Posttraumatic Stress Disorder, Exposure to Combat, and Lower Plasma Cortisol Among Vietnam Veterans: Findings and Clinical Implications

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Several clinical studies suggest that individuals with posttraumatic stress disorder (PTSD) experience neuroendocrine system alterations, resulting in significantly lower plasma cortisol. To test this hypothesis, morning serum cortisol was compared among a national sample of Vietnam "theater" veterans ($n = 2,490$) and a sample of Vietnam "era" veterans ($n = 1,972$) without service in Vietnam. Analysis of covariance was used to compare cortisol concentrations after adjusting for 9 covariates (education, income, race, age, smoking status, alcohol use, illicit drug use, medication use, and body mass index). Adjusted cortisol was lower among theater veterans with current PTSD but not era or theater veterans with lifetime PTSD. Among theater veterans, cortisol was inversely related to combat exposure, with veterans exposed to heavy combat having the lowest concentrations. Analysis of plasma cortisol, together with other clinical data, may be instrumental in the future diagnosis and treatment of stress disorders.

Recognition of the effects of severe psychological distress has a long history in psychology and medicine. For example, nearly 80 years ago, soldiers with adverse psychological reactions after combat were believed to be afflicted with "shell shock," resulting from artillery bombardment (Salmon, 1919). Later the concept of combat fatigue was used to categorize soldiers exhibiting adverse psychological reactions after combat, because it was thought that exhaustion played a role in this condition (Hanson, 1949). Between the 1950s to 1970s, the term "war neurosis" was often used to characterize soldiers' adverse psychological reactions after combat experiences (Mullins, 1973). A review of the psychiatric literature during this latter period found a variety of symptoms associated with different explanatory concepts, with war neurosis used to link a range of psychological problems associated with combat, including irritability, jumpiness, disturbed sleep, hysteria, disorientation, and panic attacks (Kormos, 1978).

Understanding of the effects of traumatic stress remained limited, in part, because rigorous studies of the long-term effects of combat were not available until many years after World War II (Archibald, Long, Miller, & Tuddenham, 1962; Archibald & Tuddenham, 1965; Dobbs & Wilson, 1960). After

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review of these and other findings related to natural disaster and concentration camp survivors, it was suggested that there was evidence that many individuals developed specific functional psychiatric disorders after extreme stress exposures, which were not present before these experiences (Dohrenwend, 1975).

Initial studies of Vietnam veterans provided additional evidence linking severe stress exposures in Vietnam—and exposure to combat in particular—to a host of mental health problems (Boscarino, 1981; DeFazio, Rustin, & Diamond, 1975; Foy, Sipprelle, Rueger, & Carroll, 1984; Laufer, Gallops, & Frey-Wouters, 1984; Nace, Meyers, O'Brien, Ream, & Mintz, 1977), although negative findings also were reported (Boscarino, 1979; Robins, Davis, & Goodwin, 1974). However, controversies about combat-associated stress disorders remained because of methodological problems associated with many early Vietnam veteran studies (Boscarino, 1995).

Recently, two national studies confirmed that Vietnam combat veterans had a higher prevalence of posttraumatic stress disorder (PTSD) and that this was due chiefly to combat experienced in Vietnam (Boscarino, 1995; Centers for Disease Control, 1988, 1989a, 1989c, 1989f; Kulka et al., 1990a, 1990b). There have been other recent national studies of Vietnam veterans, and these have reported similar results (Goldberg, True, Eisen, & Henderson, 1990).

In summary, for years clinicians observed that some individuals exposed to combat exhibited certain "neuroses" afterward, including hyperalertness, exaggerated startle responses, sleep disturbances, and other psychological difficulties (Wilson & Raphael, 1993a). These symptoms were eventually incorporated into the Diagnostic and Statistical Manual of Mental Disorders (3rd ed.; DSM–III; American Psychiatric Association, 1980). As noted, recent large-scale national studies confirmed that Vietnam veterans had a higher prevalence of PTSD and that this was caused by exposure to combat in Vietnam (Kulka et al., 1990a, 1990b).

The research in this article relates to the biological basis of

PTSD. The research question is, Do individuals with PTSD exhibit altered neuroendocrine functions related to changes in the body's stress response system? One important biomarker for neuroendocrine activity is plasma cortisol—a key neuroendocrine regulatory biochemical in the body's stress response system (Greenspan & Baxter, 1994). There are reasons to expect alterations in neuroendocrine system functions in chronic PTSD cases, because long-term changes in the hypothalamic–pituitary–adrenal system and the sympathetic arm of the autonomic nervous system have been noted after exposure to extreme stress (Chrousos & Gold, 1992; van der Kolk & Saporta, 1993). Understanding the biology of PTSD and the nature of human stress has important implications for both clinical psychology and clinical medicine.

Conceptualization and Recent Research Findings

"Biophysiopsychology" of the Human Stress Response

Evidence suggests that the physiologic arousal often observed during recollection of traumatic events and the startle response to loud noises sometimes exhibited by combat veterans are related to alterations in the neuroendocrine functions associated with changes in the sympathetic–adrenomedullary and hypothalamic–pituitary–adrenocortical axes of the human stress response system (Kolb, 1993; van der Kolk & Saporta, 1993). In the case of PTSD, it has been proposed that these neuroendocrine alterations may reflect the consequences of an extreme state of physiopsychological conditioning often observed in animal models after severe stress exposures (van der Kolk, Greenberg, Boyd, & Krystal, 1985). In addition, other evidence suggests that the general stress response is probably a critical mammalian mechanism for environmental adaptation and survival (Chrousos & Gold, 1992; Hofer, 1987). For example, research with human infants indicates that neuroendocrine systems are responsive to environmental stress from birth (Gunnar, 1992), and research with nonhuman infants suggests that stress reactions are basic for learning in all mammals (Hofer, 1987).

A number of interrelated neurochemical processes, as well as glandular and organ systems responses, appear to be activated during stress exposures that are organized into a systemic response. In particular, the sympathetic–adrenomedullary and hypothalamic–pituitary–adrenocortical systems have been identified as two of the major axes of this response system (Boyce & Jemerin, 1990). Furthermore, although the stress response is initiated in the central nervous system (CNS), it is subsequently carried out by multiple endocrine mechanisms that have wide-ranging effects on the body and nervous system (Boyce & Jemerin, 1990; Greenspan & Baxter, 1994).

Studies show that the sympathetic–adrenomedullary system is activated when stimuli are perceived as highly threatening (Boyce & Jemerin, 1990; Chrousos & Gold, 1992). When this occurs, higher brain centers, such as the cortex and limbic structures, activate the sympathetic arm of the autonomic nervous system. In the second phase, sympathetic activation of the adrenal medulla occurs, resulting in the secretion catecholamines (epinephrine and norepinephrine) into the blood stream. The effects of catecholamine secretion prepares the body to react to

danger, and these include increases in heart rate, oxygen supply, blood glucose, blood clotting, mental alertness, and anxiety (Boyce & Jemerin, 1990; Chrousos & Gold, 1992).

