Current Concepts

POST-TRAUMATIC STRESS DISORDER

RACHEL YEHUDA, PH.D.

THE terrorist attacks on the World Trade Center and the Pentagon on September 11, 2001, represented an amalgam of interpersonal violence, loss, and disaster. Tens of thousands of people ran for their lives in fear, were exposed to graphic scenes of death, or lost loved ones. It is estimated that well over 100,000 people directly witnessed the events, and many people around the world were also exposed to these horrifying scenes through the media.[1] The attacks were followed by the imminent threat of subsequent attacks, the prospect of war, and bioterrorism. These events have influenced and will continue to influence the clinical presentation of patients seeking health care services, and post-traumatic stress disorder (PTSD) will develop in a substantial number of people. On the basis of data obtained after the 1995 bombing of the Murrah Federal Building in Oklahoma City, which was previously the deadliest act of terrorism in America, one could predict PTSD will develop in approximately 35 percent of those who were directly exposed to the September 11 attacks.[2] In addition, many persons with prior exposure to traumatic events may have a recrudescence of PTSD symptoms triggered by news of catastrophic events and their distressing effects. Since traumatized persons with PTSD are far more likely to visit primary care physicians for their symptoms than mental health professionals, primary care practitioners will play an important part in identifying and treating this disorder.

DEFINITION OF PTSD

The defining characteristic of a traumatic event is its capacity to provoke fear, helplessness, or horror in response to the threat of injury or death.[3] People who are exposed to such events are at increased risk for PTSD as well as for major depression, panic disorder, generalized anxiety disorder, and substance

From the Division of Traumatic Stress Studies and Department of Psychiatry, Mount Sinai School of Medicine and Bronx Veterans Affairs Medical Center, New York. Address reprint requests to Dr. Yehuda at Bronx Veterans Affairs Medical Center, 130 Kingsbridge Rd., Bronx, NY 10468, or at rachel.yehuda@med.va.gov.

abuse, as compared with those who have not experienced traumatic events.[4] They may also have somatic symptoms and physical illnesses, particularly hypertension, asthma, and chronic pain syndromes.[5,6]

To be given a diagnosis of PTSD, a person has to have been exposed to an extreme stressor or traumatic event to which he or she responded with fear, helplessness, or horror and to have three distinct types of symptoms consisting of reexperiencing of the event, avoidance of reminders of the event, and hyperarousal for at least one month (Table 1).[3] Reexperiencing of the event refers to unwanted recollections of the incident in the form of distressing images, nightmares, or flashbacks. Symptoms of avoidance consist of attempts to avoid reminders of the event, including persons, places, or even thoughts associated with the incident. Symptoms of hyperarousal refer to physiological manifestations, such as insomnia, irritability, impaired concentration, hypervigilance, and increased startle reactions.[2]

Within the first month after a traumatic experience, traumatized persons may meet the diagnostic criteria for acute stress disorder. Although acute stress disorder is not always followed by PTSD, it is associated with an increased risk of PTSD.[7]

The symptoms of PTSD are readily identifiable by a primary care physician. Because there is substantial overlap between the symptoms of PTSD and those of depression and other anxiety disorders, however, the diagnosis is easily missed unless specific inquiries are made about the occurrence of a traumatic event. Often practitioners are reluctant to ask their patients about events that might be distressing or that might involve shame or secrecy, and patients will not usually mention such topics without prompting. By providing patients with the opportunity to disclose such events, practitioners break down an important barrier to treatment by legitimizing the event as a valid explanation for symptoms. Exposure to a traumatic event can often explain the presence of nonspecific symptoms such as palpitations, shortness of breath, tremor, nausea, insomnia, unexplained pain, and mood swings, as well as a reluctance to undergo certain types of examinations (e.g., rape victims may feel uncomfortable undergoing a gynecologic examination) and behavior such as nonadherence to treatment, which may be a manifestation of avoidance.[8] Thus, otherwise unexplained physical symptoms or behavior may prompt clinicians to question patients about the possibility of traumatic experiences and the specific symptoms of PTSD.

