THE NATIONAL CENTER
FOR PTSD
VAM&ROC 116D
WHITE RIVER JUNCTION
VERMONT 05001 USA
802-296-5132
FTS 834-1132

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BIOLOGICAL ASPECTS OF PTSD: LABORATORY AND CLINICAL RESEARCH

All research reviewed in this issue of the *PTSD Research Quarterly* concerns laboratory and clinical findings on biological aspects of PTSD. In addition to abstracts and citations of peer-reviewed articles published since 1988, we have included citations of important papers presented at national scientific meetings during the past year. While recognizing the considerable difference between peer-reviewed and other data, we believe that PTSD researchers may benefit from our publicizing selected unpublished results. Because the 41 selected abstracts and citations are listed separately and because both lists are alphabetized, designated abstracts will be indicated by "A" (e.g., van der Kolk et al., A), whereas citations will be indicated by "C" (e.g., Kudler et al., C).

There is growing literature suggesting that PTSD is associated with abnormalities in a number of distinct biological systems, including the central and peripheral sympathetic nervous system (SNS), the hypothalamic-pituitary-adrenocortical (HPA) axis, the endogenous opioid system, and the diurnal sleep cycle. Comprehensive, provocative, and theoretical review articles and two very recent books assessing these results are listed on page 5.

Regarding the SNS, Pitman et al. (A, C) have replicated earlier findings that Vietnam veterans with PTSD exhibit increased psychophysiologic reactivity when instructed to imagine actual combat experiences in which they had participated. Another psychophysiological abnormality associated with PTSD is an enhanced acoustic startle eyeblink response in traumatized children (Ornitz & Pynoos, 1989; see *PTSD Research Quarterly*, *1 (1)*, 1990) and in Vietnam veterans with PTSD, Rausch et al. (C). Finally, Paige et al. (A) measured event-related brain potentials (ERPs) and found that Vietnam combat veterans with PTSD could be distinguished from combat veteran non-PTSD controls by a "reducer" pattern of P2 component amplitudes. The PTSD patients also exhibited a lower threshold for autonomic arousal.

Psychophysiological findings are bolstered by neuroendocrine/neuropharmacological findings showing that excessive SNS reactivity is associated with increased adrenergic function (McFall et al., A; Mason et al., A). Other reports suggesting adrenergic dysfunction in PTSD are reports of excessive plasma dopamine levels at rest (Hamner & Diamond, C) and excessive plasma MHPG levels following exercise (Hamner et al., C) in combat veterans with PTSD. Dramatic evidence suggesting CNS adrenergic dysfunction was reported by Southwick et al. (C), who observed that the alpha-2 antagonist yohimbine precipitated panic attacks and flashbacks in a significant percent of Vietnam combat veterans with PTSD but not in healthy controls.

Because one would predict that a hyperadrenergic state would produce down-regulation of adrenergic receptors, it is of great interest that such changes have been observed. Lerer et al. (A) observed reduced beta adrenergic receptor binding in the blood platelets of Israeli combat veterans. Similar results have been obtained in studies on platelet alpha-2 receptors. Perry (C) observed reduced alpha-2 receptor binding in abused children and adolescents, and Yehuda et al. (C) observed that Vietnam combat veterans with PTSD had significantly fewer alpha-2 binding sites than depressed, anxious, or control subjects. Finally, DeMet et al.'s (A) finding that panic disorder but not PTSD patients appear to up-regulate A_1-adenosine receptors suggests that there may be some specificity to the aforementioned beta and alpha-2 receptor abnormalities observed in PTSD.

Although most studies on HPA axis function in PTSD patients indicate abnormalities in this system, research in this area does not show the same overall consistency as do results on SNS and adrenergic function. Lower urinary and plasma cortisol levels have been found in PTSD patients by some investigators (Halbreich et al., A, C; Mason et al., A; Yehuda et al., A), although other groups (Hoffman et al., A; Pitman & Orr, C) found no difference in plasma cortisol levels between PTSD combat veterans and control subjects. The report by Rahe et al. (C) on higher plasma and saliva cortisol levels among American hostages freed from Iran is equivocal because there is no diagnostic information about the presence or absence of PTSD. Combining SNS and HPA abnormalities, Mason et al. (A) reported that PTSD patients ex- hibit a significantly higher urinary norepinephrine/cortisol ratio than patients with other psy-chiatric disorders.