Activation of the hypothalamic–pituitary–adrenocortical axis appears to result from continuous exposure to internal or external noxious stimuli (Boyce & Jemerin, 1990). When this occurs, systemic responses include release of corticotropin-releasing hormone (CRH) from the median eminence of the hypothalamus, which stimulates secretion of the adrenocorticotropic hormone (ACTH) in the anterior lobe of the pituitary. ACTH, in turn, activates the adrenal cortex, resulting in the secretion of glucocorticoids (Boyce & Jemerin, 1990). In humans, the major active glucocorticoid is cortisol. This substance has wide-ranging effects on the body. These include its effects on metabolism, its anti-inflammatory properties, and its immunosuppressive effects (Boyce & Jemerin, 1990). Recently, it has been suggested that stress-induced alterations in cortisol regulate the body's response to severe stress to protect against the destructive effects that would result if these neurochemical mechanisms were overstimulated (Boyce & Jemerin, 1990).

There are other substances involved in the stress response, such as the morphinelike activities of the CNS peptide, beta-endorphin (Boyce & Jemerin, 1990; van der Kolk et al., 1985); however, space limits discussion of these here. Nevertheless, although the stress response appears complex, as noted subsequently, biological knowledge of this system seems to coincide with both physiological laboratory studies (Blanchard, Kolb, Pallmeyer, & Gerardi, 1982; Malloy, Fairbank, & Keane, 1983; Pitman, Orr, Forgue, de Jong, & Claiborn, 1987; Shalev, Orr, & Pitman, 1993) and higher order psychological models as they relate to both classical (Kolb, 1993) and operant conditioning processes (Keane, Zimering, & Caddell, 1985).

It has been observed that chronicity and excessiveness of stress system activation can lead to pathogenesis, causing weight loss, depression, hypogonadism, and immunosuppression (Chrousos & Gold, 1992; Greenspan & Baxter, 1994). In the case of PTSD, it has been suggested that this condition may cause chronically reduced secretion of CRH (Chrousos & Gold, 1992; Greenspan & Baxter, 1994), because this substance seems to act as a catecholamine regulator through a negative feedback process of some sort (Chrousos & Gold, 1992).

Recent Findings With PTSD-Positive Veterans

To date, several studies with small hospital- and clinic-based samples of male Vietnam veterans have found lower cortisol concentrations among veterans with PTSD. One study reported that combat veterans with PTSD had significantly lower urinary free-cortisol levels in comparison with other groups of veteran psychiatric patients (Mason, Giller, Kosten, Ostroff, & Podd, 1986). Another study of veterans with PTSD also found that they had significantly lower urinary free-cortisol levels in comparison to healthy control participants (Yehuda et al., 1990). Furthermore, investigators have reported that male veterans with PTSD had substantially more lymphocyte glucocorticoid receptors than healthy comparison participants, which is consist with lower urinary cortisol excretions (Yehuda, Lowy, Southwick, Shaffer, & Giller, 1991). In addition, increased urinary catecholamine excretions also were observed among PTSD-diagnosed veterans, in

comparisons with healthy control participants (Yehuda, South-wick, Giller, Ma, & Mason, 1992). Increased plasma norepineph-rine concentrations were also observed among veterans with PTSD in response to auditory combat stimuli administered in an experimental setting (Blanchard, Kolb, Prins, Gates, & McCoy, 1991). It also has been reported that the ratio of urinary norepi-nephrine to urinary cortisol could effectively discriminate PTSD veterans from other groups of psychiatric patients (Mason, Giller, Kosten, & Harkness, 1988).

In summary, existing research is consist with the hypothesis that PTSD victims are typically in a basal state of cortisol hypoarousal that, however, is associated with higher catecholamine levels and heightened responses of the stress system to certain stimuli—par-ticularly traumatic memories and other phenomena associated with the original traumatic events (Chrousos & Gold, 1992).

Method

Participants

The participants for this study were from the Vietnam Experience Study (VES). Participants were selected from a random sample of male U.S. Army veterans who served during the Vietnam War (Centers for Disease Control, 1988, 1989a, 1989c, 1989f). For aid in comparability, veterans selected for this study included only men who entered the mil-itary for the first time between 1965 and 1971, served only one enlist-ment term, had at least 16 weeks of active service, achieved a military specialty other than "trainee," and had a pay grade no higher than E-5 when discharged.[1] Altogether, 48,513 records meeting these criteria were randomly selected from 4.9 million U.S. Army records for this period. From these, two groups—theater veterans, who served in Viet-nam, and era veterans, who did not—were randomly selected among all veterans known not to be deceased and were traced using a variety of methods. From these two samples, 87% of the theater veterans (7,924) and 84% of the era veterans (7,364) were located and interviewed by telephone. Next, among those veterans interviewed, a random subsam-ple was selected for personal interviews and medical examinations. Al-together, 75% of the theater veterans (2,490) and 63% of the era veterans (1,972) participated in this phase. The personal interviews and the physical exams were administered at one medical facility between June 1985 and September 1986. Because participation rates differed between theater and era veterans, a detailed analysis was conducted using origi-nal military records and the telephone interview data. Statistical com-parisons indicated that the nonresponse rates did not bias the study results (Centers for Disease Control, 1989b).

Study Variables

PTSD

Posttraumatic stress was defined using the Diagnostic Interview Schedule (DIS; Robins, Helzer, & Cottler, 1987), a standardized ques-tionnaire designed to assess the prevalence of psychiatric conditions ac-cording to DSM–III criteria (American Psychiatric Association, 1980; Robins et al., 1987). Studies of the reliability and validity of the DIS have been published (Robins, Helzer, Croughan, & Ratcliff, 1981; Rob-ins, Helzer, Ratcliff, & Seyfried, 1982). The DIS was administered by trained psychology technicians under the supervision of licensed clini-cal psychologists. Two categories of PTSD were examined in this article.

Any PTSD in lifetime (ANY PTSD-EVER). This was defined as having ever met the full diagnostic criteria for either combat- or non-combat-related PTSD in a lifetime on the basis of DSM–III criteria.

Any PTSD in past year (ANY PTSD-YEAR). This was defined as

having one or more of the diagnostic criteria for combat- or noncombat-related PTSD in the previous year, once having ever met the full diag-nostic criteria for combat- or noncombat-related PTSD in a lifetime, on the basis of DSM–III criteria. This diagnostic category represents a partial PTSD diagnosis, because the full diagnostic criteria were not available in this study for a 1-year time frame.

Combat Exposure

This was a self-reported measure of combat exposure related to pre-vious research with Vietnam veterans (Laufer et al., 1984). This scale was based on a weighted sum of 12 questions related to personal combat experiences ($M = 23.82$, $SD = 16.36$; range, 0–72). Higher scores on this scale indicated greater combat exposure. A point-biserial correla-tion between this score and whether the theater veteran had a combat-related military occupation (e.g., infantry, cavalry, or artillery) was sig-nificant ($r = .47$, $p < .0001$). It has recently been reported that these types of scales are reliable and valid measures of combat exposures among Vietnam veterans (Janes, Goldberg, Eisen, & True, 1991). Ad-ditional information on this scale is available (Centers for Disease Con-trol, 1989c, 1989f). For this study, combat exposure was divided into quartiles ranging from "no or low" to "very heavy" combat exposures.