TABLE 1. DIAGNOSTIC CRITERIA FOR PTSD.*

A person must have been exposed to a traumatic event.
   The event involved a perceived or actual threat to the person's own life or physical integrity or that of another, such as a physical or sexual
       assault, rape, a serious accident, a natural disaster, combat, being taken hostage, torture, displacement as a refugee, sudden unexpected
       death of a loved one, and witnessing a traumatic event.
   The person's response to the event involved fear, helplessness, or horror.
The person persistently reexperiences the event in at least one of several ways:
   The person has intrusive recollections of the event.
   The person has nightmares.
   The person has flashbacks, which are particularly vivid memories that occur while he or she is awake and make him or her act or feel as
       though the event was recurring.
   The person has intense psychological distress in response to reminders of the traumatic event.
   The person has intense physiological reactions in response to reminders of the event (including palpitations, sweating, difficulty breathing,
       and other panic responses).
The person avoids reminders of the event and has generalized numbness of feeling, as indicated by the presence of at least three of the following:
   The person actively avoids pursuits, people, and places that remind him or her of the event.
   The person avoids thinking of or talking about the event.
   The person is unable to recall aspects of the event.
   The person has lost interest in or participates less in activities.
   The person has felt detached or estranged from other people since the event.
   The person has a restricted range of emotions or a feeling of numbness.
   The person feels as though his or her life has been foreshortened or as though there is no need to plan for the future, with respect to his
       or her career, getting married, or having children.
The person has symptoms of increased arousal, as evidenced by the presence of at least two of the following:
   The person has difficulty falling or staying asleep (sometimes related to fear of having nightmares).
   The person is irritable and has feelings or outbursts of anger.
   The person has difficulty concentrating.
   The person has become more vigilant and concerned about safety.
   The person has exaggerated startle reactions in response to sounds or movements.
The three types of symptoms must be present together for at least one month.
The disorder must cause clinically significant distress or impairment in social, occupational, or other areas of functioning.

*There are three subtypes of PTSD. Acute PTSD refers to symptoms that last less than three months. Chronic PTSD refers to symptoms that last three months or longer. Delayed-onset PTSD refers to symptoms that begin at least six months after a traumatic event. Adapted from the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition.[3]

EPIDEMIOLOGIC ASPECTS

Before the September 11 attacks, studies of the prevalence of PTSD in the United States demonstrated that 5 to 6 percent of men and 10 to 14 percent of women had had PTSD at some time in their lives, making it the fourth most common psychiatric disorder.[4,9-11] Events that give rise to PTSD typically involve interpersonal violence (e.g., rape, assault, and torture) or exposure to life-threatening accidents (e.g., motor vehicle accidents) or disasters (e.g., fires and earthquake). Although the disorder is far more likely to occur after direct than indirect exposure to trauma,[3] PTSD can occur in persons who have witnessed a violent injury to or the unnatural death of another person and those who have learned that a loved one was involved in such an event,[12] provided there is sufficient associated terror or shock.[2] Factors that contribute to the intensity of the response to a psychologically traumatic experience include the degree of controllability, predictability, and perceived threat[13]; the relative success of attempts to minimize injury to oneself or others; and actual loss.[14] If the patient is wounded or exposed to pain, heat, or cold, the biologic and psychological experience can be intensified.[15]

Events that involve interpersonal violence give rise to PTSD more often than events such as motor vehicle accidents and natural disasters. For example, PTSD developed in 55 percent of persons who reported being raped, as compared with 7.5 percent of those involved in accidents[4] and 2 percent of those who learned of traumatic events.[16] One study reported that PTSD developed in approximately 14 percent of those who experienced the sudden, unexpected death of a loved one,[16] making this event the single most frequent traumatic event to occur in both men and women, accounting for 39 percent of cases of PTSD in men and 27 percent of cases in women.[17]

Although women have a higher lifetime prevalence of PTSD, it is not clear whether this finding reflects an increased vulnerability to the disorder or the fact that seemingly similar events are experienced differently by men and women. Women are more likely than men both to be molested and to have PTSD in response to molestation (Table 2).[4] However, PTSD also develops more often in women than men after a physical assault, such as mugging, despite the fact that these events are far less common in women (Table 2).[4,16] In contrast, although women are more than 10 times as likely as men to be raped, the prevalence

of PTSD after rape is actually higher in men (65 percent vs. 46 percent).[4] These statistics argue against an increased vulnerability to the disorder in women and instead suggest that certain experiences may involve different degrees of actual threat and physical injury. Nonetheless, because of the extremely high frequency of sexual and physical assault among women, more than 50 percent of cases of PTSD among women appear to result from such events, whereas only 15 percent of cases among men result from this type of trauma.[17] The rates of PTSD in response to events such as accidents, natural disasters, or death of a loved one (Table 2) are statistically similar among men and women and suggest that the incidence of PTSD may be similar among men and women in the aftermath of September 11.