Because HPA activity is generally increased in major depressive disorder (MDD), there is considerable interest in comparisons of HPA function in PTSD and MDD. Aforementioned reports on lower cortisol levels in PTSD show that patients who meet criteria for both PTSD and MDD also have lower cortisol levels. Furthermore, patients with PTSD and MDD tend to show suppression follow-

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ing a dexamethasone challenge, whereas patients with MDD alone are more likely to show non-suppression after dexa-methasone (Halbreich et al., A, C). Similarly, Olivera & Fero (A) reported that dexamethasone non-suppression did not occur in any PTSD patients except for a fraction of PTSD patients who also met criteria for MDD. Finally, Smith et al. (A) reported that PTSD patients show a blunted adrenocorticotropin (ACTH) response to corticotropin-releasing hormone (CRH), as do patients with MDD, panic disorder, or anorexia nervosa.

Another neuroendocrine abnormality observed in combat veterans with PTSD is significant elevation in serum testosterone levels, in contrast to the reduced level seen in MDD (Mason et al., C).

Opioid system dysfunction is suggested by three intriguing articles. Pitman et al. (A) and van der Kolk et al. (A) reported a naloxone-reversible analgesic response following exposure to a videotaped segment from the movie *Platoon* among combat veterans with PTSD. These results are reviewed in context of the inescapable shock model of PTSD. Hoffman et al. (A) observed lower plasma endorphin levels among PTSD patients, suggesting that chronic endogenous opioid depletion may be a factor in PTSD.

Sleep abnormalities in PTSD have been reviewed by Ross et al. (1989; see *PTSD Research Quarterly, 1 (1)*, 1990). Consistent with the hypothesis proposed in that article, these investigators recently reported excessive REM activity among Vietnam combat veterans with PTSD (Ross et al., C). Kaminer & Lavie (C), however, did not find increased REM activity among Holocaust survivors with PTSD. Furthermore, Kramer & Kinney (C) have observed disturbed dreaming in Vietnam combat veterans with PTSD during non-REM sleep. Other reports on the quality of sleep of PTSD patients describe repetitive nightmares, spontaneous awakenings, and insomnia (Inman et al., C; Rosen et al., C). Finally, Kaminer & Lavie (C) reported a dramatic lack of dream recall among well-adjusted survivors of the Nazi Holocaust both in contrast to survivors with a post-traumatic syndrome and in contrast to age-matched controls.

Among a number of intriguing clinical reports, one with major medical implications is the finding by Shalev et al. (A) that Israeli combat veterans with PTSD exposed to a multi-stage incremental-load ergometric test exhibit low effort tolerance, cardiac reserve, and physical fitness in contrast to combat veterans without PTSD. With regard to the SNS arousal associated with drug withdrawal, Risse et al. (A) reported that patients undergoing alprazolam withdrawal experienced severe exacerbation of PTSD intrusive recollections and arousal symptoms. In a neuropathological review among WWII French combat veterans, Crocq et al. (C) reported that cranial injuries were more closely associated with PTSD symptoms than non-cranial injuries.

Despite numerous published articles on open trials of different drugs in PTSD (which are summarized in many of the review articles listed on page 5), there have been very few controlled pharmacological trials. We have abstracted all relevant literature in this regard, which consists primarily of double-blind comparisons of antidepressants: tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs). Results have been mixed. Frank et al. (A, C) reported that an 8-week course of both the MAOI phenelzine and the TCA imipramine were significantly better than placebo in reducing intrusive symptoms such as nightmares, intrusive recollections, and flashbacks. Phenelzine was superior to imipramine in this regard. In contrast, Davidson et al. (A) reported modest reduction in PTSD symptoms following 8 weeks of treatment with the TCA amitriptyline in comparison to placebo. They noted that amitriptyline showed far greater antidepressant and anxiolytic than anti-PTSD potency in this study. Reist et al. (A) reported no difference between TCA and placebo following a 4-week double-blind cross-over trial of desipramine. Finally, Shestatzky et al. (A) also reported negative findings following a 4-week double-blind cross-over trial comparing the MAOI phenelzine with placebo. An instructive note by Kudler et al. (C) points out a number of important factors in measuring the results of treatment of PTSD, including the quality of assessment instruments and the apparent necessity for the clinical trial to last at least 8 weeks.

We conclude by citing three additional drug trials of interest. Famularo et al. (A) demonstrated the efficacy of propanolol with an off-on-off design in 11 children with PTSD. Wolf et al. (C) reported on two successful open trials of the anticonvulsant carbamazepine in combat veterans with PTSD and related those results to the kindling hypothesis of PTSD, and McDougle et al. (C) presented data on a successful open trial of fluoxetine, noting that global improvement was especially related to reduction of PTSD avoidant symptoms.