Plasma Cortisol Levels

Serum cortisol samples were evaluated using a double antibody radio-immunoassay system ($M = 18.20$ $\mu g/dl$, $SD = 5.52$ $\mu g/dl$; range, 3.70–48.00 $\mu g/dl$). Blood samples were collected at 7 a.m. on the second day of testing. (The first day of testing included the study orientation and completion of consent forms.) Blood collection was preceded by an over-night fast, with only drinking water permitted (Centers for Disease Con-trol, 1989b, 1989d). However, participants were instructed that for 3 days before examinations they should not eat red meat, pork, or sweets; drink any alcohol or use any mouthwash; take any multivitamins or Vitamin C supplements; or take any nonprescriptive drugs unless absolutely neces-sary. (Participants were told to continue taking medications or drugs pre-scribed by a physician.) They were also told not to start any new exercise programs. The Aria HT cortisol system was used to analyze serum corti-sol concentrations (Becton Dickinson, 1985, Orangeburg, New York). With this system, diluted serum is incubated in the presence of radioac-tive (labeled) antigen and an antibody specific for cortisol to attain an equilibrium between nonbound antigen (labeled and unlabeled) and bound antigen (labeled and unlabeled). This incubation mixture then flows through a solid-phase elutable absorbent. The labeled and unla-beled cortisol not bound to the soluble antibody during incubation binds to the antibody chamber, whereas the labeled and unlabeled cortisol bound to the soluble antibody during the incubation passes through the antibody chamber and into the bound flow cell, where the labeled cortisol molecules are counted by a gamma detector. An eluting agent then passes through the antibody chamber to free the bound cortisol. The cortisol (labeled and unlabeled) freed from the antibody chamber by the eluting solution flows into the free flow cell where it is counted. Specimens that were not used immediately were properly stored and refrigerated. All lab-oratory determinations were monitored by using bench and masked re-peat quality control procedures under the supervision of board-certified clinical pathologists (Centers for Disease Control, 1989d, 1989e). Labo-ratory testing was preformed at the Clinical and Research Division, De-partment of Laboratories, Lovelace Medical Foundation, Albuquerque,

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[1] Approximately 3 million men and 7,000 women served in the Viet-nam theater during the war, with the latter serving primarily as nurses (Kulka et al., 1990a, 1990b). The mental health status of female veter-ans was assessed in a separate study (see Kulka et al., 1990a, 1990b).

New Mexico. Additional information on the laboratory procedures is available (Centers for Disease Control, 1989d).

Control Variables

For this study, nine variables were used as control variables because they potentially could be confounding factors associated with plasma cortisol concentrations (Greenspan & Baxter, 1994). These variables were developed from data collected during the interviews and physical examinations. They include the following variables.

Current illicit drug use. This was based on reported drug use in the previous 12 months. This was coded as none (87.6%), used marijuana only at least once a day for a week or more (9.5%), and used hard drugs (e.g., heroin, cocaine, amphetamines, etc.) at least once a day for a week or more (2.3%).

Current alcohol use. This is an estimate of the number of drinks consumed in the past month that is based on the number of days on which the veteran drank in the past month and the average number of drinks consumed per day when the veteran drank ($M = 36.82$, $SD = 63.35$; range, 0 to 960). Because this measure was positively skewed (skewness = 4.81), it was transformed using a logarithmic transformation, which is normally recommended for this variable (de Lint & Schmidt, 1973).

Current smoking. This variable was based on the veteran's smoking history. It was coded as never smoked (26.0%), ex-smoker (29.0%), and current smoker (45.0%).

Current prescribed medication use. This was an indicator variable for current use of physician-prescribed medications. This was coded as yes (18.8%) and no (81.2%).

Body mass index (BMI). This variable was based on the veteran's current squared weight:height ratio ($M = 26.86$, $SD = 4.47$; range, 16.00 to 67.00).

Age at interview. This was based on the veteran's age at the interview ($M = 37.83$, $SD = 2.53$; range, 31 to 48).

Annual household income. This was based on the total reported household income in the past year. This was coded as less than $10,000 (9.8%), $10,001–$20,000 (18.1%), $20,001–$30,000 (27.3%), $30,001–$40,000 (23.7%), $40,001–$50,000 (10.4%), and over $50,000 (10.8%). The median category was substituted for missing.

Race. This was based on the veteran's reported race and was as follows: White (81.9%), Black (11.8%), Hispanic (4.5%), and "other" (Asian, Pacific Islander, Native American, and Alaskan native; 1.9%). For this analysis Black, Hispanic, and "other" were combined into one category.

Level of education. This was based on the veteran's total years of formal education at the time of the interview ($M = 13.29$, $SD = 2.30$; range, 1 to 18). Additional information on the development, reliability, and validity of the variables used in this analysis and laboratory procedures are available elsewhere (Boscarino, 1995; Centers for Disease Control, 1989a, 1989b, 1989c, 1989d, 1989e, 1989f).

Statistical Methods

Descriptive and multivariate statistical analyses for this article were performed using SPSS for Windows Version 6.01 (SPSS, 1994) and STATA Release 3.1 (Stata Corporation, 1994). The analysis of covariance (ANCOVA) was used to adjust plasma cortisol concentrations for potential confounding factors. All ANCOVAs were based on a linear model in which the control variables (i.e., alcohol use, drug use, BMI, and demographics) were entered simultaneously (Neter, Wasserman, & Kutner, 1990). Univariate confidence intervals provided were based on "ordinary" confidence interval estimation methods (Blalock, 1972). Finally, Statistical Analysis System (SAS) for Windows, Version 6, was used to generate the DIS diagnostic codes for PTSD (SAS Institute, 1993).

Because only PTSD and combat exposure level "treatment" effects were hypothesized, no additional factors were included in the ANCOVAs: They contain one factor for each type of PTSD (two categories) or one factor for combat exposure (four categories), respectively, plus the nine control variables as covariates. Given this model, while the problem of the equality of slopes is not a concern here, homogeneity of variance still is a factor for consideration. Statistical tests for the homogeneity of variance (Neter et al., 1990) indicated that the model for theater veterans by combat exposure level had unequal group variances. Consequently, the following steps were undertaken, all recommended to stabilize the group variances in this situation (Cohen & Cohen, 1983; Neter et al., 1990). First, the dependent variable was transformed using a logarithmic and then a square-root transformation and separate ANCOVAs were conducted respectively. Next, two separate weighted least squares linear regressions were conducted. In the first, the inverse of the residual group variances were used as regression weights; in the second, the inverse of the group variances were used (Neter et al., 1990). All four of these transformed models produced results very similar to the original (untransformed) data. Consequently, the untransformed ANCOVA results are presented here.

Hypotheses

The primary hypothesis in this article is that veterans with a lifetime or current PTSD diagnosis have lower plasma cortisol concentrations. Because combat exposure was found to be positively related to PTSD (Boscarino, 1995), a secondary hypothesis is that plasma cortisol is inversely related to the degree of combat exposure reported. Here, the alpha level to reject the null hypothesis was set at .05.

Results

Table 1 shows that theater veterans had a higher lifetime and current prevalence of PTSD and that they were less educated (all $ps < .05$). They also consumed more alcohol and were more likely to use illicit drugs (both $ps < .05$). These disparities reinforce the need to adjust for differences between the veteran groups, because some of these could be confounders, only coincidentally related to plasma cortisol through another variable not on the causal pathway hypothesized (Hennekens & Buring, 1987). Noteworthy here is that the lifetime prevalence of PTSD among era veterans is 3%, which is the approximate figure reported in the general (nonveteran) population (Helzer, Robins, & McEvoy, 1987). As can be seen, the overall cortisol levels between era and theater veterans were not significantly different (see Table 1).

