Psychological Bulletin
2007, Vol. 133, No. 1, 25–45


0033-2909/07/$12.00 DOI: 10.1037/0033-2909.133.1.25

# If It Goes Up, Must It Come Down? Chronic Stress and the Hypothalamic-Pituitary-Adrenocortical Axis in Humans

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The notion that chronic stress fosters disease by activating the hypothalamic-pituitary-adrenocortical (HPA) axis is featured prominently in many theories. The research linking chronic stress and HPA function is contradictory, however, with some studies reporting increased activation, and others reporting the opposite. This meta-analysis showed that much of the variability is attributable to stressor and person features. Timing is an especially critical element, as hormonal activity is elevated at stressor onset but reduces as time passes. Stressors that threaten physical integrity, involve trauma, and are uncontrollable elicit a high, flat diurnal profile of cortisol secretion. Finally, HPA activity is shaped by a person's response to the situation; it increases with subjective distress but is lower in persons with posttraumatic stress disorder.

*Keywords:* stress, trauma, cortisol, HPA axis



Exposure to chronic stress markedly increases vulnerability to adverse medical outcomes. This holds true across a wide variety of mental and physical conditions. For example, persons facing chronic stress are more likely to develop an episode of clinical depression, experience symptoms of an upper respiratory infection following viral exposure, suffer from a flare up of an existing allergic or autoimmune condition, and show accelerated progression of chronic diseases such as acquired immunodeficiency syndrome and coronary heart disease (Miller & Cohen, 2005; Monroe & Hadjiyannakis, 2002; Pereira & Penedo, 2005; Rozanski, Blumenthal, & Kaplan, 1999; Wright, Rodriquez, & Cohen, 1998). This phenomenon is apparent across the entire lifespan. From early in childhood to late in adulthood, chronic stress is accompanied by worse health (Coe & Lubach, 2003; Kiecolt-Glaser & Glaser, 2001; Repetti, Taylor, & Seeman, 2002; Taylor, Repetti, & Seeman, 1997), and the magnitude of this effect is substantial: In some cases, exposure to chronic stress triples or quadruples the chances of an adverse medical outcome (S. Cohen et al., 1998; Sandberg, Jarvenpaa, Penttinen, Paton, & McCann, 2004).

Scientists have long been interested in understanding the biological mechanisms by which chronic stress "gets under the skin" to affect health outcomes. One potential mechanism that has received widespread and persistent attention is the hypothalamic-pituitary-adrenocortical (HPA) axis. This hormonal response system is present in organisms ranging from birds to humans and can be activated by a broad array of mental and physical stressors (McEwen, 1998; McEwen & Stellar, 1993; Weiner, 1992). Activation occurs when neurons in the paraventricular nucleus of the hypothalamus secrete corticotropin-releasing hormone (CRH). This molecule travels through the hypophyseal portal circulation to the anterior pituitary gland, which responds to its presence by secreting a pulse of adrenocorticotropin hormone (ACTH). The ACTH signal is carried through the peripheral circulation to the adrenal glands, which synthesize and release cortisol in a tissue layer called the *zona fasciculata*. Of the hormones released as part of this cascade, cortisol has been the subject of the most research attention, probably because of its widespread regulatory influences. Cortisol plays a key role in the central nervous system, where it is involved in learning, memory, and emotion; in the metabolic system, where it regulates glucose storage and utilization; and in the immune system, where it regulates the magnitude and duration of the inflammatory responses and the maturation of lymphocytes (Sapolsky, Romero, & Munck, 2000). Moreover, these are just the most prominent examples of cortisol's actions; its influence also extends to multiple other systems in the body (Weiner, 1992).

These observations have prompted scientists to advance numerous theories over the past 50 years linking stressors, cortisol, and disease. Common to each of these models is the notion that cortisol is a critical biological intermediary; it is seen as a primary mechanism through which chronic stressors get inside the body to bring about disease. Models of this type have been articulated for psychiatric disorders such as depression and schizophrenia (McEwen, 2000; E. F. Walker & Diforio, 1997); medical conditions such as cancer, arthritis, and diabetes (Bjorntorp & Rosmond, 1999; Sephton & Speigel, 2003; Heijnen & Kavelaars, 2005); and lifestyle problems such as obesity (Epel et al., 2000) and fatigue (Bower, Ganz, & Aziz, 2005). Cortisol has also been implicated as a primary suspect in more general models of stress and disease (S.

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Our efforts on this project were generously supported by the Michael Smith Foundation for Health Research; the Canadian Institutes of Health Research; the National Heart, Lung, and Blood Institute; the National Alliance for Research on Schizophrenia and Depression; and the UBC Human Early Learning Partnership.

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Cohen, Kessler, & Underwood, 1995), the idea being that it serves as a gateway to a broad array of conditions brought on by undesirable circumstances.

In the vast majority of these models, stress triggers disease by increasing output of cortisol, thereby exposing bodily tissues to elevated concentrations of the hormone. If sustained, this process is thought to lead to tissue damage and subsequent dysregulation of biological systems. In contrast to these models, there also is now a handful of theories positing that stress-induced declines in cortisol output are the culprit mechanism (Heim, Ehlert, & Hellhammer, 2000; Sternberg, Chrousos, Wilder, & Gold, 1992; Yehuda, 2000). These models are generally advanced to explain how stress could exacerbate conditions in which deficient cortisol signaling contributes to disease pathogenesis (Raison & Miller, 2003). This may be the case with rheumatoid arthritis, chronic fatigue syndrome, and posttraumatic stress disorder (PTSD). Thus, current theories view cortisol deviations in both directions as potentially detrimental; whether elevations or declines are pathogenic depends on the condition.

## Chronic Stress and Cortisol Output

With cortisol so prominently featured in models of stress and disease, much effort has been devoted to understanding how undesirable circumstances modify its secretion. The earliest research with human subjects indicated that chronic stress (e.g., being a soldier in combat or having a child with pediatric cancer) was associated with reduced daily output of cortisol (Bourne, Rose, & Mason, 1967, 1968; Friedman, Mason, & Hamburg, 1963). These findings were puzzling to researchers, because they contradicted a central dogma of the period—that stress markedly increased cortisol secretion. This dogma had emerged from decades of research in animal models by Selye and his descendants (e.g., see Selye, 1956). As a result, the findings of reduced cortisol output were set aside, and work in this area languished for 10–15 years. At that time, new research emerged showing that chronic stresses such as bereavement, unemployment, and man-made disasters were accompanied by elevated levels of cortisol output (Arnetz et al., 1987; Baum, Gatchel, & Schaeffer, 1983; Kosten, Jacobs, & Mason, 1984; Schaeffer & Baum, 1984). Perhaps because they were consistent with the large body of evidence from animal studies, these findings captivated the attention of researchers and provided an empirical foundation for models of stress, cortisol, and disease that followed. For the next 10–15 years, research and theory in this area flourished, guided by the implicit assumption that HPA activity increases robustly with stress.

However, in the mid to late 1990s, a series of studies emerged of patients suffering from PTSD, and they reported the surprising result that combat veterans, Holocaust survivors, and other trauma victims had reduced cortisol secretion as well as a host of other indicators of abnormal HPA activity (Yehuda, Boisonuae, Lowy, & Giller, 1995; Yehuda, Kahana, et al., 1995; Yehuda, Resnick, Schmeidler, Yang, & Pitman, 1998; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996). This pattern was not uniformly observed in studies of PTSD (see e.g., Hawk, Dougall, Ursano, & Baum, 2000; Lemieux & Coe, 1995; Pitman & Orr, 1990). The most robust evidence came from patients who had chronic, intractable PTSD and had been exposed to trauma many years before cortisol assessment. Nevertheless, this pattern of reduced cortisol output and blunted HPA activity was sufficiently common that some researchers began viewing it as a unique feature of (and a potential cofactor in) PTSD (Yehuda, 2000; Yehuda, Resnick, Kahana, & Giller, 1993). In the years that followed, broader evidence of this phenomenon began to emerge; low cortisol output was documented in chronically stressed but nonpsychiatric populations, such as victims of domestic violence and caregivers for ill family members (Miller, Cohen, & Ritchey, 2002; Seedat, Stein, Kennedy, & Hauger, 2003; Vedhara et al., 2002). Again, not all studies of chronic stress reported findings in this direction. However, by 2000, stress-related hypocortisolism had begun to attract considerable attention, and Heim, Ehlert and Hellhammer (2000) published a seminal review article on the topic. A number of other articles on this phenomenon soon followed (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Gunnar & Vazquez, 2001; Raison & Miller, 2003), and today the field is squarely focused on hypocortisolism.

Despite the enthusiasm, these findings have created significant confusion in the field. It is unclear how the recent findings can be integrated with older studies to arrive at a general conclusion about how HPA functions are influenced by chronic stress. Does cortisol output increase, as older work suggests? Or does it decline, as newer research indicates? Or perhaps more interestingly, is it capable of doing both? That is, might the nature and direction of the cortisol response depend on features of the stressor or on characteristics of the person who is coping with it? The answers to these questions have significant implications for research and theory across many areas of inquiry. Hence, the goal of this review is to synthesize findings over the past 50 years of research and generate answers to what was once considered a simple question: How is activity of the HPA axis modified by exposure to chronic stress?

## What Shapes HPA Activity Following Exposure to Chronic Stress?

If chronic stress is capable of increasing or decreasing HPA activity, what are some of the critical features that govern which outcome occurs? It is surprising that there has been little effort to develop psychological hypotheses that can explain this process. Thus, a second objective of this review is to outline and evaluate five hypotheses that may help to sort out some of the confusion in the literature. These hypotheses focus on (1) the time elapsed since stressor onset, (2) the nature of the threat posed, (3) the core emotions likely to be elicited by the stressor, (4) the controllability of the stressor, and (5) the psychiatric characteristics of the person.

### *1. Time Since Onset*

One possibility is that chronic stress both increases and decreases HPA activity, but does so at different times over the course of a threat. Shortly after the stress has begun, the axis may become activated, resulting in elevated cortisol output. However, with the passage of time, the body could mount a counter-regulatory response such that cortisol output rebounds below normal. This is a biologically plausible explanation, because the HPA axis is regulated by a potent negative feedback circuit, in which elevated levels of cortisol suppress output of CRH and ACTH by acting on glucocorticoid receptors in the hippocampus, hypothalamus, and

pituitary. It is also a plausible explanation for the conflicting findings in the literature. Although hypotheses about the importance of timing have been articulated by several researchers (Fries et al., 2005; Hellhammer & Wade, 1993; Miller et al., 2002), they have not yet been tested with a proper longitudinal design. Thus, the existing literature may only seem contradictory because it is composed of a series of cross-sectional studies, each of which assesses its participants at a slightly different point in time with respect to stressor onset. In the current article, we use meta-analysis to evaluate this hypothesis. To the extent that it is correct, a correlation should emerge between timing and HPA activity, with more distant traumas being associated with hypocortisolism, and the reverse being true of recent-onset stress.



