# Stress: A Risk Factor for Serious Illness

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**The body's principal adaptive responses to stress stimuli are mediated by an intricate stress system, which includes the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathoadrenal system (SAS). Dysregulation of the system, caused by the cumulative burden of repetitive or chronic environmental stress challenges (allostatic load) contributes to the development of a variety of illnesses including hypertension, atherosclerosis, and the insulin-resistance–dyslipidemia syndrome, as well as certain disorders of immune function. The brain's limbic system, particularly the hippocampus and amygdala, is also intimately involved in the stress response. Chronically elevated corticosteroid levels induced by persisting stress may adversely affect hippocampal structure and function, producing deficits of both memory and cognition. The ability of stress to cause illness in humans is most clearly exemplified by post-traumatic stress disorder (PTSD), which consists of a predictable constellation of distressing behavioral symptoms and physiological features. An appreciable proportion of the observed variance in vulnerability to PTSD is attributable to genetic factors. The relationship of this disorder to its precipitating cause—a recent, severely traumatic event—is unambiguous. The neuroendocrinology of PTSD is noteworthy, being characterized in many adult victims by enhanced negative feedback sensitivity of glucocorticoid receptors in the stress response system, and lower than normal urinary and plasma cortisol levels. Adult patients with PTSD also have been shown to exhibit exaggerated catecholamine responses to trauma-related stimuli. On the other hand, severely maltreated prepubertal children with PTSD continue to excrete greater than normal urinary cortisol, catecholamines, and dopamine years after disclosure of the causative abuse.**



THE TERM *STRESS* has several different meanings; hence, whenever it is used, it is important to distinguish between stress viewed as a *cause* (the condition or adverse circumstance that threatens [or is perceived to threaten] an individual's physiological and/or psychological integrity), and stress as an *effect* (the resulting state of disturbance or distress).

To understand how stress can give rise to illness, it is necessary to examine the mechanisms employed by the body to adapt to stressful stimuli, and to consider ways in which these initially protective adaptations can sometimes go astray—with damaging health consequences.

## NEUROENDOCRINE RESPONSES TO STRESS

The body's principal physiological responses to stress stimuli are mediated by the sympathoadrenal system (SAS), functionally separable into the sympathetic nervous system (SNS) and the adrenal medulla (AM), and the hypothalamic-pituitary-adrenocortical (HPA) axis. Such responses are automatically generated and coordinated in the brain; however, as Dinges[1] has pointed out, "there is also recognition that humans *cognitively* assess potential stressors for their perceived or real threat potential, and the brain then orchestrates the physiological and behavioral responses to the stressor."

A schematic representation of the stress system (adapted from Chrousos[2]) is provided in Fig 1. As shown on the right side of the figure, acute activation of the SAS gives rise to increased production by the adrenal medulla of epinephrine (E) and norepinephrine (NE). Increased activity of the SNS also occurs, with enhanced release of NE and neuropeptide Y (NPY) from sympathetic nerve terminals. Activation of the SAS also results in an increase in secretion of interleukin-6 (IL-6), one of the cytokines that link the stress system and various inflammatory and immunologic processes. IL-6 plays a prominent role in inducing C-reactive protein production, a major host defense against bacterial pathogens.[3] As shown on the left side of the figure, acute activation of the HPA axis involves increased secretion in the hypothalamus of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). AVP potentiates CRH activity, suppresses urine production, supports cardiovascular function, and is reported to elevate mood, memory, and selective attention.[4] When it travels from the paraventricular nucleus (PVN) to the anterior pituitary gland, CRH stimulates production of corticotropin (ACTH), causing the adrenal cortex to release more cortisol. In addition to its role as principal regulator of the HPA axis, CRH is also an activator of the SAS and SNS.[5]

It needs to be emphasized, however, that the stimuli for secretion of the so-called stress hormones are by no means limited to stressful events but more commonly consist of ordinary lifestyle factors such as alcohol, smoking, exercise, and disrupted sleep patterns, to say nothing of the 24-hour cortisol rhythm.[6] As Spiegel et al[7] have shown, in the sleep-debt condition, glucose tolerance becomes impaired, evening cortisol concentrations are raised, and the activity of the SNS is increased.

