Understanding the Neurobiology of Fear Conditioning and Emergence of Posttraumatic Stress Disorder Psychobiology

Commentary on Blanchard et al.

Joseph A. Boscarino, PhD, MPH,†‡ and Charles R. Figley, PhD§*

Abstract: In this article, we discuss the historical evolution of posttraumatic stress disorder (PTSD) after the Vietnam War, with a focus on an article by Blanchard, Kolb, Prins, Gates, and McCoy (*J Nerv Ment Dis* 179:371–373, 1991) published in this Journal in 1991 entitled Changes in Plasma Norepinephrine to Combat-Related Stimuli Among Vietnam Veterans With Posttraumatic Stress Disorder. In this commentary, we discuss the significance of this brief article and the developments in the PTSD field before, during, and after the Blanchard publication. Within this context, we discuss the eventual recognition in both the clinical and scientific fields that PTSD had a major neurobiological foundation. Finally, we examine the key implication of these discoveries from an epidemiological, a clinical, and a public health perspective.

Key Words: Posttraumatic stress disorder, Vietnam War, veterans, epidemiology, *Diagnostic and Statistical Manual of Mental Disorders*, psychobiology.

(*J Nerv Ment Dis* 2012;200: 740–744)

During the long publication history of *The Journal of Nervous Mental Disease*, 88 articles that have focused on the Vietnam War have been published, including studies of Vietnam veterans and war refugees. The first one published in this Journal on Vietnam veterans was on the prevalence of depressive disorder among US Army returnees by Helzer et al. in September 1976. The most recent one published was authored by Benedek in August 2011. The Benedek article was a tribute to the late Dr Eugene Brody's tenure as editor-in-chief of this Journal and was titled Posttraumatic Stress Disorder from Vietnam to Today: The Evolution of Understanding During Eugene Brody's Tenure at *The Journal of Nervous and Mental Disease.* Because both of us were active on the professional scene in the 1970s when the posttraumatic stress disorder (PTSD) emerged as a diagnostic construct (J. A. B. at Yale and C. R. F. at Purdue) and both of us are Vietnam veterans with an interest in PTSD psychobiology, we comment on a brief article by Blanchard et al. published in this Journal in 1991. This article was entitled Changes in Plasma Norepinephrine to Combat-Related Stimuli Among Vietnam Veterans With Posttraumatic Stress Disorder.

At the time the Blanchard et al. article was published in 1991, about the midpoint of the end of the Vietnam War and where we are today, there were 36 articles published in this Journal in that decade related to the Vietnam War. Although most of these articles in the 1990s focused on descriptive and clinical studies of PTSD among veterans, two focused on the biological aspects of PTSD, including the Blanchard et al. article. The Blanchard et al. article was published a little more than 10 years after the PTSD diagnosis was promulgated with the publication of the *DSM-III* (American Psychiatric Association, 1980). Around this time, the Department of Veterans Affairs had established a number of PTSD research centers at major academic centers around the country, and, as we discuss below, the results of several large-scale Vietnam veteran studies were made publicly available.

The research by Blanchard et al. (1991) studied plasma norepinephrine samples obtained before and after exposure to auditory stimuli reminiscent of combat. These investigators contrasted responses to these stimuli between two groups of male Vietnam veterans with combat experience:

*Center for Health Research, Geisinger Clinic, Danville, PA; †Departments of Medicine and Pediatrics, Mount Sinai School of Medicine, New York, NY; ‡Department of Psychiatry, Temple University School of Medicine, Philadelphia, PA; and §Disaster Mental Health, School of Social Work, and Traumatology Institute, Tulane University, New Orleans, LA.

Send reprint requests to Joseph A. Boscarino, PhD, MPH, Senior Investigator-II, Center for Health Research, Geisinger Clinic, 100 N. Academy Ave, Danville, PA 17822-4400. E-mail: jaboscarino@geisinger.edu.

ISSN: 0022-3018/12/20009-0740

DOI: 10.1097/NMD.0b013e318266b5ea

one group, with PTSD, and one group, with no mental disorders. Their results showed a significant 30% rise in plasma norepinephrine for the PTSD group, with no change in the comparison group.