Table 2 shows unadjusted and adjusted plasma cortisol concentrations first grouped by the two PTSD classifications and then by combat exposure level. For both era and theater veterans, a lifetime diagnosis of PTSD is not significantly related to lower cortisol levels. Because only 1.7% of era veterans had a current PTSD (see Table 1), these data are highly unbalanced and, therefore, this group cannot be analyzed effectively with ANCOVA (Neter et al., 1990). Hence, these data are not presented in Table 2. It should be noted that a total of 0.8% ($n = 20$) and 1.0% ($n = 25$) of theater veterans, respectively, had a lifetime diagnosis of a "noncombat" PTSD only or a lifetime diagnosis of a noncombat PTSD and a combat PTSD combined. In addition, 0.6% of era veterans ($n = 11$) had a combat PTSD, probably related to "live-fire" exercises or combat patrols in other theaters of operation, such as in Korea. Again, in

Table 1
Profile of Vietnam-Era and Vietnam-Theater Veterans

Variable	Vietnam-era veterans (n = 1,972)		Vietnam-theater veterans (n = 2,490)	
	% or M	95% CI	% or M	95% CI
Diagnosis				
Any PTSD-ever	3.0	2.3–3.9	15.5	14.1–17.0*
Any PTSD-year	1.7	1.2–2.4	11.8	10.5–13.1*
Alcohol abuse-year[a]	13.6	12.1–15.2	15.6	14.2–17.1
Drug abuse-year[a]	3.9	3.1–4.9	3.9	3.1–4.7
Age (M)	37.8	37.7–38.0	37.8	37.7–37.9
% College graduates	24.9	23.1–26.9	18.9	17.4–20.5*
% Non-White[b]	18.9	17.2–20.7	17.5	16.0–19.1
Household income of $20,000 or less	27.4	25.4–29.4	28.3	26.5–30.1
Current status				
Smoking	43.2	41.0–45.4	46.4	44.5–48.4
Mean no. of drinks per month	33.6	31.0–36.1	39.4	36.7–42.1*
Illicit drug use	10.4	9.0–11.8	13.2	11.9–14.6*
Prescriptive drug use	18.0	16.3–19.7	19.5	18.0–21.1
Mean level BMI	26.7	26.6–26.9	26.9	26.8–27.1
Mean level of unadjusted cortisol (μg/dl)[c]	18.1	17.8–18.3	18.3	18.1–18.5

Note. CI = confidence interval; PTSD = posttraumatic stress disorder; BMI = body mass index.
[a] Similar to current PTSD, also based on having met one of the diagnostic criteria for alcohol or drug abuse in the past year, ever having met the full diagnostic criteria for either, respectively, in a lifetime. [b] Non-White includes Black, Hispanic, and other. [c] The unadjusted differences in cortisol between era and theater veterans were not significant, $F(1, 4461) = 1.24$, $p = .266$. The "adjusted" differences in cortisol between era and theater veterans also were not significant, $F(1, 4411) = 0.81$, $p = .367$.
* $p < .05$ statistical difference between groups, based on nonoverlapping 95% confidence intervals.

both situations small cell sizes make ANCOVA impractical and, hence, these subgroup results are not presented.

Table 2 shows that theater veterans with a 1-year partial PTSD diagnosis had both lower unadjusted plasma cortisol concentrations, $F(1, 2488) = 3.97$, $p = .047$, and adjusted plasma cortisol concentrations, $F(1, 2454) = 4.16$, $p = .041$. In addition, the bottom of Table 2 shows an inverse dose–response relationship for combat exposure for both unadjusted cortisol, $F(3, 2486) = 6.04$, $p = .0004$, and adjusted cortisol, $F(3, 2444) = 5.71$, $p = .001$, where higher exposures are associated with lower cortisol concentrations (see Figure 1). The Scheffe test for post hoc multiple comparisons (Winer, Brown, & Michels, 1991) was used to determine which categories of combat exposure were significantly lower. This test is necessary to avoid Type I statistical errors that would result from using multiple t tests to determine this. The Scheffé test indicated that those in the "heavy" and "very heavy" combat exposure groups had significantly lower cortisol than those in the "none or low" combat exposure group ($p < .05$).

Discussion

In part, the findings presented replicate previous research with small samples of veterans and other studies: Theater veterans with a current (partial) PTSD had lower cortisol levels. However, a lifetime PTSD diagnosis (among either group of veterans) was not associated with lower cortisol, although unadjusted cortisol differences approached significance among

theater veterans, $F(1, 2486) = 2.65$, $p = .104$. These results suggest that cortisol hypoactivity could be related to the recency of PTSD symptoms; that is, the effects of traumatic stress may have extinguished for some veterans over time, but for those with a current PTSD, cortisol hypoactivity was present. In addition, it is also possible that combat-related PTSD may somehow be different than noncombat-related PTSD. This is important because about 95% of theater veterans with PTSD had a combat PTSD, whereas only about 20% of era veterans with PTSD had this type of PTSD (recall, however, that the latter was not due to Vietnam service). The number of era veterans with PTSD, unfortunately, was too small to explore this issue in more detail. Perhaps the most important finding, however, was that combat exposure levels were associated with cortisol concentrations in the inverse dose–response direction hypothesized (see Figure 1). This seems to suggest that traumatic stress exposure years ago may have resulted in neuroendocrine system dysfunction, which now also manifests itself through current (partial) PTSD symptoms. Nevertheless, the lack of positive findings for lifetime PTSD warrants further comment.

Research suggests that use of the DIS and the *DSM–III* criteria in the VES project may have resulted in underdiagnosis of PTSD (Kulka, 1990a). Consequently, misclassification bias may confound the findings presented. To explore this, I conducted logistic regressions predicting both lifetime and current (partial) PTSD. Logistic regression is appropriate for analysis of binomial-distributed events, such as PTSD, and does not de-

Table 2

Plasma Cortisol by Veteran Status, PTSD Diagnosis, and Combat Exposure: Unadjusted and Adjusted Results

| | Unadjusted | | | | Adjusted[a] | | | |
| | | | Plasma cortisol level (μg/dL) | | | | Plasma cortisol level (μg/dL) | |
Theater, PTSD, and combat status	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*
Era veterans: Any PTSD-ever								
No	1,911	97.0	18.10	5.53	1,885	97.0	18.11	5.54
Yes	60	3.0	17.80		59	3.0	17.93	
		$F(1, 1969) = 0.17, p = .678$				$F(1, 1933) = 0.06, p = .805$		
Theater veterans: Any PTSD-ever								
No	2,102	84.6	18.36	5.51	2,085	84.6	18.35	5.51
Yes	386	15.4	17.86		379	15.4	17.91	
		$F(1, 2486) = 2.65, p = .104$				$F(1, 2453) = 2.02, p = .155$		
Theater veterans: Any PTSD-year								
No	2,197	88.4	18.36	5.51	2,179	88.4	18.36	5.51
Yes	293	11.6	17.68		286	11.6	17.66	
		$F(1, 2488) = 3.97, p = .047$				$F(1, 2454) = 4.16, p = .041$		
Theater veterans: Combat exposure								
None/low	579	23.4	19.07	5.51	577	23.4	19.05	5.51
Moderate	542	21.8	18.33		538	21.8	18.33	
Heavy	719	28.8	17.98		703	28.8	17.98	
Very heavy	650	25.9	17.86		639	25.9	17.87	
		$F(3, 2486) = 6.04, p = .0004$				$F(3, 2444) = 5.71, p = .001$		

Note. PTSD = posttraumatic stress disorder.
[a]Cortisol was adjusted for education, income, race, age, smoking status, alcohol use, medication use, illicit drug use, and body mass index using an analysis of covariance. Here the two PTSD categories and the four combat exposure categories shown for the four models, respectively, were used as single factors in the adjusted models. All other variables were used as covariates.