The activity of the stress system is modulated by negative feedback loops involving its humoral products. Thus, glucocorticoids and mineralocorticoids enter the brain and, by binding to appropriate receptors in the hippocampus and other sites, act to restrain CRH production. Mineralocorticoid receptors (MR) play an important part in the feedback control of the HPA axis, promoting maintenance of basal HPA activity. Recently, Arvat et al[8] demonstrated in normal young women that intravenous administration of the MR antagonist canrenoate was followed by progressive rises in plasma levels of ACTH, cortisol, and dehyroepiandrosterone (DHEA). ACTH, cortisol, and DHEA responses to human CRH (and also to AVP) were enhanced by prior canrenoate administration.

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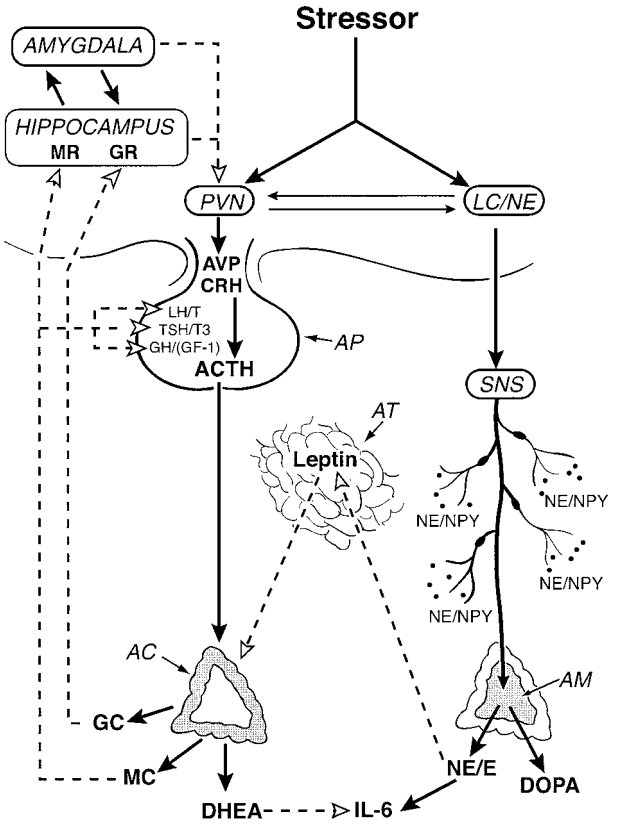


**Fig 1. A diagrammatic representation of elements of the stress response system. Stress stimuli activate the reciprocally innervated hypothalamic-pituitary-adrenal (HPA) axis and sympathoadrenal system (SAS). Activation of the HPA axis involves release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the paraventricular nucleus (PVN) of the hypothalamus, generating increased secretion of adrenocorticopic hormone (ACTH) in the anterior pituitary (AP). ACTH, in turn, stimulates increased secretion of glucocorticoid (GC) and mineralocorticoid (MC) hormones, and dehydroepiandrosterone (DHEA) from the adrenal cortex (AC). GC and MC modulate HPA axis activity via negative feedback effects on gluco- and mineralocorticoid receptors (GR and MR) in the hippocampus, as well as in other parts of the stress-response system. Activation of the SAS (locus ceruleus [LC]/norepinephrine [NE]/sympathetic nervous system [SNS]) causes increased release of NE and neuropeptide-Y (NPY) from sympathetic nerve terminals, and of NE, E, and dihydroxyphenylalanine (DOPA) from the adrenal medulla (AM). Activation of the HPA axis causes suppression of the growth hormone/insulin-like growth factor-1 (GH/IGF-1), luteinizing hormone/testosterone (LH/T), and thyrotropin/triiodothyronine (TSH/$T_3$) axes. Activation of the SAS/SNS results in increased interleukin-6 (IL-6) secretion, which is subject to inhibition by DHEA. Leptin, from adipose tissue (AT), directly inhibits secretion of GC, while increased NE and E secretion tends to reduce serum leptin levels. Straight lines indicate stimulation; dashed lines inhibition. (Adapted with permission from Chrousos.[2])**