PSYCHOLOGICAL ASPECTS

The psychological and biologic response to a traumatic event is determined by the characteristics of both the event and the person involved.[18] The initial response of fear is inherently biologic, but it can be influenced by the person's subjective interpretation of the event, which in turn is influenced by the person's previous experiences and other risk factors.[19]

Experiencing or learning about a traumatic event challenges a person's sense of safety, leading to feelings of vulnerability and powerlessness.[19,20] Recovery from the event involves confronting human vulnerability in a way that promotes the development of resilience. However, the body's biologic responses in the aftermath of a traumatic event may perpetuate a state of fear that interferes with the restoration of feelings of safety, particularly if the result leads to further events, such as war.[21] Living in a state of perpetual fear can overwhelm a person's coping resources and lead him or her to avoid thoughts and feelings associated with the traumatic event. Avoidance reduces opportunities to extinguish or diminish fear responses — for example, through exposure to information that could correct exaggerated beliefs[20] about the safety of the world and the fragility of the person — and prevents the development of effective coping strategies, resulting in further social, interpersonal, or occupational disruption.

Horror, anger, sadness, humiliation, and guilt can also occur in response to trauma.[19] Many people blame themselves for failing to act in ways that could have averted the event or mitigated the circumstances of the event. No matter what the emotional response, the process of recovery requires acknowledgment of changes that have occurred as a result of the traumatic event. Although many traumatized persons attempt to avoid distressing emotions related to their experiences, being able to confront them will promote habituation, so that over time, their thoughts

TABLE 2. PREVALENCE OF TRAUMATIC EVENTS AND RATES OF PTSD IN RESPONSE TO SUCH EVENTS AMONG MEN AND WOMEN.

TRAUMATIC EVENT	PREVALENCE OF EVENT		RATE OF PTSD IN RESPONSE TO EVENT	
	MEN	WOMEN	MEN	WOMEN
	percent			
Rape*	0.7	9.2	65.0	45.9
Molestation*	2.8	12.3	12.2	26.5
Physical assault*	11.1	6.9	1.8	21.3
Accident*	25.0	13.8	6.3	8.8
Natural disaster*	18.9	15.2	3.7	5.4
Combat*	6.4	0.0	38.8	—
Witnessed death or injury†	40.1	18.6	9.1	2.8
Learned about a traumatic event†	63.1	61.8	1.4	3.2
Sudden death of loved one†	61.1	59.0	12.6	16.2
Any traumatic event*	60.7	51.2	8.1	20.4
Any traumatic event†	92.2	87.1	6.2	13.0

*Data are from Kessler et al.[4]

†Data are from Breslau et al.[16,17]

about and emotional responses to the event will become less distressing.[22]

BIOLOGIC ASPECTS

The elucidation of the biologic changes related to PTSD has shed light on the question of why some people recover from traumatic events whereas others do not. Patients with chronic PTSD have increased circulating levels of norepinephrine[23] and increased reactivity of α_2-adrenergic receptors.[24] These alterations, in tandem with the finding that thyroid hormone levels are increased in patients with PTSD,[25] may help explain some of the somatic symptoms of the disorder. Recent neuroanatomical studies have identified alterations in two major brain structures — the amygdala and hippocampus — in patients with PTSD. Positron-emission tomography and functional magnetic resonance imaging have shown that the reactivity of the amygdala and anterior paralimbic region to trauma-related stimuli is increased[26,27] and the reactivity of the anterior cingulate and orbitofrontal areas is decreased.[28] These areas of the brain are involved in fear responses. Differences in hippocampal function[29] and in memory processes presumed to be dependent on the hippocampus have been found, suggesting a neuroanatomical substrate for the intrusive recollections and other cognitive problems[30] that characterize PTSD.