pend on multivariate normal distributions and equal variances required of least squares models (Hosmer & Lemeshow, 1989). The first set of logistic regressions shown in Table 3 (left panel) predicts PTSD from theater status, controlling for age, income, education, and race. The second set (right panel) predicts PTSD from theater status controlling for demographics, plus preservice factors (e.g., childhood delinquency), service entry characteristic (e.g., whether volunteered for Vietnam service),
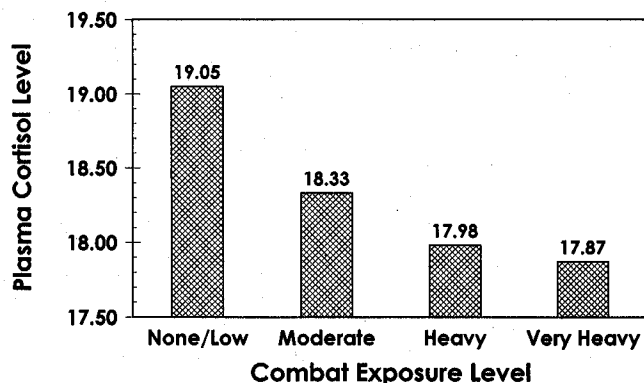

Figure 1. Adjusted plasma cortisol concentrations (in micrograms per deciliter) among theater veterans by combat exposure levels. (See Table 2, Footnote a.)

military adjustment (e.g., whether disciplined in the military), and other postservice factors (e.g., current marital status). This analysis also is repeated for combat exposure as well among theater veterans only. Adjustment for preservice and service entry characteristics are normally important in evaluating the mental health status of Vietnam veterans, because of selection biases associated with Vietnam service (Boscarino, 1995). These adjustments, including those for postservice factors, are described elsewhere (Boscarino, 1995). It is important to note that these adjustments produce very conservative estimates of PTSD, because they overadjust for factors. Table 3 summarizes the logistic regression results in terms of the odds ratio, which indicates the odds of having an outcome given an exposure and is equivalent to the "relative risk" of having an outcome when the outcome is rare in a population (Hennekens & Buring, 1987).

As can be seen in Table 3, the odds of a lifetime or current (partial) PTSD among theater veterans are about five to seven times higher than era veterans (the reference group). However, among "heavy combat" theater veterans, the odds are greater than 20 to 40 times higher of having either of these, in comparison to "none or low combat" theater veterans (the reference group). This confirms that degree of combat exposure is a major predictor of DIS- or *DSM-III*-diagnosed PTSD. Given this, it is not surprising that combat exposure is associated with cortisol concentrations in this study. However, as noted, there is evidence that the DIS and *DSM-III* criteria may not have been reliable for diagnosing some PTSD cases. To further evaluate this, I conducted two separate

Table 3
Logistic Regressions Predicting Any PTSD-Ever and Any PTSD-Year From Theater Status and Combat Exposure, Adjusted for Demographics and Other Factors

Theater, PTSD, and combat status	Adjusted for demographics				Adjusted for demographics and other factors		
	n	% PTSD[a]	OR	95% CI	*n*	OR	95% CI
Any PTSD-ever based on theater status							
Era (ref.)	1,971	3.0	1.00		1,971	1.00	
Theater	2,488	15.5	6.00***	4.5–7.9	2,488	5.84***	4.4–7.8
Any PTSD-ever based on combat status (theater veterans only)							
None/low (ref.)	579	1.4	1.00		579	1.00	
Moderate	541	8.3	6.47***	3.0–13.8	541	5.35***	2.4–11.5
Heavy	711	14.5	12.16***	5.9–25.3	711	9.85***	4.6–20.6
Very heavy	649	35.3	38.82***	19.0–80.0	649	28.60***	13.3–60.1
Any PTSD-year based on theater status							
Era (ref.)	1,972	1.7	1.00		1,972	1.00	
Theater	2,490	11.8	7.76***	5.4–11.1	2,490	7.58***	5.2–11.0
Any PTSD-year based on combat status (theater veterans only)							
None/low (ref.)	579	0.9	1.00		579	1.00	
Moderate	542	5.9	7.17***	2.7–18.3	542	5.32**	2.0–13.9
Heavy	711	11.1	14.37***	5.7–35.6	711	10.00***	3.9–25.1
Very heavy	650	27.2	42.16***	17.2–103.6	650	24.75***	9.6–62.4

Note. All odds ratios presented are adjusted first by age, income, education, and race (under the heading "Adjusted for demographics") and then by preservice, military adjustment, and postservice adjustment factors (under the heading "Adjusted for demographics and other factors"). The latter adjustments produce conservative odds ratios because they "overadjust" results. Both the veteran status and the combat exposure predictor variables were dummy coded here with the first category as the reference category. The general form and structure of these logistic regression models are discussed in detail elsewhere (Boscarino, 1995). PTSD = posttraumatic stress disorder; OR = odds ratio; CI = confidence interval; ref. = reference group.
[a]Percentage with PTSD in each category based on bivariate cross-tabulations.
**$p < .001$. ***$p < .0001$.

ANCOVAs in which cortisol was analyzed by combat exposure, but this time lifetime and current PTSDs were used as covariates, respectively. As seen in Table 4, the results for combat exposure are still significant in both models. It should be noted that neither current PTSD, $F(1, 2443) = 1.39$, $p = .238$, nor lifetime PTSD, $F(1, 2442) = 0.11$, $p = .739$, were significant in either of these models. This suggests that the problem here may be with using PTSD diagnoses that are based on the DIS and *DSM-III*, not with using cortisol as a biomarker of traumatic stress per se. Of course, without a better measure of PTSD, this hypothesis cannot be further elaborated.

Biological and Higher Order Psychological Explanations of PTSD

On the basis of these findings, two key questions for clinicians might be as follows: (a) What higher order concepts are needed, if any, to explain PTSD on a psychological level where symptoms present themselves? (b) How are the "lower order" biological explanations, that were suggested earlier, linked to higher order psychological explanations of PTSD? It is believed that the answers to these questions may lie in the observation that psychological-level explanations of PTSD appear to parallel "conditioned fear" re-

sponses often observed in humans and in animal models (van der Kolk et al., 1985; van der Kolk & Saporta, 1993). For those exposed to traumatic stressors, it has been suggested that these may act as unconditioned aversive stimuli that evoke severe autonomic physiological distress. Consequently, previously neutral external stimuli (e.g., aspects of the physical environment) and internal stimuli (e.g., physiological states, emotions, and cognitions) that accompanied the traumatic stressor, may function as "conditioned" stimuli capable of producing profound psychological and physiological distress when the traumatic stressors are no longer present (Keane et al., 1985). This model suggests that individuals may not only avoid the unconditioned stimuli (i.e., the traumatic event), but also engage in behaviors necessary to avoid the aversively conditioned external and internal stimuli indirectly associated with it.