As Fig 1 indicates, the HPA axis and the SAS are functionally interrelated. CRH, for example, causes an increase in the activity of tyrosine hydroxylase and of the firing rate in the locus ceruleus (LC), as well as NE release in LC projection areas. Asakura et al[9] have suggested that, in depressed patients, hyperactivation of the CRH-NE systems may be involved in generating anxiety, sympathetic activation, and hyperarousal.

## EFFECTS OF STRESS ON HIPPOCAMPAL STRUCTURE AND FUNCTION

The hippocampus is one of a group of subcortical structures (including the amygdala) that make up the brain's limbic system—a system located in the boundary between the *telencephalon* (the anterior subdivision of the forebrain comprising the cerebral hemispheres and associated structures) and the *diencephalon* (the posterior subdivision of the forebrain, which includes the thalamus and hypothalamus).

According to McEwen,[10] "The hippocampus participates in verbal memory and is particularly important for the memory of 'context', the time and place of events that have a strong emotional bias. . .Impairment of the hippocampus decreases the reliability and accuracy of contextual memories. . .preventing access to the information needed to decide that a situation is not a threat. . .The hippocampus also regulates the stress response and acts to inibit the response of the HPA axis to stress."

Feldman and Weidenfeld[11] have reported that electrical stimulation of the dorsal hippocampus causes a long-lasting inhibition of the ACTH and adrenocortical responses to stressful (photic) stimuli in freely moving rats. Principal cells in the hippocampus contain high concentrations of glucocorticosteroid as well as MRs. MR occupation maintains steady electrical activity in hippocampal neurons. As Joels[12] puts it, "These slow and persistent corticosteroid actions will alter network function within the hippocampus, thus contributing to behavioral adaptation in response to stress." Such modulation of hippocampal activity by corticosteroids affects hippocampal inhibitory interneurons, which control HPA axis activity.

The dorsal hippocampus appears necessary for formation of fear memory to both explicit and contextual cues.[13] Neurons in the ventral hippocampus that bear the γ-aminobutyric acid-A (GABA-A) receptor are important for fear conditioning to a context. It seems likely that these hippocampal functions play a role in the development of post-traumatic stress disorder (PTSD).

The amygdala is involved in coordinating stress behaviors and modulating memory consolidation. It is also important in memory of fear-producing experiences and generation of aversive behavior.[14] Recently, Kim et al[15] examined the role of the amygdala in mediating stress effects in rats (produced by restraint and tailshock) on hippocampal long-term potentiation and memory. Their findings indicate that an intact amygdala is necessary for the expression in the hippocampus of these stress-induced effects.

The human hippocampus is particularly prone to atrophy in the presence of excess glucocorticoid production (eg,, Cushing's syndrome, PTSD, and depressive illness).[14] To date, the only known example of reversal of hippocampal atrophy in man is in patients with successfully treated Cushing's disease.[16]

Hippocampal atrophy can also occur in the absence of elevated glucocorticoid levels. It has been known for some time that stress early in postnatal life may result in long-term memory deficits and selective loss of hippocampal neurons. Brunson et al[17] administered CRH to the brains of immature rats and reproduced the same effect, reducing memory function throughout life. The memory deficits were associated with loss of hippocampal CA3 neurons and did not require the concomitant presence of elevated glucocor-

ticoid levels for their occurrence. The authors suggest that CRH may play a critical role in mediating the effects of early-life stress on hippocampal integrity and function. In adults, acute stress can impair short-term memory by increasing cortisol secretion, thereby suppressing memory-mediating mechanisms in the hippocampus and temporal lobe. This effect is potentially reversible; however, chronic stress can kill hippocampal neurons.[14] Brain imaging studies have shown hippocampal atrophy in patients with such stress-related disorders as recurrent depression and PTSD (see below).