Although the Blanchard et al. study was modest by today's standards ($N = 21$), it represented one of about a dozen studies published in the late 1980s and early 1990s that helped change how we thought about PTSD. Specifically, it suggested that PTSD was more than a psychological state—it had a biological foundation. Below, we review developments in the PTSD field before, during, and after the publication of the Blanchard et al. article in 1991 and discuss how we got to where we are today in the field.

EMERGENCE OF PTSD AS A DIAGNOSTIC CONSTRUCT

Although the involvement of the United States in the Vietnam War officially ended in 1975, the impact of that conflict affected society in many ways (Boscarino, 2007). The Vietnam veterans returned home from a conflict that was controversial and unpopular. It became clear to health care professionals during the war and shortly afterward that many returning veterans were experiencing postwar adjustment problems (Boscarino, 2007). During the early postwar period, the work of one of us stood out as a classic in stress research because it documented well the emotional and psychological trauma many veterans began to manifest by the war's end (Figley, 1978b). On the basis of this work, *Stress Disorders Among Vietnam Veterans: Theory, Research and Treatment,* and that of others, health care researchers and medical professionals in the late 1970s formulated specific etiological models of the pathogenesis of mental disorders among Vietnam veterans (Boscarino, 2007). These efforts eventually culminated in the inclusion of PTSD in the *DSM-III*. The symptoms of this disorder came to include increased arousal after an event, re-experiencing of an event, and avoidance of stimuli associated with an event, all of which begin after a traumatic event exposure. Once the diagnosis of PTSD emerged in the early 1980s, more accurate assessments of the scope and nature of traumatic stress injuries (and related disorders) among Vietnam veterans and others were possible. These studies of Vietnam veterans, as we suggest below, have led to research developments and have accelerated the accumulation of knowledge related to the psychobiology of PTSD.

Although clinical evidence of the adverse psychological effects of combat exposure go back as far as the US Civil War, the etiology of these syndromes were neither clearly understood nor well defined (Boscarino, 2007). However, after reviewing war trauma studies and other findings related to natural disaster and concentration camp survivors, in 1975, Dohrenwend concluded that there was clear and compelling evidence that many individuals develop functional psychiatric disorders after extreme stressor exposures that were not present before these exposures. In 1973, two years before Dohrenwend's article was published, Robert Jay Lifton's classic book, *Home from the War: Vietnam Veterans—Neither Victims nor Executors*, was published (Lifton, 1973). Thus, within the span of about 5 years, several major works related to the mental health status of Vietnam veterans and others exposed to psychological trauma were published, including the *DSM-III* manual (American Psychiatric Association, 1980). These publications created a major paradigm shift in American psychiatry, which would eventually affect the practice of psychiatry worldwide (Boscarino, 2007).

INITIAL VIETNAM VETERAN STUDIES

Initial studies of the postwar experiences of Vietnam veterans provided the first clinical and scientific evidence linking combat exposures in Vietnam to postservice adjustment difficulties also observed among previous veterans (Figley, 1978a, 1978b; Figley and Southerly, 1980; Figley and Sprenkle, 1978; Stretch and Figley, 1984). One difficulty was that these early studies were limited because of selection biases associated with using nonrepresentative samples. Another problem was the use of nonstandardized mental health measures or the use of measures that assessed only mental health symptoms. Thus, although clinicians had observed that individuals exposed to combat exhibited certain syndromes, linking these symptoms to past combat exposure was problematic because of existing methodological shortcomings at the time (Boscarino, 2007).

When *DSM-III* was being written in the 1970s, however, clinicians and others involved with Vietnam veterans were successful in eventually incorporating these syndromes into *DSM-III* under the diagnostic nomenclature defining PTSD, originally labeled the "post-Vietnam syndrome" (Boscarino, 2007). Once PTSD was included in *DSM-III*, undertaking large-scale, systematic mental health studies of Vietnam veterans were feasible and had other research and clinical benefits. During this early research period, the "Legacy Study," (Frey-Wouters and Laufer, 1986) which, although not based on a true probability study, stood out as a landmark investigation. This is because it included more than 1000 subjects (both Vietnam veterans and civilians) and used several standard symptom scales common in the 1960s and 1970s. At the time, this study provided the best assessment of the mental health status of Vietnam veterans and served as a bench mark for future studies (Boscarino, 2007). However, because the Legacy Study was considered primarily a "convenience" sample, questions about bias remained.