### 2. Nature of Threat

Another possibility is that different forms of stress elicit different patterns of hormonal response. A number of theorists have argued that biological responses are stressor specific, having been shaped over time to maximize success at coping (Kemeny, 2003; Weiner, 1992). For example, a distinction can be made between forms of stress that pose a threat to the physical self (e.g., being in the midst of combat) and those that represent a threat to the social self (e.g., being in the midst of a divorce). According to specificity hypotheses, these situations should elicit different patterns of HPA activity because they pose different adaptational demands, which cortisol helps to support metabolically. Support for this view was recently obtained in a meta-analysis of cortisol responses to acute stress: Subjects exposed to laboratory situations that were high in social threat exhibited robust increases in cortisol secretion (Dickerson & Kemeny, 2004). When the situation had few elements of social threat, little in the way of a cortisol response was evident. The authors theorized that preserving social standing is a central motivation of humans; when this standing is threatened by a demanding situation, the HPA axis is mobilized to help manage the threat or its longer term consequences. It may also be useful to differentiate between traumatic and nontraumatic forms of stress. The former are defined as experiences that involve "actual or threatened death or serious injury, or a threat to the physical integrity of self or others" and have a special capacity to elicit feelings of "intense fear, helplessness, or horror" (American Psychiatric Association, 2000, pp. 427–428). Because they are able to elicit such intense and distinct emotions, traumas may bring about more pronounced alterations in HPA function or qualitatively different profiles of hormonal output than do chronic, but nontraumatic, stressors. In the current review, meta-analysis is used to evaluate whether these distinctions—physical versus social and trauma versus nontrauma—help to explain the mixed findings in the literature on chronic stress and HPA outcomes.

### 3. Emotions Elicited by Stress

A related hypothesis is that the direction and magnitude of the HPA response is governed by the emotion(s) elicited by the situation. According to this view, emotions represent the psychological mechanism connecting stressors to biology, so they should be the most powerful determinant of changes in HPA functions. One emotion that has been repeatedly discussed in this regard is shame. In studies in which subjects are exposed to acute stress in a laboratory setting, the extent of cortisol reactivity increases in a linear fashion with shame (Dickerson & Kemeny, 2004; Gruenewald, Kemeny, Aziz, & Fahey, 2004). Thus, feelings of shame appear to foster HPA activation during acute bouts of stress. It is interesting that the available evidence suggests an opposite pattern with more long-term, severe stress. At least in combat veterans who suffer from PTSD, shame is inversely related to daily cortisol output (Mason et al., 2001). This has led some researchers to suggest that shame may be a critical mechanism in stressor-related hypocortisolism. Feelings of loss also have been discussed as potential moderators. Life stress that involves a major loss has been shown to predict the onset of major depression (Kendler, Hettema, Butera, Gardner, & Prescott, 2003), and it has been argued that it does so by activating the HPA axis to persistently secrete cortisol (Meinlschmidt & Heim, 2005; Nicolson, 2004; Petitto, Quade, & Evans, 1992). Thus, the meta-analysis will examine whether two key emotional themes of chronic stress—shame and loss—can differentiate between studies that find increases versus decreases in HPA function.

### 4. Controllability of Stress

Controllability represents another important dimension of chronic stress that has been proposed to influence HPA axis responsivity (Heim, Ehlert, & Hellhammer, 2000). In the context of acute stress, uncontrollability amplifies cortisol secretion, both in humans and in animals (Dickerson & Kemeny, 2004; Sapolsky, 1998). However, with stress that is more severe and persists longer, uncontrollability is thought to result in diminished HPA activity. This blunting may underlie the withdrawal and disengagement behaviors that often accompany uncontrollable chronic stress (Gold & Chrousos, 2002; Heim, Ehlert, & Hellhammer, 2000; Mason et al., 2001). Conversely, it may be a manifestation of the physiological toughening or steeling oneself that can occur when a person cannot escape from a difficult situation (Dienstbier, 1989; Gunnar & Vazquez, 2001a). By contrast, stress that has some element of controllability may activate the HPA axis, as its hormonal products provide metabolic support for active coping efforts (Gunnar & Vazquez, 2001a; Mason et al., 2001). Hence, to the extent that these theoretical formulations are accurate, the meta-analysis should yield positive associations between controllability and HPA products, which would help to explain variability in the existing literature.

### 5. Individual Psychiatric Sequelae

A final possibility is that the psychiatric consequences of chronic stress, rather than features of the stress itself, are what govern the magnitude and direction of any HPA axis response. For example, research indicates that if a person exposed to trauma develops PTSD, he or she is likely to exhibit hypocortisolism (Yehuda, 2000; Yehuda, Resnick, et al., 1993). In contrast, depression following a trauma has been associated with increased cortisol output (Kaufman et al., 1997, 1998; Raison & Miller, 2003). Even when a trauma victim does not develop a full-blown psychiatric condition, research has suggested that the extent of subjective distress is positively associated with HPA activation (Baum, Cohen, & Hall, 1993; Davis et al., 2004; Rahe, Karson, Howard, Rubin, & Poland, 1990). To examine the contribution of

psychiatric conditions and normative distress, we also conducted a separate meta-analysis involving only persons exposed to chronic stress. It asked the question, do individuals who experience chronic stress and develop a psychiatric diagnosis, or report greater subjective distress, differ in HPA function from those who experience chronic stress but do not develop a diagnosis or report distress?

## Defining and Measuring Chronic Stress

Most of the work in this area has relied on stimulus-based definitions of *chronic stress*, in which a target population is facing circumstances that most people would consider troubling and ongoing. Typical designs feature soldiers in the midst of combat, refugees displaced by war, victims of sexual assault, family caregivers for the ill, and people who have lost their jobs or spouses. Although these situations differ in a number of important respects, we believe they all can be viewed as chronic forms of stress. By *stress* we mean situations that the average person would appraise as threatening and exceeding his or her ability to cope (Lazarus & Folkman, 1984). By *chronic* we mean that the eliciting stimulus remains in the environment for an extended period of time (e.g., the family member who needs care indefinitely) or, alternatively, that the threat a stimulus poses to the self looms for an extended period of time (e.g., the sense of danger that follows a sexual assault), even if the stimulus itself does not. This definition grows out of the taxonomy proposed by Baum, Cohen, and Hall (1993), which views chronic stress as being composed of a stimulus from the environment, a person's appraisal of that stimulus, and biobehavioral responses that support coping efforts. These dimensions are understood to be independent, and each can vary in duration from acute to chronic. As a result, this view of chronic stress encompasses situations in which the stressor persists for an extended period of time, as well as situations that last for a very short time but are likely to be seen as threatening for much longer.

## Defining and Measuring HPA Activity

HPA activity can be assessed in a variety of ways. The most common method is to measure output of cortisol. This can be done by collecting saliva (which contains biologically active cortisol, unbound to carrier proteins), blood, urine, or cerebrospinal fluid (all of which contain bound and unbound cortisol). Each of these fluids provides a slightly different temporal window on cortisol activity (Baum & Grunberg, 1995). Levels of hormone in blood and saliva reflect HPA activity in the past 10–60 min. Because it is usually collected over a 15–24-hr period, urinary cortisol provides a broader and more integrative profile of activity. In addition, cortisol has a diurnal rhythm (highest in the early morning, lowest in the evening), so the timing of assessments is an important factor. Some studies measure cortisol at specific times of the day (e.g., morning cortisol, evening cortisol). Others collect samples at multiple times throughout the day and either average across the day (as an indication of total cortisol output across the day) or calculate a slope (as an indication of cortisol's rhythm across the day). Studies can also measure hormonal output at different points in the HPA axis. In addition to cortisol, measures can be taken of CRH (via cerebrospinal fluid) or ACTH (via blood) as additional indicators of HPA activity.

An alternative approach is to perform hormonal challenges. Researchers can introduce molecules such as CRH and ACTH into the system, as well synthetic versions of cortisol like dexamethasone, and measure secretion of downstream hormonal products. Normally, when cortisol levels are elevated, hypothalamic secretion of CRH declines, and this in turn diminishes ACTH and cortisol release. Challenge protocols are thus used to evaluate the sensitivity of the HPA axis's negative-feedback circuit. Different molecules are used to assess the integrity of each axis component. CRH challenges provide a window into pituitary function, whereas ACTH challenges index sensitivity of the adrenals. Dexamethasone acts for the most part at the pituitary. In each of these tests, a response is considered "normal" when the challenge molecule suppresses circulating concentrations of the target hormone below a specified threshold in the hours following administration. For challenge protocols involving dexamethasone, cortisol is the target hormone, and it is measured 8–17 hr after drug administration. For CRH challenges, ACTH and cortisol secretion are measured over a shorter window, usually 1–2 hr after drug administration. An "abnormal" response to these protocols occurs when a participant's secretion of the target hormone is not influenced (or declines only modestly) following introduction of the challenge molecule.

A final approach to measuring the HPA axis involves evaluating its influence on target tissues. For a hormone like cortisol to influence a biological system, it must bind to a specific receptor located inside a cell. The newly formed receptor-hormone complex translocates to the nucleus, where it is capable of modifying the cell's program of genetic expression. To estimate how sensitive bodily tissues might be to cortisol's regulatory influence, researchers in this area have sometimes measured the number of glucocorticoid receptors. This assessment is typically performed in white blood cells, as they can be easily extracted from humans and represent a target tissue of considerable theoretical interest. To the extent that a person's cells express higher numbers of receptors, he or she is assumed to be more sensitive to cortisol's actions in that tissue. It also bears noting that receptor expression is directly influenced by cortisol exposure; when high levels of the hormone are present, cells typically downregulate receptor numbers to maintain homeostasis. Thus, number of receptors is also sometimes understood as a marker of a tissue's recent exposure to cortisol.