SELECTED ABSTRACTS

DAVIDSON, J., KUDLER, H., SMITH, R., MAHORNEY, S.L., LIPPER, S., HAMMETT, E., SAUNDERS, W.B., & CAVENAR, J.O. (1990). **Treatment of posttraumatic stress disorder with amitriptyline and placebo.** *Archives of General Psychiatry, 47,* 259-266. Amitriptyline hydrochloride was compared with placebo in 46 veterans with chronic PTSD. Treatment continued up to 8 weeks, and efficacy was measured by five observer and two self-rated scales. Percent recovery rates were higher for amitriptyline than placebo on two measures. In patients who completed 4 weeks (n = 40), better outcome with amitriptyline was noted on the Hamilton depression scale only. In the group completing 8 weeks of treatment (n = 33), the drug was superior to placebo on Hamilton depression, Hamilton anxiety, Clinical Global Impression severity, and Impact of Event scales. There was no evidence for drug effects on the structured interview for PTSD. Drug-placebo differences were greater in the presence of comorbidity in general, although recovery rates were uniformly low in the presence of major depression, panic disorder, and alcoholism. At the end of treatment, 64% of the amitriptyline and 72% of the placebo samples still met diagnostic criteria for PTSD.

DEMET, E., STEIN, M.K., TRAN, C., CHICZ-DEMET, A., SANGDAHL, C., & NELSON, J. (1989). **Caffeine taste test for panic disorder: adenosine receptor supersensitivity.** *Psychiatry Research, 30,* 231-242. The present study introduces a novel measure of adenosine receptor sensitivity that is based on the action of specific receptor blockers (e.g., caffeine) to potentiate the ability to detect threshold quinine concentrations. The test is used to compare gustatory adenosinergic responses to caffeine challenges in normal controls and patients with panic disorder or PTSD. Panic disorder patients had an exaggerated response to the caffeine challenge that was not found in controls or PTSD patients, although the latter had higher anxiety scores on psychometric tests. The results are related to a model in which A_1-adenosine receptors up-regulate in an attempt to modulate hyperactive excitatory neuronal systems.

FAMULARO, R., KINSCHERFF, R., & FENTON, T. (1988). **Propranolol treatment for childhood posttraumatic stress disorder, acute type.** *American Journal of Diseases of Children, 142,* 1244-1247. We report 11 cases of PTSD. Each child had been physically abused or sexually abused or both and presented in an agitated, hyperaroused state. Using a B-A-B (off-on-off) medication design in a clinical setting, the children were treated with beta-adrenergic antagonist propranolol. Scores on an inventory of symptoms of PTSD indicated that patients exhibited significantly fewer symptoms while receiving medication than either before or after they received medication.

FRANK, J.B., KOSTEN, T.R., GILLER, E.L., & DAN, E. (1988). **A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder.** *American Journal of Psychiatry, 145,* 1289-1291. In a double-blind, randomized clinical trial, the efficacy of imipramine and of phenelzine was compared with that of placebo in 34 male veterans with PTSD. Both medications reduced PTSD symptoms.

HALBREICH, U., OLYMPIA, J., CARSON, S., GLOGOWSKI, J., YEH, C.M., AXELROD, S., & DESU, M.M. (1989). **Hypothalamo-pituitary-adrenal activity in endogenously depressed post-traumatic stress disorder patients.** *Psychoneuroendocrinology, 14,* 365-370. We studied the hypothalamo-pituitary-adrenal (HPA) system in Vietnam veterans with PTSD who also met Research Diagnostic Criteria for endogenous depression (MDD-ED). Over half also abused alcohol, and many complained of pain-confounding factors usually associated with increased HPA activity. Nonetheless, not even one patient had elevated basal plasma cortisol concentrations or an abnormal dexamethasone suppression test (DST); the subjects' post-dexamethasone cortisol values and plasma cortisol per ng plasma dexamethasone were in the low-normal range. These results highlight the biological heterogeneity of endogenous depression and its possible influence by past psychological trauma, and they raise questions about the use of current typological criteria for research purposes.