It would seem, therefore, that stress-induced activation of the HPA axis, if sufficiently severe and prolonged, is capable of producing long-term deficits of both memory and cognition associated with atrophy of the hippocampus, as well as of other brain areas.[18,19]

## STRESS-RELATED ILLNESS

### *Healthy Versus Pathologic Stress*

A distinction needs to be made between "healthy" and "pathologic" responses to stress. Everyday interaction of animals with their environments inevitably exposes them to a variety of stress stimuli. Indeed, to develop properly animals require such exposure on a continuing basis. The stress system must have evolved to help individuals respond appropriately and effectively to a variety of threatening environmental challenges, including actual attack. Among the many behavioral and physiological responses to such situations is rapid activation of the SAS and the HPA axis, giving rise to behavioral and physiological responses calculated to help the organism survive under emergent conditions. The early response to acute stress is protective, enhancing immune function, promoting memory of dangerous events, increasing blood pressure and heart rate to meet the physical and behavioral demands of fight or flight, and making fuel more readily available to sustain intensified activity. At the same time, overactivity of the stress system contributes to the chronic wear and tear that render the organism more vulnerable to disability and illness.[20] Observations of the behavior of animals in their natural habitats have shown that the stress system was designed to deal with circumstances requiring an immediate response to a physically threatening situation of limited duration. Nature did not anticipate situations in which the stress system would be activated for prolonged periods by stimuli such as an ominous letter from the Internal Revenue Service, a bitterly contested divorce, the perceived obligation to care for an obstreperous spouse with Alzheimer's disease, or a sudden financial reverse. Nor could nature have foreseen that the development of the man's unique brain would also render its possessor vulnerable to imagination-generated stress.

### *Role of Stress in Pathogenesis*

To gain a better understanding of how stress can lead to illness, it is useful to invoke the concept of *allostatic load*, first introduced in 1993 by McEwen and Stellar.[21] In their words, "The (cumulative) strain on the body produced by repeated ups and downs of physiologic response, as well as by the elevated activity of physiologic systems under challenge and the changes in metabolism and the impact of wear and tear on a number of organs and tissues, can predispose the organism to disease. We define this state of the organism as *allostatic load*." Stress is one of the factors (including lifestyle, sleep patterns, etc) that contribute to allostatic load.

According to Seeman et al,[22] the mechanism by which allostatic load gives rise to illness involves three levels of events. "At the first level are primary mediators, eg, chemical messengers such as cortisol, norepinephrine, and epinephrine. A second level of events is represented by. . .primary effects, eg, cellular events, like enzymes, receptors, ion channels, or structural proteins induced genomically or phosphorylated via second messenger systems, that are regulated. . .by the primary mediators. A third level is represented by secondary mediators, eg, more integrated processes such as blood pressure, heart rate, and metabolic profiles that are the outcome of effects of one or more primary mediators. The final [result] of this cascade of events would be the actual disease outcomes."

Although a growing number of illnesses have been found to be associated with dysregulation of the stress system, the precise role of stress in their causation usually is not clear. Illness itself is often a powerful stressor. The best evidence that stress (including psychological stress) can give rise to actual illness comes from a number of well-controlled studies in laboratory animals showing that investigator-applied stress predictably results in the development of a distinct disease. For example, experimentally induced psychosocial stress reliably causes atherosclerosis and hypertension in primates and mice.[23]

In most of the stress-related diseases that affect humans, stress does not appear to be the sole or even the principal causative factor. Rather, it contributes—to a variable degree—to the pathogenesis, precipitation, exacerbation, or prolongation of the illness or condition in question. Although the role of stress in causation of various diseases may have been overestimated by some authors, there is little doubt that, in many cases, stress plays a critical role in determining clinical outcome. Examples of ways in which stress can increase risk of several important diseases in man are shown in Table 1.