The biologic alterations observed in PTSD do not uniformly resemble those associated with other types

of stress (Fig. 1). For example, cortisol levels have been lower than normal in some studies of patients with PTSD, even decades after a traumatic event.[32,33] Paradoxically, however, levels of corticotropin-releasing factor in cerebrospinal fluid appear to be increased.[34] This pattern differs from the patterns associated with brief and sustained periods of stress and with major depression, which are typically associated with increased levels of both cortisol and corticotropin-releasing factor (Fig. 1). In PTSD the sensitivity of the negative-feedback system of the hypo-thalamic–pituitary–adrenal axis is increased, as reflected by the exaggerated suppression of cortisol in response to dexamethasone administration[35,36] and the increased sensitivity of lymphocyte glucocorticoid receptors.[37] These findings contrast with the well-demonstrated phenomenon of reduced cortisol suppression in response to dexamethasone[38] and findings of reductions in glucocorticoid-receptor sensitivity in major depressive disorder.[39]

The psychological and biologic data support the hypothesis that the development of PTSD is facili-
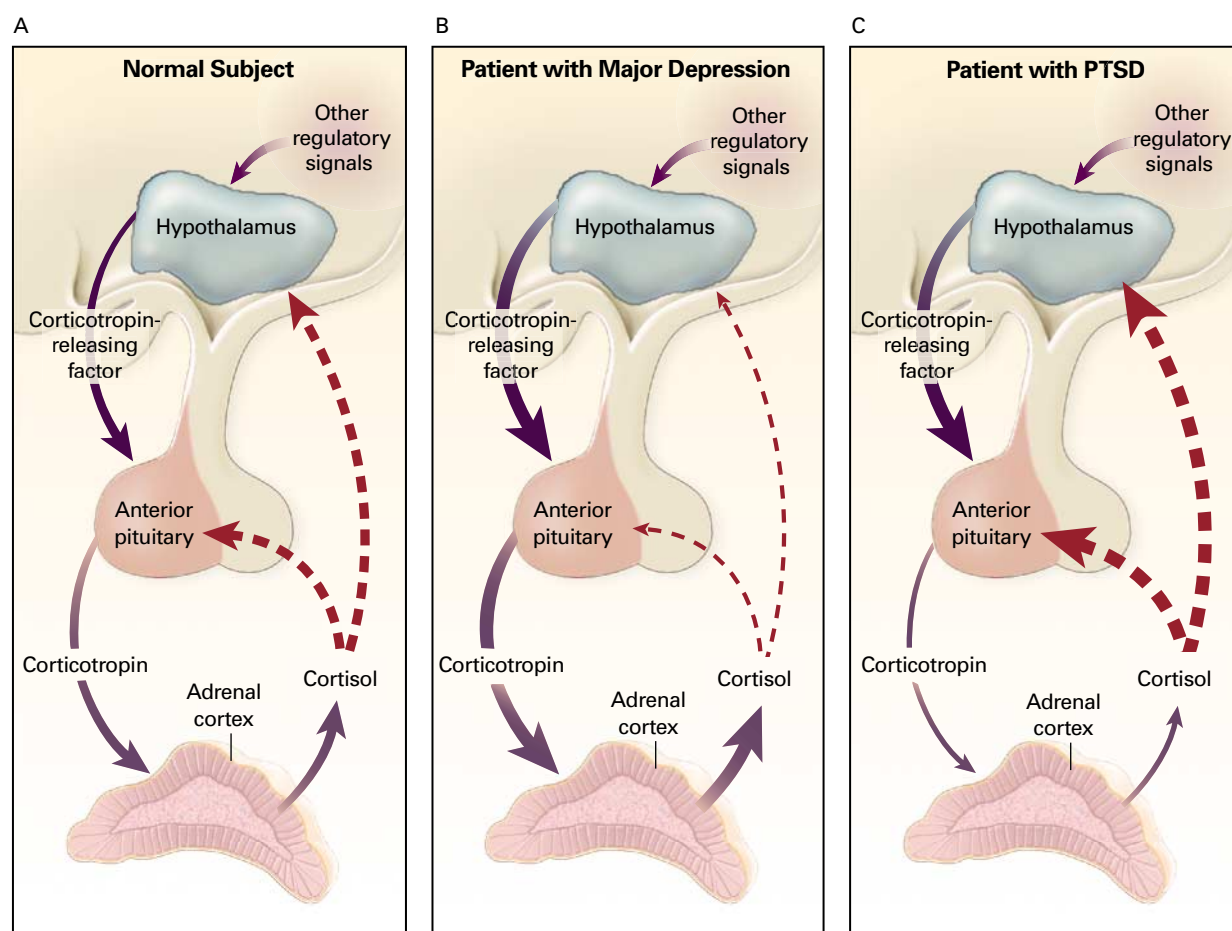