# Method

## *Literature Search*

Articles for the meta-analysis were initially identified through searches of the PubMed, Ovid MEDLINE, PsycInfo, EMBASE, and Evidence-Based Medicine Reviews databases for the years 1950–2005. Each search crossed keywords reflecting chronic stress (*assault*, *abuse*, *bereavement*, *caregiver*, *stress*, *trauma*, *unemployed*, *veteran*, and *war*) with those reflecting HPA outcomes (*cortisol*, *ACTH*, *CRH*, *adrenocortical*). To augment the yield of the database search, we also combed reference sections of review articles in the area (Chrousos & Gold, 1992; Dickerson & Kemeny, 2004; Heim, Ehlert, & Hellhammer, 2000; Raison & Miller, 2003; Yehuda, 2000; Yehuda, Resnick, et al., 1993). As well, we did a cited-reference search on the ISI Web of Science, which involved entering the 10 most highly cited studies we found into the database and then having it locate articles that listed those studies in their reference sections.

To be eligible for inclusion in the meta-analysis, a study had to enroll subjects exposed to chronic stress, measure an indicator of HPA axis function, and provide enough data for us to compute effect sizes. We defined *chronic stress* as persistent circumstances that would normatively be appraised as threatening and exceeding coping resources (Lazarus & Folkman, 1984). To qualify as chronic, either the stressor itself needed to persist for a period lasting at least 1 month, or the circumstance needed to involve a brief event such as a natural disaster that was likely to be appraised as threatening for a similar duration. This definition is consistent with the broad view of chronic stress proposed by Baum et al. (1993). It encompasses situations in which the stressor persists for an extended period of time (e.g., caregiving for a family member with dementia), as well as situations that last for a very short time but are likely to be seen as threatening for much longer (e.g., being the victim of a sexual assault). In summary, for a situation to be included in the meta-analysis, either the stimulus and/or the presumed threat appraisal had to persist for 1 month. We also required the chronic stressor to be psychological in nature. Situations that were undesirable because of their physical health implications—such as long-term cold, pain, or disease—were excluded from the meta-analysis for two main reasons. First, our interest was in situations that primarily involved psychological stress. Second, exposure to stimuli like cold, pain, and disease can directly modify functions of the HPA axis, and this makes it difficult (if not impossible) to untangle the relative influences of the mental versus physical aspects of stress.

With these eligibility criteria in place, our search efforts yielded 171 articles. A sizable number of these articles had to be excluded from the meta-analysis because they did not focus on a discrete chronic stressor ($k$ = 24 studies). This created difficulties because the goal of our analysis was to identify features of chronic stress, such as its core emotional themes, that give rise to distinct profiles of HPA axis function. If a study included people facing divergent kinds of chronic stress, such as a job loss and combat experience, we were unable to assign it codes on these dimensions. (That is, unless it presented distinct statistics for each form of stress, in which case it was included in the meta-analysis.) A handful of articles also had to be excluded because they did not provide sufficient information for us to compute effect sizes ($k$ = 13), or they were not designed with an appropriate control or baseline condition that was free of chronic stress ($k$ = 15). To meet our criteria for good design, studies had to include a control sample free of chronic stress or compare subjects before and after they encountered difficulties. We also included studies in which all subjects had been exposed to stress, but the focus was on whether psychiatric symptoms explained variability in HPA outcomes. These studies were used to perform meta-analyses on the roles of PTSD, major depression, and normative distress. After studies had been excluded for these reasons, the pool of eligible articles totaled 119.

## Coding Strategy

The eligible studies were coded to derive features of the participants, the kinds of stress they faced, and the HPA outcomes being assessed. Coding was done by consensus of Edith Chen and Gregory E. Miller.

*Participant features.* The coder extracted information regarding the size, mean age, gender balance, and psychiatric condition of the participants in each study.

*Stressor features.* Four major features of each form of chronic stress were coded, corresponding to the hypotheses outlined in the introduction. To classify the nature of the threat, coders rated each form of stress according to whether it posed a physical (*likely* vs. *unlikely*) and a social threat (*likely* vs. *unlikely*). *Physical threats* were defined as stimuli that had the potential to diminish bodily integrity and bring about injury, disease, or mortality. *Social threats* were defined as stimuli that could diminish a person's social standing or interrupt a major social role that he or she occupies. Studies were also categorized according to whether they focused on traumatic stressors (*likely* vs. *unlikely*). In line with current diagnostic standards for PTSD, *traumas* were defined as situations in which a person was likely to have experienced or witnessed "events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others" (American Psychiatric Association, 2000).

To extract the core emotional theme of each form of stress, coders rated the likelihood that it would result in loss and humiliation. *Loss* was coded when there was an actual or potential loss of life to self or a close other or when the stress threatened an important relationship or social role. *Humiliation* was coded when the stress had the potential to cause shame or disgrace or leave the victim feeling devalued in the eyes of important others in his or her life. Ratings were made on a binary scale, with endpoints of *likely* and *unlikely*. The extent of control each kind of stress afforded participants was also coded. *Control* was defined as the ability to end the stress when desired. Because chronic stress never affords much in the way of control, coders assigned ratings of either *uncontrollable* or *possibly controllable* in this category.

The temporal features of stress were coded in two ways. To estimate the duration of stress exposure, coders recorded the number of months since onset, because this is when HPA activity presumably begins. When this value was not provided, we either requested it from authors or estimated it using historical knowledge. The latter strategy was mostly used in studies of combat exposure in Vietnam, for which we estimated duration as months between the date of article publication and the height of U.S. involvement in the war (December 1968). Preliminary analyses of this variable revealed that it was distributed in a nonnormal fashion, so all values were log-10 transformed prior to use in the meta-analysis. To evaluate whether HPA functions differ according to the persistence of stress, we also recorded whether the stressor stimulus was *present* versus *absent* at the time of assessment. Circumstances that were still unfolding or required ongoing coping—such as caregiving for a disabled relative or seeking a job while unemployed—were rated by coders as being present. Those in which the outcome had already been determined—such as combat experience 30 years prior or adults who were abused as children—were rated by coders as being absent.

## The Meta-Analysis

Meta-analysis is a tool for synthesizing research findings. Its first stage involves computing an effect size for each study that is identified. The effect size reflects the magnitude of the relationship between predictor and outcome variables of interest, in this case, forms of chronic stress and various HPA axis functions. It is important to note that an effect size reflects the strength of an association and not its statistical significance; as such, it is not dependent upon the size of the sample from which it derives. In the next stage of meta-analysis, article-specific effect sizes are combined to derive an aggregate estimate across the literature.

*Study-level effect sizes.* We used Cohen's $d$ as the effect size metric in this meta-analysis. We computed effect sizes for individual studies using descriptive statistics presented in the original published reports. When these statistics were not available, we requested them from authors. This strategy was successful in most circumstances. To compute $d$ from descriptive statistics in between-subjects designs, we subtracted the control group mean from the chronic stress group mean and divided this value by the pooled standard deviation (Rosenthal, 1994). To compute $d$ from descriptive statistics in within-subject designs, we subtracted the group mean at baseline from the group mean during stress and divided this quantity by the sample standard deviation at baseline. In cases in which descriptive statistics were not available, we computed $d$ from inferential statistics using standard formulae (Rosenthal, 1994). These formulae had to be modified slightly for studies that used within-subject designs, because effect sizes are systematically overestimated when they are calculated from repeated-measures test statistics (Dunlap, Cortina, Vaslow, & Burke, 1996). In these situations, we derived effect size estimates using the formula $d = t_c\,[2(1 - r)n]^{1/2}$, where $t_c$ corresponds to the value of the $t$

statistic for correlated measures, and $r$ corresponds to the value of the correlation between outcome measures at pretest and posttest (Dunlap et al., 1996). Because very few studies reported the value of $r$, we used a value of .40 to compute effect sizes in this meta-analysis. To ensure that the meta-analytic findings were robust to variations in $r$, we conducted follow-up analyses using $r$ values ranging from .20 to .60. Very similar findings emerged from these analyses, suggesting that the values we present below are reliable estimates of effect size.

*Aggregate effect sizes.* The study-level effect sizes were subsequently aggregated by use of fixed-effects models in the software program Comprehensive Meta-Analysis Version 2 (Borenstein & Rothstein, 1999). We chose fixed-effect procedures because they are well suited to the goals of our review: to take stock of the data that have accumulated in this area over 50 years and to begin testing hypotheses about stressor and person features that give rise to distinct HPA profiles. When a meta-analysis has aims of this nature—to sort out existing findings, but not generalize more broadly—fixed-effects procedures are the method of choice (Hedges & Vevea, 1998). These models also have the (general) advantage of greater statistical power (Cohn & Becker, 2003), especially in cases in which the number of studies being synthesized is small. All that said, some caution needs to be exercised when the results of fixed-effects analyses are interpreted. Although they can help to sort out conflicts among existing studies, their findings need to be replicated in novel samples before large-scale generalizations can be made.

Separate fixed-effects models were computed for each HPA outcome included in the meta-analysis. Each model yielded an aggregate effect size $d$, which reflects the difference between chronic stress and control groups in standard deviation units. $d$ values of .20, .50, and .80 correspond roughly to small, medium, and large effects, respectively (J. Cohen & Cohen, 1983). Each $d$ statistic was weighted before aggregation by multiplying its value by the inverse of its variance; this procedure enabled larger studies to contribute to effect size estimates to a greater extent than smaller ones. Weighting effect sizes is important because larger studies provide more accurate estimates of true population parameters (Shadish & Haddock, 1994). After each aggregate $d$ had been derived, we evaluated whether it was significantly different from zero, using the criteria that its corresponding $z$ value had to be greater than 1.96 and that its 95% confidence intervals could not include zero (Rosenthal, 1991; Shadish & Haddock, 1994). We also computed a heterogeneity coefficient with each model to evaluate whether it was composed of studies with similar findings. The heterogeneity coefficient is referred to as $Q$, and it is chi-square distributed with $k - 1$ degrees of freedom, where $k$ is the number of studies included. When a $Q$ statistic indicated there was significant variability across a group of studies, we examined whether person or stressor features explained the disparity. In cases in which the proposed moderator was scaled nominally or ordinally, we stratified studies using coder ratings and computed separate fixed-effects models for each subgroup. When the proposed moderator was continuous—for example, months since stressor onset—a fixed-effects meta-regression equation was constructed. These equations are similar to standard linear regression equations, except that the unit of analysis is "study" rather than "participant."

*Handling missing data.* Occasionally studies failed to report the descriptive or inferential statistics needed to compute an effect size. In some of these cases, the authors noted that there was a significant difference between chronic stress and control groups. When this occurred, we computed effect sizes assuming that $p$ values were equivalent to .05. This represents a conservative approach because the actual $p$ values were probably smaller. In other cases, the authors noted that chronic stress and control groups did not differ with respect to an HPA outcome, but failed to provide any further statistical information. When this occurred, we computed effect sizes assuming that there was no difference at all between the groups, that is, a $d$ value of 0.00. Because there is seldom no difference at all between two groups, this also represents a conservative strategy. Imputation was used in $< 5\%$ of cases.

