Posttraumatic stress disorder (PTSD) is a psychiatric condition that can occur following exposure to extreme trauma. According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), a traumatic event is defined as one that threatens an individual’s life or physical integrity and involves a subjective response of fear, helplessness, or horror. By definition, intense fear or terror are essential components in response to a life-threatening event, and individuals who are exposed to such events are at increased risk for developing PTSD and other related conditions, such as major depressive disorder and generalized anxiety disorder, compared with those who have not experienced a traumatic event. Approximately 60% of individuals in the United States are exposed to at least 1 potentially life-threatening event or severe trauma that could lead to the development of PTSD during the course of their lives. Certainly, rates of exposure to trauma in other parts of the world are much higher. Traumatic events may include violent physical assault, torture, natural disasters, accidents, rape, terrorist attack, or military combat. Recent world events, including the terrorist attacks on the World Trade Center and the Pentagon, suggest that thousands of individuals may have been exposed to the threat of death or the loss of loved ones or witnessed horrifying images of death. Consequently, the prevalence of PTSD may be higher than estimated in epidemiologic studies.

Following exposure to extreme trauma, individuals who are diagnosed with PTSD develop 3 distinct types of symptoms reflecting difficulties in regulating memories or emotional content. The person persistently reexperiences images, thoughts, or perceptions of the event in the form of nightmares or flashbacks. These intrusive symptoms are highly disturbing as the individual may see, hear, and smell details associated with the traumatic event (i.e., re-experience, not just recall, the event). Other characteristic symptoms include persistent avoidance of stimuli (i.e., people, places, thoughts) associated with the trauma and numbing of general responsiveness. Patients also experience hyperarousal associated with difficulty falling asleep, irritability, impaired concentration, hypervigilance, and exaggerated startle response.

Not surprisingly, the incidence of PTSD is quite high, with an estimated lifetime prevalence of between 8% and 9% in the United States. Approximately 10% to 14% of
women and 5% to 6% of men may develop PTSD during their lifetimes. Based on data from the National Comorbidity Survey, about 60% of men and 50% of women are exposed to a traumatic event that can potentially result in the diagnosis of PTSD. Of these individuals, 8.2% of men and 20.4% of women develop PTSD. However, looking at the data another way suggests that more than 90% of men and almost 80% of women exposed to life-threatening trauma do not progress to PTSD (Figure 1). Some individuals are clearly vulnerable to the development of PTSD, whereas others are more resilient. This raises the question of whether PTSD best reflects the absence of resilience factors or the presence of risk factors. As the field begins to look at the biological similarities of PTSD and other psychiatric disorders, it becomes important to de-emphasize trauma and stress, because these factors produce heterogeneous symptoms or diagnostic entities, and focus instead on specific outcomes. Indeed, PTSD does not appear to be a reflection of the normal response to stress, as demonstrable neurochemical changes have been observed in these patients, some of which are inconsistent with those observed in persons experiencing acute or chronic stress. This article examines the issue of why some individuals are at risk for developing PTSD after a traumatic event, whereas others appear to be resilient and can recover from the trauma without psychiatric sequelae.

**NATURE AND INTENSITY OF TRAUMA RESPONSE**

Kessler and associates noted that the rate of PTSD development was influenced in part by the nature of the trauma. In both men and women, rape was the trauma most often associated with the development of PTSD; approximately 50% of individuals developed PTSD following rape regardless of gender. In contrast, less than 5% of individuals developed PTSD after experiencing a natural disaster. Simply, the rate of PTSD appeared to be influenced by the nature of the event. The findings from Kessler and coworkers often are interpreted as reflecting the idea that trauma severity is responsible for the differences in prevalence rates of PTSD by trauma type. However, this raises the question of how trauma severity is measured and what the characteristics are that render rape a more salient producer of PTSD than disaster. Indeed, if development of PTSD is associated with trauma severity, the method of measuring trauma severity becomes important.