Chrousos[2] has reviewed evidence showing that stress-induced chronic increases in cortisol, catecholamines, and interleukin-6, together with chronic suppression of the growth hormone/insulin-like growth factor-, luteinizing hormone/testosterone-, and thyrotropin/triiodothyronine-axes (see Fig 1) provide a hormonal milieu conducive to the development of visceral obesity (and the insulin-resistance-dyslipidemia syndrome), hypertension, atherosclerosis, osteoporosis, and immune dysfunction. Additional stress-related illnesses include such conditions as depression,[24] irritable colon,[25] and peptic ulcer.[26] Stress is associated with increased substance (including alcohol) abuse.[27]

Stress has been shown to hamper control of both type l and type 2 diabetes mellitus.[28,29] It has been implicated in precipitation of Grave's disease[30] and exacerbation of multiple sclerosis.[31] Fibromyalgia, chronic fatigue syndrome, and myofascial pain syndrome[32] as well as rheumatoid arthritis[33] are all associated with the type of stress system dysregulation that is characterized by a decrease in stress system activity. Patients with fibromyalgia have been found to have an impaired ability to activate the HPA axis as well as the sympathoadrenal system.[34]

### *Post-traumatic Stress Disorder*

The ability of stress to cause illness in human beings is most clearly exemplified by PTSD, in which acute exposure to a

**Table 1. Mechanisms by Which Activation of the Stress System May Increase Risk of Myocardial Infarction, Stroke, High Blood Pressure, Cardiac Arrhythmia, Visceral Obesity, and Exacerbate Diabetes**

| Stress Response | Clinical Effect |
|---|---|
| Epinephrine ↑ | ↑ Platelet aggregation→thrombosis of coronary/ cerebral arteries→*myocardial infarction/stroke* |
| SNS tone ↑<br>Norepinephrine secretion ↑<br>Cortisol secretion ↑ | ↑ Peripheral vasoconstriction→<br>↑ peripheral vascular resistance→*hypertension* |
| Epinephrine ↑<br>SNS activity ↑ | ↑ Heart rate→ ↑ myocardial irritability→<br>↑ risk of *cardiac arrhythmia* |
| SNS activity ↑<br>Epinephrine secretion ↑<br>Cortisol secretion ↑ | ↑ Insulin resistance + ↑ gluconeogenesis→<br>*impaired diabetes control* |
| Cortisol secretion ↑<br>GH/IGF-1 ↓ LH/testosterone ↓<br>TSH/$T_3$ ↓ | ↑ Visceral obesity→insulin resistance syndrome→<br>↑ dyslipidemia→*atherosclerosis* |

Abbreviations. SNS, sympathetic nervous system; GH, growth hormone; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; TSH, thyrotropin; $T_3$, triiodothyronine.

severely traumatic event is followed within days or weeks by development of a distinct syndrome with a characteristic behavioral and physiological pattern. According to Frances,[35] the diagnosis of PTSD is made after a person experiences one or more overwhelming traumatic event(s) and reacts with fear or disorganized behavior, followed by complaints of 3 clusters of categorical symptoms for at least 1 month: (1) intrusive re-experiencing of the trauma(s); (2) persistent avoidance of stimuli associated with the trauma; and (3) persistent symptoms of increased physiological arousal.