*Handling dependent data.* Meta-analysis assumes that each study-level effect contributing to an aggregate estimate is statistically independent (Rosenthal, 1991). We took a number of steps to avoid violating this assumption. First, when the same data appeared to have been published in multiple articles, we contacted authors to determine the extent of sample overlap. Second, in a handful of studies, multiple chronic stresses were assessed, and each was compared with the same pool of control subjects. In these cases the average $d$ across stresses was used for aggregate estimates, unless a specific analysis permitted us to use stressor-specific values in a nondependent fashion. Finally, a small group of studies used longitudinal designs, assessing HPA outcomes on multiple occasions over the course of stress. For these studies, we used the average $d$ across occasions to derive aggregate estimates.

## Results

### Preliminary Findings

The meta-analysis is based on 107 independent studies from a total of 119 published manuscripts. A total of 8,521 individuals participated in these research projects. On average, 53% of participants were male, 47% were female, and their average age was 38.39 ($SD = 16.23$). They faced many forms of chronic stress: 38 of the studies focused on combat/war experience (35.5%), 27 involved abuse/assault (25.2%), 15 involved death or loss of a major relationship (14.0%), 10 involved caregiving experiences (9.3%), 8 involved natural disasters (7.5%), and 5 involved job loss and/or unemployment (4.7%). Table 1 provides a summary of how each kind of stress was rated along the various dimensions of our coding scheme.

With respect to outcomes, the most common HPA indicator was morning cortisol ($k = 65$; 60.7% of studies), followed by daily output of cortisol ($k = 33$; 30.8%), then afternoon/evening cortisol measures ($k = 31$; 29.0%), postdexamethasone cortisol ($k = 21$; 19.6%), ACTH ($k = 16$; 15.0%), post-CRF cortisol ($k = 7$; 6.5%), post-CRF ACTH ($k = 6$; 5.7%), cortisol rhythm ($k = 5$; 4.7%),

Table 1
*Ratings of Features for Commonly Assessed Stressors*

| Characteristic | Studies of combat/war | Studies of abuse/assault | Studies of death/loss | Studies of caregiving | Studies of disaster | Studies of job loss |
|---|---|---|---|---|---|---|
| Months since onset (*Mdn,* range) | 300.0 (1–720) | 69.5 (1–400) | 61.4 (1–360) | 42.0 (6–144) | 12.0 (1–78) | 18.0 (8–24) |
| Physical threat rated as likely (%) | 100.0 | 100.0 | 8.3 | 0.0 | 62.5 | 0.0 |
| Social threat rated as likely (%) | 30.0 | 50.0 | 91.7 | 100.0 | 12.5 | 100.0 |
| Trauma rated as likely (%) | 100.0 | 100.0 | 36.4 | 0.0 | 100.0 | 0.0 |
| Rated as likely to be uncontrollable (%) | 100.0 | 100.0 | 91.7 | 22.2 | 87.5 | 33.3 |
| Feelings of loss rated as likely (%) | 100.0 | 44.0 | 100.0 | 100.0 | 75.0 | 100.0 |
| Feelings of shame rated as likely (%) | 26.7 | 100.0 | 16.7 | 0.0 | 12.5 | 100.0 |

glucocorticoid receptor numbers on lymphocytes ($k = 4$; 3.7%), CRF ($k = 3$; 2.8%), and white blood cell function following glucocorticoid administration ($k = 3$; 2.8%). Several outcomes were included in only 1–2 studies, including post-ACTH cortisol, postdexamethasone ACTH, postdexamethasone glucocorticoid receptor numbers, and cortisol or ACTH challenge studies that administered other types of HPA-challenge molecules. On average, studies in the meta-analysis reported on two different HPA indicators ($M = 2.0$, $SD = 1.3$), though nearly half of them presented only a single outcome (60 of 119, or 50.4%).

### *General Findings: Chronic Stress and HPA Functions*

Table 2 presents aggregate effect sizes for each outcome. We have collapsed the findings across stressor and person features, to provide a general indication of how chronic stress modifies HPA axis functions. Note that to derive estimates of this nature, we had to restrict the analyses to studies that included stress and control conditions and to outcomes that were assessed in three or more separate studies. The results indicate that exposure to chronic stress is associated with significantly lower concentrations of morning cortisol ($d = -0.08$), and more pronounced suppression of cortisol following dexamethasone challenge ($d = -0.23$). It is also associated with greater concentrations of afternoon/evening cortisol ($d = 0.18$), a flatter diurnal rhythm ($d = 0.39$), and a higher daily volume of cortisol output ($d = 0.31$). Collectively, these findings suggest that chronic stress is accompanied by a dysregulated pattern of hormone secretion, with lower than normal morning output but higher than expected secretion across the rest of the day. This pattern gives rise to a flattened diurnal rhythm. In healthy persons not exposed to chronic stress, cortisol usually displays a robust diurnal rhythm, with values highest in the morning and lowest in the evening.

Several additional outcomes were assessed in the literature. Although there was evidence that cerebrospinal fluid concentrations of CRH were significantly increased ($d = 0.66$), ACTH levels in participants facing chronic stress were similar to those in nonexposed controls. There also were no stress-related differences in hormonal response to CRH challenge or in the number of glucocorticoid receptors expressed by white blood cells.

Inspection of the heterogeneity statistics ($Q$) in Table 2 revealed significant variability in the studies composing each aggregate $d$. This was true in all cases, except diurnal cortisol rhythm and CRH concentration. Thus, our next step was to explain the sources of this variability, using the stress–person hypotheses outlined earlier as a guide. The results of these analyses are presented below. Note that because only a handful of outcomes have been assessed regularly in this literature, we limit moderator analyses to categories in which five or more studies are available. This is the case for morning, afternoon/evening, and daily volume of cortisol; for ACTH measured at any time of day; and for the cortisol response to dexamethasone challenge. With all other outcomes, there were too few data points to make moderator analysis feasible.

Table 3 summarizes the stressor and person features of studies that were included in each outcome category. As is evident from the data in this table, the kind of stress was generally similar across categories. War/combat and abuse/assault were the most frequently studied difficulties. Experiences with caregiving and bereavement were next most common, followed by natural disasters and job loss, which accounted for only a handful of studies in each category. On average, a good deal of time had elapsed since the onset of these stressors, though the range of durations was quite broad within each category. Stress was more likely to pose a physical versus social threat, was generally rated as being uncontrollable, and was more likely to elicit feelings of loss than shame.

### *Temporal Features of Stress*

To examine the relationship between months since onset and HPA outcomes, we estimated a series of fixed-effects meta-regression equations. The results are summarized in Table 4 and illustrated in Figure 1. Analyses revealed a pattern of inverse associations for morning cortisol, daily volume, ACTH, and post-dexamethasone cortisol. As time since the onset of stress increased, effect sizes for each of these outcomes decreased. These findings are consistent with the hypothesis that when a chronic

Table 2
*Summary of Meta-Analytic Findings Across Studies and Outcomes*

| Outcome | Standardized mean difference ($d$) | $k$ | $SE_d$ | 95% CI | $p$ | $Q_w$ | $p$ |
|---|---|---|---|---|---|---|---|
| Cortisol | | | | | | | |
| Morning samples | −.08 | 54 | .03 | −.14, −.03 | <.01 | 258.13 | <.01 |
| Afternoon/evening samples | +.18 | 30 | .04 | +.09, +.26 | <.01 | 61.25 | <.01 |
| Daily output | +.31 | 27 | .05 | +.20, +.41 | <.01 | 265.72 | <.01 |
| Diurnal rhythm | +.39 | 4 | .11 | +.18, +.60 | <.01 | 4.99 | <.17 |
| Post-DST sample | −.23 | 17 | .09 | −.40, −.07 | <.01 | 27.09 | <.04 |
| Post-CRH sample | −.07 | 4 | .18 | −.41, +.28 | <.71 | 13.27 | <.01 |
| ACTH | | | | | | | |
| All samples | −.08 | 13 | .09 | −.25, +.10 | <.39 | 18.77 | <.10 |
| Post-CRH sample | +.26 | 4 | .17 | −.09, +.60 | <.15 | 19.83 | <.01 |
| CRH: All samples | +.66 | 3 | .25 | +.17, +1.16 | <.01 | 3.04 | <.22 |
| GC receptor expression | +.03 | 4 | .18 | −.32, +.39 | <.86 | 38.92 | <.01 |

*Note.* Summaries are presented for outcomes assessed in three or more studies. $Q_w$ is the heterogeneity statistic. CI = confidence interval; DST = dexamethasone suppression test; CRH = corticotropin releasing hormone; GC = glucocorticoid.

Table 3
*Characteristics of Studies in Each Outcome Category*

| Stressor | Studies of morning cortisol | Studies of afternoon/evening cortisol | Studies of daily cortisol output | Studies of post-DST cortisol | Studies of ACTH |
|---|---|---|---|---|---|
| Types | | | | | |
| Combat/war (%) | 38.9 | 26.7 | 37.0 | 58.8 | 23.7 |
| Abuse/assault (%) | 24.1 | 36.7 | 22.2 | 17.6 | 23.7 |
| Death/loss (%) | 14.8 | 16.7 | 7.4 | 17.6 | 23.7 |
| Caregiving (%) | 11.1 | 10.0 | 14.8 | 0.0 | 23.7 |
| Natural disaster (%) | 3.7 | 6.7 | 14.8 | 5.9 | 7.7 |
| Unemployment (%) | 7.4 | 3.3 | 3.7 | 0.0 | 0.0 |
| Features | | | | | |
| Months since onset (*Mdn,* range) | 60 (1–720) | 97 (1–720) | 72 (1–720) | 300 (1–360) | 78 (1–300) |
| Physical threat rated as likely (%) | 40.7 | 73.3 | 20.8 | 88.2 | 61.5 |
| Social threat rated as likely (%) | 24.1 | 33.3 | 21.9 | 17.6 | 76.9 |
| Trauma rated as likely (%) | 22.2 | 73.3 | 74.0 | 100.0 | 76.9 |
| Rated as likely be uncontrollable (%) | 50.0 | 83.3 | 25.9 | 100.0 | 85.2 |
| Feelings of loss rated as likely (%) | 46.3 | 63.3 | 22.2 | 76.5 | 69.2 |
| Feelings of shame rated as likely (%) | 27.8 | 53.3 | 11.1 | 25.4 | 30.8 |

*Note*. DST = dexamethasone suppression test; ACTH = adrenocorticotropin hormone.



stressor first arises, there is an initial activation of the HPA axis, which results in elevated levels of ACTH and cortisol. However, as time passes, this activity diminishes, and cortisol secretion rebounds to below normal.

