

Burnout and Risk of Cardiovascular Disease: Evidence, Possible Causal Paths, and Promising Research Directions

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Burnout is characterized by emotional exhaustion, physical fatigue, and cognitive weariness, resulting from prolonged exposure to work-related stress. The authors review the accumulated evidence suggesting that burnout and the related concept of vital exhaustion are associated with increased risk of cardiovascular disease and cardiovascular-related events. The authors present evidence supporting several potential mechanisms linking burnout with ill health, including the metabolic syndrome, dysregulation of the hypothalamic–pituitary–adrenal axis along with sympathetic nervous system activation, sleep disturbances, systemic inflammation, impaired immunity functions, blood coagulation and fibrinolysis, and poor health behaviors. The association of burnout and vital exhaustion with these disease mediators suggests that their impact on health may be more extensive than currently indicated.

Keywords: burnout, stress, depression, cardiovascular disease

Burnout, a unique affective response to stress, is a multidimensional construct consisting of emotional exhaustion, physical fatigue, and cognitive weariness, which together represent the core components of burnout (Schaufeli & Buunk, 2003; Shirom, 2003). The literature on burnout regards it as a result of continuous and prolonged exposure to stress, particularly work-related stress. The construct of burnout, thus defined, does not overlap with related affective dysfunctions, such as depression and anxiety (cf. Breninkmeijer, Van Yperen, & Buunk, 2001; D. C. Glass & McKnight, 1996; Leiter & Durup, 1994; McKnight & Glass, 1995), nor does it overlap with facets of the coping process, such as psychological withdrawal, or with aspects of the self, for example self-efficacy (Shirom, 2003). Moreover, it is conceptually distinct from a temporary state of fatigue that passes after a resting period. Burnout may occur outside of the occupational domain, and indeed burnout has been studied in a variety of fields, including sports, parenthood, and marriage (e.g., Pines, 1987). Our review is concerned primarily with burnout in work organizations.

When measured on several occasions in longitudinal studies, burnout was found to have moderate to high correlations over time.

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The cross-time (diachronic) correlations were found to range from .50 to .60 even with a time interval extending up to 8 years (Bakker, Schaufeli, Sixma, Bosveld, & Van Dierendonck, 2000; Burisch, 2002; Melamed, Shirom, & Froom, 2003; Peiro, Gonzalez-Roma, Tordera, & Manas, 2001; Toppinen-Tanner, Kalimo, & Mutanen, 2002; Van Dierendonck, Schaufeli, & Buunk, 2001). These results suggest that regardless of sample makeup, cultural context, and length of time of the follow-up survey, the phenomenon of burnout exhibits remarkable stability, attesting to its chronic nature. Most research suggests that job environment features, among them the chronic job stress of workload, are more strongly related to burnout than are personality factors such as neuroticism or demographic factors such as age (Lee & Ashforth, 1996; Schaufeli & Enzmann, 1998). Using a measure of emotional exhaustion, a recent study of twins concluded that genetic factors are probably not important in explaining burnout; nevertheless, the study suggested the existence of a familial clustering for burnout due to environmental factors, which explained 22% of its variance (Middeldorp, Stubbe, Cath, & Boomsma, 2005). Yet another study of twins (Fitzpatrick, Reed, Goldberg, & Buchwald, 2004), using a measure of excess fatigue and exhaustion, found an association between prolonged fatigue and self-reports of heart disease (after controlling for demographic variables and depression); however, this association was not influenced by a common genetic factor, thus corroborating the findings of the former study.

In several advanced market economies, for instance, the United States, the Netherlands, and the United Kingdom, there has been a sharp rise in the incidence of stress-related workers' compensation claims in recent years (cf. Schaufeli & Enzmann, 1998). In some countries, chronic fatigue is a legitimate base for a compensation claim (Schaufeli, 2003). In Sweden, “burnout” is used as a diagnosis in medical certificates (Hallsten, 2005). Schaufeli and Enzmann (1998) estimated that about 4%–7% of the Dutch working population suffered from severe burnout. In deriving this estimate, Schaufeli and Enzmann assumed that those who report experienc-

ing symptoms of burnout at work most of the time (e.g., feeling drained and used up, feeling that one's emotional resources are depleted) represent cases of severe burnout, and they conducted a reanalysis of several large-scale studies of professionals in the Netherlands. It has been suggested that the situation in the Netherlands is typical of most developed western countries (Landsbergis, 2003). Hallsten (2005) used cutoff criteria similar to those of Schaufeli and Enzmann and found that the estimated proportion of burnout among employees in a representative sample of the Swedish population is 7.4%, almost identical to the prevalence of serious burnout reported in similar studies in Finland. In Japan, work-related excess fatigue is considered one of the major occupational health problems (Kawakami & Haratani, 1999). Reviews of burnout among human service professionals, such as teachers (Guglielmi & Tatrow, 1998) and resident physicians (Thomas, 2004), suggest that burnout levels among these professionals are high and may be associated with poor health. Accumulated evidence shows that burnout may transfer from one employee to another, either directly or indirectly (for a recent review of the evidence, see Bakker, Demerouti, & Schaufeli, 2003). Therefore, burnout at work can be regarded as a major public health problem and a cause for concern for health care policymakers.

Until recently, researchers studying burnout focused on its interpersonal, attitudinal, and organizational consequences (Burke & Richardson, 1996, 2000; Cordes & Dougherty, 1993; Schaufeli & Enzmann, 1998). In the past decade, however, growing evidence has pointed to burnout's negative repercussions on health. Previous reviews on this topic have focused mainly on burnout and risk to mental health (see Leiter & Maslach, 2001; Schaufeli & Enzmann, 1998; Shirom, 2003). In this review, we focus on recently accumulated evidence suggesting that burnout might pose a risk to physical health as well. Most of the studies in this area, however, have explored the possible association between burnout and risk of cardiovascular disease (CVD) and cardiovascular-related events (among them, recurrent myocardial infarction [MI], coronary bypass surgery, percutaneous transluminal coronary angioplasty [PTCA], repeat PTCA, increase of coronary atherosclerosis, coronary stenosis and restenosis, and cardiac death). Therefore, we have chosen to focus on CVD and risk factors for CVD. We have also included in our review a few studies that suggest burnout may be associated with other health impairments and bodily disorders.

Our objectives in the present review are to provide an integrated overview of current knowledge regarding the link between burnout and CVD risk and cardiovascular-related events and to describe plausible pathways of this link. In addition, we propose potentially promising avenues for future research in this area. We start with the theoretical basis for distinguishing between stress, chronic stress, and burnout. We then discuss the concept of burnout and distinguish between burnout and related affective dysfunctions, mainly depression. Evidence that suggests burnout and depression may be differentiated at the physiological level is introduced in a later section of our review. We present the evidence concerning the effects of burnout on cardiovascular health. We then present the potential mechanisms linking burnout and CVD. Finally, we discuss the implications and directions for future research.

Stress, Chronic Stress, Burnout, and Depression: A Conceptual Clarification

Stress and Chronic Stress

Although the definition of *stress* has long been debated, a strong commonality among the various conceptual approaches has been noted. They are all interested in how environmental demands tax or exceed the adaptive capacity of individuals, in turn leading to psychological and biological changes that may place these individuals at risk of disease (Baum & Posluszny, 1999; Cohen, Kessler, & Gordon, 1997, p. 3; Lazarus, 1999). The work-related characteristics, events, or conditions that give rise to stress appraisals are often referred to as *stressors*; subjective evaluations of the stressfulness of stressors are often referred to as *stress appraisals* or *stress perceptions*; and the affective, behavioral, and biological responses to the former components of the stress process are often referred to as *strains* or *stress responses* (Hart & Cooper, 2001; Kahn & Byosiere, 1992; Pearlin, 1999). Several widely used theories in stress research are based on the conceptual distinction between perceived stress and psychological and physiological strain (Beehr & Glaser, 2005; Edwards, 1998; French, Caplan, & Harrison, 1982; Pearlin, 1999). One of the most influential models of the stress process, proposed by Lazarus and Folkman (Folkman & Lazarus, 1985; Folkman, Lazarus, Gruen, & DeLongis, 1986), argues that stress appraisals involving potential harm or threat may elicit a range of strains, including self-reported depression, as well as changes in health practices, such as smoking, and changes in how complex tasks are performed (Cohen et al., 1997).

The stress literature covers many types of stresses, including sudden traumas, critical life events, daily hassles, and chronic stresses, and it has been suggested that these types may be placed on a continuum that reflects their relative discreteness and time boundaries (Wheaton, 1999). Chronic stress is a type of stress that lasts for a long time, occurring repeatedly or continuously, often due to constant stressors embedded in the work situation or work environment (Baum, Garofalo, & Yali, 1999). Examples of chronic stresses at work, each of which has been extensively studied, include overload, within- or cross-role conflicts, injustice, inequity, uncertainty, underreward, threats of regular physical abuse, ambiguity, job insecurity, job complexity, structural constraints, and sexual harassment (Wheaton, 1997). Substantial empirical evidence links several specific chronic stresses to CVD risk factors and CVD. (For recent reviews in this area, see Belkic, Landsbergis, Schnall, & Baker, 2004; Karasek & Theorell, 1990, 1996; Krantz & McCeney, 2002; Kuper, Marmot, & Hemingway, 2002; Rosmond, 2005.) As suggested by these reviews, specific chronic stresses are prospectively linked with increased risk of CVD morbidity and mortality (e.g., Belkic et al., 2004; Kopp & Rethelyi, 2004; Strike & Steptoe, 2004) and with elevated levels of CVD risk factors (Rosmond, 2005). However, very few attempts have been made to study the combined effect of individuals' experience of chronic stresses at work on CVD risk factors and CVD-related outcomes (Belkic, 2003). This is probably due to the inherent difficulty of combining the effects of different chronic stresses that may be related to strain linearly or nonlinearly, additively or interactively, and with singular or multiple dose-response functions. For example, Belkic et al. have constructed an Occupational Stress Index, consisting of 58 equally weighted factors that are additively combined to a total score gauging the

total burden of the work environment on an individual worker (Belkic, Schnall, Savic, & Landsbergis, 2000). These 58 factors were conceptualized to reflect several stress dimensions, for example underload, high demand, strictness, time pressure, and conflict or uncertainty. Another example is an instrument constructed to gauge stress at work, the Occupational Stress Indicator (Evers, Frese, & Cooper, 2000), which includes 15 scales and 94 items in its revised and abridged version. A major limitation of such attempts is their lack of theoretical and empirical consideration of the actual reality of work environments, which are characterized by nonlinear relationships and complex interactions among types of stress (Cummings & Cooper, 1998; Edwards, 1998; Kohn & Schooler, 1973). We argue below that if one is interested in identifying individuals who may be adversely affected by many and diverse types of chronic stresses, then the assessment of burnout seems to be a viable approach.

Chronic Stress and Burnout

Given the multiplicity of chronic stresses at work (Kahn & Byosiere, 1992), differential experiencing of them in specific job families or occupations (Fletcher, 1991), and their relatively unknown interactions (Lepore & Evans, 1996), most researchers in studies designed to predict CVD end points or CVD risk factors have focused on a specific subset of stresses (e.g., Ming et al., 2004). Although there have been attempts to construct and use a general measure of stress (Spielberger & Reheiser, 1994; Stanton, Balzer, Smith, Perra, & Ironson, 2001), researchers have used measures of general job satisfaction, psychophysiological symptoms, or self-rated health to assess chronic stress at work (Hart & Cooper, 2001, p. 95). Focusing on burnout as an affective response to chronic stresses at work, a type of strain most likely to reflect the combined influence of chronic stresses, offers a promising, complementary research strategy to those presented above.

This approach to burnout research is supported by insights offered by several theories. One of the basic tenets of Hobfoll's conservation of resources (COR) theory (Hobfoll, 1989) is that individuals who lack strong resources are most likely to experience cycles of resource losses that may lead to chronic depletion of emotional, cognitive, and physical resources, namely, to progressive burnout (Hobfoll & Shirom, 2000). Lazarus's theory of the relational meaning of stress suggests that the depletion of coping resources during the coping process leads to a negative emotional reaction (Lazarus, 1999, 2001). The action theory suggests that unlike structural resources, such as professional skills and technical aids, a person's energetic resources, like vigor, emotional vitality, and cognitive liveliness, are limited, rapidly consumed during the process of coping with stress, and take time to replenish. This theory therefore proposes a rational model of resource management (Frese & Zapf, 1994). Hockey (1993, 1997) has suggested that researchers may use the extent to which individuals' coping resources have been depleted to assess the total burden of work-related demands; he regarded coping resources as including individuals' reservoirs of physical, mental, and emotional (i.e., interpersonally related) energy. As suggested by Ursin and Eriksen (2004), a cumulative process of chronic stress at work may drain an individual's energy, leading to a state of exhaustion. In accordance with these theoretical views, burnout may be used as a proxy variable to assess the extent to which individuals have experienced

work-related chronic stresses that progressively depleted their coping resources. It does not follow from this view of burnout, however, that it is causally predicted by chronic stress. Indeed, most longitudinal research on burnout lends support to the thesis that chronic stressors at work and burnout are reciprocally related over time (e.g., de Jonge et al., 2001; de Lange, Taris, Kompier, Houtman, & Bongers, 2004, 2005; Demerouti, Bakker, & Bulters, 2004; Houkes, Janssen, de Jonge, & Bakker, 2003; Janssen & Nijhuis, 2004; Schaufeli & Bakker, 2004). Other longitudinal studies, however, have supported a unidirectional effect of chronic stress on burnout (e.g., Michielsen, Willemsen, Croon, De Vries, & Van Heck, 2004; Schaufeli, Bakker, Hoogduin, Schaap, & Klader, 2001; Teuchmann, Totterdell, & Parker, 1999).