HOFFMAN, L., BURGES WATSON, P., WILSON, G., & MONTGOMERY, J. (1989). **Low plasma ß-endorphin in posttraumatic stress disorder.** *Australian and New Zealand Journal of Psychiatry, 23,* 269-273. We compared serum cortisol, ACTH, and plasma beta-endorphin in 21 PTSD patients and 20 controls. Although we found no important disturbance in diurnal rhythms, the PTSD patients had significantly higher A.M. serum cortisols compared with controls. Both A.M. and P.M. plasma beta-endorphins in PTSD patients were significantly lower compared with controls. These data suggest that plasma beta-endorphin may be a marker for PTSD and that chronic endogenous opioid depletion may play a role in the pathogenesis and perpetuation of this disorder.

LERER, B., BLEICH, A., BENNETT, E.R., EBSTEIN, R.P., & BALKIN, J. (1990). **Platelet adenylate cyclase and phospholipase C activity in posttraumatic stress disorder.** *Biological Psychiatry, 27,* 735-740. Adenylate cyclase and phospholipase C activity were examined in platelet membranes obtained from 19 male subjects with combat-related PTSD and 35 age- and gender-matched healthy controls. Basal and forskolin-stimulated adenylate cyclase activity were significantly lower in the PTSD group whereas aluminum chloride plus sodium fluoride (AlCl3 | NaF)- and prostaglandin E_1 (PGE_1)-stimulated responses were normal. There was no difference in phospholipase C activity between the two groups. The lower basal and forskolin-stimulated adenylate cyclase responses replicate a previous report and suggest that PTSD may be associated with an abnormality of the catalytic subunit of the receptor-adenylate cyclase complex.

MASON, J.W., GILLER, E.L., KOSTEN, T.R., & HARKNESS, L. (1988). **Elevation of urinary norepinephrine/cortisol ratio in posttraumatic stress disorder.** *The Journal of Nervous and Mental Disease, 176,* 498-502. We have previously reported the unusual combination of low urinary free cortisol levels with high urinary norepinephrine excretion in PTSD patients in comparison with four other patient groups: major depressive disorder, endogenous type; bipolar I, manic; paranoid schizophrenia; undifferentiated schizophrenia. Cortisol levels alone did not distinguish PTSD from paranoid schizophrenia patients and norepinephrine levels alone did not distinguish PTSD from bipolar I, manic, patients. In further consideration of these findings, we have found that combining the values for the two systems in a norepinephrine/cortisol (N/C) ratio provides a measure that significantly distinguishes PTSD from all the other patient groups throughout the hospitalization period. The N/C ratio was more than twice as high in the PTSD group than in all the other patient groups in the first sample following hospital admission, in the mean sample during hospitalization, and in the last sample before discharge. The mean N/C ratio for the PTSD group was 2.54, compared with a mean of .99 for the other four groups. which ranged from .81 to 1.18. The diagnostic sensitivity was 78% and the specificity was 94% for correct classification of PTSD in our sample. These preliminary findings yield further encouragement for exploring multivariate strategies, using hormonal ratios or profiles, in an effort to increase the diagnostic sensitivity of neuroendocrine criteria in the assessment of psychiatric patients.

MCFALL, M.E., MURBURG, M.M., KO, G.N., & VEITH, R.C. (1990). **Autonomic responses to stress in Vietnam combat veterans with posttraumatic stress disorder.** *Biological Psychiatry, 27,* 1165-1175. This study tested the hypothesis that combat veterans with PTSD experience sympathetic nervous system activation in response to war-related laboratory stimuli. Circulating plasma catecholamines, vital signs, and affect ratings were measured in 10 Vietnam combat veterans with PTSD and 11 control subjects, during and after viewing combat and noncombat stress films. PTSD subjects responded more strongly than controls to the combat film, with greater increases in plasma epinephrine, pulse, blood pressure, and subjective distress. The increases in autonomic activity of PTSD subjects were more pronounced and long lasting in response to the combat film than to the noncombat film, but type of film had no systematic effect on control subjects' responses. These findings are consistent with biological models that posit sympathoadrenal activation in re-

sponse to memory-evoking cues of traumatic events in PTSD.

OLIVERA, A.A. & FERO, D. (1990). **Affective disorders, DST, and treatment in PTSD patients: clinical observations.** *Journal of Traumatic Stress, 3,* 407-414. A study of 109 chronic PTSD patients found 65 suffered current major affective disorders. Of these 65, 84.8% had major depression and 15.2% had bipolar disorder. Nonsuppression of the DST occurred only in those cases with concurrent major affective disorder; the incidence of nonsuppression was 32.3%. Treatment effectively attained clinical improvement and conversion of nonsuppressor to suppressor state in these cases. The DST, cortisol suppression index, and inhibition of cortisol production index were useful to support the clinical diagnosis of major affective disorders in PTSD patients, in an exclusively clinical setting.