As another method of evaluating the impact of timing, we categorized stressor as present or absent at the time of HPA assessment. Within-category meta-analyses revealed that in studies in which the stressor was still present, morning cortisol ($d = 0.12$), afternoon/evening cortisol ($d = 0.18$), and daily output of cortisol ($d = 0.54$) were all significantly higher than controls. By contrast, in studies in which the initial stimulus was no longer present, morning cortisol ($d = -0.17$) and postdexamethasone cortisol ($d = -0.24$) were significantly lower, although afternoon/evening cortisol was higher ($d = 0.21$). Similar to the analyses of months since onset, these findings suggest the possibility that chronic stress initially boosts cortisol output but that, as time passes and the initial stimulus is removed, secretion rebounds to below normal concentrations.

### *Nature of Stress*

Table 5 describes the results of analyses focusing on the nature of the stress. In studies in which the stress was likely to involve a threat to the physical self, morning ($d = -0.16$) and postdexamethasone cortisol ($d = -0.31$) were reliably lower, and afternoon/evening ($d = 0.22$) and daily output of cortisol ($d = 0.46$) were reliably higher. Overall, these data suggest the possibility of a flattened diurnal rhythm in which morning output is somewhat reduced, but there is less decline across the rest of the day than would be expected. This pattern results in a significantly elevated daily volume of secretion. In studies in which physical threat was rated as unlikely, there was little in the way of reliable findings, except that morning cortisol was higher ($d = 0.11$).

In studies in which the stress was likely to threaten the social self, morning ($d = 0.27$) and afternoon/evening ($d = 0.26$) cortisol output was higher than in nonexposed controls. These findings suggest that social threats may activate the HPA axis during the day hours. In contrast, in studies in which social threats were unlikely, both morning ($d = -0.17$) and postdexamethasone cortisol ($d = -0.30$) were significantly lower, and afternoon/evening cortisol ($d = 0.15$) and daily volume ($d = 0.42$) were higher. These latter findings are difficult to interpret because "unlikely social threat" is a nonspecific category that tells us little about the circumstances of the stress.

The studies focusing on traumatic stressors yielded a pattern that was identical to those focusing on physical threats. They showed reliably lower morning ($d = -0.16$), and postdexamethasone

Table 4
*Meta-Regression of Hypothalamic-Pituitary-Adrenocortical Outcomes On Time From Stressor Onset*

| Outcome | Slope coefficient | *k* | *SE* | 95% CI | *p* |
|---|---|---|---|---|---|
| Cortisol | | | | | |
| Morning samples | −.13 | 52 | .04 | −.21, −.05 | <.01 |
| Afternoon/evening samples | −.02 | 25 | .06 | −.13, +.10 | <.76 |
| Daily output | −.80 | 27 | .08 | −.95, −.65 | <.03 |
| Post-DST sample | −.29 | 17 | .10 | −.49, −.09 | <.01 |
| ACTH—all samples | −.29 | 13 | .11 | −.50, −.08 | <.01 |

*Note.* CI = confidence interval; DST = dexamethasone suppression test.

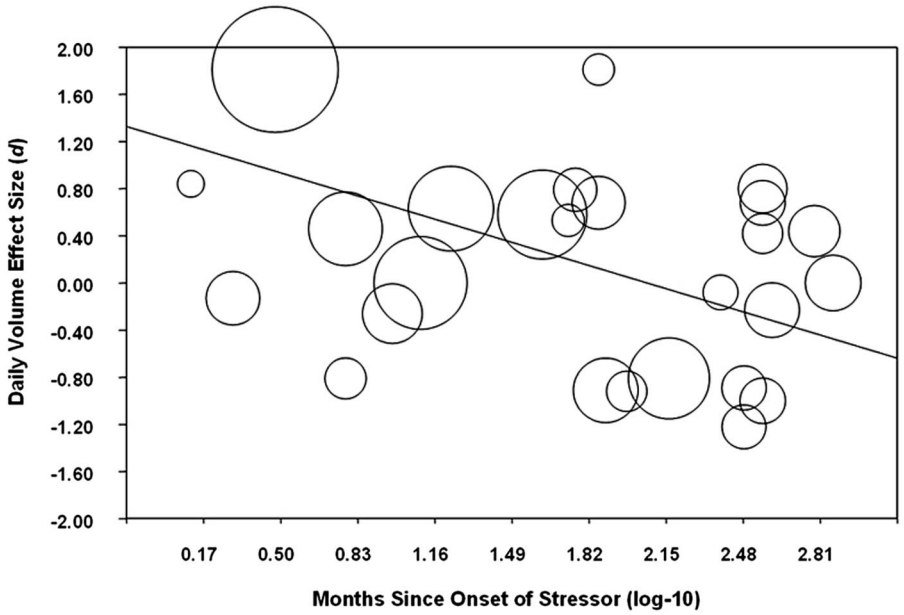


*Figure 1.* Regression of effect sizes for daily volume on time since stressor onset. Each circle in the plot represents an individual study, and its size is directly proportional to its weight in the analysis.

cortisol ($d = -0.24$), and significantly higher afternoon/evening ($d = 0.22$) and total daily cortisol ($d = 0.51$). Again, this pattern suggests a flat diurnal rhythm in which morning output is reduced, but there is less decline in the afternoon/evening than would be expected, leading to higher daily output. In studies in which trauma was unlikely following a stressor, the only reliable finding to emerge was higher morning cortisol ($d = 0.16$).

### *Emotions Elicited by Stress*

We next examined whether the emotion(s) likely to be elicited by each form of chronic stress was associated with HPA outcomes. Table 5 shows that when chronic stress involved a likely loss, both morning ($d = -0.09$) and post-DST (dexamethasone suppression test) cortisol ($d = -0.32$) were reliably lower than in nonexposed controls, whereas afternoon/evening cortisol was reliably higher ($d = 0.20$). This pattern suggests that loss is associated with a flatter cortisol profile across the day. In contrast, for situations in which loss was unlikely, afternoon/evening cortisol ($d = 0.17$) and daily output ($d = 1.11$) were higher.

When chronic stress was likely to involve shame, afternoon/evening levels of cortisol ($d = 0.16$) were significantly higher than in controls. This suggests that forms of stress likely to elicit shame activate the HPA axis, similar to what was found for threats to the social self. By contrast, stress rated as unlikely to elicit shame was associated with a pattern of lower morning ($d = -0.17$) and

Table 5
*Effect Sizes (d) for Hypothalamic-Pituitary-Adrenocortical Outcomes According to Stress Features*

| | Cortisol | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Morning samples | | Post-DST samples | | Afternoon/evening samples | | Daily output | | ACTH: All samples | |
| Nature of threat | *d* | *SE* | *d* | *SE* | *d* | *SE* | *d* | *SE* | *d* | *SE* |
| Physical threat | −0.16** | 0.04 | −0.31** | 0.09 | +0.22** | 0.05 | +0.46** | 0.07 | −0.10 | 0.13 |
| Social threat | +0.27** | 0.05 | +0.01 | 0.09 | +0.26** | 0.08 | −0.04 | 0.11 | 0.17 | 0.23 |
| Traumatic stressor | −0.16** | 0.04 | −0.24** | 0.09 | +0.22** | 0.05 | +0.51** | 0.07 | −0.03 | 0.11 |
| Uncontrollable | −0.15** | 0.03 | −0.24** | 0.09 | +0.24** | 0.05 | +0.43** | 0.06 | −0.03 | 0.11 |
| Potentially controllable | +0.21** | 0.07 | — | | −0.03 | 0.10 | −0.04 | 0.11 | −0.14 | 0.14 |
| Loss | −0.09** | 0.03 | −0.32** | 0.10 | +0.20** | 0.06 | −0.06 | 0.07 | −0.17 | 0.10 |
| Shame | +0.07 | 0.05 | −0.01 | 0.16 | +0.16** | 0.06 | 0.07 | 0.09 | 0.22 | 0.18 |

*Note.* Values are standardized mean differences (*d*) with standard errors. Effect sizes are indicated for stress in which physical threat, social threat, trauma, loss, and shame were rated as likely. For controllability, effect sizes are indicated for stress that was uncontrollable and potentially controllable. Dashes indicate there were too few studies to estimate an effect size. DST = dexamethasone suppression test; ACTH = adrenocorticotropin hormone.
** $p < .01$.

post-DST cortisol ($d = -0.32$) and higher afternoon/evening ($d = 0.20$) and daily cortisol output ($d = 0.44$). This is the "high–flat" profile seen with other stress dimensions. However, because unlikely shame is a nonspecific category, these data are difficult to interpret.

### *Controllability of Stress*

Table 5 also presents the results of analyses for controllability. In studies in which the stress was rated as uncontrollable, there was evidence of reliably lower morning ($d = -0.15$) and post-DST cortisol ($d = -0.24$), and reliably greater afternoon/evening cortisol ($d = 0.24$) and daily output ($d = 0.43$), all relative to nonexposed controls. Again, these data suggest a flattened rhythm in which morning output is reduced, but the typical decline across the day was less than expected, resulting in high overall volume. By contrast, in studies in which the stress was potentially controllable, morning cortisol was reliably higher ($d = 0.21$). These findings suggest that when a person has a chance to control the outcome of chronic stress, his or her HPA axis is activated in the morning hours.

### *Individual Psychiatric Sequelae*

Table 6 presents the results of meta-analyses on psychiatric features of the victim. The studies composing these analyses generally compared individuals who had or had not developed a psychiatric condition following exposure to chronic stress. Among the studies that focused on major depressive disorder, there was evidence of significantly higher postdexamethasone cortisol ($d = 1.13$). These findings suggest that in the context of chronic stress, clinical depression interferes with the negative-feedback circuit of the HPA axis, allowing cortisol to partially escape from dexamethasone suppression.

The analyses also indicated that among people who developed PTSD after stress exposure, postdexamethasone cortisol ($d = -0.25$) and total daily output ($d = -0.34$) were reliably lower, and afternoon/evening cortisol was reliably higher ($d = 0.47$). These findings indicate that compared with healthy adults who have been exposed to identical chronic stress, patients with PTSD are generally hypocortisolemic and have enhanced sensitivity to molecules that engage the HPA axis negative-feedback circuitry.

Some studies also investigated the role of distress in predicting HPA outcomes in persons facing chronic stress. These studies measured subjective distress as an individual difference variable, and typically correlated distress with HPA outcomes in a sample in which everyone was facing the same ongoing difficulty. In these samples more subjective distress was associated with lower morning ($d = -0.08$), higher afternoon/evening ($d = 0.45$), and greater daily output of cortisol ($d = 0.58$). This pattern suggests that subjective distress is associated with a dysregulated (flat, high) pattern of cortisol secretion.