On the basis of the above theoretical ideas, we consider burnout as a unique affective response to chronic stress at work. At the core of burnout is the depletion of individual energetic resources, as represented by feelings of physical fatigue, emotional exhaustion, and cognitive weariness (e.g., Cordes & Dougherty, 1993; Pines, Aronson, & Kafry, 1981; Shirom, 2003). Two meta-analytic studies investigated the empirical relations between burnout and chronic stress. Lee and Ashforth (1996) accumulated correlations from studies using the Maslach Burnout Index (MBI; Maslach, 1982; Maslach & Jackson, 1981; Maslach & Leiter, 1997) and found that its Emotional Exhaustion scale had corrected mean correlations of .65, .53, .50, and .21 with workload, role conflict, work pressure, and role ambiguity, respectively. With the exception of work pressure, these metacorrelations were all heterogeneous, indicating that moderators were likely to be present. Lee and Ashforth argued that these relatively high metacorrelations may in part be due to a methodological artifact, namely, the stress-oriented phrasing of several items in the MBI's Emotional Exhaustion scale. Another meta-analytic study (Collins, 1999) covered three different burnout measures and six different types of chronic stressors and used a substantively larger number of samples relative to the meta-analytic study of Lee and Ashforth. Collins (1999) found considerably lower metacorrelations between overall burnout and the chronic stressors covered in her study, mostly ranging in the .30s, and also between the Emotional Exhaustion scale of the MBI and these chronic stresses, mostly in the .40s. Both meta-analytic studies support the view that burnout and chronic stress represent two distinct constructs.

Conceptualizing and Measuring Burnout

The dominant instrument in burnout research is the MBI and its successors, constructed by Maslach et al. (Maslach, 1982; Maslach & Jackson, 1981; Maslach & Leiter, 1997) on the basis of the view that burnout represents a syndrome consisting of three dimensions: emotional exhaustion, depersonalization, and reduced personal accomplishment. *Emotional exhaustion*, which refers to feelings of depleted emotional resources, is regarded as the basic individual energy component of the syndrome (Maslach, Schaufeli, & Leiter, 2001). *Depersonalization*, which refers to negative, cynical, or excessively detached responses to other people at work, was viewed by Maslach et al. (2001) as representing the interpersonal component of burnout, but it may also indicate a specific coping style following exhaustion (Moore, 2000; Shirom, 2003). The third dimension suggested by Maslach et al. is *reduced personal accomplishment*, which refers to feelings of decline in competence

and productivity and to a lowered sense of self-efficacy. This dimension represents the self-evaluation component of burnout (Maslach, 1998, p. 69), but it may also represent an individual difference variable, such as self-efficacy (Cordes & Dougherty, 1993) or self-esteem (Schaufeli & Buunk, 2003). The three-factor structure of the original MBI and its successors has been generally confirmed in many studies (for a review, see Schaufeli & Enzmann, 1998, pp 50–54). It has been argued that the psychometric confirmation of the three-factor structure of the MBI (or its successors, such as the General Survey [MBI-GS]) may reflect the fact that these factors were empirically derived from an arbitrary set of items and were not based on a priori theory (Moore, 2000; Schaufeli, 2003; Schaufeli & Buunk, 2003; Shirom, 2003) or on the possibility that each of the three components resides in a different conceptual domain (Shirom, 2003). As Moore (Moore, 2000) argued, researchers who use the unidimensional version of the MBI or its successors may inadvertently be constricting the assessment of burnout to those exhausted employees who also exhibit depersonalization and diminished personal effectiveness reactions, which may or may not be associated with the core meaning of burnout, that is, mental and emotional exhaustion. Indeed, in accordance with this view, the authors of the MBI (Maslach et al., 2001) and other researchers (Brenninkmeijer & Van Yperen, 2003) have advocated against aggregating all three components of the MBI or its successors.

The second most popular burnout measure, the Burnout Measure (BM), was constructed by Pines et al. (Pines, 1993; Pines, Aronson, & Kafry, 1981) on the basis of their view that burnout is a state of physical, emotional, and mental exhaustion caused by long-term involvement in emotionally demanding situations. Although this conceptualization of burnout is analogous to the one proposed by Shirom (1989, 2003), the BM has some inherent difficulties. Several studies reached the conclusion that the BM is not suitable for measuring burnout as a distinct phenomenon because it confounds the core of burnout, exhaustion of the individual's energetic resources, with depression and anxiety (Enzmann, Schaufeli, Janssen, & Rozeman, 1998; Shirom & Ezrachi, 2003). To the best of our knowledge, there are practically no studies that have related the BM and very few studies that have related the MBI to any aspect of physical health. In this review we focus on burnout measures that actually have been used in studies designed to investigate the physical health consequences of burnout, namely, the Shirom–Melamed Burnout Measure (SMBM; Lerman et al., 1999; Toker, Shirom, Shapira, Berliner, & Melamed, 2005) and the vital exhaustion measure (VE), as described below.

Shirom (Shirom, 1989, 2003) defined *burnout* as a constellation of an individual's feelings that he or she is emotionally exhausted, physically fatigued, and cognitively worn-out, basing this definition on the COR theory (Hobfoll & Shirom, 1993, 2000). Burnout thus (as assessed by the SMBM) is a combination of physical fatigue, emotional exhaustion, and cognitive weariness, representing the depletion and draining of three closely interrelated and individually possessed energetic resources (Hobfoll & Shirom, 2000) that can be gauged by a single burnout score. *Physical fatigue* refers to feelings of tiredness and low levels of energy in carrying out daily tasks at work. *Emotional exhaustion* refers to the interpersonal aspect of burnout, namely, feeling that one lacks the energy needed to invest in relationships with other people at work.

Cognitive weariness refers to feelings of slow thinking and reduced mental agility.

Appels and his colleagues introduced the construct of vital exhaustion, which refers to a state characterized by excess fatigue, lack of energy, increased irritability, sleep disturbances, and feelings of demoralization. Vital exhaustion, a construct conceptually akin to burnout, has been assessed by two versions of the Maastricht Questionnaire (MQ), the 21-item version (Appels, Hoppener, & Mulder, 1987) and the 9-item version (Kop, Hamulyak, Pernot, & Appels, 1998), and by using the Maastricht Interview for Vital Exhaustion, a standardized interview (Meesters & Appels, 1996). The short form of the MQ, the 9-item measure, has 5 items reflecting physical exhaustion, 2 items tapping sleep disturbances, 1 item gauging anxiety, and 1 gauging depression. Therefore, findings based on the full MQ (21 items) and those based on the short 9-item version differ in the respective weights of the above major components. Recently, it has been shown that like burnout, vital exhaustion is also associated with work stress (Schnorpfeil et al., 2002).

Empirical data indicate that various measures of burnout are closely correlated. The SMBM was found to be closely correlated ($r = .68$) with the MQ (Lerman et al., 1999) and to be closely correlated ($r = .74$) with the Emotional Exhaustion scale of the MBI (Grossi, Perski, Evengard, Blomkvist, & Orth-Gomer, 2003) and with the BM ($r = .74$) (Soares & Jablonska, 2004). These correlations suggest that most burnout scales probably measure a common factor representing emotional and physical exhaustion (cf. Collins, 1999; Lee & Ashforth, 1996).

Burnout and Depression

All approaches toward conceptualizing burnout include a component of felt fatigue or low levels of physical energy. These symptoms also appear as one of the nine criteria for diagnosis of a major depressive disorder and as one of the seven criteria leading to diagnosis of low-level depression or dysthymia (Aggen, Neale, & Kendler, 2005; Suls & Bunde, 2005). Moreover, the same symptoms appear in some depression symptomatology scales, such as the Beck Depression Inventory (Beck, Steer, & Carbin, 1988; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Therefore, this common symptom of fatigue or loss of energy suggests the possibility of a degree of overlap between burnout and depression and has led to the suggestion that these constructs are essentially interchangeable (Hemingway & Marmot, 1999). This problem is aggravated when measures of burnout include other symptoms of depression, such as sleep disturbances or distress, as is the case with the VE, or feeling sad or blue, as is the case with the BM. This is a major difference between the SMBM and the VE. Yet another salient difference between the SMBM and the VE is that the SMBM arose from an a priori theoretical model, whereas the VE arose from clinical observations, much like the MBI (Appels, 2004).

Empirical evidence shows that burnout measures, including the VE, have positive moderate correlations with depression. On the basis of 12 studies, Schaufeli and Enzmann (1998) found that the emotional exhaustion component of burnout (gauged by the MBI) and depression share on average 26% of their variance. Schaufeli and Enzmann reported in their meta-analysis that the relationships between depression and the other MBI components, depersonal-

ization and personal inefficacy, are much weaker, sharing 13% and 9% of their variance, respectively. Subsequent research provided additional evidence that burnout and depression are positively and moderately correlated (Bakker, Schaufeli, et al., 2000; Brenninkmeijer, Van Yperen, & Buunk, 2001; Iacovides, Fountoulakis, Moysidou, & Ierodiakonou, 1999; Sears, Urizar, & Evans, 2000; Thomas, 2004), with correlations similar to those reported by Schaufeli and Enzmann. In a similar vein, vital exhaustion was found to correlate with depression. In a prospective study of a large sample of healthy men, Appels and Mulder (1988) found that vital exhaustion was composed of three factors—fatigue, depressive affect, and irritability—and that the risk of subsequent myocardial infarction was attributable to the fatigue dimension of vital exhaustion. Kop et al. (1998) found a correlation of .62 between vital exhaustion and a measure of depression in a very large and representative sample of Hungarian adults. Kop et al. also reported that vital exhaustion and depression were differentially associated with behavioral risk factors for CVD. In a study of a representative sample of the employees of an aircraft manufacturer in Germany, Kudielka, von Kanel, Gander, and Fischer (2004) found that vital exhaustion and a common depression scale loaded on different factors and concluded that depressive symptoms, as well as dysphoric mood, were distinct from the concept of vital exhaustion, thus supporting an earlier study by Appels et al. (van Diest & Appels, 1991). In contrast to the above pattern of results, studies of the relationships between depression and vital exhaustion in patients with MI found that the two concepts are highly correlated and that this correlation did not diminish after controlling for age, sex, and comorbidity (McGowan et al., 2004; Wojciechowski, Strik, Falger, Lousberg, & Honig, 2000). Nevertheless, studies of patients with CVD may reflect the impact of the disease on both depression and vital exhaustion. A recent review of depression as a risk factor for CVD (Suls & Bunde, 2005) concluded that vital exhaustion and depression are not synonymous, because vital exhaustion does not include sadness, guilt, hopelessness, and feelings of worthlessness, which are considered basic features of depression.

The burden of the evidence reviewed above, including a meta-analytic study, leads to the conclusion that burnout and depression are two distinct constructs. Conceptually, burnout is distinct in that it is dependent on the quality of the social environment at work (Schaufeli & Enzmann, 1998), whereas depression is a global state that pervades virtually every aspect of an individual's environment. On the basis of COR theory, Hobfoll (e.g., Hobfoll & Shirom, 2000) proposed that during the early stages of burnout, when individuals still try to engage in active coping to prevent further losses of energetic resources and to replenish those lost, burnout may co-occur with anxiety, whereas in the later stages of burnout, when and if these active coping behaviors prove ineffective, burnout may be accompanied by depressive symptoms. Empirically, we discuss below the evidence suggesting that the two constructs exhibit different physiological pathways to CVD risk factors. In addition, factor analytic studies of items measuring burnout and depression (Leiter & Durup, 1994; Schaufeli & Enzmann, 1998) have generally found each construct to load on different factors, indicating that they probably tap different domains. Studies that explored the factor structure of vital exhaustion and of vital exhaustion with depression arrived at a similar conclusion. The D. C. Glass and McKnight (1996) review of 18

studies suggested that depressive affect and burnout may share a common etiology and that their shared variance may be due to their concurrent development. Still, this meta-analytic study (D. C. Glass & McKnight, 1996) concluded that burnout and depressive symptomatology are not redundant concepts and that their shared variance does not indicate complete isomorphism.

Burnout and Risk of CVD

The evidence concerning the association between burnout or vital exhaustion and risk of CVD and cardiovascular-related events comes from some case-control (cross-sectional) studies but largely from longitudinal (prospective) studies. This evidence suggests that even after adjusting for potential confounding variables, the relative risk (RR) associated with burnout and vital exhaustion approached, was equal to, and sometimes (depending on the outcome studied) even exceeded the risk conferred by classical risk factors, such as age, body mass index (BMI), smoking, blood pressure, and lipid levels.