LATER VIETNAM VETERAN STUDIES

As part of Public Law 98-160, the US Congress in 1983 mandated that research on Vietnam veterans be undertaken to determine "the prevalence and incidence of post-traumatic stress disorder and other psychological problems in readjusting to civilian life." In addition to Public Law 98-160, the US Congress passed other public laws mandating studies of the "health effects" of Vietnam service. As a consequence of these new laws, several well-designed cohort studies of Vietnam veterans were undertaken during the late 1980s (Boscarino, 2007). These studies avoided many of the shortcomings of previous research, chiefly because of the advancements in study sampling and measurement that evolved from earlier research. One of these measurement advances included the availability of the Diagnostic Interview Schedule (DIS), which, for the first time, permitted the gathering of *DSM-III* psychiatric diagnoses by means of population surveys, something previously not possible (Robins et al., 1981). This later research confirmed that Vietnam combat veterans had higher rates of postwar adjustment difficulties, mental health disorders, and medical morbidity and a higher postwar mortality than did noncombat veterans or comparable nonveterans (Boscarino, 2007). Importantly, these studies indicated that the postwar adjustment difficulties and the health problems experienced by these veterans were often caused by combat exposures in Vietnam, not by the selection biases or the measurement inadequacies that had affected earlier studies (Boscarino, 1995).

Among these newer generation of studies was the National Vietnam Veterans Readjustment Study (NVVRS). This national study, which involved a large random sample of Vietnam "theater" and nontheater veterans (in addition to civilian nonveterans), was considered one of the most comprehensive psychosocial assessments at the time it was conducted in the late 1980s. The NVVRS findings were a wake-up call for the American mental health community. Among other things, the NVVRS suggested that 15% of male Vietnam veterans (9% of female veterans) were current PTSD patients and that 31% of male veterans (27% of female veterans) had PTSD in their lifetimes (Kulka et al., 1990). The NVVRS further confirmed that the PTSD-positive veterans often had disrupted lives in almost every domain, including in employment and in family relationships.

As significant as the psychosocial consequences of the war were for the Vietnam veterans, their postwar experiences went beyond only psychosocial outcomes. For example, the Vietnam Experience Study (VES), another national landmark study conducted in the late 1980s, revealed that Vietnam veterans had higher rates of postwar mortality in the first 5 years after discharge, primarily because of suicides, homicides, drug overdoses, and motor vehicle accidents (Centers for Disease Control, 1987). Furthermore, the VES findings related to the postwar morbidity experienced by these veterans confirmed that Vietnam theater veterans as a group had higher rates of health care use and reported themselves to be in poorer physical health in comparison with veterans without Vietnam service (Center for Disease Control, 1988a, 1988b). In addition, when the postwar health status of Vietnam veterans was examined by whether the veteran had PTSD, PTSD-positive veterans had substantially higher postwar rates (*i.e.*, 50%–150% higher prevalence) of many major chronic diseases, including circulatory, nervous system, digestive, musculoskeletal, and respiratory diseases, even controlling for the major risk factors for these conditions (Boscarino, 1997).

Another compelling study that provided additional evidence linking PTSD to adverse health outcomes was a VES study that examined the causes of death among 15,288 male US Army veterans 30 years after military service (Boscarino, 2006). These findings indicated that postwar mortality for all-cause, cardiovascular, external causes (including motor vehicle accidents, accidental poisonings, suicides, homicides, and injuries), and cancer was associated with PTSD among Vietnam theater veterans. For Vietnam "era" veterans with no Vietnam service, PTSD was associated with all-cause mortality. This study suggested, among other things, that Vietnam veterans with PTSD were at about twice the risk of postwar death from multiple causes 30 years after military service than were veterans without PTSD (Boscarino, 2006).

What can be concluded from this research is that, although combat exposure and service in Vietnam had a negative impact on the veteran's health status, it was whether the veteran developed PTSD from these exposures that had the greatest adverse impact on health status in the long-term.