### *Where Is the Action?*

The meta-analyses yielded robust support for several of our hypotheses: (a) Time elapsed since onset was inversely related to most outcomes; (b) forms of stress that posed a physical threat, were traumatic in nature, and were uncontrollable elicited a specific hormonal profile; and (c) there was a consistent pattern of HPA output among those who developed PTSD after trauma. In an effort to untangle these findings, and discern the critical determinants of HPA response, we ran a final wave of meta-analyses. They were guided by three specific questions, each meant to isolate the influence of a single factor. As a result of the small pool of studies in this literature, these analyses were limited to the most frequently assessed outcomes: morning cortisol and daily output.

*Question 1: To what extent does PTSD status explain the other findings?* Research in this area has been dominated by a focus on PTSD, and patients with this disorder were often subjected to physically threatening and uncontrollable stress, which by diagnostic necessity was traumatic in nature. So it could be that psychiatric diagnosis, rather than stress features, is the critical determinant of HPA response. Thus, we stratified articles on the basis of whether patients did versus did not suffer from PTSD, and then we computed another series of meta-analyses testing the major hypotheses. The results of these analyses convincingly demonstrated that PTSD does not account for the influences of timing, stress nature, and controllability. In the subset of studies in which no patients suffered from PTSD, months since onset remained negatively associated with morning cortisol (slope = −0.11, $SE = 0.05$, $p < .02$) and with daily output (slope = −0.65, $SE = 0.08$, $p < .001$). The earlier findings with physically threatening stress

Table 6
*Effect Sizes (d) for Hypothalamic-Pituitary-Adrenocortical (HPA) Outcomes According to Psychiatric Status*

| | Cortisol | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Morning samples | | Afternoon/evening samples | | Daily output | | Post-DST samples | | ACTH: All samples | |
| Status | *d* | *SE* | *d* | *SE* | *d* | *SE* | *d* | *SE* | *d* | *SE* |
| PTSD | −0.03 | 0.09 | +0.47* | 0.24 | −0.34** | 0.14 | −0.25* | 0.13 | 0.00 | 0.10 |
| MDD | — | | +0.30 | 0.20 | — | | 1.13** | 0.38 | — | |
| Subjective distress | −0.08* | 0.04 | +0.45** | 0.12 | +0.58** | 0.13 | — | — | | |

*Note.* Values are standardized mean differences (*d*) with standard errors. Effect sizes indicate disparity in HPA outcome attributable to psychiatric status over and above stress exposure. Dashes indicate there were too few studies to estimate an effect size. DST = dexamethasone suppression test; ACTH = adrenocorticotropin hormone.
* $p < .05$. ** $p < .01$.

also were preserved: In non-PTSD samples, this kind of stress was associated with lower morning cortisol ($d = -0.17$, $SE = 0.04$, $p < .001$) and with higher daily output ($d = 0.61$, $SE = 0.07$, $p < .001$). The same was true of the findings for uncontrollability. As was the case for the larger body of studies, in non-PTSD samples, uncontrollable stress was accompanied by lower morning cortisol ($d = -0.15$, $SE = 0.03$, $p < .001$) and higher daily output ($d = 0.68$, $SE = 0.08$, $p < .001$). Together, these results suggest that the meta-analytic findings are not simply reducible to the influence of PTSD on HPA response.[1]

*Question 2: Can the relative influences of physical threat, trauma exposure, and stressor controllability be separated?* Throughout the meta-analysis, these three factors yielded similar patterns. They were all associated with lower morning cortisol, blunted responses to dexamethasone, higher afternoon/evening cortisol, and greater daily output. Despite attempts to separate the influence of these factors, they are highly confounded in the existing literature. Stressors that were rated as physically threatening were almost always rated as traumatic and uncontrollable and vice versa. This left too few instances of divergence for any meaningful separation to be achieved. Thus, the pool of studies at present does not allow us to determine whether it is physical threat, trauma, controllability, or some combination of these factors that gives rise to a distinct HPA profile.

*Question 3: Is the impact of timing distinct from that of stressor controllability?* Readers may wonder whether more distant kinds of stress, such as combat experience and sexual assault, tended to be rated as more uncontrollable. If the answer to this question was yes, isolating the relative influence of these factors would be important. However, in our coding scheme, controllability was rated at the time the stressor was present in the victim's life, not at the time the cortisol assessment was performed. This prevented timing and controllability from becoming confounded. This fact is borne out to some extent by the meta-analytic findings. For example, more distant stress was associated with lower daily cortisol output, whereas the opposite was true of uncontrollable stress. Nevertheless, to empirically assess whether the contributions of these variables were independent, we estimated associations between time since onset and HPA outcomes within the types of stress that were rated as uncontrollable. These analyses indicated that months since stressor onset continued to be negatively associated with morning cortisol (slope $= -0.08$, $SE = 0.04$, $p < .07$) and with daily output (slope $= -0.71$, $SE = 0.07$, $p < .001$) even when all the stress was uncontrollable. Thus, timing and controllability appear to shape HPA outcomes independently.

## Discussion

We began this article by posing what has long been viewed as a simple question: How is activity of the HPA axis modified by exposure to chronic stress? Despite many claims that a simple answer to this question exists, the meta-analytic findings suggest that the situation is far more complex. Chronic stress has the capacity to increase or decrease HPA activity, and the pattern one sees depends on features of the stress and the person facing it. In the sections that follow, we discuss each of the stressor and person features tested in the meta-analysis, focusing on what the available evidence documents, what still needs to be discovered, and how researchers can best go about doing that.

### *Summary and Integration*

*Time since onset.* One of the most robust findings of the meta-analysis was that time since onset was negatively associated with HPA activity. That is, the more months that had elapsed since the stress first emerged, the lower a person's morning cortisol, daily volume, ACTH, and postdexamethasone cortisol. Similarly, when chronic stressors were still present in a person's environment (e.g., unemployment), morning, afternoon/evening, and daily cortisol output were significantly higher. By contrast, in cases in which the stressful stimulus was no longer present (e.g., combat situations), morning cortisol and postdexamethasone cortisol were significantly lower. These findings are consistent with the hypothesis that when chronic stress first begins, there is an initial activation of the HPA axis, which results in elevated concentrations of ACTH and cortisol. However, the findings suggest that as time passes, this activity diminishes, and cortisol secretion rebounds to below normal. A time-dependent pattern of this nature is consistent with theories advanced by several researchers (Fries et al., 2005; Miller et al., 2002; Hellhammer & Wade, 1993).

Besides revealing the influence of timing on the HPA response, these findings clarify a major source of confusion in the literature. Across the last 5 decades, researchers have alternated between depictions of "hypercortisolism" and "hypocortisolism." The meta-analysis indicates that rather than being contradictory, these depictions are probably all accurate, but simply reflect different timepoints during the stress process. Studies focusing on recent and ongoing stress have generally documented increases in HPA output (Arnetz et al., 1987; Baum et al., 1983; Kosten et al., 1984; Schaeffer & Baum, 1984), whereas those focusing on distant traumas have often found the opposite (Yehuda, Teicher, et al., 1996; Yehuda, Boisonuae, et al., 1995; Yehuda et al., 1998, Yehuda, Kahana, et al., 1995). Of course, this has not been true uniformly (Seedat et al., 2003; Miller et al., 2002; Vedhara et al., 2002), and these exceptions suggest timing is not the only critical factor. However, the general pattern of the meta-analytic findings suggests that it is, in the aggregate, a partial determinant of how the HPA axis responds to chronic stress.

That said, our analysis of timing suffers from an important limitation. Because of the dearth of longitudinal research in this area, it relied heavily on studies with cross-sectional designs. Thus, although the question we sought to answer was whether the pattern of HPA activity changes as time since onset elapses, the available research forced us to modify it to "Do studies with shorter intervals since stress onset show different patterns of HPA activity than studies with longer intervals?" The difficulty with this sort of

[1] Readers may wonder whether PTSD accounts for the distinct HPA profile associated with stressors coded as traumatic. Unfortunately, we are unable to answer this question with the available literature, as nearly all the studies of trauma involved patients with PTSD. Thus, there was not a sufficient quantity of trauma studies with non-PTSD subjects to compute effect sizes and disentangle the influence of these factors. Note also that the disparate findings for trauma coding in the *Nature of Stress* section and the PTSD coding in the *Individual Psychiatric Sequelae* section are likely due to the differences in methodology: The trauma analyses compared individuals who experienced a likely trauma with nonexposed controls, whereas the PTSD analyses compared individuals who did versus did not develop PTSD after being exposed to stress.

analysis is that time and study are confounded; it is therefore possible that some other study feature is the actual determinant of HPA response. We view this as an unlikely possibility, but it cannot be ruled out definitively.[2] Thus, an important direction for future research will be to substantiate the meta-analytic findings using prospective longitudinal designs. So far, only a handful of research projects have enrolled subjects shortly after stress onset and followed them over time to determine whether activity of the HPA axis shifts (Anisman, Griffiths, Matheson, Ravindran, & Merali, 2001; Gerra et al., 2003; Spratt & Denney, 1991; Theorell et al., 1992). We recognize that this represents a logistically difficult undertaking, because most chronic stress arises unexpectedly, it takes time to locate and assess victims, and it can be difficult to keep such participants enrolled for a long time. However, research of this nature is absolutely necessary if we are to stringently evaluate the impact of timing and develop realistic accounts of its influence. This work will need to answer questions such as the following: At what point in time does HPA activity begin to decline from its peak? When does it drop below a person's baseline? At what point does it reach asymptote and stop declining? In short, the next wave of studies will need to discern the shape of the time function, and they can best do so using prospective longitudinal designs with repeated assessments.

*Nature of stress.* The meta-analysis also examined whether HPA activity varies according to the nature of the threat posed by the chronic stress. We found that stress that threatens physical integrity, like combat, elicits a diurnal profile of cortisol secretion that is high and flat. Although morning output is slightly lower, secretion in the afternoon/evening and evening is higher, leading to greater total daily hormone output. An identical pattern was found for stress that was traumatic in nature. These findings make sense when viewed from a functional perspective. In the midst of stress that poses a threat to survival, there would be adaptive value in maintaining persistently elevated HPA activity. This system's hormonal products facilitate cognitive, metabolic, immunologic, and behavioral adaptations that maximize the chances of survival (Sapolsky et al., 2000; Weiner, 1992). When such a threat is not looming, the organism can afford a diurnal rhythm, in which hormonal availability declines across the day.