Figure 1. Response to Stress in a Normal Subject (Panel A), a Patient with Major Depressive Disorder (Panel B), and a Patient with PTSD (Panel C).

In normal subjects (Panel A) and in patients with major depression (Panel B), brief or sustained periods of stress are typically associated with increased levels of both cortisol and corticotropin-releasing factor. In each panel the thickness of the interconnecting arrows denotes the magnitude of the biologic response. Corticotropin-releasing factor stimulates the production of corticotropin, which in turn stimulates the production of cortisol. Cortisol inhibits the release of corticotropin from the pituitary and the release of corticotropin-releasing factor from the hypothalamus. It is also responsible for the containment of many stress-activated biologic reactions. In patients with PTSD (Panel C), levels of cortisol are low and levels of corticotropin-releasing factor are high. In addition, the sensitivity of the negative-feedback system of the hypothalamic–pituitary–adrenal axis is increased in patients with PTSD rather than decreased, as often occurs in patients with major depression.[31]

tated by a failure to contain the biologic stress response at the time of the trauma, resulting in a cascade of alterations that lead to intrusive recollections of the event, avoidance of reminders of the event, and symptoms of hyperarousal. This failure may represent an alternative trajectory to the normal process of adaptation and recovery after a traumatic event. Prospective studies have shown that patients in whom PTSD[40,41] or symptoms of PTSD[31] develop have attenuated increases in cortisol levels in the immediate aftermath of a traumatic event, which may be related to prior exposure to a traumatic event or other risk factors.[42] They also have higher heart rates in the emergency room and one week later than persons in whom PTSD does not develop.[43] These findings suggest that patients with PTSD have a greater degree of activation of the sympathetic nervous system.

Decreased cortisol levels at the time of a traumatic event could prolong the availability of norepinephrine to synapses in both the periphery and the brain,[44,45] which in turn might affect the consolidation of the memory of the incident. Adrenergic activation in the face of low cortisol levels facilitates learning in animals.[46] If this process also occurs in traumatized persons, the memory of the event not only would be strongly encoded, but also would be associated with strong, subjective feelings of distress. This feeling would most likely facilitate the development of altered perceptions and thoughts in the aftermath of the event, particularly those associated with the perception of danger or ability to cope with a threat. These altered perceptions would further delay recovery by leading to a failure to quell fearful responses, which would further strengthen maladaptive cognitive responses to trauma and fear, perpetuate the symptoms of PTSD, and trigger a series of secondary biologic changes. Indeed, the exaggerated startle reaction is not usually seen in patients with PTSD until one month after the event, reflecting the progression of at least some biologic aspects.[47] Further research may enable us to identify those at greatest risk for PTSD on the basis of combined biologic and psychological characteristics.

TREATMENT

Counseling

An important component of treating traumatized persons is the provision of education, a feeling of safety, and support, which can be done by primary care providers. Education helps patients understand the nature of their condition and the process of recovery. Patients should be made to understand that their symptoms represent a psychobiologic reaction to overwhelming stress rather than a character flaw or a sign of weakness. Clinicians can provide a noncritical ear and emphasize that patients are not alone.