Using vital exhaustion as a predictor variable, Appels and his associates conducted the first systematic research study in this area using objective indicators of physical morbidity: vital exhaustion was predictive of future MI in apparently healthy men and women, independent of the classic risk factors (Appels, Falger, & Schouten, 1993; Appels & Mulder, 1988). For example, in a 4.2-year follow-up of apparently healthy men, vital exhaustion was predictive of future MI, even after controlling for blood pressure, smoking, cholesterol levels, age, and use of antihypertensive drugs (Appels & Mulder, 1988). A case-control study of women with first MI found that the RR for MI associated with vital exhaustion was 2.75, even when adjusting for several potent confounding variables (Appels et al., 1993). In a prospective study of adults (41–66 years) in a Dutch village, vital exhaustion was found to be associated with triple risk of fatal and nonfatal MI (new cases as well as recurrent MI), after controlling for host of potential confounding variables including previous MI (Schuitemaker, Dinant, Van Der Pol, & Appels, 2004). In another prospective study of a community sample, vital exhaustion was found to be a risk factor for ischemic heart disease (with a RR ranging from 1.36 to 2.10, depending on the questionnaire items selected) and all-cause mortality (Prescott et al., 2003). Vital exhaustion was also found to be associated with excess coronary heart disease (CHD) mortality (adjusted rate ratio = 2.07; Cole, Kawachi, Sesso, Paffenbarger, & Lee, 1999). In other studies, vital exhaustion also was found to be associated with a 1.3- to 1.9-fold increased risk of incident stroke (Schuitemaker, Dinant, Van Der Pol, Verhelst, & Appels, 2004; Schwartz, Carlucci, Chambless, & Rosamond, 2004) and to be a precursor of sudden cardiac death (with a RR = 2.28 or 2.81, depending upon the reference group; Appels, Golombeck, Gorgels, De Vreed, & Van Breukelen, 2002; Appels & Otten, 1992).

Vital exhaustion has also been associated with outcomes in cardiac patients. Feelings of exhaustion in patients undergoing coronary angioplasty were associated with a twofold increased risk of developing subsequent cardiac events within 1.5 years after the initially successful intervention (Kop, Appels, Mendes de Leon, de Swart, & Bar, 1994). In a similar vein, vital exhaustion was found to predict the recurrence of cardiac events and subsequent chest pain and coronary stenosis in women with acute myocardial infarction (Koertge et al., 2002). Other studies have also indicated

that burnout may be a risk factor for CHD. In a recent case-control study, women with CHD reported a higher level of burnout compared with matched control subjects. The women with CHD also showed lesser coping abilities (Hallman, Thomsson, Burell, Lisspers, & Setterlind, 2003), replicating an earlier case-control study in which burnout was found to be associated with increased risk of CHD for both men (RR = 3.1) and women (RR = 3.4; Hallman, Burell, Setterlind, Oden, & Lisspers, 2001). Using data from the prospective study of healthy men mentioned above, Appels and Schouten (1991a) found that a single question measuring burnout, "Have you ever been burned out?," was found to be predictive of MI risk (RR = 2.13). It should be pointed out that the reliability of this burnout measure is unknown.

In summary, there is sufficient evidence that comes from several prospective cohort studies linking burnout and vital exhaustion with risk of CVD and cardiovascular-related events. The RR associated with burnout and vital exhaustion is of similar magnitude to that of the classical risk factors for CVD. Are the links between burnout or vital exhaustion and CVD plausible from a biological viewpoint? We consider in the next section the possible pathways that could explain how burnout and vital exhaustion might increase the risk of CVD and cardiovascular-related events.

Potential Mechanisms Linking Burnout and CVD

In the following, we review the evidence for the possible pathways linking burnout or vital exhaustion and CVD and additional physical morbidities. These pathways include burnout and vital exhaustion and their possible associations with various components of the metabolic syndrome, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, sleep disturbances, inflammation, immunity, blood coagulation and fibrinolysis, and poor health behaviors. We present each mechanism as a distinct pathway only for sake of simplicity. It is well documented that many of these pathways may be interrelated (Calabrese, van der Wal, & Levi, 2003; Esman, 2003; Kop et al., 2002; Levi, van der Poll, & Buller, 2004; Vgontzas et al., 2003).

Burnout and the Metabolic Syndrome

The metabolic syndrome includes five components that tend to co-occur: obesity (especially abdominal obesity), dyslipidemia (high levels of triglycerides and low levels of high-density lipoprotein cholesterol), elevated levels of glucose (resulting from insulin resistance and/or glucose intolerance), and elevated blood pressure (cf. Meigs, 2003). Recently, markers of inflammation and accelerated homeostasis or impaired fibrinolysis have been added to this list (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004; Miranda, Defronzo, Callif, & Guyton, 2005). The metabolic syndrome is considered a major risk factor for CVD (including stroke). Furthermore, most people with this syndrome are insulin resistant, conferring increased risk of Type 2 diabetes. When diabetes becomes clinically apparent, CVD risk rises sharply. In addition to risk of CVD and Type 2 diabetes, individuals with metabolic syndrome are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstone, asthma, sleep disturbances, and some forms of cancer (Grundy, Brewer, Cleeman, Smith, & Lenfant, 2004).

Although there is no consensus on the specific clinical thresholds for establishing a medical diagnosis for each of the five components, the presence of three or more is considered an elevated risk for heart disease. Burnout has been found to be associated with some of these components. In a study of 104 disease-free male employees of a high-tech company, burnout was found to be correlated with elevated risk factors for CVD (Melamed, Kushnir, & Shirom, 1992). Specifically, this study reported a positive association between burnout and fasting glucose levels and that the combination of high burnout and tension was significantly associated with increased total cholesterol, low-density lipoprotein cholesterol, triglycerides, and uric acid, and marginally with electrocardiogram abnormality. In another study of healthy employees (Shirom, Westman, Shamai, & Carel, 1997), burnout in men was found to be predictive of cholesterol changes, evidenced 2–3 years later. In this prospective research, emotional exhaustion (as gauged by the SMBM) among female employees was positively correlated whereas physical fatigue was negatively correlated with cholesterol and triglycerides levels (Shirom et al., 1997). Similarly, vital exhaustion also was found to be associated with atherogenic lipid profile, particularly reduced high-density lipoprotein cholesterol levels (Koertge, Ahnve, Schenck-Gustafsson, Orth-Gomer, & Wamala, 2003; Wirtz et al., 2003). These associations were obtained independent of BMI. No association was found between burnout or vital exhaustion and elevated BMI or obesity (Appels et al., 1993; Appels & Mulder, 1988; Melamed et al., 1992). The elevated glucose and lipids levels in burned-out individuals may be indicative of sympathetic activation (Bravo, 1989). Some direct evidence for the this possibility comes from a study by van Doornen and van Blokland (1989) in which vital exhaustion correlated positively with epinephrine reaction to real-life stressors as well as with cholesterol base level, stress-induced cholesterol change, and norepinephrine levels. It was suggested that the relationship between vital exhaustion and cholesterol parameters may originate in norepinephrine-induced lipolysis. Using the MBI, De Vente and his colleagues (De Vente, Olf, Van Amsterdam, Kamphuis, & Emmelkamp, 2003) did not find a significant difference in resting blood pressure values when comparing burnout patients and healthy control subjects, and a similar lack of association between blood pressure and burnout was reported for the SMBM (e.g., Melamed et al., 1992) and the VE (e.g., Appels et al., 1993; Wirtz et al., 2003). Thus, it was interesting to find that in burnout and vital exhaustion there is no co-occurrence of dyslipidemia and elevated blood pressure. This finding, however, is not exceptional. A recent study using confirmatory factor analysis to specify and test the factor structure of the metabolic syndrome showed that although blood pressure was found to be an element of the metabolic syndrome, the strength of this relationship was weaker than those of the other components (Shen et al., 2003).

Burnout and Dysregulation of the HPA Axis

Bruce McEwen (1998, 1999, 2003) introduced the concept of "allostasis," which refers to the notion of achieving stability through change and denotes adaptation to the challenges of daily life mediated by the HPA axis, the autonomic nervous system, the metabolic system, and the immune system. He has suggested that overactivity or dysregulated activity on the HPA axis plays a significant role in the cascade of events leading to pathological

changes resulting from overactive or inefficiently managed allostatic response (McEwen, 1998, 1999, 2003). Components of the HPA axis response to both physical and psychological stress include production of corticotrophin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. Acting via the portal circulation, CRH, in conjunction with arginine vasopressin, induces the pituitary to produce adrenocorticotrophic hormone (ACTH), which enters the bloodstream and causes the adrenal glands to release glucocorticoids, mainly cortisol in humans. When produced in response to stress, glucocorticoids have a myriad of effects on the body, primarily mediated via intracellular receptors (for further elaborations, see Black & Garbutt, 2002; McEwen et al., 1997; Tsigos & Chrousos, 2002).

In stressful situations, however, other components of the stress system are also activated, including specifically the locus ceruleus–norepinephrine system (central sympathetic system). The HPA axis and the efferent sympathetic–adrenomedullary system are anatomically and functionally interconnected, and during stress they can interact at different levels (Kvetnansky et al., 1995). The HPA axis and the efferent sympathetic–adrenomedullary system represent the effector limbs via which the brain influences all body organs when exposed to threatening stimuli (Tsigos & Chrousos, 2002). Glucocorticoids participate in the control of whole body homeostasis and of the organism's response to stress and play a key regulatory role in the basal activity of the HPA axis and the termination of the stress response by acting in the extrahypothalamic centers, the hypothalamus and the pituitary gland (de Kloet, 1991; Tsigos & Chrousos, 2002).

Of particular relevance to the present review are the HPA axis–immune system interactions (see Black & Garbutt, 2002; McEwen et al., 1997; Tsigos & Chrousos, 2002). These interactions may play a pivotal role in the association between burnout and immunity or inflammation, reviewed later. A cumulative body of evidence points to the bidirectional communication between the central nervous system (CNS) and the immune system, indicating that cytokines are among the principal messengers in this network (Black & Garbutt, 2002; Maier, 2003; Maier & Watkins, 1998; Tsigos & Chrousos, 2002). Stressors of all kinds, whether traumatic or psychological, are associated with concurrent activation of the HPA axis and the sympathetic nervous system, and the product of these systems then alters the function of the immune organs and cells and activates cytokine production and other humoral mediators of inflammation (Black & Garbutt, 2002; Maier & Watkins, 1998; Tsigos & Chrousos, 2002). Conversely, cytokines and other humoral mediators of inflammation are potent activators of the central stress response, constituting the afferent limb of a feedback loop via which the immune–inflammatory system and the CNS communicate (Chrousos, 1995).

All three inflammatory cytokines, tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6), can cause stimulation of the HPA axis alone or in synergy with each other (Chrousos, 1995). Evidence suggests that IL-6—the main endocrine cytokine—plays a major role in the immune stimulation of the HPA axis, especially in chronic stress (Tsigos & Chrousos, 2002). Conversely, activation of the HPA axis has profound inhibitory effects on the inflammatory–immune response because virtually all the components of the immune response are inhibited by cortisol. Alterations in leukocyte traffic and function, decreases in production of cytokines and mediators of inflammation, and

inhibition of the effects of the cytokines and mediators on target tissues are among the main immunosuppressive effects of glucocorticoids (Chrousos, 1995; Elenkov, Webster, Torpy, & Chrousos, 1999). The hypothesized beneficial role of glucocorticoids in constraining the very processes (such as catabolic, antireproductive, and immunosuppressive processes) to which they initially contributed prevents the occurrence of a host of potential adverse health effects that could have resulted if these processes were to continue unabated after crisis resolution (Raison & Miller, 2003; Tsigos & Chrousos, 2002).

Compelling evidence suggests that exposure to acute psychological stress increases cortisol levels (for review, see Dickerson & Kemeny, 2004). Nonetheless, the empirical evidence for the role of the HPA axis in chronic stress is contradictory, because findings of both enhanced cortisol concentrations and hypocortisolism have been reported (Kaspers & Scholz, 2004). Several studies have examined the association between burnout and cortisol levels, with some inconsistent results, but the majority of past studies show burnout to be more consistently associated with hypocortisolism. Two studies were conducted in patient populations. In one study conducted by Moch, Panz, Joffe, Havlik, and Moch (2003) among women, appreciably lower urinary free-cortisol excretion was found in patients compared with control subjects. This trend of functional hypocortisolism persisted after 4 months of follow-up. The second study, conducted in a composite sample of men and women, found that basal salivary cortisol levels and cortisol reactivity recovery measures were similar for burnout patients and control subjects (De Vente et al., 2003).

An innovative series of studies (e.g., J. C. Pruessner, Hellhammer, & Kirschbaum, 1999; J. C. Pruessner et al., 1997, M. Pruessner, Hellhammer, Pruessner, & Lupien, 2003; Schulz, Kirschbaum, Pruessner, & Hellhammer, 1998) carried out at the Center for Psychobiological and Psychosomatic Research at the University of Trier (Trier, Germany) has shown cortisol response to awakening to be a reliable assessment of HPA activity. Awakening seems to represent an endogenous stimulation for the HPA axis, and cortisol response to awakening shows good intraindividual stability over time, independent of factors such as sleep duration, sleep quality, disrupted sleep, body mass index, alcohol consumption, and hormone replacement therapy (Clow, Thorn, Evans, & Hucklebridge, 2004; J. C. Pruessner et al., 1997), but it may be dependent on time of awakening and several other possible confounding variables (for review, see Clow et al., 2004).