The meta-analysis also indicated that stress posing a threat to the social self, like divorce, was associated with significantly higher cortisol at specific times in the day, including the morning and afternoon/evening. Why might this be the case? One potential explanation is that activation helps individuals mobilize resources to preserve their social standing when it is threatened. Researchers have argued that the need to be part of a social group is a fundamental human motivation and that people are driven to behave in ways that further their belongingness and group affiliation (Baumeister & Leary, 1995). A recent meta-analysis found support for this hypothesis by showing that cortisol secretion is boosted acutely when people are confronted with social evaluative threats, that is, situations that have the potential to diminish one's standing in the eyes of others (Dickerson & Kemeny, 2004). These findings have been recently extended into a real-world context: Adults participating in competitive ballroom dancing, which involves a high degree of social evaluation, show marked increases in cortisol output that are not due to the physical components of dancing (Beulen, Chen, Rohleder, Wolf, & Kirschbaum, in press). These increases are much greater than those observed when the dancers are practicing without an audience. Collectively, these findings suggest that social stressors, whether they are acute or chronic, reliably activate the HPA axis. One question that remains looming in this area of research, however, is why the observed elevations are not sufficient to yield higher daily cortisol volumes. Perhaps the hormonal consequences of social threats are limited to daytime hours, when people are actively coping with them or ruminating about them. If this was the case, and cortisol excretion was normal during sleep, it could explain the lack of daily volume findings.

There are several limitations to the evidence provided by the meta-analysis in this area. Most important is our inability to determine the relative influences of physical threat, trauma exposure, and stress controllability. These factors overlap almost completely in the existing research, and this is also likely to be true in real-world contexts. Nevertheless, research that could isolate the influence of these dimensions would be extremely valuable. Second, although our approach of rating stress according to physical versus social threat proved to be useful, one should bear in mind that most studies in the meta-analysis focused on one or the other. Follow-up research is needed that compares HPA responses utilizing the same measures, taken at the same time points, for both physical and social stress within the same study. This would allow direct comparison of the HPA profiles for each type of stress. Moreover, assessment of the presumptive mediators of these phenomena would advance this research considerably. In the case of stress that poses a physical threat and is traumatic in nature, the potential mediators of hormone release might include fearful emotions. For stress that is more social in nature, reduced social standing would seem to be critical, as would the self-conscious emotions it elicits. To the extent that the influence of these mediators can be documented, and the concerns identified above can be addressed, the validity of stressor-specificity hypotheses will be enhanced considerably.

*Controllability of stress.* Many researchers have proposed that one primary dimension of what makes a situation stressful is its controllability (Heim, Ehlert, & Hellhammer, 2000; Dickerson & Kemeny, 2004; Mason et al., 2001; Sapolsky, 1998; Weiner, 1992). We tested this hypothesis by categorizing each kind of chronic stress as either uncontrollable or potentially controllable. Uncontrollable stress elicited a flat, high diurnal pattern of cortisol secretion. This was manifested by a lower morning output and higher afternoon/evening secretion, which was sufficient to produce a significant elevation in total daily volume. These findings are generally consistent with the research on acute stress, which indicates that situational controllability is inversely related to cortisol output (Dickerson & Kemeny, 2004). However, they run counter to a number of recent theories seeking to explain hypocortisolism. These models suggest that when people encounter chronic stress that is uncontrollable, HPA activity declines mark-

[2] In an effort to detect evidence of confounding, we examined whether the timing variable related to other methodological characteristics. There were no systematic relationships between timing and mean age of participants, percent who were female, nature of chronic stress, and type or quality of cortisol assessment. While these findings do not eliminate the possibility of confounding, they rule out some of the more plausible scenarios of it.

edly, and a constellation of withdrawal and disengagement behaviors emerge (Gold & Chrousos, 2002; Heim, Ehlert, & Hellhammer, 2000; Mason et al., 2001). There also has been speculation that diminished HPA activity emerges because people have toughened themselves in preparation for later stress (Dienstbier, 1989; Gunnar & Vazquez, 2001a). Despite the intuitive appeal of these theories, the meta-analytic findings do not support their basic prediction. One potential explanation is that most of these theories were formulated to explain blunted HPA activity in patients suffering from psychiatric disorders like atypical depression and PTSD (Gold & Chrousos, 2002; Heim, Ehlert, & Hellhammer, 2000; Mason et al., 2001). The theories may apply specifically to populations with psychiatric disorders, and our meta-analytic findings indicate that these processes may work differently in normal individuals facing chronic stress. Alternatively, these theories may have been derived from studies that relied largely on morning cortisol assessments. As seen in our meta-analysis, morning cortisol was lower for uncontrollable stress; however, across the whole day, cortisol was higher during uncontrollable stress.

Turning to chronic stress that was rated as potentially controllable, the meta-analysis yielded evidence of significantly higher morning cortisol. This stands in contrast to the lower morning cortisol observed in conjunction with uncontrollable stress. How might these findings be explained? When a person is facing a challenge that is potentially controllable, he or she may engage in active coping behaviors, with the hope that they will eradicate the stressor or attenuate its impact. Higher levels of morning cortisol may help to mobilize biological systems for coping activities that will occur the rest of the day. Although this explanation is intuitively appealing, caution needs to be exercised in this area, as the findings were restricted to a single index of hormone secretion. It remains unclear whether controllable stress has effects on cortisol only at specific times of the day, or whether findings for controllable stress are less reliable than for other HPA outcomes. Clearly, further research is needed to sort this out and evaluate this coping mobilization hypothesis.

Two limits of these analyses should be noted. The first is that the relative influences of uncontrollability, traumatic experience, and physical threat cannot be separated in this literature. The second is that our coding system is likely to have some built-in "noise" because it does not consider individual circumstances. Judgments of controllability are likely to vary a great deal across people, even when they are coping with ostensibly similar difficulties. For example, unemployment is a more controllable situation for a person with a marketable set of skills holding out for the right job than it is for someone laid off from an unskilled factory position in a tight labor market. Because our coding system could not contextualize individual ratings in this way, we almost certainly underestimated relations between control and hormonal outcomes. Future research can circumvent this difficulty and more precisely evaluate the impact of control by collecting subjective assessments of this construct from participants.

*Emotions elicited by stress.* The meta-analysis also examined whether feelings of shame or loss were associated with specific patterns of HPA activity. Situations likely to elicit shame (e.g., sexual abuse) were associated with significantly higher afternoon/evening cortisol, whereas those evoking loss (e.g., death of spouse) were accompanied by a flattened diurnal profile. This consisted of lower morning cortisol and higher afternoon/evening cortisol.

What might these findings indicate? For situations that elicit feelings of shame, high afternoon/evening cortisol may be a result of troubling social interactions across the day, in which one's standing within the social hierarchy has been diminished (Dickerson & Kemeny, 2004). It also could reflect rumination about such interactions. These possibilities would explain why no reliable shame findings emerge for morning cortisol; within the first hours of the day, people have not yet had time for rumination or troubling interactions. Nevertheless, the absence of other reliable hormonal alterations for shame makes us reluctant to speculate further or offer definitive conclusions. For stress that evokes feelings of loss, a flattened cortisol profile may reflect social isolation or a withdrawal from regular social activities. Social contact with others programs many of the body's circadian rhythms, including those regulating the secretion of hormones like cortisol (Stetler, Dickerson, & Miller, 2004; Stetler & Miller, 2005). Thus if major losses significantly alter an individual's social activities, this could result in a dysregulated cortisol rhythm that remains flat across the day, rather than a diurnal profile that is regulated by social contact.

A major difficulty with the emotion findings is that they were not robust across outcomes. Shame was associated with only a single parameter, whereas the effects of loss were somewhat stronger, extending to three different outcomes. These findings could reflect what happens in real-world contexts; perhaps emotions are not a central determinant of the HPA response. However, we are more inclined to believe that the relatively weaker findings in this area stem from limitations of our coding system. In the same way that controllability ratings were decontextualized, our emotion ratings were made for situations more generally and could not account for individual differences in affective response. Thus, research would benefit greatly if future studies assessed the degree to which participants experience shame, loss, and other emotions during the course of chronic stress. Researchers could then test whether the intensity and/or frequency of negative emotional experiences is associated with HPA patterns. Future studies should also compare different negative emotional experiences within one study to determine whether emotions such as shame, loss, and sadness have unique HPA signatures.

*Individual psychiatric sequelae.* There was consistent evidence that the psychiatric sequelae of chronic stress are reliable determinants of HPA activity. Individuals who developed a major depressive episode in the midst of chronic stress showed markedly higher cortisol after the dexamethasone-suppression test. This effect was quite large: They showed postdexamethasone cortisol levels more than one standard deviation greater than healthy adults who were also in the midst of chronic stress. This finding is consistent with the larger corpus of evidence on affective disorders, which shows that depression is associated with dexamethasone non-suppression, particularly in patients suffering from severe, melancholic subtypes of this disorder (Haskett, 1993). Despite the robust pattern of findings with dexamethasone, no other hormonal outcomes were studied in conjunction with depression. This will be an important undertaking for future research endeavors.

Individuals who developed PTSD in the aftermath of chronic stress showed a reliable pattern of hormonal alterations. Compared with healthy adults who had been exposed to the same form of chronic stress, they showed lower daily output of cortisol, enhanced suppression of cortisol following dexamethasone adminis-

tration, and higher levels of cortisol in the afternoon/evening. These findings parallel the existing literature on PTSD, which documents hypocortisolism and enhanced sensitivity of the HPA negative feedback circuit (Yehuda, 2000; Yehuda, Resnick, et al., 1993).

Finally, the meta-analysis provided evidence that subjective distress is related to the magnitude of HPA alterations. To the extent that people reported higher levels of distress, they showed greater total daily output and afternoon/evening cortisol, though morning levels were somewhat lower. These findings suggest that even when a person does not develop a full-blown psychiatric condition, the extent of distress is positively associated with HPA activation. This is consistent with theories positing that distress is an important pathway linking stress and endocrine response (S. Cohen et al., 1995; Baum et al., 1993).

The major limitation of work in this area is that it has been largely cross-sectional in nature. This design feature makes it impossible to determine whether hormonal alterations are caused by an individual's psychiatric response or simply reflect trait features of the person that were present before the symptoms (or perhaps even the chronic stress) emerged. Indeed, research by Yehuda and colleagues has shown that reduced output of cortisol is evident in young adults at risk for PTSD, none of whom have exhibited symptoms of the disorder or have been directly exposed to trauma (Yehuda et al., 2000). These findings have generated speculation that blunted hormonal responses to stress may facilitate the development of PTSD (Yehuda, 2000; Yehuda, Resnick, et al., 1993). To the extent that further research shows these hypotheses to be accurate, it will demonstrate that relations between psychiatric response and HPA activity can play out in multiple directions. Regardless of how the work on PTSD evolves, future research in this area needs to be prospective and follow people over the course of a few years starting shortly after stress onset. Work of this sort will help untangle the complex relations between chronic stress, psychiatric response, and HPA activity.