EMERGENCE OF PTSD PSYCHOBIOLOGY

As suggested in the Blanchard et al. study (Blanchard et al., 1991), there are reasons to expect alterations in neuroendocrine system functioning in chronic PTSD patients because changes in the hypothalamic-pituitary-adrenal system (HPA) and in the sympathetic arm of the autonomic nervous system had been observed after severe stressor exposures (Tsigos and Chrousos, 2002; Yehuda and LeDoux, 2007). Evidence suggests that the adverse physiological arousal often observed during recollection of traumatic events is associated with alterations in neuroendocrine functions linked to sympathetic-adrenomedullary and hypothalamic-pituitary-adrenocortical stress axis activation (Tsigos and Chrousos, 2002; Yehuda and LeDoux, 2007). In the case of PTSD, it is thought that these neuroendocrine alterations reflect the consequences of a state of physiopsychological "conditioning" that occurs after stressor exposures. Furthermore, although this conditioning response is initiated in the CNS, it is subsequently carried out by multiple endocrine mechanisms that have wide-ranging effects on the body and the nervous system. One large-scale study, also based on the VES and involving thousands of veterans, found not only that Vietnam theater veterans with PTSD had lower cortisol levels but also that past combat exposure levels were associated with plasma cortisol concentrations in an inverse "dose-response" relationship, suggesting neuroendocrine system dysregulation (Boscarino, 1996).

The research with Vietnam combat veterans suggests, in effect, that PTSD-positive veterans tend to have lower cortisol levels. Paradoxically, however, they also tend to have higher catecholamine concentrations, together with heightened responses of the stress system to traumatic memories and other stimuli associated with the original trauma (Blanchard et al., 1991; Yehuda and DeDoux, 2007). Thus, the physiological findings for PTSD-positive Vietnam veterans suggest that past traumatic stress exposures have resulted in neuroendocrine alterations that may make veterans potentially susceptible to a host of inflammatory diseases, although the specific biological pathways for these associations are uncertain at this time (Boscarino, 2012). Consistent with these clinical findings, it has recently been reported that PTSD was associated not only with early-onset ischemic heart disease (Boscarino, 2008) but also with autoimmune diseases, including psoriasis and rheumatoid arthritis (Boscarino, 2004; Boscarino et al., 2010).

In summary, PTSD among Vietnam veterans has been associated with significant alterations in their neurophysiology and with an increased risk of many chronic diseases. However, the specific causal pathways for these diseases, and whether these can be prevented or not, are uncertain at this time (Boscarino, 2011, 2012).

TRAUMATIC STRESS STUDIES WITH OTHER POPULATIONS

After the first Persian Gulf War (PGW) in 1991, large scale epidemiological studies were used to evaluate the health impact of this conflict for military personnel who served in that theater (Hallman et al., 2003). This PGW research has established a link between service in the PGW and mental illness, postservice injury, chronic fatigue syndrome, and other multisymptom conditions. Although the reasons for these associations are still being investigated, the results from this research are being used to inform a new generation of veterans, the men and women deployed to the Afghanistan and Iraq theaters of war after the September 11, 2001, attacks (Hoge et al., 2006). For these recent conflicts, military personnel were being assessed both before deployment and after return, something rarely done in the past but often desired after combat exposures had occurred (Boscarino, 2007). These newer prospective cohort studies offer both researchers and clinicians alike much more robust data with which to assess the impact of war zone stressor exposures.

Finally, after the September 11 attacks in New York City (NYC) in 2001, investigative teams funded by the National Institutes of Health to assess this event, including our team, used prospective cohort studies together with *DSM* measurements that were originally developed for Vietnam veterans and other trauma populations (Boscarino and Adams, 2009; Boscarino et al., 2006, 2011, 2012b, 2012c). In short, the field of "psychiatric epidemiology" has emerged as a subspecialty within the field of biomedical research (Tsuang et al., 2011), informed, in part, by the original work with Vietnam veterans over the previous decades and the development of the *DSM-III* and the DIS (Boscarino, 2007). This epidemiological research is now being used to study the impact of traumatic stress exposures among a broad range of populations.