Several studies have shown that chronic stress in general, and work-related stress in particular, is associated with increased cortisol response to awakening (Lundberg & Hellstrom, 2002; J. C. Pruessner et al., 1999; Schulz et al., 1998; Wust, Federenko, Hellhammer, & Kirschbaum, 2000). J. C. Pruessner et al. (1999), however, studied the effects of both perceived stress and burnout on cortisol response to awakening in the same subjects—a group of male and female teachers. Consistent with previous findings, perceived stress correlated with increased cortisol levels during the first hour of awakening. On the other hand, teachers scoring high on burnout scales had a lower cortisol response after awakening and showed lower overall cortisol secretion. Thus, this finding showed for the first time that whereas perceived stress is associated with hypercortisolism, burnout is associated with hypocortisolism. Furthermore, the results of this study showed that teachers with low morning cortisol levels also manifested supersuppression

of cortisol to dexamethasone (an artificial glucocorticoid) and reported the highest number of physical complaints. Of interest, supersuppression of cortisol to dexamethasone was also observed in bodily disorders associated with fatigue, such as fibromyalgia (Griep et al., 1998). Evidence of hypocortisolemia was found in individuals in a state of vital exhaustion and no longer able to cope with environmental stress (Keltikangas-Jarvinen, Raikkonen, Hautanen, & Adlercreutz, 1996). A similar trend was also uncovered in a later study in which, compared with control subjects, vitally exhausted subjects had lower basal cortisol levels, especially in the evening. Furthermore, exhausted subjects tended to show decreased cortisol responses to challenging tasks (Nicolson & van Diest, 2000).

Different results were obtained by Melamed et al. (1999), who found that chronic burnout (measured by the SMBM) was associated with elevated cortisol levels throughout the day. A similar trend was found in a case-control study of 22 patients scoring high for burnout (measured by the MBI) and 23 healthy control subjects; burnout was associated with elevated cortisol levels during the first hour after awakening (De Vente et al., 2003). In a study by Ekstedt, Akerstedt, and Soderstrom (2004), burnout was found to correlate positively with cortisol levels at awakening but not with the mean cortisol levels during the 60 min after awakening. Somewhat more complex results were recently reported by Grossi et al. (Grossi, Perski, Ekstedt, & Johansson, 2004). Patients who scored high on burnout (assessed by the SMBM) had higher cortisol levels than did the group with low burnout at awakening and at 15 and 60 min after awakening. The mean increase in cortisol tended to be smaller in the group with high burnout. Taken together, the above findings suggest that burnout may be associated with higher or lower baseline cortisol levels. Yet, irrespective of the baseline levels, it seems that persons scoring high on burnout scales tend to have decreased cortisol responsiveness to the awakening stimulus.

Hellhammer in 1990 (as cited by Heim, Ehlert, & Hellhammer, 2000) uncovered yet another form of perturbation in the regulation of the HPA axis. Within a group of nurses studied, those who suffered from burnout and multiple bodily complaints manifested a flattened diurnal cortisol curve characterized by decreased basal salivary cortisol in the morning along with relatively high cortisol levels in the afternoon and evening. It is interesting that such a flattened cortisol curve has also been observed in some individuals exposed to chronic stress (Miller, Cohen, & Ritchey, 2002; Rosmond, Dallman, & Bjorntorp, 1998), in members of the general population (Stone et al., 2001), and in older individuals as well (Steiger, 2003). New evidence from a 5-year follow-up of subjects in the Rosmond et al. (1998) study suggests that the flattened diurnal cycle of cortisol may have negative implications on health; it was found to be prospectively associated with an increased incidence of cardiovascular-related events and Type 2 diabetes (Rosmond et al., 2003).

Recently, it was proposed that the failure of adult hippocampal neurogenesis may provide the biological and cellular basis for altered brain plasticity in burned-out individuals (Eriksson & Wallin, 2004). *Neurogenesis* refers to the formation of new neurons in the human adult brain, a newly discovered dimension of brain plasticity with enormous consequences for memory and learning. This new theory views burnout, representing a decreased ability to cope with chronic stress because of dwindling resources, as an

exponent of a decrease in adult neurogenesis involving disturbed hippocampal regulation of the HPA axis (Eriksson & Wallin, 2004). Eriksson and Wallin (2004) reviewed many animal studies that have suggested the rate of neurogenesis in the adult hippocampus may provide an important neurobiological correlate of experienced stress. This novel hypothesis involving burnout as a proxy variable to gauge overall exposure to stress, neurogenesis in the brain, and HPA dysregulation provides support for the vicious cycle between chronic stress and burnout, predicted by the COR theory and further supported by several longitudinal studies referred to above that found chronic stress and burnout to be reciprocally related.

Possible Health Consequences of Hypocortisolism in Burned-Out Individuals

In most models of chronic stress and its association with inflammation, insulin resistance, Type 2 diabetes, metabolic syndrome, arteriosclerosis, and CVD, elevation of glucocorticoids is implicated along with activation of other neuroendocrine pathways (Black, 2002, 2003; Black & Garbutt, 2002). Yet, convincing evidence shows that hypocortisolism may also have damaging effects and may be a relevant factor in the pathogenesis of bodily disorders, inasmuch as a lack of cortisol availability may promote increased vulnerability to bodily disorders, such as autoimmune disorders, inflammation, chronic pain, asthma, and allergies (Heim et al., 2000; Raison & Miller, 2003). HPA hyporesponsiveness has been found in patients suffering from rheumatoid arthritis (Chikanza, Petron, Kingsley, Chrousos, & Panayi, 1992), fibromyalgia (Crofford et al., 1994), long-lasting chronic fatigue syndrome (CFS; Cleare, 2004), and posttraumatic stress disorder (Yehuda, 1997, 2002), known to be stress-related disorders.

The damaging effects on body function induced by insufficient glucocorticoid signaling (resulting from decreased hormone bioavailability, e.g., hypocortisolism, or from reduced responsiveness to glucocorticoids) may be related in part to the role of glucocorticoids in restraining activation of the immune system and other components of the stress response, including the sympathetic nervous system and CRH (Raison & Miller, 2003; Tsigos & Chrousos, 2002). Thus, a permanent lack of the protective effects of cortisol in traumatized or chronically stressed individuals may promote a disinhibition of immune functions, resulting in increased vulnerability to infectious agents and in the development of autoimmune disorders, inflammation, and other bodily disorders mentioned above (Heim et al., 2000). The negative consequences of an enhanced inflammatory response are seen, for example, in Lewis rats; these animals are very susceptible to autoimmune and inflammatory disturbances because of a genetically determined hyporesponsiveness of the HPA axis (Sternberg, 1997).

Thus, it seems plausible that the reported association between burnout or vital exhaustion and increased CVD risk may in part be the outcome of various forms of HPA dysregulation observed in burned-out or exhausted individuals. The findings of Rosmond et al. (2003) support this hypothesis, in that they suggest that the flattened diurnal cortisol curve, as observed in some burned-out persons, may reflect an increased risk of cardiovascular-related events and Type 2 diabetes. In addition, burnout may be associated with increased atherosclerosis. Such a possibility emerges from several converging findings. Burnout was found to be associated

with decreased cortisol response to awakening (J. C. Pruessner et al., 1999). Such an attenuated response was found to be positively associated with intima media thickness in women (Eller, Netterstrom, & Hansen, 2001). Furthermore, the hypocortisolism observed in some burned-out or exhausted persons may induce low-grade inflammation, as suggested above. Indeed, burnout was found to be associated with biomarkers of inflammation (as illustrated below). Inflammation is now documented as part of the atherosclerotic process (Koenig, 2001; Libby, Ridker, & Maseri, 2002; Ross, 1999) and hence elevated risk of CVD. Finally, it has been suggested that HPA dysregulation may play a causative role in some clinical sleep disorders, such as insomnia (Buckley & Schatzberg, 2005). Other evidence, discussed below, points to an association between burnout or vital exhaustion and sleep disturbances and disorders, which may be an additional pathway of the link between burnout or vital exhaustion and CVD.

Burnout, Vital Exhaustion, and Sleep Disturbances and Disorders

In a study by Melamed et al. (1999), burnout was found to be associated with an unpleasant sensation of tension and restlessness at work, postwork irritability, sleep disturbances, and complaints of waking up exhausted. These findings suggest that burned-out persons have an inability to unwind after working hours. In a more recent study, burnout was found to be positively associated with poor quality of sleep, a sensation of not feeling refreshed on awakening, and incidence of sleepiness and/or fatigue during the day (Grossi et al., 2003). Another study showed that burned-out subjects had a higher frequency of arousals during sleep compared with others (Soderstrom, Ekstedt, Akerstedt, Nilsson, & Axelsson, 2004). Similarly, vital exhaustion also was found to be associated with sleep disturbances. Polysomnographic recordings made in a sleep laboratory have indicated that the deep sleep stage was significantly diminished in exhausted subjects compared with control subjects, suggesting that the normal restoration processes that take place during sleep (A. W. Smith & Baum, 2003) are impaired in exhausted subjects (van Diest & Appels, 1994). In addition, exhausted subjects reported more sleep complaints, shorter sleep duration and frequent napping, and poor sleep quality than did vital subjects (Nicolson & van Diest, 2000; van Diest, 1990). Supportive evidence for the chronic fatigue characterizing burned-out and exhausted subjects was obtained in a study by Nicolson and van Diest (2000), in which daily fatigue ratings (made on a visual analog scale) positively correlated with vital exhaustion. Such persistent fatigue certainly has negative implications regarding the quality of life of exhausted subjects and the potential impact on performance and creativity. Taken together, the insomnia and nonrefreshing sleep manifested by the burned-out or exhausted persons may partly explain the chronic physical and mental fatigue characterizing such persons.

Sleep research indicates that the dysregulation of the HPA axis and the sleep disturbance (mainly insomnia) manifested in burned-out individuals may be interrelated. Chronic insomnia in young adults was found to be associated with increased plasma levels of ACTH and cortisol (Vgontzas et al., 2001). The association between elevated evening and nocturnal cortisol levels and impaired nighttime sleep was observed in a number of studies (Rodenbeck, Huether, Ruther, & Hajak, 2002; Vgontzas et al., 2003). Likewise,

several of the studies of burned-out persons cited above found elevated afternoon and evening cortisol levels (Hellhammer, 1990, as cited by Heim et al., 2000; Melamed et al., 1999). Furthermore, a similarity between burned-out persons and insomniac patients was also observed with regards to cortisol response to awakening. Burned-out teachers showed lower cortisol response after awakening (J. C. Pruessner et al., 1999), and the same trend was recently found in primary insomnia patients (Backhaus, Jungmann, & Hohagen, 2004). Taken together, these findings suggest that the observed link between burnout or vital exhaustion and sleep disturbances may be mediated by perturbation of the HPA axis. However, because most studies are cross-sectional, cause-effect relationships remain to be elucidated by future longitudinal and experimental research.

These findings may yet uncover additional pathways by which burnout may be associated with increased risk of CVD. Insomnia in general (Carney, Freedland, & Jaffe, 1990; Schwartz et al., 1999; van Diest, 1990), and waking up exhausted in particular (Appels & Schouten, 1991b), were found to be risk indicators of future MI. Furthermore, sleep complaints predicted coronary artery disease mortality in men (Mallon, Broman, & Hetta, 2002). Thus, another pathway of the link between burnout or vital exhaustion and CVD risk may be through the association, in some individuals, with insomnia and sleep disturbances. Nonetheless, there is evidence to suggest that the association between burnout or vital exhaustion and CVD risk persists even after adjusting for insomnia and sleep medication use (Cole et al., 1999). New studies have shown an association between sleep disturbances and biomarkers of the inflammatory process (Vgontzas & Chrousos, 2002; Vgontzas et al., 2003), suggesting another possible pathway of the link between burnout and health.

Burnout and Inflammation

Consequent to the findings that classical risk factors (hypertension, poor lipids profile, smoking, lack of physical exercise, and overweight) only partly explain the incidence of CVD, ongoing efforts have been devoted to identifying new risk factors. Inflammation represents the newest addition to the list of CVD risk factors. Recent studies provide evidence indicating a link between inflammation, atherosclerosis, and CVD (Hansson, 2005; Koenig, 2001; Libby, Ridker, & Maseri, 2002; Ross, 1999) and the pathogenesis of Type 2 diabetes (Pickup, 2004). There is also evidence that chronic inflammation may play an important role in linking diabetes and CVD. Considerable support can be found in the literature for the relationship between markers of inflammation, abnormalities of glucose metabolism, and CVD end points (Resnick & Howard, 2002).

There is compelling evidence that chronic stress or repeated episodes of acute psychological stress may induce inflammatory reactions (Black & Berman, 1999), perhaps explaining part of the approximately 40% of atherosclerotic patients with no other known risk factors (for a review of the evidence and the suggested mechanisms of the link, see Black, 2002, 2003; Black & Garbutt, 2002; Kop, 2003). Among the proposed pathways is the role of psychological stress in inducing the acute phase response. The acute phase response is part of the innate immune inflammatory response (for further elaboration, see Black, 2003; Segerstrom & Miller, 2004), representing the way the body responds to any type

of tissue damage and infection, that is, with a series of specific physiological reactions designed to repair the damage, contain the offending organism(s), promote wound healing, and recruit host defense mechanisms (Black, 2003). A number of proteins, called acute phase proteins, are produced by the liver. Some proteins are "positive"; that is, their plasma concentration increases in response to injury and infection, and they play a role in the inflammatory process. The major acute phase proteins are C-reactive protein (CRP) and serum amyloid A. Other proteins are "negative"; that is, their plasma concentration decreases in response to injury and infection, and they are important carriers of proteins such as albumin, corticosteroid-binding globulin, and metal-binding protein such as transferrin (see Gabay & Kushner, 1999, for review).