Seedat and Stein[36] have cited new studies that confirm prevalence rates of 7% to 12% of PTSD in the general US population. It has been reported that more than 60% of men and 51% of women experience at least one major traumatic event in their lifetimes. Approximately 8% of men and 20% of women exposed to such traumatic situations fall victim to PTSD.[37]

A study of generalized anxiety disorder symptoms, panic disorder symptoms, and PTSD in 3,327 monozygotic and dizygotic male-male twin pairs has shown that additive genetic influences common to symptoms of generalized anxiety disorder and panic disorder accounted for 21.3% of the genetic variance in PTSD. Additive genetic influences specific to PTSD accounted for 13.6% of the genetic variance in PTSD. The remaining variance was attributed to unique environmental factors.[38]

The September 11, 2001, terrorist destruction of New York City's World Trade Center created a flood of new victims of PTSD. An article published in the *New York Times* 3 weeks later under the headline "For Haunted Survivors, the Towers Fall Again and Again,"[39] provides a poignant description of the psychological anguish that characterizes PTSD.

> "Inez Graham is at war with her memory. She spends her days sobbing and afraid, battling images of flames and falling debris and trying to quell the soundtrack of screams in her head. A ringing phone, a plane overhead or a passing truck makes her hunker down in fear. She refuses to go outside. She tells friends not to visit and says the smell of smoke, like some unseen phantom, lingers around her home."

Although most (if not all) PTSD victims appear to suffer from some form of neuroendocrine abnormality, the hormonal picture may vary depending on such factors as age, sex, duration of illness, genetic makeup, proximate emotional status, presence of one or more comorbidities, and the diagnostic paradigm employed by the investigator. In a series of studies of PTSD patients starting more than a decade ago, Yehuda and associates[40-42] have reported that, compared to normal subjects and depressed patients, combat veterans with PTSD of long standing have significantly lower mean 24-hour urinary cortisol excretion, a more sharply defined diurnal rhythm of cortisol secretion, with larger peak-to-trough differences, lower mean basal plasma cortisol levels at several times during the circadian cycle, and greater numbers of lymphocyte cytosolic glucocorticoid receptors.

Veterans with PTSD also showed enhanced suppression of cortisol in response to low doses of dexamethasone.[43] Similarly, Holocaust survivors with PTSD (28 men and 34 women) were found to have significantly lower mean 24-hour urinary cortisol excretion than Holocaust survivors without PTSD and subjects not exposed to the Holocaust.[44] (It should be noted, however, that, in 1990, Pitman and Orr[45] reported *elevated* 24-hour cortisol secretion in some PTSD patients.)

In contrast to the findings of Yehuda et al in adults, severely maltreated but medically healthy prepubertal male and female children with PTSD have been shown to excrete greater quantities of urinary free cortisol than healthy controls, years after disclosure of abuse.[46] Moreover, the same subjects excreted significantly greater concentrations of norepinephrine (NE), epinephrine (E), and dopamine (DA) in urine than nonabused anxious, but otherwise healthy, controls. According to the authors, neuroendocrine differences between child and adult PTSD may be explained by maturation effects or a long-term adaptation of the HPA axis after the traumatic experience.

The participation of the autonomic nervous system in the adaptive response to severe trauma is also an important component of the neuroendocrine picture that characterizes PTSD. It has been known since 1918 that combat veterans with "shell shock" exhibit overactivity of the SNS. Contemporary studies of patients examined in emergency rooms immediately following trauma have demonstrated increased heart rate, as well as lower cortisol levels, at the time of the event in individuals who later develop PTSD, compared to those who do not.[47]

In a symptom provocation study of veterans with PTSD, Liberzon et al[48] found that, compared to controls, PTSD victims showed heightened responsivity to trauma-related clues in certain response modalities. PTSD patients exhibited higher skin conductance, heart rate, plasma cortisol, and catecholamines at baseline (possibly in anticipation of the expected challenge), and exaggerated E and NE responses to combat sounds. However, the investigators were unable to detect evidence of ACTH hyperreactivity to trauma-related cues.

More research will be needed to explain and reconcile the apparent discrepancies described above; however, it is conceivable that adult PTSD patients could display exaggerated responses of both E and NE to certain stress stimuli while maintaining a reduced 24-hour urinary output of cortisol.