Avoidance of the aversively conditioned stimuli may be reinforced by aversive arousal reduction (i.e., negative reinforcement). This may function to encourage further avoidance in the future. Avoidance may produce a temporary reduction in aversive arousal but may prevent the extinction that would occur over time, hence contributing to the chronicity often observed with this disorder (Wilson & Raphael, 1993a). In addition to aversive conditioning, other conditioning factors are believed to contribute to the psycho-

Table 4
Plasma Cortisol: Theater Veterans by Combat Exposure Levels Adjusted for PTSD-Year and PTSD-Ever, Respectively

Combat status, theater veterans only	Adjusted for PTSD-year[a]		Plasma cortisol level (µg/dL)		Adjusted for PTSD-ever[a]		Plasma cortisol level (µg/dL)	
	n	%	M	SD	n	%	M	SD
Theater veterans: Combat exposure								
None/low	577	23.4	19.01	5.51	577	23.4	19.05	5.51
Moderate	538	21.8	18.31		537	21.8	18.35	
Heavy	703	28.8	17.97		703	28.8	17.98	
Very heavy	639	25.9	17.93		639	25.9	17.90	
		$F(3, 2443) = 4.74, p = .003$				$F(3, 2442) = 5.10, p = .002$		

Note. PTSD = posttraumatic stress disorder.
[a]In addition to adjusting for PTSD, cortisol was adjusted for education, income, race, age, smoking status, alcohol use, medication use, illicit drug use, and body mass index using an analysis of covariance. The four combat exposure categories shown for the two models were used as a single factor in the adjusted models, respectively. All other variables were used as covariates.

pathogenesis of this disorder, such as higher order conditioning and stimulus generalization. The latter is believed to be responsible for the broad range of anxiety reactions typically found in PTSD victims. For example, many sudden loud noises have the potential to provoke aversive arousal in PTSD-positive combat veterans, not just gunfire (Butler et al., 1990; Keane et al., 1985).

Other Evidence: Implications for Clinical Psychology

Experimental laboratory studies provide evidence for not only conditioning in PTSD but also suggest key "physiopsychological" linkages. For example, one study compared the responses of Vietnam theater veterans to a series of videotaped scenes of combat that increased in intensity (Malloy et al., 1983). Veterans who were positively diagnosed with PTSD showed more behavioral avoidance of the material, had greater heart rate and skin resistance responses, and reported more subjective distress than non-PTSD veterans. Another study found that PTSD-positive Vietnam veterans showed significantly more behavioral avoidance and physiologic arousal (e.g., they had higher heart rate, systolic blood pressure, and electromyogram responses) to combat sounds that increased in intensity (Blanchard et al., 1982). Another study has also produced similar physiologic arousal using "scripts" describing each veteran's combat experiences (Pitman et al., 1987). These results have been recently replicated with PTSD-positive Israeli civilians (Shalev et al., 1993). As noted previously, PTSD-positive Vietnam veterans were more likely to have higher levels of circulating catecholamines in response to combat-associated stimuli presented in laboratory settings, suggesting higher states of emotional and physiological stimulus arousal (Blanchard, Kolb, & Prins, 1991).

Additional clinical insights on PTSD also are available within the treatment literature. For example, general learning theory suggests that, if stress victims are gradually exposed to stress-related conditioned stimuli (under the proper conditions), symptoms should decrease because desensitization to the stressor could occur (Mahoney, 1974; Sherman, 1973). Although specific approaches vary, this is one of the general ther-

apies recommended for treatment of PTSD, together with counseling on anxiety reduction and coping techniques (Committee on Veterans Affairs, 1988; Fairbank & Nicholson, 1987). A common treatment technique often reported helpful in PTSD therapy with veterans is one in which the patient is taught to verbalize the traumatic experience with the help of a support group consisting of other veterans (Grady, 1990). This process would allow the veteran to redefine external and internal stimuli that affect psychological arousal, develop better self-control, and with assistance, desensitize himself or herself to a range of thoughts, actions, and situations associated with traumatic events. Recently, a negative association was reported for veterans with PTSD and their current level of social support, reinforcing this hypothesis; that is, Vietnam combat veterans with lower current social support had a higher prevalence of current PTSD (Boscarino, 1995). Given the findings presented and the evidence discussed, this association is consistent with a "biophysiopsychological" model of PTSD and also is consistent with other medical research findings (Veiel & Baumann, 1990).

In short, the treatment approach recommended for PTSD is consistent with the observation that most psychotherapy is more a form of learning than medical treatment (Frank & Frank, 1991). Then psychotherapy works, the changes that take place are primarily cognitive, and the physiological and behavioral changes that follow are often related to these cognitive changes, or how patients think (Mahoney, 1974; Sherman, 1973). Nevertheless, the findings presented in this article suggest that more than cognitive explanations are needed to understand PTSD and, most importantly, treat it effectively. In addition to higher order cognitive explanations of downward causality, the findings presented suggest lower order biological explanations of upward causality also seem necessary, suggesting that a conceptual synthesis may be warranted (Kolb, 1993). The possible interaction between social support and traumatic stress is intriguing and may explain the high rates of PTSD among Vietnam veterans (see Kulka et al., 1990a, 1990b), given low community support during and after the war (Polner, 1971). Clearly, this finding may have important clinical implications for the future treatment of both combat-related and

noncombat-related stress victims, which leads to another key observation. This is that human stress responses likely fall along a continuum, with PTSD on the extreme end of this stress gradient and minor stressors on the other end (Boscarino, 1995). Given this logic, the standard PTSD diagnostic scheme is probably limited for studying the complexity of human stress phenomena (Boscarino, 1995).

Conclusion

All living organisms seem to survive by maintaining a complex equilibrium that is challenged by environmental forces (Chrousos & Gold, 1992). For both humans and some nonhuman primates, at least, activation of complex biophysiopsychological processes appear to bring about critical behavioral and cognitive changes that improve the ability to survive. Identification of some biochemical effectors of this stress-response system and the biological mechanisms responsible for producing and releasing some informational substances have been discussed. In brief, both physical and emotional stressors appear to activate responses designed to stimulate alertness, vigilance, cognition, as well as appropriate aggression. Increases in cardiovascular activity lead to elevations in blood pressure and heart rate, whereas increases in respiratory rate, gluconeogenesis, and lipolysis promote enhanced physiological and cognitive functions (Chrousos & Gold, 1992).

The findings reported in this article document possible long-term biological alterations related to the stress response among a large national sample of Vietnam veterans: Some men exposed to heavy combat appear to have altered neuroendocrine system functions 20 years after this exposure. Although the data presented provide evidence for the biological basis for PTSD, they also are consistent with higher order psychological explanations of this disorder too. In fact, both explanations seem necessary, because systemic biological alterations that have psychoactive expressions through cognitive, emotional, and behavioral outcomes also require psychological knowledge. This realization is not revolutionary. In the alcohol field, it has been recognized for years that, although ethanol has specific pharmacologic properties, individual interpretations of these effects are influenced by individual expectancies derived through social groups (Critchlow, 1986). These psychological variables likely explain the key subjective role apparently played by "social support" in alleviating PTSD symptoms (Boscarino, 1995; Grady, 1990), and also are consist with conditioning models of PTSD as well (Keane et al., 1985).

This study has some limitations. First, it is possible that the participants in this study may differ because of uncontrolled selection biases. As a consequence of these unknown selection biases, they may have lower plasma cortisol concentrations, not because of exposure to traumatic stress. Second, the biology of the human stress response is very complex. It is possible that the findings reported were due to interactions between different biological systems and that plasma cortisol is only a proxy for more important biological processes. Third, not all veterans contacted agreed to participate in this study. Thus, nonresponse bias could have affected the results somehow, although nonresponse analyses failed to detect this (Centers for Disease Control, 1989b). Fourth, the effects found, while often in the hypothesized direction, were relatively small. Consequently, by itself, plasma cortisol may not be an optimal biomarker for PTSD. Additional laboratory indicators are likely needed, such as the norepinephrine:cortisol ratio measure recently reported (Mason et al., 1988). Fifth, as mentioned, use of DIS and *DSM-III* criteria also may be a limitation in this study too.