Certain cytokines produced during inflammatory processes, in particular IL-6, but also IL-1 β , TNF- α , interferon- α , transforming growth factor β , and possibly IL-8, are the chief stimulators for production of acute phase proteins (Gabay & Kushner, 1999). Corticosteroids and catecholamines, the major stress mediators, enhance this induction of acute phase proteins (Black, 2003). A number of studies indicate that stress alone can induce the acute phase response and the elaboration of many of the acute phase proteins. Certain hormonal substances, such as norepinephrine and glucagons, may also induce an acute phase response. Black et al. (Black, 2002, 2003; Black & Garbutt, 2002) have suggested that repeated episodes of acute or chronic psychological stress can periodically invoke or maintain the acute phase response and, subsequently, a chronic inflammatory process, which eventually culminates in atherosclerosis and CVD (Black, 2003; Maier & Watkins, 1998).

Recent studies have examined and demonstrated the existence of an association between burnout or vital exhaustion and elevation of selected acute phase proteins, most notably CRP (Kop et al., 2002; Toker, Shirom, et al., 2005; Wirtz et al., 2003) and fibrinogen (Kop et al., 2002; Toker, Shirom, et al., 2005). Plasma CRP is produced by hepatocytes, predominantly under the control of cytokine IL-6. CRP has been found to be a powerful biomarker of systemic inflammation and a consistent predictor of CHD risk (Koenig et al., 1999; Kuller, Tracy, Shaten, & Meilahn, 1996; Ridker, Hennekens, Buring, & Rifai, 2000; Ridker, Rifai, Rose, Buring, & Cook, 2002; Rifai, 2001; Rifai & Ridker, 2003; Tracy et al., 1997), stroke, peripheral arterial disease, sudden cardiac death among healthy individuals with no history of CVD, and recurrent events and death in patients with acute or stable coronary syndromes (Bassuk, Rifai, & Ridker, 2004). CRP also has been found to be associated with the risk of developing hypertension (Sesso et al., 2003) and Type 2 diabetes (Hu, Meigs, Li, Rifai, & Manson, 2004) and to correlate with several components of the metabolic syndrome (Bermudez, Rifai, Buring, Manson, & Ridker, 2002; Toker, Rogowski, et al., 2005). Fibrinogen is a circulating glycoprotein that acts at the final step in the coagulation response to vascular and tissue injury, for which it controls for blood loss (for recent reviews and pathophysiological pathways, see Herrick, Blanc-Brude, Gray, & Laurent, 1999). It may increase up to fourfold in response to inflammatory or infectious triggers (Fey & Fuller, 1987). Epidemiological data support an independent association between elevated concentrations of fibrinogen and cardiovascular morbidity and mortality (Danesh, Collins, Appleby, & Peto, 1998; Faxon et al., 2004), due to its involvement in atherosclerotic processes (for a review, see Hackam & Anand, 2003). In

addition to its role in cardiovascular processes, fibrinogen has been studied in relation to psychosocial factors such as acute stressors and job strain (for recent reviews and pathophysiological pathways, see Strike & Steptoe, 2004; Theorell, 2002; von Kanel, Mills, Fainman, & Dimsdale, 2001).

Other studies have found that more upstream markers of the inflammation cascade, namely, proinflammatory cytokines such as IL-1, TNF- α , and IL-6, are independent predictors of CVD risk. Such cytokines are thought to play an important role in atherogenesis and in the development of acute coronary syndrome (C. K. Glass & Witztum, 2001; Libby, 2001). TNF- α and IL-1 have been associated with CVD severity (Hasdai et al., 1996; Lantini et al., 1994), recurrent coronary events in coronary patients (Ridker, Rifai, Pfeffer, et al., 2000), and heart failure (Mann, 2001). Baseline plasma concentration of IL-6 was shown to predict future mortality in apparently healthy men after controlling for cardiovascular risk factors (Ridker, Rifai, Stamper, & Hennekens, 2000). Another study has shown that IL-6 predicts MI and coronary death over a 5-year period (Luc et al., 2003).

Cytokines are among the principal messengers responsible for the bidirectional communication between the CNS and the immune system, and cytokine levels are regulated in part by brain functions (Maier, 2003). A body of evidence indicates that proinflammatory cytokines are associated with psychological stress (Black, 2003). Recent studies have explored the association between burnout or vital exhaustion and the concentrations of such cytokines. A positive association between vital exhaustion or burnout and proinflammatory cytokine levels has been observed in a number of studies (Appels, Bar, Bar, Bruggeman, & de Baets, 2000; Grossi et al., 2003). The results of the study by Appels et al. (2000) conducted among coronary artery disease patients treated with directional coronary angioplasty because of severe angina showed that exhausted depressed patients had higher levels of proinflammatory cytokines IL-1 β and TNF- α and marginally higher IL-6 levels, compared with nonexhausted depressed patients. The shortcoming of this study is that its design precludes distinguishing whether the difference between the two groups is due to exhaustion or depression. The Grossi et al. (2003) study conducted among apparently healthy women found that women suffering from burnout (as gauged by the SMBM) manifested higher levels of TNF- α independent of confounders, including depression. The burned-out women also showed higher levels of glycosylated hemoglobin (HbA1c) compared with their counterparts. The significance of this latter parameter is discussed below in the section on burnout and Type 2 diabetes. The authors concluded that among women, burnout seems to involve enhanced inflammatory responses and oxidative stress.

A recent study by Wirtz et al. (2003) pointed to one mechanism that maintains high levels of IL-6 production in exhausted men. The researchers showed that highly exhausted subjects required larger quantities of dexamethasone to inhibit lipopolysaccharide-stimulated IL-6 release than did the nonexhausted men. Release of IL-6 without dexamethasone was similar in the two groups. This reduced sensitivity to glucocorticoids indicates that the same amount of glucocorticoid was less effective in reducing the stimulated production of IL-6. The implication of these findings is that the monocytes of highly exhausted men are more likely to continue producing IL-6 after encountering an inflammatory stimulus than are those of nonexhausted individuals. Such glucocorticoid resis-

tance was also observed in chronic psychological stress (Bauer et al., 2000; Miller et al., 2002).

Further evidence corroborating a possible association between burnout and inflammation is the finding of a relationship between burnout and leukocyte adhesiveness–aggregation (LAA; Lerman et al., 1999). LAA is a sensitive marker for detecting inflammation and assessing its intensity (Rotstein et al., 2002). The search for LAA as a marker of inflammation is based on the notion that white blood cells become activated and sticky during the inflammatory response (Frenette & Wagner, 1996a, 1996b). LAA probably represents both the enhanced expression of cell adhesion molecules during cell activation as well as the appearance of plasmatic adhesive proteins during the acute phase response (Rotstein et al., 2002). Additional evidence indicates a high correlation between LAA and erythrocyte aggregation (Shapira et al., 2001), and there is also evidence regarding red blood cell aggregability in patients with hyperlipidemia, diabetes mellitus, hypertension, and acute MI (Berliner, Zeltser, Rotstein, Fusman, & Shapira, 2001; Shapira et al., 2001). Taken together, the above findings suggest that burnout and vital exhaustion may be associated with CVD risk through the presence of smoldering low-grade inflammation. This is another hypothesis that awaits further research and confirmation.

The possible association between burnout or vital exhaustion and sustained or recurrent acute phase response and elevated concentration of proinflammatory cytokines may suggest yet another and perhaps complementary source of the chronic emotional and/or physical fatigue characterizing exhausted or burned-out persons. The corresponding behavioral, mood, and cognitive concomitants of the acute phase response and the elevated levels of proinflammatory cytokines include a feeling of lack of well-being, somnolence, general malaise, listlessness, sickness, tiredness, and inability to concentrate (Black, 2003; Dantzer, 2004; Gabay & Kushner, 1999; Maier & Watkins, 1998), which are similar to the symptoms of burnout and vital exhaustion.

Burnout and Immunity

A significant body of evidence supports the association between stress and immunity and susceptibility to infectious disease (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Marsland, Bachen, Cohen, & Manuck, 2001; McEwen, 1998; Segerstrom & Miller, 2004). This association was convincingly demonstrated in a study of healthy individuals who were given nasal drops containing one of five respiratory viruses (Cohen, Tyrell, & Smith, 1991). The study showed that stress increases the risk of infectious respiratory illness in a dose–response manner. Stress-related reactivation of Epstein–Barr virus infection has also been shown (Metha, Pierson, Cooley, Dubow, & Lugg, 2000). Furthermore, chronic stress modulates antibody titers to herpes simplex virus infection (Glaser & Kiecolt-Glaser, 1997) and specific immunity to varicella–zoster virus infection (Irwin et al., 1998). On the basis of this evidence, new studies have been initiated to explore the effect of burnout on the immune system and its possible association with infectious disease. Such association may have negative implication to cardiovascular health, given the convincing clinical evidence that the simultaneous or subsequent infection with several pathogens is a major factor involved in the pathogenesis of atherosclerosis. The main infectious agents found to be implicated in coronary artery disease and atherosclerosis are Chlamydia pneu-

monia, *Helicobacter pylori*, and cytomegalovirus (Ludewig, Krebs, & Scandella, 2004).

In a study of office workers (Nakamura, Nagase, Yoshida, & Ogino, 1999), burnout assessed by the MBI showed that higher depersonalization was associated with reduced cellular immunity marked by lower natural killer (NK) cell activity and lower proportionality of CD57+CD16+ to total lymphocytes. The NK cells are a subset of large granular lymphocytes and make up approximately 15% of the lymphocyte population. The NK cells act early in the immune response before specificity can be generated. They mediate the first-line defense by direct cytotoxicity against infectious agents and virally infected cells without apparent prior sensitization. This nonspecific recognition categorizes NK cells as part of innate immunity (Forlenza & Baum, 2003). CD57+CD16+ is a subset of the NK cells, identified by a cell surface marker combination. The reduced cellular immunity observed in this study of office workers was independent of health behaviors (e.g., smoking, alcohol use, obesity) or work stress (Nakamura et al., 1999). The study by Nakamura et al. (1999) is particularly important because it showed once again that burnout might have different outcomes than does work stress. Furthermore, the finding of the Nakamura et al. study is consistent with the findings of the extensive review by Segerstrom and Miller (2004) indicating that chronic stressors are associated with suppression of both cellular and humoral immunity. It suggests that burned-out or exhausted persons may be at risk of reduced immunocompetence and may be potentially prone to a variety of infectious diseases, such as upper respiratory infection and different types of viral infections.

There is some initial evidence to support this contention. In a study conducted during the Gulf War, Kushnir and Melamed (1992) found that prewar burnout (measured by the SMBM) was associated with wartime threat appraisal (worry) and upper respiratory infections (namely, acute, mild catarrhal syndrome, for which the principal signs and symptoms include rhinorrhea, nasal congestion, cough, and sore throat; other manifestations, such as fever, malaise, sneezing, and hoarseness, are more variable). A more recent prospective study of 12,140 employees (Mohren et al., 2003) found that burnout (measured by the MBI) was associated with common infections: common cold, flu-like illnesses and gastroenteritis (intestinal flu, a syndrome caused by infection with one of several viruses, usually characterized by vomiting, watery diarrhea, and abdominal cramps). The largest effect was found for gastroenteritis, both at baseline and at 3-year follow-up, and only with the exhaustion subscale of the MBI. The findings of another recent study have implication to coronary artery disease risk. Van der Ven et al. (2003) have found that seropositivity to the herpes viruses, including the varicella–zoster virus and cytomegalovirus but not the herpes simplex virus, occurred significantly more often in exhausted individuals than in control subjects. Moreover, vitally exhausted individuals had significantly more multiple herpes virus infections than did the control subjects. These viruses are characterized by lifelong latency that may reactivate in the case of impaired cellular immunity. Thus, the association found here might have implications for atherosclerosis, given the findings reviewed by Ludewig et al. (2004). However, there still is ongoing debate in the literature concerning whether microbial infections determine the development and progression of atherosclerotic disease. Black (2003) maintained that none of the above-mentioned

infectious agents has been consistently and convincingly established as a causal agent leading to atherosclerosis and CVD. Calabrese et al. (2003) argued that it is still unclear whether these microorganisms are truly an etiologic factor rather than just innocent bystanders. Consequently, the pathway leading from burnout or vital exhaustion to CVD via vulnerability of burned-out individuals to viral infections awaits further confirmation by future prospective studies.

Vital Exhaustion, Blood Coagulation, and Fibrinolysis

Epidemiological investigations have demonstrated that coagulation and fibrinolytic factors contribute to the development of MI (Danesh et al., 1998; Tracy, 2003). Exposure to acute and chronic stress has been shown to affect the balance between coagulation factors that generate fibrin (Von Villebrand factor, Factors VII and VIII, fibrinogen) and the removal of fibrin by the fibrinolytic system (tissue plasminogen activator antigen and plasminogen activator inhibitor [PAI-1] activity), purported to be one of the pathophysiological pathways by which psychological stressors may lead to CHD (Markowe et al., 1985; Moller & Christensen, 1991; Patterson et al., 1995; von Kanel et al., 2001).