PAIGE, S.R., REID, G.M., ALLEN, M.G., & NEWTON, J.E.O. (1990). **Psychophysiological correlates of posttraumatic stress disorder in Vietnam veterans.** *Biological Psychiatry, 27,* 419-430. We measured event-related brain potential component amplitudes and heart rate (HR) to four intensities of randomly presented tones in two matched groups of drug-free male Vietnam veterans: 12 patients diagnosed with PTSD and 6 normal combat veterans. Subjects were evaluated with structured diagnostic interviews and anxiety and depression rating scales. We found a significant group X intensity interaction for P2 peak amplitude at CZ. Subjects were classified as augmenters or reducers: positive P2 slopes as a function of stimulus intensity implying augmentation and negative slopes implying reduction. Nine of 12 PTSD subjects were reducers (sensitivity of 75%) and 5 of 6 normals were augmenters (specificity of 83.3%). By the third and fourth second following tone onset, the mean HR of PTSD subjects increased more than twice that of the normals. HR change scores were significantly responsive to the manipulation of stimulus intensity and to the difference between our two groups. P2 reduction differentiates Vietnam veterans with combat-related PTSD from combat veteran controls, and PTSD subjects are more autonomically arousable than their combat veteran peers.

PITMAN, R.K., ORR, S.P., & STEKETEE, G.S. (1989). **Psychophysiological investigations of posttraumatic stress disorder imagery.** *Psychopharmacology Bulletin, 25,* 426-431. Physiological responses to self-generated imagery of past traumatic combat experiences were assessed in medication-free Vietnam combat veterans, classified on the basis of DSM-III-R criteria into PTSD ($n = 25$), non-PTSD anxiety disorder (Anxious, $n = 7$), or no-mental-disorder (Healthy, $n = 15$) groups. "Scripts" describing each subject's combat experiences were read to him in the laboratory, and he was instructed to imagine the events the scripts portrayed, while heart rate, skin conductance, and frontalis electromyogram were recorded. PTSD subjects' responses to their combat imagery were significantly higher than those of both control groups. A discriminant analysis identified 64 percent of PTSD subjects as physiological responders, and 100 percent of Anxious and 94 percent of Healthy subjects as nonresponders. A pilot study of imaginal flooding in three PTSD and two Healthy pilot subjects suggested that more prolonged, therapist-assisted imagery might increase the sensitivity of psychophysiological measures to PTSD, and that motor and endocrinological measures might also be of value in characterizing the disorder.

PITMAN, R.K., VAN DER KOLK, B.A., ORR, S.P., & GREENBERG, M.S. (1990). **Naloxone-reversible analgesic response to combat-related stimuli in posttraumatic stress disorder.** *Archives of General Psychiatry, 47,* 541-544. We tested the hypothesis that exposure to a stimulus resembling the original traumatic event would induce naloxone-reversible analgesia in patients with PTSD. Eight medication-free Vietnam veterans with PTSD and eight veterans without PTSD, matched for age and combat severity, viewed a 15-minute videotape of dramatized combat under naloxone hydrochloride and placebo conditions in a randomized double-blind crossover design. In the placebo condition, the subjects with PTSD showed a 30% decrease in reported pain intensity ratings of standardized heat stimuli after the combat videotape. No decrease in pain ratings occurred in the subjects with PTSD in the naloxone condition. The subjects without PTSD did not show a decrease in pain ratings in either condition. The results are consistent with the induction of opioid-mediated stress-induced analgesia in the patients with PTSD.

REIST, C., KAUFFMANN, C.D., HAIER, R.J., SANGDAHL, C., DEMET, E.M., CHICZ-DEMET, A., & NELSON, J.N. (1989). **A controlled trial of desipramine in 18 men with posttraumatic stress disorder.** *American Journal of Psychiatry, 146,* 513-516. Eighteen male U.S. veterans meeting DSM-III criteria for PTSD completed a 4-week double-blind, crossover study comparing administration of 200 mg/day of desipramine with placebo. Response was measured by using the Beck Depression Inventory, the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, and the Impact of Events Scale. Overall, the only apparent response to desipramine was in some symptoms of depression; there were no changes in anxiety and other PTSD symptoms.