To understand the risks of PTSD genetically, we recently assessed the cumulative burden of polymorphisms located within four genetic loci previously associated with PTSD among patients at risk of PTSD (Boscarino et al., 2012a). For this, we completed diagnostic interviews and collected DNA samples among 412 randomly selected patients to determine whether *FKBP5*, *COMT*, *CHRNA5*, and *CRHR1* single nucleotide polymorphisms (SNPs) were cumulatively associated with the risk of PTSD. In bivariate analyses, we found that a count of specific PTSD risk alleles located within the *FKBP5, COMT, CHRNA5,* and *CRHR1* genetic loci (allele range, 0–6; mean count [SD] = 2.92 [1.36]) was associated with lifetime (t[409] = 3.430, p = 0.001) and early-onset PTSD (t[409] = 4.239, p = 0.000028). In logistic regression, controlling for demographic factors, personality traits, and trauma exposures, risk allele count remained associated with both lifetime

(odds ratio [OR], 1.49; $p = 0.00158$) and early-onset PTSD (OR, 2.37; $p = 0.000093$). Interaction effects were also detected, whereby individuals with higher risk allele counts and higher trauma exposures had an increased risk of lifetime PTSD (allele count × high trauma, $p = 0.026$) and early-onset PTSD (allele count × high trauma, $p = 0.016$). Those with no or few risk alleles seemed resilient to PTSD, regardless of exposure history.

In summary, we found that a cumulative risk allele count involving SNPs located within the *FKBP5, COMT, CHRNA5,* and *CRHR1* genes, respectively, was associated with PTSD. Furthermore, level of trauma exposure interacted with risk allele count, such that PTSD was increased in those with higher risk allele counts and higher trauma exposures (Boscarino et al., 2012a).

The *FKBP5* polymorphisms are known to regulate the cortisol-binding affinity and nuclear translocation of the glucocorticoid receptor. The *COMT* polymorphisms have been found to affect fear extinction and are thought to play a role in the etiology of anxiety disorders. The *CHRNA5* gene has been associated with smoking and nicotine dependence. PTSD is known to be associated with cigarette smoking. This locus has recently been associated with PTSD and is likely involved in mammalian fear circuitry (Boscarino et al., 2012a). Research suggests that the *CRHR1* gene regulates HPA axis function in conjunction with exposure to early life trauma. It has been suggested that corticotrophin-releasing hormone is associated with alterations in memory formation in PTSD and that this hormone influences hippocampus regulation of the HPA axis. Because the four SNPs studied encompass fear circuitry, addiction biology, and other key neurobiological circuits, we think these genetic findings may have implications for neuropsychiatric research and treatment related to PTSD (Boscarino, 2012; Boscarino et al., 2012a).

IMPLICATIONS FOR RESEARCH AND TREATMENT

Synthesizing the scientific findings related to the postwar experience of Vietnam veterans during the past 3 decades suggests that, generally, neurobiological models are required to understand the impact of this experience and that there is the need for multifactorial PTSD models, in particular. Such models are consistent with the observation that both pharmacotherapy and cognitive behavioral psychotherapy are reported effective in treating PTSD (Boscarino, 2007). In the case of pharmacotherapy, the pathophysiology of PTSD seems to involve the cholinergic, noradrenergic, and other biological pathways involving the amygdala and mammalian fear circuitry systems (Boscarino et al., 2012a). Consequentially, drugs known to potentiate or block these biological mechanisms have been found to have a positive effect (Yehuda and LeDoux, 2007).

In the case of cognitive behavioral therapy, this approach has been effective in reducing PTSD-related symptoms and can be traced back to an innovation introduced by Wolpe (1958). Desensitization and elimination of the link between stressful stimuli and unwanted cognitive states can be achieved by increasing self control of aversive arousals, by enhancing anxiety management, and by other known behavioral-psychological techniques (Boscarino, 2007). Although the underlying interventional mechanisms differ for pharmacological versus cognitive behavioral therapy (*e.g.*, pharmacokinetic versus psychological), the outcomes are similar. That is, the psychopathology and the underlying pathophysiology would be reduced and fewer adverse patient symptoms would be manifested, hence, lowering the risk of other adverse outcomes (Boscarino, 2007).