Such intervention can help build a therapeutic alliance and help patients see the need for therapy. Traumatized persons are notoriously reluctant to seek help for their symptoms, particularly from mental health practitioners. This reluctance may result from a lack of awareness on the part of patients that their symptoms are linked to a traumatic event or from concern that they will be seen as "damaged" or emotionally unstable. Many survivors fear that there may be job-related consequences of the disclosure or treatment of a traumatic event; for example, a police officer may lose the right to carry a weapon, and a politician may be viewed as insufficiently stable. Supportive counseling by primary care providers can help address many of these barriers to further care.

Alleviating the symptoms of PTSD usually requires the use of specialized techniques that help patients confront fears and emotional responses to the traumatic event in a more structured format, without becoming overwhelmed. Treatment involves reducing the level of distress associated with memories of the event and quelling the resultant physiological reactions. Research has demonstrated the effectiveness of such techniques as exposure therapy (helping patients confront painful memories and feelings), cognitive therapy (helping patients process their thoughts and beliefs), anxiety management, and interpersonal therapies (helping patients understand the ways in which the traumatic event continues to affect relationships and other aspects of their lives). Group therapy may also be helpful in reducing isolation and stigma.[48]

Medications

Medications can also benefit traumatized persons and can be prescribed by a primary care physician. Results of randomized clinical trials demonstrate that medications such as selective serotonin-reuptake inhibitors,[49,50] tricyclic antidepressants,[51] and monoamine oxidase inhibitors[52] alleviate the symptoms of PTSD and are associated with improvements in overall functioning. Serotonin-reuptake inhibitors are a first-line medication because they are safer and better tolerated than other types of psychotropic medications. Sertraline (Zoloft) and, more recently, paroxetine (Paxil) are the only agents that have been approved by the Food and Drug Administration for the treatment of PTSD. The Expert Consensus Guidelines on the treatment of PTSD[53] recommend that if there is no response to an eight-week trial of a serotonin-reuptake inhibitor, treatment should be switched to nefazone (Serzone) or venlafaxine (Effexor); if there is a partial response, a mood stabilizer such as divalproex (Depakote) should be added. These recommendations are based on the results of a survey of prominent physicians with clinical experience in PTSD, but

such algorithms are not empirically based, since there have been no double-blind, placebo-controlled studies of either nefazodone or venlafaxine.

Benzodiazepines should be avoided or used very judiciously in patients with PTSD. Randomized, double-blind trials found that alprazolam (Xanax) was not significantly better than placebo in patients with chronic PTSD[54] and that neither alprazolam nor clonazepam was better than placebo immediately after a traumatic event.[55]

Further research is needed to determine whether some groups of patients with PTSD have a preferential response to one type of treatment. The decision to use psychotherapy, pharmacotherapy, or a combination of the two depends on the overall clinical picture. Pharmacologic agents targeting the specific constellation of biologic alterations in PTSD have not yet been developed. Rather, pharmacotherapy for PTSD has involved administering agents with established efficacy in other mood and anxiety disorders.

Referral

Primary care physicians may choose to refer patients for specialized treatment if initial interventions have not been successful or patients have side effects from medication. Some traumatized persons may also have suicidal thoughts and behavior, other serious psychiatric problems, substance abuse, and ongoing stress in addition to that relating to the event that precipitated PTSD. As noted above, another complicating factor in the referral process is the reluctance of patients to be treated by mental health professionals. The establishment of mental health treatment programs in primary care settings represents an important future goal.

SUMMARY

Although most people will gradually recover from the psychological effects of a traumatic event, PTSD will develop in a substantial proportion. PTSD appears to represent a failure to recover from a nearly universal set of emotions and reactions and is typically manifested as distressing memories or nightmares related to the traumatic event, attempts to avoid reminders of the trauma, and a heightened state of physiological arousal. Studies of the biologic mechanisms of PTSD have delineated circumscribed alterations in brain regions, such as the amygdala and hippocampus, that are associated with fear and memory, as well as changes in hormonal, neurochemical, and physiological systems involved in coordinating the body's response to stress. The treatment of PTSD involves educating the patient about the nature of the disorder, providing a safe and supportive environment for discussing traumatic events and their impact, and relieving the distress associated with memories and re-

minders of the event. A variety of approaches, such as exposure therapy, cognitive therapy, and pharmacotherapy, have been found to be effective in the treatment of PTSD.

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