Several studies have shown the association between vital exhaustion and changes in blood coagulation and fibrinolysis. Raikkonen, Keltikangas-Jarvinen, Adlercreutz, and Hautanen (1996) observed significant associations between feelings of exhaustion and impaired fibrinolytic capacity (increased synthesis of PAI-1) in healthy men. This finding was replicated in a later study by Kop et al. (1998). A more recent study showed that vital exhaustion was associated with undesirable changes in coagulation and fibrinolytic measures. Exhausted persons showed elevated coagulation measures (prothrombin fragment 1+2 and fibrinogen) throughout the day and decreased fibrinolytic capacity during the early morning (van Diest, Hamulyak, Kop, van Zandvoort, & Appels, 2002). The authors of these studies concluded that these haemostatic changes may promote thrombus formation and provide one of the potential pathways by which vital exhaustion is related to MI and its circadian variations.

Burnout and Health Behaviors

Poor health behaviors (e.g., lack of physical exercise, smoking, and alcohol consumption) have been suggested as one of the pathways of the link between psychosocial stress and physical health (Vitaliano, Zhang, & Scanlan, 2003). For example, risky behaviors have been found capable of modifying immune system processes (Kiecolt-Glaser & Glaser, 1988). Schaufeli and Enzmann (1998, p.88) were able to find four studies that have investigated the linkages among health behaviors (coffee consumption, alcohol consumption, caloric intake, substance abuse, and smoking) and emotional exhaustion (as measured by the MBI), and all of them reported null or very small correlations. We were able to find two recent studies that found significant correlations between alcohol consumption and emotional exhaustion or burnout, both focusing on dentists in different countries (Gorter, Eijkman & Hoogstraten, 2000; Winwood, Winefield, & Lushington, 2003). Melamed et al. (1992), in a study of 104 disease-free male employees in the high-tech industry, found that a high level of tension burnout was associated with poor health habits, including smoking

and lack of participation in physical leisure activities, which is consistent with the findings of Gorter et al. (2000).

A recent study provides an indication of a possible synergistic effect between health behaviors and burnout or vital exhaustion on CVD risk. A follow-up study of a large cohort of initially healthy individuals uncovered a synergistic effect of smoking and vital exhaustion on ischemic stroke risk. In a multivariate analysis, current smoking and high vital exhaustion were found to be independent risk factors for ischemic stroke, with corresponding hazard ratios of 1.76 and 1.94, respectively. However, their combination yielded a hazard ratio of 2.71 (Schwartz et al., 2004). Thus, the relationships between health-related behaviors and vital exhaustion or burnout and their potential synergistic effect on cardiovascular health appear to be a promising area of further research.

Association of Burnout and Vital Exhaustion With Other Bodily Disorders

Burnout and Type 2 Diabetes

Type 2 diabetes is a complex disorder characterized by impaired secretion of insulin and increased resistance to insulin and is associated with a two- to fourfold increased risk of CHD and a fourfold increase in mortality from CHD (Haffner & Cassells, 2003), as well as increased risk of peripheral vascular disease, renal failure, and blindness (Bailes, 2002; Beckman, Creager, & Libby, 2002). The past two decades have witnessed an explosive increase in the number of people diagnosed with diabetes worldwide, particularly with Type 2 diabetes (Seidell, 2000; Zimmet, Alberti, & Shaw, 2001).

It is believed that stress plays a significant role in the etiology of Type 2 diabetes, but only a few studies have systematically tested this assertion (Surwit & Schneider, 1993). Some studies have shown that the risk of developing Type 2 diabetes is higher in certain occupations (Cobb & Rose, 1973; Morikawa et al., 1997). Other studies that focused on working hours have yielded conflicting results (Kawakami et al., 2000; Nakanishi et al., 2001). Though no studies directly examined the association between work stress and clinically diagnosed Type 2 diabetes, several did demonstrate a link between chronic stress and risk factors for diabetes and related diseases. For example, greater job strain and lower social support in the workplace were found to be associated with increased concentrations of HbA1c (Kawakami et al., 2000; Netterstrom, Kristensen, Damsgaard, Olsen, & Sjol, 1991). HbA1c measures average glycemic levels over a time scale of weeks, whereas plasma glucose varies greatly on a given day and from day to day and is thus a more accurate and stable measure than are fasting blood glucose levels (Goldstein et al., 2003). Yet, the use of HbA1c as a diagnostic test for diabetes is not recommended—rather, this measure is recommended to monitor the effectiveness of glycemic therapy (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Other scholars, however, have suggested that high levels of HbA1c should be taken into account in the diagnosis of Type 2 diabetes (Barr, Nathan, Meigs, & Singer, 2002). Elevated HbA1c was found as a cardiovascular risk factor in both nondiabetic and diabetic individuals (Palumbo, Bianchi, Miccoli, & Del Prato, 2003; Selvin et al., 2004).

There are some indications that burnout might be associated with risk of Type 2 diabetes. Using the SMBM, Grossi et al. (2003) found that burnout was associated with elevated HbA1c among women, independent of confounders, including depression. In a study of apparently healthy men, Raikkonen et al. (1996) found that a cluster of certain characteristics related to vital exhaustion, namely, feelings of excessive tiredness, lack of energy, irritability, demoralization, and hostility, were linked to the development of insulin resistance syndrome, a risk factor for Type 2 diabetes. Direct support for the possible link of burnout and Type 2 diabetes was obtained in a recent study by Melamed et al. (2003). This study was conducted among white-collar Israeli workers. After excluding those who had a history of diabetes mellitus or other chronic diseases, 633 workers were followed up for a period of 3–5 years. During this period there were 17 new cases of treated Type 2 diabetes. Burnout measured by the SMBM was found to be associated with increased risk of Type 2 diabetes (odds ratio = 1.83, 95% confidence interval = 1.20–2.77), even after controlling for age, sex, body mass index, smoking, period of follow-up, and job category. Thus, this finding suggests that burnout might be a risk factor for Type 2 diabetes. This may constitute yet another path, albeit indirect, of the link between burnout and CVD risk.

Burnout and Reproductive Functions

The scientific literature points to another domain in which stress has an adverse impact—the risk of male infertility. Research findings show that stress has a negative impact on semen quality (Clarke, Klock, Geoghegan, & Travassos, 1999; Giblin, Poland, Moghissi, Ager, & Olson, 1988; Harrison, Callan, & Hennessey, 1987). On the basis of this finding a novel case-control study was recently initiated to explore the possibility that burnout would also have a negative effect on male fertility. The results confirmed this suspicion. Men with infertility problems (on the basis of combined criteria of sperm concentration and quantity and quality of motility) were found to have significantly higher burnout scores (on the SMBM) compared with control subjects (Sheiner, Sheiner, Carel, Potashnik, & Shoham-Vardi, 2002). If this finding is replicated, it will be an indication of yet another potential area of burnout-related health impairment, with negative implications for marital relationships, marital satisfaction, and quality of life.

Burnout and Self-Rated Health

Self-rated health is a simple and valid proxy measure of health status (McGee, Liao, Cao, & Cooper, 1999) because it has been found to consistently predict mortality even after adjustment for physical ill health at baseline (Idler & Kasl, 1991). It is most commonly measured with a single question, in which respondents are asked to assess their general state of health with a few response options, such as “very poor,” “poor,” “fair,” “good,” and “very good,” with a dose–response association commonly demonstrated in predicting all-cause mortality (cf. Kaplan et al., 1996). The VE has been linked to self-reported ill health or disease states. Using a measure of self-reported general health in a two-wave study of healthy men in Sweden, Halford, Anderzen, and Arnetz (2003) found this measure to correlate negatively with vital exhaustion. Self-rated health also has been found to be closely correlated with burnout in other studies (Gorter et al., 2000; Kahill, 1988; Soder-

feldt, Soderfeldt, Ohlson, Theorell, & Jones, 2000). In a longitudinal study of staff burnout in a psychiatric hospital, self-reported frequency of serious illness shared 10% of the variance with the Emotional Exhaustion scale of the MBI, after controlling for social support and other confounders (Corrigan et al., 1994), and a similar result was obtained for the relationship of these variables in another study (Bhagat, Allie, & Ford, 1995). In a search for the biological basis for self-rated health, a recent study found that self-rated health is related to levels of circulating proinflammatory cytokines (Lekander, Elofsson, Neve, Hansson, & Uden, 2004); this finding is consistent with similar findings for burnout and vital exhaustion, cited above. This rather important association between burnout and poor self-rated health suggests that burnout may reflect impaired physical health.

Discussion

Reliable and long-standing evidence indicates that experiencing chronic work or life stress has a detrimental effect on physical health (for recent reviews, see Black, 2003; Black & Garbutt, 2002; Dougall & Baum, 2001; Hemingway & Marmot, 1999; Ketterer, Mahr, & Goldberg, 2000; Kuper et al., 2002; T. W. Smith & Ruiz, 2002). On the basis of this literature, the working hypothesis guiding current research on burnout, vital exhaustion, and health is that burnout may pose a risk to physical health through wear and tear on body tissues and organs resulting from chronic overactivity or dysregulated activity of the stress system.

The evidence reviewed here supports this assumption and suggests that burnout and vital exhaustion pose an increased risk of incident MI, stroke, and sudden cardiac death. Both burnout and vital exhaustion have also been found to be related to other bodily disorders, such as Type 2 diabetes and impairment of reproductive function, as well as to poor self-rated health (a valid measure for health status), through interrelated mediating mechanisms. The association of burnout and vital exhaustion with various disease mediators suggests, as elaborated below, that the impact of these factors on health may be more extensive than is currently indicated. It is plausible that those displaying burnout symptoms are more adversely affected by chronic stress than are others not displaying these symptoms. There is some physiological evidence, presented below, that provides initial support for this statement.

We acknowledge several notable gaps in the literature covered by our review. First, as we noted, most of the prospective studies that have linked burnout and vital exhaustion with CVD end points have used the VE, a measure suspected of being in part confounded with sleep disturbances, depressive symptomatology, and irritation or anxiety. Second, burnout and vital exhaustion may have different roles in the development versus progression of CVD: This possibility has not been systematically explored in the literature. Third, it is possible that burnout and vital exhaustion may indicate early manifestations of the atherosclerotic process, not yet clinically diagnosed (Macleod & Carroll, 2003; Suls & Bunde, 2005). To the best of our knowledge, this reverse-causation hypothesis has not yet been addressed in prospective studies of initially disease-free individuals. Fourth, we have discussed the conjecture that a third variable, specifically inflammatory processes, may be implicated in both burnout and CVD. Yet another possible third variable, not yet adequately addressed in the literature that we reviewed, is adverse life circumstances or material

deprivation (Macleod & Carroll, 2003). However, we consider this hypothesis to be less plausible because burnout has been documented to be positively associated with schooling or educational attainment and negatively associated with work experience (Schaufeli & Enzmann, 1998), both proxies of rather advantageous life circumstances (Gallo & Matthews, 2003). Fifth, there is paucity of research concerning the potential modifying role of gender. Much more work needs to be done before we can fully understand gender differences in the association between burnout and CVD risk uncovered in the Shirom et al. (1997) study and in a few other works cited here. Finally, a novel cardiovascular risk factor like burnout, even if amenable to modification and capable of being incorporated in an intervention strategy (Leiter & Maslach, 2000; Maslach, 2003), has little public health utility unless it is shown in randomized controlled trials that the alleviation of burnout has favorable effects on CVD end points. Such controlled trials have yet to be conducted. Despite these gaps, we maintain that the eight prospective studies that we have reviewed, augmented by several case-control studies referred to above, provide solid support to the hypothesis that the state of burnout and vital exhaustion can increase damage to the cardiovascular system. Furthermore, existing knowledge summarized above documents several interactive physiological pathways linking burnout and vital exhaustion with established risk factors of CVD and coronary events.

Burnout and Vital Exhaustion and Their Association With Interrelated Disease Mediators

For burnout to be considered risk in the etiology and progression of CVD, plausible mechanisms must exist that explain the physical health effects of burnout. Our review identified several such disease mediators. Integrating the findings of an association between burnout or vital exhaustion and various disease mediators suggests that many are interrelated, pointing to the convergent validity of these findings. The findings reviewed here indicate that burnout and vital exhaustion are associated with several components of the metabolic syndrome, inflammation biomarkers, and impaired coagulation and fibrinolysis. Furthermore, burnout and vital exhaustion have also been associated with more upstream markers of the inflammation cascade, such as IL-1, IL-6, and TNF- α , which were shown to be independent predictors of CVD risk. Past studies uncovered an association between components of the metabolic syndrome and biomarkers of inflammation, such as CRP, which additively are strong predictors of cardiovascular risk among apparently healthy individuals (e.g., Bassuk et al., 2004; Ridker, Buring, Cook, & Rifai, 2003). Evidence also indicates that the metabolic syndrome is associated with homeostatic components, such as fibrinogen and PAI-1, and all are associated with atherosclerotic risk (Miranda et al., 2005). Furthermore, baseline CRP, fibrinogen, and particularly PAI-1 were found to be significantly associated with risk of diabetes (Dandona, Aljada, Chaudhuri, Mohanty, & Garg, 2005; Festa, D'Agosto, Tracy, & Haaffner, 2002), indicating that chronic inflammation may also be a risk factor for development of Type 2 diabetes. This evidence reveals a link between inflammation, atherosclerosis, acute coronary syndrome, and stroke, as well as the pathogenesis of Type 2 diabetes, which may be one of the possible pathways of the link between burnout or vital exhaustion and the disease outcomes listed above.