The severity of a traumatic experience is generally defined by subjective emotional response and varies between individuals based on perception. A number of factors contribute to the intensity of the response to trauma and may affect the development of PTSD in certain individuals (Table 1). The degree of controllability, predictability, and perceived threat intensifies the fear response or the terror for the person involved. The relative success of attempts to minimize injury is associated with development of PTSD: the more successful the attempt to minimize the stressful event, the less the likelihood of PTSD. Other factors that influence the intensity of the response include actual loss to self; loss of a loved one or even property; exposure to pain, heat, or cold; and a sense of failure to act in ways that might have mitigated the circumstances of the event. In one study, the individual’s appraisal of threat to life was highly predictive of PTSD development. This highlights the fact that development of PTSD is not just associated with exposure to trauma, but with how the events are interpreted and how the person acts in the immediate aftermath of the trauma. Determining who will and who will not develop PTSD in response to trauma is complex and involves identifying not just a single risk factor, but multiple risk factors that can work together.

**Table 1. Factors Contributing to the Intensity of Response to Trauma**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of controllability, predictability, perceived threat (eg, intensity of fear)</td>
<td>60.7</td>
</tr>
<tr>
<td>Actual loss</td>
<td>91.9</td>
</tr>
<tr>
<td>Relative success of attempts to minimize injury</td>
<td>51.2</td>
</tr>
<tr>
<td>Exposure to pain, heat, cold</td>
<td>20.4</td>
</tr>
<tr>
<td>Perceived sense of failure to act in ways that might have mitigated the circumstances of the event (ie, intensify guilt, anger, humiliation)</td>
<td>79.6</td>
</tr>
</tbody>
</table>

*Data from Yehuda.*

Initial review of the Kessler et al. study suggests that PTSD is twice as prevalent in women as in men (20.4% vs. 8.2%), implying that women are more vulnerable to PTSD. However, it may also be that the actual experiences during specific traumatic events are different for women compared with men. When considering the incidence of personal attacks, men are assaulted (11.1%) far more often than women (6.9%), but men rarely develop PTSD as the result of an assault (1.8%), whereas this is an event that often results in PTSD in women (21.3%). Similar results...
have been reported by Breslau, who has interpreted the findings as suggesting that women are at increased risk for PTSD following assaultive violence (54% incidence in women vs. 15% in men). That there is greater risk for PTSD among women following assaultive violence is not in dispute. The question is whether this increase is due to the characteristics of the person experiencing the assault or to the fact that the event itself is fundamentally different. For example, when a 200-lb (91-kg) man assaults another 200-lb man, this may be a very different experience than when a 200-lb man assaults a 110-lb (50-kg) woman. Interestingly, women are more likely to experience rape, humiliation, guilt, and inability to minimize injury. But when men experience this event, they do develop PTSD in roughly equal proportions (65% in men and 45.9% in women), suggesting that both genders are highly traumatized by sexual assault. Furthermore, the likelihood of experiencing a natural disaster (18.9% vs. 15.2%) and the prevalence of developing PTSD following a natural disaster are similar between men and women (3.7% vs. 5.4%, respectively), possibly because there is no particular a priori reason to assume that these events are experienced differently in men and women as they usually involve similar types of losses, emotions, and outcomes. Thus, it is clear that numerous factors affect an individual’s perception of trauma and may influence the development of PTSD.

**PTSD IS NOT A DICHOTOMOUS VARIABLE**

Another challenge in addressing risk and resilience is the fact that the presence or absence of PTSD following a trauma is not best conceptualized as a dichotomous variable. Although technically it is not possible to diagnose PTSD in the immediate aftermath of a trauma because of the diagnostic stipulation that symptoms occur for at least 1 month, it is true that up to 94% of trauma survivors initially exhibit some degree of acute PTSD symptoms. Over time, most survivors experience a reduction in symptoms, which persist in a few individuals. After 9 months, the percentage of individuals with PTSD symptoms decreases to 42%. Thus, PTSD may represent the failure to recover from a universal set of reactions. Using such a “recovery” model for PTSD, it could be assumed that during a specific time period immediately following the traumatic event, the manifestation of symptoms is normal. Pathology could be defined as the presence of symptoms after that period (i.e., arbitrary cut-off point that has not been determined). On the other hand, it is possible that failure to recover from acute symptoms is part of an alternative trajectory to the normative response in patients who develop PTSD. Thus, failure to contain or control the initial biological response to stress leads to a cascade of events resulting in symptoms of hyperarousal, recollection of intrusive events, and avoidance of reminders. The second alternative provides a more reasonable basis for understanding PTSD as a disorder with preexisting risk factors.