Thus, one would expect that because trauma-related symptoms were reduced through pharmacotherapy or psychotherapy, the risk of adverse health outcomes would also decrease. Recent research has partially confirmed this hypothesis in NYC after the September 11 attacks. For example, we reported that NYC adults that received emergency crisis counseling at work shortly after the attacks had not only better mental health outcomes but also better outcomes in binge drinking and alcohol dependence, lowering the possibility of adverse health outcomes in the future (Boscarino et al., 2006, 2011).

CONCLUSION

We suggest that just as what has been true with other areas of medicine—orthopedic surgery, plastic surgery, and emergency medicine—developments in military medicine and in veterans' health care, in particular, often are translated into medical advances for nonmilitary populations. Although the findings discussed chiefly involved veterans' exposure to combat, these results are applicable to other trauma-exposed populations. Thus, despite the medical and the mental health suffering caused by the Vietnam War—or perhaps because of it—the postwar experiences of the Vietnam veterans have resulted in significant scientific and professional practice advances in our knowledge of the nature and the consequences of human stress exposures. These advances will likely lead to future medical advances not currently imagined. We think that the Blanchard et al. study represented the commencement of our understanding of the neurobiology of PTSD and fear conditioning, thanks, in part, to *The Journal of Nervous and Mental Disease* and to Dr Brody's tenure as editor-in-chief.

DISCLOSURES

This research was supported, in part, by grants from the National Institute of Mental Health (Grant No. R21-MH-086317 Boscarino PI).

The authors declare no conflict of interest.

REFERENCES

American Psychiatric Association (1980) *Diagnostic and statistical manual of mental disorders* (3rd ed). Washington, DC: American Psychiatric Association.

Benedek DM (2011) Posttraumatic stress disorder from Vietnam to today: The evolution of understanding during Eugene Brody's tenure at the Journal of Nervous and Mental Disease. *J Nerv Ment Dis*. 199:544–552.

Blanchard EB, Kolb LC, Prins A, Gates S, McCoy GC (1991) Changes in plasma norepinephrine to combat-related stimuli among Vietnam veterans with posttraumatic stress disorder. *J Nerv Ment Dis*. 179:371–373.

Boscarino JA (1995) Post-traumatic stress and associated disorders among Vietnam veterans: The significance of combat exposure and social support. *J Trauma Stress*. 8:317–336.

Boscarino JA (1996) Posttraumatic stress disorder, exposure to combat, and lower plasma cortisol among Vietnam veterans: Findings and clinical implications. *J Consult Clin Psychol*. 64:191–201.

Boscarino JA (1997) Diseases among men 20 years after exposure to severe stress: Implications for clinical research and medical care. *Psychosom Med*. 59: 605–614.

Boscarino JA (2004) Posttraumatic stress disorder and physical illness: Results from clinical and epidemiologic studies. *Ann N Y Acad Sci*. 1032:141–153.

Boscarino JA (2006) Posttraumatic stress disorder and mortality among U.S. Army veterans 30 years after military service. *Ann Epidemiol*. 16:248–256.

Boscarino JA (2007) Vietnam veterans, postwar experiences and health outcomes. In Fink G (Ed), *Encyclopedia of stress* (2nd ed, pp 830–838). New York: Academic Press.

Boscarino JA (2008) A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: Implications for surveillance and prevention. *Psychosom Med*. 70:668–676.

Boscarino JA (2011) PTSD and cardiovascular disease link: Time to identify specific pathways and interventions. *Am J Cardiol*. 108:1052–1053.

Boscarino JA (2012) PTSD is a risk factor for cardiovascular disease: Time for increased screening and clinical intervention. *Prev Med*. 54:363–364.

Boscarino JA, Adams RE (2009) PTSD onset and course following the World Trade Center disaster: Findings and implications for future research. *Soc Psychiatry Psychiatr Epidemiol*. 44:887–898.

Boscarino JA, Adams RE, Figley CR (2011) Mental health service use after the World Trade Center disaster: Utilization trends and comparative effectiveness. *J Nerv Ment Dis*. 199:91–99.

Boscarino JA, Adams RE, Foa EB, Landrigan PJ (2006) A propensity score analysis of brief worksite crisis interventions after the World Trade Center disaster: Implications for intervention and research. *Med Care*. 44:454–462.