Burnout and vital exhaustion were shown to be associated with sympathetic nervous system activation (elevation of norepinephrine levels; van Doornen & van Blokland, 1989), as well as with dysregulation of the HPA axis (which may take many forms, such as reduced cortisol response to awakening, flattened cortisol curve, increased or decreased basal cortisol levels, and/or reduced glucocorticoid sensitivity or glucocorticoid resistance). The product of the activities of these components in the stress response alters the function of the immune organs and activates cytokine production and other mediators of inflammation and, hence, the link to the disease mediators discussed earlier. As indicated, there is evidence that various forms of HPA axis dysregulation may be associated with increased risk of CVD and diabetes. For example, the flattened diurnal cortisol curve, as observed in some burned-out persons, may reflect an increased risk of cardiovascular-related events and Type 2 diabetes (Rosmond et al., 2003). Attenuated response to awakening was found to be positively associated with intima media thickness in women (Eller et al., 2001). Furthermore, the hypocortisolism observed in some burned-out or exhausted persons may induce low-grade inflammation, as discussed above.

Findings of other studies showed that burnout and vital exhaustion are associated with sleep disturbances (such as a feeling of waking up exhausted) and disorders (e.g., insomnia). Moreover, there is complementary evidence of an association between vital exhaustion and objective signs of sleep disturbances (documented by polysomnographic recording). This evidence partly overcomes the potentially inflated association between vital exhaustion and self-reported sleep problems arising from the fact that both the full and the short MQ scales measuring vital exhaustion include several items that tap sleep problems, thus confounding these scales. One of the mediators of the link with sleep problems may be via HPA dysregulation, which has been suggested as playing a causative role in some clinical sleep disorders, such as insomnia (Buckley & Schatzberg, 2005; Vgontzas et al., 2001, 2003).

The above sleep problems, in addition to their impact on daily functioning and quality of life, were also shown to constitute an increased risk of CVD and sudden cardiac death (as outlined earlier). Several pathways have been suggested, all also found to be associated with burnout or vital exhaustion. One of them is through the association of sleep disturbances and disorders with mediators of the inflammatory process. Accordingly, Vgontzas et al. have shown that chronic insomnia is associated with a shift of IL-6 and TNF secretion from nighttime to daytime (Vgontzas et al., 2002). A recent study has shown that persistent insomnia is a predictor of hypertension (Suka, Yoshida, & Sugimori, 2003). Another recent study has shown that microarousals during sleep are associated with increased levels of lipids, cortisol, and blood pressure (Ekstedt et al., 2004), whereas in a previous study, burned-out subjects were shown to have a higher frequency of arousals during sleep compared with others (Soderstrom et al., 2004). In summary, these findings, taken together, suggest that burnout and vital exhaustion may be associated with increased risk of CVD and Type 2 diabetes through different but interrelated pathways.

For the reasons outlined in the introduction, we focused on two measures of burnout, the SMBM and the VE, because these two measures have been predominantly represented in the literature that considers the relation between burnout and physical health. We noted a considerable degree of convergence between findings

obtained with the VE and with the SMBM, hence supporting the earlier assertion that these scales probably tap a common factor. We did, however, caution that the VE is confounded with depression, anxiety, and sleep disturbances, so that findings of studies using the VE do not necessarily lead to remedial interventions focusing on a well-defined culprit. This lack of a clear relation has to do with the fact that the VE combines items that primarily gauge burnout with a few additional items that appear to represent depression, anxiety, and sleep disturbances. In comparison, the SMBM covers three interrelated types of energetic resources, was constructed based on COR theory, and is therefore probably not confounded with anxiety and sleep disturbances. Still, the SMBM may to some extent overlap with depression, because, as we noted, the definition of a depressive disorder includes fatigue or loss of energy as 1 of its 10 criteria, and low energy is one of the seven criteria leading to a diagnosis of low-level depression (Aggen et al., 2005; Suls & Bunde, 2005). Below, we review evidence that indicates burnout and depression are probably associated with CVD and CVD mediators through different physiological pathways. Irrespective of this evidence, we argue that in considering the effects of burnout on CVD risk factors and CVD morbidity and mortality, future researchers should include in their studies a measure of depressive symptomatology to control for the effects of depression. For example, in a cross-sectional study of a large sample, after controlling for the potential confounders of depression and anxiety, it was found that in women, burnout as assessed by the SMBM was positively associated with CRP and fibrinogen concentrations (Toker, Shirom, et al., 2005).

Burnout and Depression Are Differentially Linked to Disease Mediators

It is interesting that burnout and depression may be associated with similar health end points. Depression, like burnout, was found to be associated with increased risk for CVDs (Lett et al., 2004; Suls & Bunde, 2005; Wulsin & Singal, 2003), diabetes (Brown, Varghese, & McEwen, 2004), and sleep disturbances (Adrien, 2002; Walsh, 2004). Converging evidence, however, indicates that the mechanisms of the link may be different. For example, the study by Kop et al. (1998) indicated that depressive symptomatology and vital exhaustion are differentially related to behavioral risk factors for coronary artery disease and that their measures of vital exhaustion and of depression were differentially associated with risk factors for CVD. We reinterpret these (Kop et al., 1998) findings as reflecting the added value of burnout over and above that of depression for predicting risk factors and disease states.

In general, burnout or vital exhaustion and depression are found to be differentially related to physiological parameters. For example, the findings reviewed here suggest that burnout is generally associated with hypocortisolism, increased feedback inhibition of the pituitary–adrenal level of the HPA axis, and supersuppression of cortisol by dexamethasone (J. C. Pruessner et al., 1999). This is contrary to findings for major depression, which in some patients is characterized by hypercortisolemia and nonsuppression of cortisol by dexamethasone (Brown, Varghese, & McEwen, 2004; Nemeroff, 1996). Furthermore, in contrast to the finding of reduced cortisol response to awakening in burned-out persons, a heightened response to awakening was recently noted in persons reporting depressive symptoms (M. Pruessner et al., 2003). As

indicated earlier, burnout does not appear to be associated with hypertension but has been found to be positively associated with hyperlipidemia. In contrast, depression has been shown to place people at higher risk of developing hypertension (Suls & Bunde, 2005, p. 285). Furthermore, several studies point to an association between depression and abdominal fat (Brown et al., 2004), whereas no association with BMI was uncovered for either burnout (Grossi et al., 2003) or vital exhaustion (Nicolson & van Diest, 2000). Brown et al. (2004) presented a large body of data indicating that for some patients, the association of depression and biomedical parameters or physical health outcomes (such as hippocampal atrophy, cognitive impairment, abdominal obesity, and loss of bone density, as well as hypertension, peptic ulcer, and diabetes) may be modulated by elevated cortisol. Furthermore, Young, Lopez, Murphy-Weinberg, Watson, and Akil (2000) reported that depressed patients show evidence of a deregulated HPA axis response during a social stress test, with elevated cortisol following a stressor as great as that of healthy control subjects, despite higher baseline cortisol levels than those of the control subjects. In contrast, as indicated earlier, Nicolson and van Diest (2000) showed that compared with control subjects, vitally exhausted subjects had lower basal cortisol levels and tended to show decreased cortisol responses to challenging tasks. Thus, all these later findings are consistent with the above findings suggesting that burnout may be associated with hypocortisolism, whereas depression is more likely to be associated with hypercortisolism.

Three studies have shown that the association between burnout and inflammation biomarkers was not mediated by depression. In one study, only vital exhaustion, and not depression, was associated with biomarkers such as CRP and white blood cell count (Kop et al., 2002). In two other studies, burnout was found to be associated in women with TNF- α (Grossi et al., 2003), CRP, and fibrinogen (Toker, Shirom, et al., 2005), even after adjusting for depression. Further studies are needed that measure burnout or vital exhaustion and depression in addition to recording a wide range of autonomic and neuroendocrine parameters as well as disease biomarkers, to elucidate whether burnout and depression are indeed physiologically differentiated.

Implications and Future Directions

Burnout May Identify Individuals at Risk

The few existing studies that simultaneously examined exposure to stress, burnout, and health outcomes indicated that measuring burnout might help identify individuals at risk. For example, the study by Nakamura et al. (1999) showed that among individuals exposed to work stress, only those who manifested burnout symptoms also showed evidence of reduced cellular immunity. Similarly, the study of teachers by J. C. Pruessner et al. (1999) indicated that individuals reporting high perceived stress showed a high cortisol response to awakening, whereas those reporting burnout had signs of hypocortisolism indexed by an attenuated cortisol response to awakening. Thus, focusing on burned-out individuals may identify those who are chronically exposed to work and life stress and who may have used ineffective means of coping with stress, leading in turn to a gradual erosion of their coping resources and to their feeling exhausted or burned out. Given the evidence pointing to the chronicity of the burnout phenomenon, it is very

likely that burned-out individuals will be at risk of physical morbidity. Further longitudinal studies that measure stress, burnout, and health outcomes are needed to validate the assertion that burned-out persons are at higher risk of impaired physical health over time.

Additional Potential Moderators of the Association Between Burnout or Vital Exhaustion and Ill Health

According to McEwen (1998), the effects of chronic stress on humans may be exacerbated by a rich diet and the use of tobacco and alcohol and may be reduced by moderate exercise. Thus, by implication, it is important to explore the possible role of health and risk behaviors in moderating the relationship between burnout or vital exhaustion and physiological outcomes. McEwen (1998) further maintained that individual sensitivity to stress is also determined by a person's general state of physical health and can lead to permanent overload (McEwen & Wingfield, 2003). Thus, an important avenue for research would be to explore whether, among persons exposed to chronic occupational or life stress, those with poor physical health more readily develop symptoms of burnout. Similarly, vital exhaustion was shown to affect outcomes such as future cardiovascular events in patients with CVD (Kortge et al., 2002; Kop et al., 1994). It would be important to determine whether this trend applies to a variety of medical conditions and procedures to identify individuals at risk.

Exploring Potential Association With Other Bodily Disorders

Many aspects of the health implications of burnout remain unexplored. The evidence suggests that individuals with metabolic syndrome apparently are susceptible to other conditions besides CVD and diabetes, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer (Grundy et al., 2004). Given the association between burnout and several components of the metabolic syndrome, it is plausible that burned-out and/or exhausted individuals may be at risk for the various bodily disorders found to be associated with the metabolic syndrome. Likewise, excessive systemic inflammation may pose a risk for diseases other than those reviewed above, such as multiple sclerosis and rheumatoid arthritis (Segerstrom & Miller, 2004), and by implication burned-out and/or exhausted individuals may also be at risk for these other diseases.

Given the association of burnout and vital exhaustion with hypocortisolism and the implication of hypocortisolism in stress-related bodily disorders (such as CFS, fibromyalgia, other chronic pain syndromes, asthma, and allergies: see Heim et al., 2000), burnout and vital exhaustion may also be associated with some of these stress-related bodily disorders. The findings of a recent study indeed provide support for one of these possibilities, as among primary care patients, burnout (measured by the SMBM) was found to be associated with 1.7-fold increased risk for musculoskeletal pain, even after controlling for possible confounding variables, including job strain (Soares & Jablonska, 2004). We are aware that the above suggestions are only tentative, yet they still may guide future research designed to explore whether burnout or vital exhaustion may be a precipitating factor in the development of bodily disorders other than those reviewed above.

Burnout and CFS

Researchers in behavioral medicine and related areas of the medical sciences have virtually overlooked the burnout syndrome when studying its more extreme form, CFS. For example, a recent compendium of research on CFS (Friedberg & Jason, 1998) does not make any reference to burnout. CFS is an illness of unknown etiology associated with significant disability; its characteristic symptoms include profound fatigue lasting for 6 months or more, impaired memory or concentration, sleep disturbances, sore throat, and other symptoms (for a discussion of the diagnosis and components of CFS, see Friedberg & Jason, 1998, pp. 49–65). Early references to the relevant disease entities often went under the symptomatic categories of asthenia, lassitude, lethargy, or listlessness. CFS is now recognized as a legitimate disease state (Shafran, 1991). Idiopathic chronic fatigue (ICF) amounts to CFS but with fewer symptoms, though studies comparing CFS and ICF patients have found few clinically meaningful differences between the two categories, and ICF is now regarded as a point on a continuum leading to CFS (Johnson, DeLuca, & Natelson, 1999).

Researchers studying the psychological pathogenesis of CFS have tended to view clinical depression as antedating the development of this disease state, because fatigue is one of the symptoms included in many measures of depression and is present in almost all cases of CFS (Shafran, 1991). However, several studies have found that CFS is distinct from depression in both the biological and psychiatric domains (Friedberg & Jason, 1998, p. 24). The medical model of CFS disregards the role of stress in bringing about the disease (Wessely, 1995). Only a small minority of those complaining of chronic fatigue are diagnosed as having CFS (Wessely, 1995). Etiologically, the role of burnout in bringing about CFS at some point is a working hypothesis that has yet to be systematically investigated (cf. Huibers et al., 2003). Huibers et al. (2003) were pioneers in this respect by exploring the relationship between burnout (gauged by the MBI) and CFS in a sample of 151 fatigued employees on sick leave. They found that the group of employees categorized as having a CFS-like condition made stronger somatic attributions concerning their illness (e.g., it is caused by a virus), whereas those categorized as burned out made stronger psychological attributions. It is a common finding in the burnout literature that those with high levels of burnout attribute their condition to their job, whereas for CFS patients, suffering from a malaise that can affect virtually all major bodily systems, the origin of their symptoms is unclear (Schaufeli & Enzmann, 1998).