If, indeed, it were possible to identify individuals who are at increased risk for PTSD in the immediate aftermath of a trauma, these individuals could be treated early to possibly prevent symptoms from emerging. In a meta-analysis conducted by Brewin and colleagues, 14 separate risk factors for PTSD were evaluated. Both pretrauma and posttrauma risk factors were found to be important, but posttrauma factors such as severity of the trauma, additional life stress, and lack of social support had a larger effect size than did factors that occurred before the trauma. On a simple level, these data suggest that prophylactic treatment following acute trauma may be beneficial in limiting or preventing the development of PTSD since they underscore the importance of posttraumatic factors in the development of PTSD. On the other hand, to the extent that the presence of posttraumatic factors represents the sum total of pretraumatic and posttraumatic factors (e.g., someone with a preexisting psychiatric disorder may also be less likely to have adequate social support), this may limit the power of prophylactic treatments.

**NEUROENDOCRINE IMPLICATIONS**

Neuroendocrine studies support the idea that factors that are present before, during, and after the trauma are all involved in the development of PTSD. An individual’s initial response to fear is clearly associated with inherent biological factors. However, response to the stressful event may be influenced by both subjective interpretation and the person’s previous traumatic experiences and risk factors. When evaluating PTSD, it is important to distinguish between the immediate effects of the trauma versus long-lasting effects. In 1914, Walter Cannon initially described the “fight or flight” response to fear, which included increased blood flow, heart rate, blood pressure, and glucose availability to muscles, allowing the person to fight or flee in response to threat.

Automatic biological reactions in response to fear or trauma occur instantaneously. In a matter of milliseconds, the amygdala determines that a sensory experience (e.g., seeing an aggressor) is perceived as harmful and mediates a biochemical and behavioral response to the threat. Thus, the amygdala is the organ that activates the fear response, initiating both neurochemical and neuroanatomical changes. The startle response is potentiated by projections from the amygdala to the reticularis pontis caudalis. Signals from the amygdala to the lateral hypothalamus and rostral ventral medulla stimulate the sympathetic nervous system, projections to the solitary tract initiate parasympathetic responses, and projections...
to the stria terminalis stimulate the hypothalamic-pituitary-adrenal (HPA) axis response.26

Activation of the HPA axis begins with the release of corticotropin-releasing factor, along with other neuropeptides, which ultimately stimulates cortisol release from the adrenal gland and adrenocorticotropic hormone release from the pituitary.27 Catecholamines and cortisol increase in a synergistic, dose-dependent manner in response to the stress.28 Catecholamine release increases the availability of energy to vital organs, whereas cortisol contains the stress response by dampening the sympathetic response. In a normal stress response, the activated sympathetic, parasympathetic, and HPA systems begin to return to basal levels within hours. Long-term effects may be observed after exposure to a subsequent stressor (i.e., sensitization). For example, if in response to a previously stressful event, the person had a successful experience, then the stress response to the current experience may be lessened. However, if the prior experience with a stressor was negative, the person may have a much greater activation of biological response to a subsequent event. An interesting contrast between the study of the normal stress response and the study of PTSD is that stress theory is based on biological effects occurring only while the stressor is still present. Once the stressful event is over, basal hormone levels should be restored to normal.29

Biological alterations associated with chronic PTSD suggest the presence of an ongoing stress response. Recent neuroanatomical studies in patients with PTSD have shown increased reactivity of the amygdala and anterior paralimbic region in response to stress and decreased reactivity of the anterior cingulate and orbitofrontal areas.30-32 In patients with PTSD, it appears that physiologic responses fail to return to the baseline, pretrauma state. In patients with long-term PTSD, neurobiological alterations suggest that the stress response is chronic and that the biological response is different from responses in normal subjects and patients with major depressive disorder (Figure 2).7 Although the stressful event has passed, these individuals continue to exhibit an enhanced startle response,
increased activation of the sympathetic nervous system, alterations in the HPA axis and hippocampus, and increased activation of the amygdala.\textsuperscript{20,33,34}