Boscarino JA, Elich PM, Hoffman SN, Zhang X (2012a) Higher *FKBP5*, *COMT*, *CHRNA5* and *CRHR1* allele burdens are associated with PTSD and interact with trauma exposure: Implications for neuropsychiatric research. *Neuropsychiatr Dis Treat*. 8:131–139.

Boscarino JA, Forsberg CW, Goldberg J (2010) A twin study of the association between PTSD symptoms and rheumatoid arthritis. *Psychosom Med*. 72:481–486.

Boscarino JA, Kirchner HL, Hoffman SN, Sartorius J (2012b) Use of the New York PTSD Risk Score to predict PTSD: Current and future research efforts. *Gen Hosp Psychiatry*. 34:317–319.

Boscarino JA, Kirchner HL, Hoffman SN, Sartorius J, Adams RE, Figley CR (2012c) Predicting future PTSD using a modified New York Risk Score: Implications for patient screening and management. *Minerva Psichiatr*. 53:47–59.

Centers for Disease Control (1987) Postservice mortality among Vietnam veterans. The Centers for Disease Control Vietnam Experience Study. *JAMA*. 257: 790–795.

Centers for Disease Control (1988a) Health status of Vietnam veterans. I. Psychosocial characteristics. The Centers for Disease Control Vietnam Experience Study. *JAMA*. 259:2701–2707.

Centers for Disease Control (1988b) Health status of Vietnam veterans. II. Physical Health. The Centers for Disease Control Vietnam Experience Study. *JAMA*. 259:2708–2714.

Dohrenwend BP (1975) Sociocultural and social-psychological factors in the genesis of mental disorders. *J Health Soc Behav*. 16:365–362.

Figley CR (1978a) Symptoms of delayed combat stress among a college sample of Vietnam veterans. *Mil Med*. 143:107–110.

Figley CR (Ed) (1978b) *Stress disorders among Vietnam veterans: Theory, research and treatment*. New York: Brunner/Mazel.

Figley CR, Southerly W (1980) Psychosocial adjustment of recently returned veterans. In Figley CR, Leventman S (Eds) *Strangers at home: Vietnam veterans since the war* (pp. 167–180). New York, NY: Praeger.

Figley CR, Sprenkle DH (1978) Delayed stress response syndrome: Family therapy implications. *J Marriage Fam Couns*. 4:53–60.

Frey-Wouters E, Laufer RS (1986) *Legacy of a war: The American soldier in Vietnam*. Armonk, NY: Sharpe Pub, Inc.

Hallman WK, Kipen HM, Diefenbach M, Boyd K, Kang H, Leventhal H, Wartenberg D (2003) Symptom patterns among Gulf War registry veterans. *Am J Public Health*. 93:624–630.

Helzer JE, Robins LN, Davis DH (1976) Depressive disorders in Vietnam returnees. *J Nerv Ment Dis*. 163:177–185.

Hoge CW, Auchterlonie JL, Milliken CS (2006) Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. *JAMA*. 295:1023–1032.

Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, Weiss DS (1990) *Trauma and the Vietnam War generation: Report of findings from the National Vietnam Readjustment Study*. New York: Brunner/Mazel.

Lifton RJ (1973) *Home from the war: Vietnam veterans—Neither victims nor executioners*. New York: Simon and Schuster.

Robins LN, Helzer JE, Croughan J, Ratcliff KS (1981) National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. *Arch Gen Psychiatry*. 38:381–389.

Stretch RH, Figley CR (1984) Combat and the Vietnam veteran: Assessment of psychosocial adjustment. *Armed Forces Soc*. 10:311–319.

Tsigos C, Chrousos GP (2002) Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *J Psychosom Res*. 53:865–871.

Tsuang MT, Tohen M, Jones P (Eds) (2011) *Textbook of psychiatric epidemiology* (3rd ed). New York: John Wiley and Sons.

Wolpe J (1958) *Psychotherapy by reciprocal inhibition*. Stanford, CA: Stanford University Press.

Yehuda R, LeDoux J (2007) Response variation following trauma: A translational neuroscience approach to understand PTSD. *Neuron*. 56:19–32.