaviors (e.g., smoking, drinking, poor nutrition, sleep disruptions, and forgetting to take medications) can impair self-care and result in abnormal glucose levels (Boyer, 2007; Clum, Nishith, & Resick, 2001; McNutt, Carlson, Persaud, & Postmus, 2002; Schnurr & Spiro, 1999).

Stress can also have direct effects on symptoms and disease management. As mentioned earlier, stress increases blood glucose levels. In Type 1 diabetes, the body does not produce enough insulin to handle the high blood glucose levels; and in Type 2 diabetes, the body cells are resistant to insulin, so blood glucose levels remain high. Therefore, high blood glucose levels associated with stress cannot be properly handled by the body (Surwit & Williams, 1996). Untreated high glucose levels are dangerous and can lead to ketoacidosis and diabetic coma (Amorosa & Swee, 2007). As with other chronic diseases, patients benefit from stress management interventions that help to decrease the stress associated with diabetes and its symptoms, improve quality of life and functioning, and improve glycaemic control in patients with either Type 1 or Type 2 diabetes (Ismail, Winkley, & Rabe-Hesketh, 2004; Plack, Herpertz, & Petrak, 2010; Winkley, Landau, Eisler, & Ismail, 2006).

## CONCLUSION

Stress is a critical crosscutting process that is basic to research, theory, and application in health psychology. It represents modifiable variance in the etiology of disease, affects nearly every behavior that contributes to good or bad health outcomes, and has direct effects on all or most bodily systems and can thereby contribute to developing health problems as well. Stress is basic to the commerce between organisms and their environments, motivating them to take action against stressors or to insulate themselves from stress effects. It also produces nonspecific catabolic arousal, driven primarily by neural-endocrine regulatory loops that support such adaptive capabilities as fight or flight. More specific aspect of stress responding, tied more closely to the stressful situation and its interaction with the organism's resources and abilities, are reflected in emotional responding and coping as well as in cognitive appraisal processes and memory.

Most people are able to adapt to stressful situations; even in the most extreme cases, it would be expected that most people would be able to cope effectively and move on to new challenges. The multiple changes that occur during stress facilitate adaptation. However, there are negative effects of stress that have been observed, including aspects of the pathophysiology of metabolic syndrome, cardiovascular disorders, infectious illnesses (including HIV disease and hepatitis), cancer, diabetes, and such autoimmune diseases as rheumatoid arthritis. These effects appear most often when stress responses are extremely intense or abnormally prolonged. They can also become manifest when resources and coping are not immediately able to overcome or displace stressful conditions. Uncontrollable stress appears to be more difficult to resist than controllable and predictable periods of threat or demand.

Quantification of contributions of stress to disease etiology and personal susceptibility to major health problems has been a slow project but has been increasingly successful in measuring harmful and beneficial effects of stress. Similarly, the ability to intervene and modify lifestyle, coping, social resources, and appraisals of major chronic illnesses, stressors, and associated conditions has continued to improve. Research during the next 10 years should continue characterizing the relationship between stress and health, with a focus on identifying long-term trajectories of stress on disease and by determining how risk and resilience factors alter this relationship. Future research should also emphasize interdisciplinary collaborations among investigators in order to examine changes among multiple stress pathways within the same sample. Such collaborations would enable researchers to apply multilevel approaches to assessing stress that will allow for more complex covariations and interactions among cognitive, behavioral, social, and physiological pathways. Researchers should also incorporate newer approaches that examine gene by environment interactions, further allowing examination of the system in its entirety rather than focusing on one specific response pathway or disease mechanism.

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