In humans, the acoustic startle reflex can be measured by the magnitude of eye blink response, heart rate, and electrodermal conductivity in response to sudden loud tones.\textsuperscript{35} In a study conducted by Orr and colleagues,\textsuperscript{36} auditory startle response was evaluated in 19 Israeli veterans with PTSD compared with 74 veterans without PTSD. Individuals were exposed to 15 consecutive 95-dB, 300-millisecond, 1000-Hz tones with 0-millisecond rise and fall times. Physiologic response was measured by orbicularis oculi electromyograms, skin conductance, and heart rate responses. Patients with PTSD had greater heart rate responses compared with non-PTSD subjects. In response to loud tones, PTSD subjects also exhibited a slower decline in skin conductance responses. Overall, individuals with PTSD exhibited increased autonomic response to loud auditory stimuli associated with higher startle response and failure to habituate compared with non-PTSD subjects.

Interestingly, some biological alterations in PTSD are observed immediately after the trauma,\textsuperscript{18} whereas others appear to be delayed.\textsuperscript{37} In one prospective study, Shalev and associates\textsuperscript{18} evaluated heart rate and blood pressure response following trauma and subsequent development of PTSD in 86 survivors who presented to the emergency department following a traumatic event. Heart rate and blood pressure were measured at the emergency room. At 1 week, 1 month, and 4 months following the traumatic event, heart rate, anxiety, depression, and PTSD symptoms were evaluated. At 4 months, 23% of patients met the diagnostic criteria for PTSD. Patients diagnosed with PTSD were found to have significantly increased heart rate at the emergency room (p < .001) and at the 1-week follow-up (p < .03), indicating that elevated heart rate immediately following trauma may be associated with development of PTSD. There were no differences in blood pressure between the groups.

However, increased startle response was not observed until 1 month after the trauma in PTSD patients. In an analysis of patients who presented to an emergency room after a psychologically traumatic event, autonomic and muscular responses to auditory tones were measured at 1 week, 1 month, and 4 months.\textsuperscript{37} At 4 months, 36 patients were classified with PTSD and 182 individuals did not have PTSD. At the 1-week follow-up, there were no physiologic differences between groups in response to auditory tones. At 1 and 4 months, patients with PTSD had increased heart rate response to startling tones. This study suggested that abnormal startle response developed along with PTSD in the months after the trauma. The data also suggest that PTSD may be an evolving illness with biological changes that are sustained or that progress over time.

**CORTISOL RESPONSE IN INDIVIDUALS WHO DEVELOP PTSD**

Cortisol is involved in both mediating the initial reaction to stress and also in limiting the sympathetic response via negative feedback inhibition on the pituitary and hypothalamus to terminate the stress response.\textsuperscript{8,39} Typically, cortisol and catecholamines increase in a dose-dependent fashion in response to acute stress; higher cortisol levels occur with higher levels of stress.\textsuperscript{28} Thus, it would be assumed that cortisol levels would be increased in patients with PTSD. Paradoxically, individuals who develop PTSD have been shown to have attenuated cortisol levels at the time of trauma compared with those who do not develop PTSD. The tendency for somewhat reduced cortisol levels appears to be maintained during the life course of trauma survivors with PTSD.\textsuperscript{17,20,40,41} Aside from modulating the stress response, cortisol is also involved in the consolidation of memory, which is particularly interesting in the development of PTSD because memory of the traumatic event is part of the pathology of the disorder. Thus, dysregulation of the HPA axis may be a marker (or risk factor) for individuals who subsequently develop PTSD.

Plasma norepinephrine levels were measured in one study during a 24-hour period in 15 men with PTSD, 12 men with major depressive disorder, and 13 control subjects with no psychiatric disorders.\textsuperscript{27} Patients with PTSD who did not have comorbid depression had increased plasma norepinephrine levels. Notably, the increase in norepinephrine may be associated with decreased cortisol levels in patients with PTSD and may increase subjective feelings of distress.\textsuperscript{42,43} In animal studies, activation of the adrenergic system in the presence of low cortisol levels is associated with learning.\textsuperscript{44} Thus, the presence of decreased cortisol levels and increased norepinephrine availability following a traumatic event could strongly encode the memory of the event, along with subjective feelings of distress.