Burnout or vital exhaustion and CFS may share a common neuroendocrine basis. Studies have found that, similar to in burnout and vital exhaustion, in CFS there is some alteration of HPA function. Most of the studies have revealed decreased basal cortisol production in persons with CFS. This finding, however, is not universal. Some studies have failed to find abnormalities in basal cortisol production in these patients, and at least in one study persons with CFS were found to have higher cortisol levels compared with healthy control subjects (Papanicolaou et al., 2004). Nevertheless, these researchers maintain that symptoms characteristic of CFS, such as fatigue, depressed mood, sleep disturbances, nausea, orthostatic intolerance, and myalgia, are shared by conditions marked by either hypocortisolism or hypercortisolism. Hypocortisolism leads to symptoms of nausea, anorexia, orthostatic intolerance, and muscle and joint pain. Hyperactivity of the HPA

axis is associated with cognitive disturbances and muscle weakness. Fatigue, depressed mood, and sleep disturbances can be found in both of these conditions (Papanicolaou et al., 2004). As indicated earlier, persons with burnout or vital exhaustion manifest several of the symptoms manifested by persons with CFS (e.g., chronic fatigue, cognitive disturbances, depressed mood, and sleep disturbances; Papanicolaou et al., 2004). Thus, the similarity between these constructs exists also at the symptomatic level. Furthermore, as in the case of burnout or vital exhaustion, CFS has been shown to be associated with increased secretion of proinflammatory cytokines, such as IL-6 and TNF- α (Papanicolaou et al., 2004), as well as an increase in autonomic nervous system activity. As indicated earlier, proinflammatory cytokines, and IL-6 in particular, have been associated with several of the symptoms listed above. On the basis of this evidence, we suggest that burnout can be a precipitating factor in the development of CFS. Alternatively, these symptoms may be one of the possible outcomes of chronic stress exposure and/or neuroendocrine dysfunction. This could be a promising area for future research.

Some Unresolved Issues and Tentative Hypotheses

The paucity of research on the neuroendocrine correlates of burnout does not permit arriving at a definite conclusion as to whether burnout and vital exhaustion are typically associated with glucocorticoid excess or insufficiency along with sympathetic nervous system activation. As indicated earlier, however, the data reviewed above suggest that burnout and vital exhaustion are more consistently associated with hypocortisolism, and in this they are similar to some neuropsychiatric and bodily disorders, such as atypical depression, fibromyalgia, rheumatoid arthritis, CFS, and post-traumatic stress disorder (PTSD) (Chrousos & Gold, 1992; Heim et al., 2000; Raison & Miller, 2003). The precise origin of hypocortisolism in burnout and vital exhaustion has not been determined. The mechanisms that may underlie the development and persistence of hypocortisolism in chronic stress or stress-related disorders, as suggested by Heim et al. (2000), are (a) reduced biosynthesis or depletion at several levels of the HPA axis (CRH, ACTH, cortisol); (b) CRH hypersecretion and adaptive down regulation of pituitary CRH receptors; (c) increased feedback sensitivity of the HPA axis; and (d) morphological changes.

It seems plausible that burnout and vital exhaustion induce CRH hypersecretion, coupled with decreased cortisol secretion, as in the case of PTSD (Yehuda, 2003). Patients with chronic PTSD have increased circulating levels of norepinephrine and increased circulating levels of α 2-adrenergic receptors (Yehuda, 2002), and this most likely is due to coactivation of the locus ceruleus–norepinephrine system (central sympathetic system). The mechanism likely to keep sustaining activation of the noradrenergic neurons of the central stress system is the absence of negative feedback from cortisol operating at the level of the pituitary and the hypothalamus, as well as at the hippocampus and amygdala levels (Chrousos & Gold, 1992; de Kloet, 1991; McEwen et al., 1997). Lower levels of cortisol may fail to inhibit activation of the pituitary gland, resulting in increased CRH stimulation in synergy with other neuropeptides, such as arginine vasopressin (Yehuda, 2003).

Basically, norepinephrine acts as a major alarm-producing neurotransmitter in the brain and inhibits neurovegetative functions,

such as feeding, grooming, and sleeping. Norepinephrine contributes to accompanying increases in autonomic and neuroendocrine responses to stress, including HPA axis activation (Chrousos, 1998). Indeed, PTSD patients also have been found to have higher catecholamine levels than do persons without PTSD exposed to trauma or nonexposed persons (Young & Breslau, 2004). All this may explain the paradox of the coexistence of hypocortisolism in PTSD patients along with irritability and hyperarousal. Thus, it seems biologically plausible that CRH and sympathetic nervous system activation may also characterize burned-out and vitally exhausted persons. Indirect supporting evidence for this assertion comes from the findings, cited earlier, of an association between burnout and vital exhaustion on the one hand and irritability, tension, and insomnia on the other. More direct evidence comes from the study by van Doornen and van Blokland (1989) showing increased epinephrine and norepinephrine responses to stress in exhausted individuals.

The possibility that burnout and vital exhaustion may be associated with elevated CRH, hypersecretion of catecholamines and other neuropeptides, and the absence of the regulating counter effects of glucocorticoids induced by insufficient glucocorticoid signaling is consistent with the observed positive association between burnout or vital exhaustion and many of the disease mediators discussed above (namely, various components of the metabolic syndrome, increased concentration of proinflammatory cytokines, and inflammation biomarkers), as well as with increased risk of Type 2 diabetes. Such a possibility may, for example, resolve the contradictory finding that basal lower cortisol levels were found in exhausted individuals, especially in the evening (Nicolson & van Diest, 2000), even though vital exhaustion is associated with insomnia and poor sleep. As indicated earlier, in most studies insomnia and poor sleep were most consistently found to be associated with elevated evening cortisol levels (Rodenbeck et al., 2002; Vgontzas et al., 2001, 2003). The thought-provoking article by Buckley and Schatzberg (2005) pointing to the role attributed to CRH, rather than to cortisol, in inducing light sleep, stressed and nonstressed waking, and insomnia may reconcile this apparent contradiction. Buckley and Schatzberg (2005) claimed that although much of the prior literature has emphasized cortisol in sleep, an inspection suggests that increased cortisol may not be the primary cause of sleep disturbance but rather a marker for increased nocturnal CRH activity. They cite evidence showing that CRH acts to decrease slow-wave sleep and to increase light sleep and awakenings. In addition, given the known relationship between CRH and the locus ceruleus–norepinephrine stress axis, an increase in central norepinephrine activity is also expected. Norepinephrine increases sleep electroencephalogram frequency (associated with increased wakefulness), and CRH reciprocally simulates the locus ceruleus–norepinephrine system. An early study by Vgontzas et al. (1998) showed activation of both limbs in the stress response (HPA axis and sympathetic system) in insomnia. Thus, the poor sleep and insomnia observed in exhausted individuals may be the outcome of elevated CRH and hypersecretion of catecholamines along with other neuropeptides, notwithstanding the low basal cortisol levels, including low evening levels.

We should point out, however, that although many of the physiological derangements found to be associated with burnout and vital exhaustion are consistent with possible coexistence of

hypocortisolism, they also may be associated with hypercortisolism. McEwen et al. (1997), as well as other researchers, have pointed out that glucocorticoids are capable both of enhancing and of inhibiting host immune responses. Under chronic stress conditions, glucocorticoids can cause enhancement of immune responses. We also recall the option raised by Papanicolaou et al. (2004) that the various symptoms manifested by burned-out or exhausted individuals may be the outcome of conditions marked either by hypocortisolism or by hypercortisolism. Thus, only specifically designed future studies that include measurements of neuroendocrine hormones (such as catecholamines and glucocorticoids) as well as administration of challenging tests such as the dexamethasone suppression test or its improved version, the dexamethasone-CRH stimulation test (Heuser, Yassouridis, & Holsboer, 1994), will be able to elucidate the predominant neuroendocrine correlates of burnout and vital exhaustion, as well as their relation to all the risk factors for physical health covered in the present review.

Suggested Physiological Basis for the Chronicity of Burnout and Potential New Avenues for Treatment

The chronicity of burnout, as documented above, is both puzzling and alarming given its negative consequences for mental and physical health. Our review of past longitudinal research on burnout supports the notion of a vicious cycle between stress appraisal and burnout, suggesting that chronic stress and burnout are reciprocally related. We have indicated that COR theory predicts this vicious cycle between chronic stress and burnout. Many recommendations in the literature for breaking this cycle focus on primary, secondary, and tertiary interventions, such as those designed to alter organizational features conducive to burnout, those for training employees in stress management, or those that provide cognitive-behavioral therapy for burned-out persons (for a review, see Maslach & Leiter, 1997; Schaufeli & Buunk, 2003; Schaufeli & Enzmann, 1998; Shirom, 2003). We suggest that such interventions may be only partially effective in eliminating burnout and vital exhaustion or may be effective mainly at the early stages of the etiology of burnout. This may be due to yet another vicious cycle, one that is based in physiology, which gradually develops between burnout and the associated physiological imbalances that feed and help to maintain the chronicity of burnout. It is possible that once that such physiological vicious cycle is established, it is less susceptible or more resistant to stress management and other behavioral interventions. Initial support for this assertion comes from the finding that stress management intervention did not alter functional hypocortisolism in burned-out patients (Moch et al., 2003).

One possible form of such a vicious cycle is a possible bidirectional association between burnout and sleep dysfunctions and disorders. It is possible that the HPA axis dysregulation and sympathetic nervous system activation associated with burnout and vital exhaustion are also associated in some individuals with sleep dysfunction, such as insomnia, nonrefreshing sleep, and waking up exhausted, which in turn exacerbates symptoms of mental and physical fatigue and further reduces resources for coping with stress, thus leading to sustained burnout. Sustained burnout preserves HPA axis dysregulation and sleep disturbances, and this self-perpetuating process persists. The clinical therapeutic

implication of such a possibility is to treat burnout and sleep disorders simultaneously in those who exhibit symptoms of both. Some avenues for combating insomnia resulting from activations of the HPA axis, including elevation of CRH, were suggested by Buckley and Schatzberg (2005) and Vgontzas et al. (2001).

Another example of possible feedback helping to sustain burnout symptoms lies in the association of burnout with increased concentrations of proinflammatory cytokines (IL-1, TNF- α , IL-6). Compelling evidence indicates such cytokines communicate with the brain to produce anxiety, depression, learned helplessness, and cognitive disturbances (Dantzer, 2004; Maier & Watkins, 1998; Reichenberg et al., 2001; Weaver et al., 2002; Wilson, Finch, & Cohen, 2002). This communication may lead to chronic negative assessment of stressors in the environment and to a vicious cycle, resulting in increased burnout. There is also evidence that IL-6 and TNF- α are somnogenic and fatigue-inducing proinflammatory cytokines (Vgontzas et al., 2002), which will exacerbate feelings of exhaustion and burnout. It is possible that measures taken to reduce inflammation might be helpful in alleviating burnout symptoms. We thus recommend that in designing future interventions to combat burnout and to reduce risks to health, a multidisciplinary approach comprising organizational, behavioral, psychological, and physiological-pharmacological approaches may prove to be more efficacious in bringing about long-term alleviation of burnout than would interventions focusing on a unidisciplinary approach.

Concluding Comment

Earlier reviews of the possible health implications of burnout have dealt exclusively with its negative impact on mental health. The evidence reviewed above reveals that burnout has deleterious consequences for physical health. Most of the relevant research in this area supports the assertion that burnout and vital exhaustion constitute an increased risk of CVD and cardiovascular-related events. Other studies provided initial evidence that both burnout and vital exhaustion are associated with risk of other bodily disorders, such as Type 2 diabetes and impairment of reproductive functions. Moreover, the association of burnout and vital exhaustion with a variety of disease mediators (namely, the metabolic syndrome, dysregulation of the HPA axis and the sympathetic nervous system activity, sleep disturbances, systemic inflammation, impaired immunity functions, blood coagulation and fibrinolysis, and poor health behaviors) suggests that their impact on health may be more extensive than is currently suggested. This suggestion should be explored in future research.

Our review of the potential disease mediators linking burnout with the above disease entities has proved beneficial in two major respects. First, it has demonstrated that the theoretically based distinctions between burnout or vital exhaustion and chronic stress and between burnout or vital exhaustion and depression can be empirically supported by the evidence we have documented for the existence of different physiological mechanisms involved in these relationships. Second, the remarkable chronicity of burnout may stem in part from the associated physiological derangements that feed back and help to maintain the chronicity of burnout. Treating the associated physiological derangements, such as sleep dysfunctions or disorders or the appearance of low-grade inflammation, may reinforce the effectiveness of more traditional psychological

and behavioral interventions to break the vicious cycle consisting of both psychological and physiological chains, which may explain the chronicity of burnout and vital exhaustion.

The documented risk to mental and physical health strongly points to the need to assess and treat burnout to prevent or at least reduce possible damage to health. The need for old and new interventions is further emphasized by the percentages of the working population reporting severe levels of burnout. One starting point would be the assessment of burnout by health care professionals, especially at occupational health clinics, where assessment of burnout can be introduced as part of the overall risk assessment for the employed population.

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