In spite of these limitations, however, the findings presented should be considered important because they are based on a large national study. To my knowledge, this has never been done before. In addition, although this research was conducted with men who have experienced combat, the generalization of these findings should not automatically be limited. Traumatic stress reactions should be expected among individuals exposed to extreme life-threatening situations, including natural disasters, violent physical attacks, wartime combat, and other situations (Wilson & Raphael, 1993b). Furthermore, as noted, it is likely that human exposure and response to stress take place along a stress continuum, with traumatic stress on one end and minor stresses and strains on the other. This realization, of course, makes the study, diagnosis, and treatment of stress-related disorders more complex than suggested in this article. Finally, future research should pursue the theoretical synthesis proposed between biological and psychological models of PTSD, as well as quantifying additional personality, situational, and diagnostic aspects of this disorder.

References

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

Archibald, H. C., Long, D. M., Miller, C., & Tuddenham, R. D. (1962). Gross stress reaction in combat—A 15-year follow-up. *American Journal of Psychiatry, 119,* 317–322.

Archibald, H. C., & Tuddenham, R. D. (1965). Persistent stress reaction after combat: A 20-year follow-up. *Archives of General Psychiatry, 12,* 475–481.

Becton Dickinson. (1985). *Instruction manual for determination of cortisol using the aria HT* (RM No. 71411). Orangeburg, NY: Author.

Blalock, H. M. (1972). *Social statistics* (2nd ed.). New York: McGraw-Hill.

Blanchard, E. B., Kolb, L. C., Pallmeyer, T. P., & Gerardi, R. J. (1982). A psychophysiological study of posttraumatic stress disorder in Vietnam veterans. *Psychiatric Quarterly, 54,* 220–229.

Blanchard, E. B., Kolb, L. C., & Prins, A. (1991). Psychophysiological responses in diagnosis of posttraumatic stress disorder in Vietnam veterans. *Journal of Nervous and Mental Disease, 179,* 97–101.

Blanchard, E. B., Kolb, L. C., Prins, A., Gates, S., & McCoy, G. C. (1991). Changes in plasma norepinephrine to combat-related stimuli among Vietnam veterans with posttraumatic stress disorder. *Journal of Nervous and Mental Disease, 179,* 371–373.

Boscarino, J. (1979). Current drug involvement among Vietnam and non-Vietnam veterans. *American Journal of Drug and Alcohol Abuse, 6,* 301–312.

Boscarino, J. (1981). Current excessive drinking among Vietnam veterans: A comparison with other veterans and nonveterans. *International Journal of Social Psychiatry, 27,* 204–212.

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

Boyce, W. T., & Jemerin, J. M. (1990). Psychobiological differences in childhood stress response. I: Patterns of illness and susceptibility. *Developmental and Behavioral Pediatrics, 11,* 86–94.

Butler, R. W., Braff, D. L., Rausch, J. L., Jenkins, M. A., Sprock, J., & Geyer, M. A. (1990). Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. *American Journal of Psychiatry, 147,* 1308–1312.

Centers for Disease Control. (1988). Health status of Vietnam veterans: 1. Psychosocial characteristics. *Journal of the American Medical Association, 259,* 2701–2707.

Centers for Disease Control. (1989a). *Vietnam Experience Study: Health Status of Vietnam Veterans: Vol. 2. Telephone interviews.* Atlanta, GA: Author.

Centers for Disease Control. (1989b). *Vietnam Experience Study: Vol. 3. Health status of Vietnam veterans. Vol. 3. Medical examinations.* Atlanta, GA: Author.

Centers for Disease Control. (1989c). *Vietnam Experience Study: Health status of Vietnam veterans: Vol. 4. Psychological and neuropsychological evaluation.* Atlanta, GA: Author.

Centers for Disease Control. (1989d). *Vietnam Experience Study: Health status of Vietnam veterans: Supplement A. Laboratory methods and quality control.* Atlanta, GA: Author.

Centers for Disease Control. (1989e). *Vietnam Experience Study: Health status of Vietnam veterans: Supplement B. Medical and psychological data quality.* Atlanta, GA: Author.

Centers for Disease Control. (1989f). *Vietnam Experience Study: Health status of Vietnam veterans: Supplement C. Medical and psychological procedure manuals and forms.* Atlanta, GA: Author.

Chrousos, G. P., & Gold, P. W. (1992). The concepts of stress and stress system disorders: Overview of physical and behavioral homeostasis. *Journal of the American Medical Association, 267,* 1244–1252.

Cohen, J., & Cohen, P. (1983). *Applied multiple regression–correlation analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Erlbaum.

Committee on Veterans Affairs, U.S. Senate. (1988). *Oversight on posttraumatic stress disorder* (Senate Hearing 100-900), pp. 25–39, 257–346. Washington, DC: U.S. Government Printing Office.

Critchlow, B. (1986). The powers of John Barleycorn: Beliefs about the effects of alcohol on social behavior. *American Psychologist, 41,* 751–764.

DeFazio, V. J., Rustin, S., & Diamond, A. (1975). Symptom development in Vietnam era veterans. *American Journal of Orthopsychiatry, 45,* 158–163.

de Lint, J., & Schmidt, W. (1973). Consumption averages and alcoholism prevalence: A brief review of epidemiological investigations. In P. C. Whitehead, C. F. Grindstaff, & C. L. Boydell (Eds.), *Alcohol and other drugs* (pp. 108–119). Toronto, Ontario, Canada: Holt, Rinehart, and Winston.

Dobbs, D., & Wilson, W. P. (1960). Observations on persistence of war neurosis. *Diseases of the Nervous System, 21,* 686–691.

Dohrenwend, B. P. (1975). Sociocultural and social-psychological factors in the genesis of mental disorders. *Journal of Health and Social Behavior, 16,* 365–392.

Fairbank, J. A., & Nicholson, R. A. (1987). Theoretical and empirical issues in the treatment of post-traumatic stress disorder in Vietnam veterans. *Journal of Clinical Psychology, 43*(Suppl.), 44–55.

Foy, D. W., Sipprelle, R. C., Rueger, D. B., & Carroll, E. M. (1984). Etiology of posttraumatic stress disorder in Vietnam veterans: Analysis of premilitary, military, and combat exposure influences. *Journal of Consulting and Clinical Psychology, 52,* 79–87.

Frank, J. D., & Frank, J. B. (1991). *Persuasion and healing: A comparative study of psychotherapy* (3rd ed.). New York: Schocken.

Goldberg, J., True, W. R., Eisen, S. A., & Henderson, W. G. (1990). A twin study of the effects of the Vietnam War on posttraumatic stress disorder. *Journal of the American Medical Association, 263,* 1227–1232.

Grady, D. A. (1990). Epilogue: A self-guide for Vietnam veterans. In R. A. Kulka, W. E. Schlenger, J. A. Fairbank, R. L. Hough, B. K. Jordan, C. R. Marmar, & D. S. Weiss (Eds.), *Trauma and the Viet-*

nam War generation: Report of findings from the National Vietnam Veterans Readjustment Study (pp. 276–308). New York: Brunner/Mazel.

Greenspan, F. S., & Baxter, J. D. (1994). *Basic and clinical endocrinology* (4th ed.). Norwalk, CT: Appleton and Lange.

Gunnar, M. R. (1992). Reactivity of the hypothalamic-pituitary-adrenocortical system to stressors in normal infants and children. *Pediatrics, 90*(Suppl.), 491–497.