In another study, a chronobiological analysis assessed cortisol regulation in 15 combat veterans with PTSD, 14 individuals with major depression, and 15 control subjects.\textsuperscript{41} Plasma cortisol concentrations were measured every 30 minutes for 24 hours. Notably, patients with PTSD exhibited lower cortisol levels compared with the other groups. These findings suggest that patients with chronic PTSD have an exaggerated sensitization of the HPA axis negative feedback loop. Of interest is whether those patients with chronic PTSD had biological alterations in the immediate aftermath of the traumatic experience.

Studies have shown that cortisol levels are lower within hours after the traumatic event in individuals who develop PTSD.\textsuperscript{15,17,20} In an analysis conducted by Delahanty and associates,\textsuperscript{15} 15-hour urine samples were collected to measure urinary cortisol levels from 99 victims of motor vehicle accidents. Urinary cortisol levels were significantly
lower in those who were subsequently diagnosed with PTSD (p < .05). In another study, blood cortisol levels were measured in a subset of 40 individuals who presented to an emergency room after a motor vehicle accident. Subjects were interviewed on the day following admission and at 10 days and 6 months after the accident. At the 6-month follow-up, 7 patients were diagnosed with PTSD, 7 had major depression, and 12 had no psychiatric disorder. The remainder of the patients had a range of diagnoses and were excluded from the analysis. Blood cortisol levels measured immediately after the accident were lowest in the individuals who subsequently developed PTSD and highest in those who developed major depression (Figure 3). These studies suggest that alterations in the HPA axis occurred immediately following the traumatic event in those who developed PTSD.

Data from animal studies have shown that previous exposure to stress can alter the HPA axis and affect response to subsequent stressful events. Studies of recently widowed individuals also suggest that the effects of prior trauma, such as death of a child, have a strong influence on development of PTSD. Results from a trauma survey conducted in Detroit also found that following an index traumatic event, development of PTSD was significantly higher in those who had prior exposure to trauma. In an interesting study conducted by Resnick and colleagues, lower cortisol levels in the immediate aftermath of rape were associated with previous assault. Blood samples were obtained from 37 women within 51 hours following a rape. PTSD status, previous assault, and index rape characteristics were assessed within a mean of 90 days following the rape. PTSD was diagnosed in 51% of the women in this study; 23% of women who did not have a history of assault and 67% of women who had a history of assault developed PTSD. Mean cortisol levels were 21.2 µg/dL in the 8 women with no history of assault who had a low severity index rape, 39.5 µg/dL in the 5 women who had not experienced a previous assault and whose index rape was rated as severe, 13.8 µg/dL in the 9 women who had experienced a previous assault and who had a low severity rape index, and 13.8 µg/dL in the 15 women who had previous assault and whose index rape was high in severity. Notably, women who had a history of rape had lower mean cortisol levels and increased likelihood of developing PTSD regardless of severity of the index rape, suggesting that prior trauma affected the response of the HPA axis in the subsequent rape. These studies suggest that lower cortisol levels in the acute aftermath of trauma may be predictive of the risk factor of prior trauma and may be associated with a previously altered neuroendocrine system that is acutely responsive to environmental challenges. Most importantly, these data show that the acute cortisol responses in individuals who are at increased risk for developing PTSD following trauma are distinctly different from those who do not develop the disorder.

**VULNERABILITY TO PTSD**

One salient question raised by these studies is whether individuals who developed PTSD had lower cortisol levels prior to the traumatic event. Adult children of Holocaust survivors represent a high-risk group because these individuals are at increased risk for PTSD in response to their own traumatic experiences. Interestingly, even in the absence of trauma, low cortisol levels have been observed in the adult offspring of Holocaust survivors with PTSD.