*Other potential moderators.* Although the meta-analysis identified several important features of stressors and persons, it was unable to consider a number of other potential moderators, which almost certainly influence the magnitude and direction of the HPA response. Development is one such factor. Exposure to chronic stress in the early years of life, when the nervous system is still developing, may result in a distinct and stable pattern of dysregulation. The importance of considering development has been highlighted in studies of rodents, in which early-life experiences have been shown to program HPA axis functions at the genomic level, such that they remain altered all the way into adulthood (Liu et al., 1997; Meaney & Szyf, 2005). At the other end of the developmental spectrum are older adults, who often face chronic stressors like caregiving, while at same time experiencing age-related changes in endocrine functions. There are good reasons to believe these factors will modify their HPA response to chronic stress (Kiecolt-Glaser & Glaser, 2001; Penedo & Dahn, 2005). Unfortunately, too few of the studies in the meta-analysis provided sufficient information for us to consider development as a moderator. Nevertheless, this line of inquiry should be a high priority for the next wave of research in this area. Genetics represents another potentially important moderator. Polymorphisms that could influence the HPA response to chronic stress are regularly being identified; some promising candidates include functional variants present in the glucocorticoid receptor, the mineralocorticoid receptor, and the serotonin transporter (Barr et al., 2004; DeRijk & de Kloet, 2005). Though work of this nature is still in its infancy, it is likely to be a fruitful avenue for research in the years to come. Finally, the impact of chronic stress on hormonal dynamics is likely to be moderated by the victim's previous exposure to stressful circumstances (Yehuda, 2004), ability to call forth effective coping strategies and social support (e.g., Miller, Cohen, & Ritchey, 2002), and need to manage other stressors that compete for his/her attention and resources. For example, a recent study found that chronic stress was associated with reduced expression of the glucocorticoid receptor, and this relationship was accentuated when an acute life event was superimposed upon the background difficulties (Miller & Chen, 2006).

### *Theoretical Implications*

These findings have several important theoretical implications. The first is that models positing an orderly and uniform HPA response to chronic stress are no longer appropriate. A new wave of theories needs to be developed to incorporate the moderating influences of timing, nature of stress, controllability, and individual psychiatric response. Such theories must provide answers to questions such as: What types of chronic stress and individual responses are required for the HPA axis to become persistently activated? How are these conditions different from those that dampen HPA activity? Although the meta-analysis does not provide sufficient information for this to be done immediately, it has identified a series of variables that are likely to figure prominently in any new theories. With further empirical research of the nature specified earlier, it should be possible to construct more elaborate and refined theories, which clearly specify the conditions when HPA activity goes up versus down.

The many theories linking stress, cortisol, and disease outcomes also will need to be refined. Most of them posit that stress nonspecifically activates the HPA axis, and by doing so, contributes to the development and progression of medical illnesses. Our results suggest that the chain of events is unlikely to unfold in such a simple fashion. Newer models will need to acknowledge that chronic stress can elicit a variety of HPA responses and that their impact on disease outcome will depend on the condition being considered. When a person is early in the course of chronic stress, for example, he or she may become vulnerable to conditions in which high cortisol is pathogenic. This seems to be true in psychiatric disorders such as depression and schizophrenia (Nemeroff, 1996; E. F. Walker & Diforio, 1997) and medical illnesses like heart disease and the metabolic syndrome (Bjorntorp & Rosmond, 1999; G. D. Smith et al., 2005). However, as time passes and cortisol output declines to below normal, these effects on disease progression would likely subside (and perhaps reverse). The person may even become vulnerable to conditions in which deficient cortisol signaling contributes to adverse outcomes, such as rheumatoid arthritis, fibromyalgia, and allergic conditions (Heim, Ehlert, & Hellhammer, 2000; Raison & Miller, 2003). These are just simplified theoretical conjectures, of course, and the clinical picture is likely to be more complex. Nevertheless, they illustrate an important theoretical lesson—that future theories will need to match kinds of chronic stress, their likely HPA concomitants, and

disease processes to arrive at biologically plausible hypotheses regarding the linkages among these constructs.

The findings also highlight the importance of developing more elaborate psychological hypotheses in this area of inquiry. Some intriguing relationships were documented between psychosocial characteristics and HPA activity; however, the cognitive, emotional, and behavioral mechanisms underlying them have yet to be identified. Future research needs to answer questions such as the following: Do potentially controllable forms of chronic stress elevate morning cortisol because of the coping efforts they mobilize? Do shame-eliciting forms of chronic stress increase afternoon/evening cortisol because of troubling social interactions or rumination about the stressor? Do loss-related forms of chronic stress dysregulate cortisol rhythms because of changes in social circadian rhythms that result from the loss? Once this has been done, more elaborate mechanistic models linking chronic stress and HPA function can be developed.

The same issues pertain to biological mechanisms that are more proximal to the HPA axis. Little theory exists to specify what goes awry in the system when it faces chronic stress. Is the high, flat pattern of cortisol secretion across the day a result of dysregulation in the suprachiasmatic nucleus, the endogenous circadian pacemaker that regulates HPA rhythms? Or does chronic stress leave the suprachiasmatic nucleus's functions intact, and instead modify downstream structures like the pituitary and/or adrenal glands? The fact that cortisol was reliably altered by exposure to chronic stress, and ACTH was not, suggests the possibility that much of the dysregulation lies at the level of the adrenals. Perhaps chronic stress modifies the sensitivity of the adrenal glands, such that cortisol is secreted at volumes disproportionate to ACTH signaling. By making use of ACTH and CRH challenge paradigms, which respectively evaluate functioning of the adrenals and the pituitary, future research can test these mechanistic hypotheses and accelerate the development of theory in this area.

### *Methodological Recommendations*

To ensure that further progress is made in this area of inquiry, the next wave of studies will need to institute a series of methodological innovations. As the summary statistics from the meta-analysis make clear, the field has relied heavily on morning cortisol as an outcome. In 25% of the studies we reviewed, it was the only HPA outcome to be assessed, and in all but a handful of studies, this was done on a single occasion. There are obvious methodological and conceptual limitations to this strategy. Single measures of a construct are notoriously unreliable, and all evidence suggests this is the case for cortisol as well (Stewart & Seeman, 2000). If future studies wish to maximize their chances of detecting stress-related disparities, they would be wise to increase the frequency of sample collection, so that multiple assessments are made each day for a period of several days. Apart from boosting statistical power to detect findings, this strategy provides a more comprehensive portrait of HPA activity. It is difficult to make accurate inferences about HPA activity being low or high from a single measure, because as our findings illustrate, the effects of chronic stress can differ in magnitude and direction over the course of the day. Guidelines for designing a sampling strategy that captures the entire diurnal rhythm of cortisol can be found online (see Stewart & Seeman, 2000).

Progress in this area also will depend on researchers' capacity to expand the repertoire of outcome variables. Half of the studies we reviewed presented findings for only a single indicator of HPA axis function. Fewer than 15% of the studies assessed ACTH. An even smaller number assessed CRH, but this is understandable, given that a medically invasive procedure (lumbar puncture) is required. Challenge paradigms also were used infrequently, and when they were, they typically involved dexamethasone suppression. By more routinely assessing output of ACTH and CRH, and performing challenge paradigms with these molecules, future research will gain detailed mechanistic insights into how stressors modify the function of structures comprising the axis. Given that much work in this area is concerned with hormonal influences on disease, there also would be much gained by assessing cortisol's impact on target tissues. Some work of this nature has already begun. A recent study found that among people facing a severe chronic stressor, the immune system's sensitivity to glucocorticoids was diminished (Miller et al., 2002). This was manifested by a reduction in dexamethasone's capacity to suppress the production of inflammatory molecules in vitro. These findings suggest that chronic stress interferes with cortisol's ability to perform an important regulatory function in the immune system. To the extent that such a deficit persists, it could enable inflammation to flourish, leading to a variety of adverse medical outcomes. More work of this nature would be valuable for the field, as it sheds light on the tissue-level consequences of differential cortisol secretion. In addition to assessing how immune system functions are influenced by glucocorticoids (DeRijk, Petrides, Deuster, Gold, & Sternberg, 1996; Rohleder, Schommer, Hellhammer, Engel, & Kirschbaum, 2001), researchers can study these processes in the vascular system through a noninvasive skin-blanching paradigm (Ebrecht et al., 2000; B. R. Walker, Best, Shackleton, Padfield, & Edwards, 1996) and in the nervous system through challenge molecules such as CRH, ACTH, and dexamethasone.

Statistical power is another design feature that warrants additional consideration. The studies in our meta-analysis had an average of 80 participants and for the most part yielded effect sizes in the .20–.50 range. These represent small- to medium-sized effects by conventional standards in behavioral science. Even at the high end of that effect-size range, however, studies need twice as many participants to have adequate power. Future research will need to boost enrollment substantially to maximize its chances of detecting alterations in the HPA axis.

### *Summary and Conclusions*

The notion that stress contributes to disease by activating the HPA axis is featured prominently in many theories. The research linking stress and the HPA axis is contradictory, however, with some studies reporting increased activation and others reporting the opposite. Our meta-analysis of this area showed that some of the variability in HPA response is attributable to stressor and person features. Timing is an especially critical element, as hormonal activity is elevated at stress onset but reduced as time passes. Stress that threatens physical integrity, is traumatic in nature, and is largely uncontrollable elicits a high, flat diurnal profile of cortisol secretion. Finally, HPA activity is shaped by the person's response to stress; cortisol output increases with the extent of subjective distress and is generally reduced in those who

develop PTSD. These findings highlight the importance of incorporating stressor and person features into models of chronic stress and HPA activity. They also suggest that relations among stress, cortisol, and disease are likely to be more complex than previously acknowledged. Because chronic stress can elicit such a wide variety of HPA responses, its impact on disease outcomes will be varied and depend on whether high versus low cortisol is pathogenic. The next wave of models will need to be refined to acknowledge this complexity. With better theories and further research of the nature suggested by the meta-analysis, the pathways through which chronic stress "gets under the skin" to influence disease will come into clearer focus.



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Received September 30, 2005
Revision received February 9, 2006
Accepted March 30, 2006 ■