Hanson, F.R. (1949). The factor of fatigue in the neuroses of combat. *Army Medical Bulletin* (Suppl. 9), 147–150.

Helzer, J. E., Robins, L. N., & McEvoy, L. (1987). Post-traumatic stress disorder in the general population: Findings of the Epidemiologic Catchment Area Survey. *New England Journal of Medicine, 317,* 1630–1634.

Hennekens, C. H., & Buring, J. F. (1987). *Epidemiology in medicine.* Boston: Little, Brown.

Hofer, M. A. (1987). Early social relationships: A psychobiologist's view. *Child Development, 58,* 633–647.

Hosmer, D. W., & Lemeshow, S. (1989). *Applied logistic regression.* New York: Wiley.

Janes, G. R., Goldberg, J., Eisen, S. A., & True, W. R. (1991). Reliability and validity of a combat exposure index for Vietnam era veterans. *Journal of Clinical Psychology, 47,* 80–86.

Keane, T. M., Zimering, R. T., & Caddell, J. M. (1985). A behavioral formulation of posttraumatic stress disorder in Vietnam veterans. *Behavior Therapist, 8,* 9–12.

Kolb, L. C. (1993). The psychobiology of PTSD: Perspectives and reflections on the past, present, and future. *Journal of Traumatic Stress, 6,* 293–304.

Kormos, H. R. (1978). The nature of combat stress. In C. R. Figley (Ed.), *Stress disorders among Vietnam veterans: Theory, research and treatment* (pp. 3–22). New York: Brunner/Mazel.

Kulka, R. A., Schlenger, W. E., Fairbank, J. A., Hough, R. L., Jordan, B. K., Marmar, C. R., & Weiss, D. S. (1990a). *The National Vietnam Veterans Readjustment Study: Tables of findings and technical appendices.* New York: Brunner/Mazel.

Kulka, R. A., Schlenger, W. E., Fairbank, J. A., Hough, R. L., Jordan, B. K., Marmar, C. R., & Weiss, D. S. (1990b). *Trauma and the Vietnam War generation: Report of findings from the National Vietnam Veterans Readjustment Study.* New York: Brunner/Mazel.

Laufer, R. S., Gallops, M. S., & Frey-Wouters, E. (1984). War stress and trauma: The Vietnam veteran experience. *Journal of Health and Social Behavior, 25,* 65–85.

Mahoney, M. J. (1974). *Cognition and behavior modification.* Cambridge, MA: Ballinger.

Malloy, P. F., Fairbank, J. A., & Keane, T. M. (1983). Validation of a multimethod assessment of posttraumatic stress disorders in Vietnam veterans. *Journal of Consulting and Clinical Psychology, 51,* 488–494.

Mason, J. W., Giller, E. L., Kosten, T. R., & Harkness, L. (1988). Elevation of urinary norepinephrine/cortisol ratio in posttraumatic stress disorder. *Journal of Nervous and Mental Disease, 176,* 498–502.

Mason, J. W., Giller, E. L., Kosten, T. R., Ostroff, R. B., & Podd, L. (1986). Urinary free-cortisol levels in posttraumatic stress disorder patients. *Journal of Nervous and Mental Disease, 174,* 145–149.

Mullins, W. S. (Ed.). (1973). *Neuropsychiatry in World War II* (Vol. 2). Washington, DC: Office of the Surgeon General.

Nace, E. P., Meyers, A. L., O'Brien, C. P., Ream, N., & Mintz, J. (1977). Depression in veterans two years after Viet Nam. *American Journal of Psychiatry, 134,* 167–170.

Neter, J., Wasserman, W., Kutner, M. H. (1990). *Applied linear models: Regression, analysis of variance, and experimental designs* (3rd ed.). Homewood, IL: Irwin.

Pitman, R. K., Orr, S. P., Forgue, D. F., de Jong, J. B., & Claiborn, J. M. (1987). Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. *Archives of General Psychiatry, 44,* 970–975.

Polner, M. (1971). *No victory parades: The return of the Vietnam veteran.* New York: Holt, Rinehart, and Winston.

Robins, L. N., Davis, D. H., & Goodwin, D. W. (1974). Drug use by U.S. Army enlisted men in Vietnam: A follow-up on their return home. *American Journal of Epidemiology, 99,* 235–249.

Robins, L. N., Helzer, J. E., & Cottler, L .B. (1987). *The Diagnostic Interview Schedule training manual, Version III-A.* St. Louis, MO: Veterans Administration.

Robins, L. N., Helzer, J. E., Croughan, J., & Ratcliff, K. S. (1981). National Institute of Mental Health Diagnostic Interview Schedule: Its history, characteristics, and validity. *Archives of General Psychiatry, 38,* 381–389.

Robins, L. N., Helzer, J. E., Ratcliff, K. S., & Seyfried, W. (1982). Validity of the Diagnostic Interview Schedule, Version 2: *DSM-III* diagnoses. *Psychological Medicine, 12,* 855–870.

Salmon, T. W. (1919). War neuroses and their lesson. *New York Medical Journal, 109,* 993–994.

SAS Institute, Inc. (1993). *SAS for Windows* (Version 6). Cary, NC: Author.

Shalev, A. Y., Orr, S. P., & Pitman, R. K. (1993). Psychophysiologic assessment of traumatic imagery in Israeli civilian patients with post-traumatic stress disorder. *American Journal Psychiatry, 150,* 620–624.

Sherman, A. R. (1973). *Behavior modification: Theory and practice.* Monterey, CA: Brooks/Cole.

SPSS, Inc. (1994). *SPSS for Windows* (Version 6.01). Chicago: Author.

Stata Corporation. (1994). *Stata* (Release 3.1). College Station, TX: Author.

van der Kolk, B., Greenberg, M., Boyd, H., Krystal, J. (1985). Inescapable shock, neurotransmitters, and addiction to trauma: Toward a psychobiology of post-traumatic stress. *Biological Psychiatry, 20,* 314–325.

van der Kolk, B. A., & Saporta, J. (1993). Biological response to psychic trauma. In J. P. Wilson & B. Raphael (Eds.), *International handbook of traumatic stress syndromes* (pp. 25–33). New York: Plenum.

Veiel, H. O., & Baumann, U. (Eds.). (1990). *The meaning and measurement of social support.* New York: Hemisphere.

Winer, B. J., Brown, D. R., & Michels, K. M. (1991). *Statistical principles in experimental design* (3rd ed.). New York: McGraw-Hill.

Wilson, J. P., & Raphael, B. (Eds.). (1993a). *International handbook of traumatic stress syndromes.* New York: Plenum.

Wilson, J. P., & Raphael, B. (1993b). Theoretical and conceptual foundations of traumatic stress syndromes. In J. P. Wilson & B. Raphael (Eds.), *International handbook of traumatic stress syndromes* (pp. 1–9). New York: Plenum.

Yehuda, R., Lowy, M. T., Southwick, S. M., Shaffer, D., & Giller, E. L. (1991). Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder. *American Journal of Psychiatry, 148,* 499–504.

Yehuda, R., Southwick, S., Giller, E. L., Ma, X., & Mason, J. W. (1992). Urinary catecholamine excretion and severity of PTSD symptoms in Vietnam combat veterans. *Journal of Nervous and Mental Disease, 180,* 321–325.

Yehuda, R., Southwick, S. M., Nussbaum, G., Wahby, V., Giller, E. L., & Mason, J. W. (1990). Low urinary cortisol excretion in patients with posttraumatic stress disorder. *Journal of Nervous and Mental Disease, 178,* 366–369.