Yehuda and associates examined trauma exposure, PTSD diagnosis, and other psychiatric diagnoses in 100 adult offspring of Holocaust survivors and 44 demographically similar comparison subjects. The prevalence of lifetime PTSD was higher in children of Holocaust survivors (31%) compared with that of the comparator group (9%). Using DSM-IV criteria for PTSD, 46% of offspring and 20% of comparators developed PTSD, indicating an increased vulnerability to PTSD in offspring of Holocaust survivors.

In a subsequent study, urinary cortisol excretion was evaluated in 35 offspring of Holocaust survivors and 15 comparator subjects who were not offspring of Holocaust survivors. Children of Holocaust survivors had lower cortisol excretion (mean = 48.3 µg/day) compared with nonoffspring (mean = 65.1 µg/day). The lowest cortisol levels were observed in the offspring with PTSD who had a parent with PTSD, suggesting that the effects of familial contribution and trauma exposure may be additive. Offspring who did not have PTSD but had a parent with PTSD also had lower cortisol levels (Figure 4). Cortisol levels were not affected by height, weight, education, age, or gender. These data indicated that low cortisol levels in offspring with and without PTSD were associated with having a parent with PTSD.
Development of PTSD is not inevitable following trauma, and the majority of individuals recover from traumatic experiences without long-term psychological sequelae. In patients who do progress to PTSD, the disorder appears to be associated with failure to recover from the acute response to a traumatic experience. The result is manifestation of the classical symptoms of avoidance of reminders of the event, increased physiologic arousal, and reexperiencing of the event. In patients with PTSD, biological studies have shown that alterations in specific regions of the brain and atypical neurochemical responses such as lower cortisol levels and increased heart rate may facilitate the development of PTSD in the immediate aftermath of a trauma. Prior traumatization, perception of the severity of the trauma, and intensity of response also may influence the likelihood for developing PTSD.

When considering the issues of risk and resilience in PTSD, one hypothesis is that the initial response to fear is biological but is influenced by subjective interpretation, which depends on the individual’s history. In this model, recovery from trauma would involve confronting human vulnerability in a way that promotes learning and resilience. The altered response to fear in vulnerable individuals can perpetuate a state of fear, leading to development of a maladaptive biological condition. The normal path is recovery, which is facilitated by a supportive environment and relief of distress associated with memories of the event. Although additional research is needed, recent findings suggest that detection of risk factors (e.g., low cortisol levels or previous trauma experience) immediately following a traumatic event may help to identify individuals who are unable to recover from the traumatic experience and are at increased risk for PTSD. It is likely that early intervention could facilitate recovery in individuals at risk for development of PTSD.

**REFERENCES**


Questions and Answers

**Question:** How soon after the traumatic event were cortisol levels measured in the PTSD studies that you described?

**Dr. Yehuda:** In the study evaluating patients after a motor vehicle accident [McFarlane AC, et al., Ann NY Acad Sci 1997;821:437–441], blood was drawn in the ambulance on the way to the hospital because blood alcohol levels are required in Australia. Thus, in that study, the cortisol levels were typically obtained within 30 minutes to 1 hour after the traumatic event. Obviously, in the studies evaluating rape victims [Resnick HS, et al., Am J Psychiatry 1995;152:1675–1677], time of cortisol measurement was dependent on when the women came to the emergency department. In one case, the patient came to the emergency department 2 days after the index rape. However, in most cases, cortisol levels were obtained within a few hours after the trauma for both populations and indicate that low cortisol levels can be seen very soon after the traumatic experience.

**Question:** In light of the new links between relative cortisol levels and hypothalamic-pituitary-adrenal (HPA) responsiveness, some of the earlier PTSD studies probably looked at changes in the HPA axis and assumed that they were linked to current phenomenology rather than prior experience. Could the older data from combat veterans be reexamined to look at the effects of previous trauma?

**Dr. Yehuda:** This possibility is something that we considered, but the problem with our earlier studies in Vietnam-era veterans is that these individuals are very reluctant to discuss anything prior to Vietnam. The information on trauma history that we obtained from these individuals was just not reliable, so we had to focus on the current effects of PTSD. However, it is interesting to speculate on the influence of previous trauma in veterans and how it may have affected development of PTSD after their experience with combat trauma.