It is not uncommon for patients exposed to intense physiological and psychological stress during intensive care to develop PTSD. Schelling et al[49] have reported preliminary evidence that administration of hydrocortisone to intensive-care patients in amounts equivalent to the maximal endocrine secretion rate during septic shock reduces the incidence of PTSD and improves emotional well-being in survivors. This observation provides support for the growing belief that low cortisol output after trauma may increase risk of PTSD. Moreover, Yehuda et al[50] have found that parental PTSD, a putative risk factor for PTSD, is associated with low cortisol levels in offspring, suggesting that ". . .low cortisol levels in PTSD may constitute a vulnerability marker related to parental PTSD. . . ." These findings provide a basis for hope that prophylactic cortisol administration might help avert PTSD in vulnerable individuals exposed to severe emotional and/or physical stress.

Pitman et al[51] have recently reported on the use of brain imaging techniques to investigate pathogenesis and pathophysiology of long-standing PTSD. Using magnetic resonance imaging (MRI), they found nonspecific white matter lesions and decreased hippocampal volume in PTSD patients. In their words, "These abnormalities may reflect pretrauma vulnerability to develop PTSD, or they may be a consequence of traumatic exposure, PTSD, and/or PTSD sequelae." (Phenytoin or tianeptine administration can block stress-induced hippocampal atrophy in laboratory animals,[14] suggesting that the use of these or similar drugs in the early treatment of PTSD might be beneficial).

Pitman et al employed positron emission tomography to measure changes in regional cerebral blood flow in PTSD patients occurring in response to symptom provocation and cognitive activation. In response to these manipulations, there was revealed ". . .greater activation of the amygdala and anterior paralimbic structures, greater deactivation of Broca's region (motor speech) and other nonlimbic cortical regions, and failure of activation of the cingulate cortex. . .in response to trauma related stimuli." The authors speculated that the cingulate cortex may act to inhibit the fear reaction and pointed out that other functional MRI studies have shown the amygdala to be hyperresponsive to fear-related stimuli in PTSD.

In a longitudinal MRI study of hippocampal volume in 37 trauma survivors with PTSD, Bonne et al[52] were unable to find any reduction in hippocampal volume 6 months after the initiating traumatic events. It may be that, in PTSD (as in depression[53]), duration predicts hippocampal volume loss.

## CONCLUSION

"Stress" is often implicated in the pathogenesis of illnesses; however, its direct culpability is not easily established. Unlike certain epidemiologic situations in which the responsible agent (eg, a micro-organism) can be identified and its virulence determined, stress—as a suspected agent of disease—is frequently indistinct and elusive. Also, because the nature of the adaptive response to any given stress may be quite variable, the vulnerability of the host becomes a major pathogenetic consideration. Finally, the duration and repetitive nature of the putative stress, as well as its severity, are frequently hard to determine. All of these limitations can seriously hinder efforts to demonstrate a clear relationship between exposure to a severe stress and a subsequent illness (This criticism may not be applicable to many cases of PTSD).

Nevertheless, well-controlled studies in laboratory animals have disclosed robust relationships between a variety of specified, investigator-applied stressors and predictable illness. In such animals, illnesses such as hypertension and atherosclerosis are reliably associated with changes in allostatic load that resemble similar patterns of response to analogous stressors in man. Yet, it has to be emphasized that stress hormones are regulated by more than "stressors" and that commonplace factors such as disrupted sleep patterns and a variety of lifestyle activities (eg, smoking, lack of exercise) contribute in cumulative fashion to allostatic load.

The epidemiologic evidence that certain acute stressors (eg, earthquake, combat) can precipitate heart attacks or PTSD in susceptible individuals is convincing. Hence, despite all the problems involved in this area of investigation, evidence continues to accumulate that stress—particularly chronic stress—may give rise to, or worsen, a number of illnesses. As we improve our ability to identify individuals who are unduly vulnerable, and understand better the ways in which the response to stress ceases to be protective and, instead, results in pathophysiology and disease, we shall also learn how to intervene in the process to prevent or mitigate such damaging outcomes.

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