RISSE, S.C., WHITTERS, A., BURKE, J., CHEN, S., SCURFIELD, R.M., & RASKIND, M.A. (1990). **Severe withdrawal symptoms after discontinuation of alprazolam in eight patients with combat-induced posttraumatic stress disorder.** *Journal of Clinical Psychiatry, 51,* 206-209. Eight patients with combat-induced chronic PTSD receiving long-term alprazolam therapy for anxiety or depression (maximum dose of 2-9 mg/day for 1-5 years) had alprazolam therapy withdrawn. Most of the patients underwent gradual medication withdrawal. All patients had a prior history of alcohol abuse or benzodiazepine dependence. During withdrawal, all patients had severe reactions including anxiety, sleep disturbance, rage reactions, hyperalertness, increased nightmares, and intrusive thoughts; and 6 of the 8 patients had homicidal ideation. As a result of this report, the authors suggest that the potential for severe withdrawal reactions, even with gradual tapering, should be considered before prescribing alprazolam therapy for this group of patients.

SHALEV, A., BLEICH, A., & URSANO, R.J. (1990). **Posttraumatic stress disorder: somatic comorbidity and effort tolerance.** *Psychosomatics, 31,* 197-203. To explore psychological and somatic distress following trauma, the authors compared 50 combat veterans with chronic PTSD with 48 age-matched combat veterans without PTSD. Both groups were evaluated on symptom reports, physical examination findings, and laboratory tests. Subjects with PTSD reported significantly more symptoms, but they did not differ from controls on their physical examination and laboratory test findings. Adverse health practices (smoking, alcohol use, and deregulation of food intake) were significantly more frequent in the PTSD group. Low effort tolerance, as has been reported in panic disorder patients, was observed in the PTSD group.

SHESTATZKY, M., GREENBERG, D., & LERER, B. (1987). **A controlled trial of phenelzine in posttraumatic stress disorder.** *Psychiatry Research, 24,* 149-155. Thirteen patients meeting DSM-

III criteria for PTSD participated in a random-assignment, double-blind crossover trial comparing phenelzine (45-75 mg/day) and placebo. Ten patients completed at least 4 weeks of each treatment phase. Clinical response to phenelzine did not differ from placebo, and overall improvement by the end of the study could not be attributed to the active drug. The findings are discussed in the light of preliminary reports suggesting that phenelzine may be an effective treatment for PTSD.

SMITH, M.A., DAVIDSON, J., RITCHIE, J.C., KUDLER, H., LIPPER, S., CHAPPELL, P., & NEMEROFF, C.B. (1989). **The corticotropin-releasing hormone test in patients with posttraumatic stress disorder.** *Biological Psychiatry, 26,* 349-355. To evaluate the hypothalamic-pituitary-adrenal axis in patients with PTSD, we measured adrenocorticotropin hormone (ACTH) and cortisol responses following administration of corticotropin-releasing hormone (CRH) in 8 combat veterans with chronic PTSD. The PTSD patients had a significantly lower ACTH response to CRH compared to a control group of normal volunteers. Blunted ACTH responses occurred in patients with PTSD alone, as well as those PTSD patients who also had major depression. The cortisol response, although reduced, was not significantly different from normal. The blunted ACTH response to CRH in PTSD patients is similar to that seen in other psychiatric disorders, such as depression, panic disorder, and anorexia nervosa.

VAN DER KOLK, B.A., GREENBERG, M.S., ORR, S.P., & PITMAN, R.K. (1989). **Endogenous opioids, stress induced analgesia, and posttraumatic stress disorder.** *Psychopharmacology Bulletin, 25,* 417-421. The hypothesis that the animal model of inescapable shock is an appropriate model for PTSD predicts that re-exposure to a traumatic stressor will precipitate opioid-mediated stress-induced analgesia in people with PTSD. Eight Vietnam veterans with PTSD and eight matched veterans without PTSD viewed a combat videotape under naloxone and placebo conditions in a randomized double-blind crossover design. In the placebo conditions, but not after naloxone, the PTSD subjects reported a 30 percent decrease in pain intensity ratings of standardized heat stimuli after the combat videotape. Point biserial correlations revealed that change in pain perception was the most highly correlated with PTSD of all variables tested, including biochemical, physiological, and self-report. These results suggest that a centrally mediated opioid response to traumatic stimuli is an important feature of PTSD. Possible implications of this finding for the psychobiology of PTSD are discussed.

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. In the present study we replicated and extended our previous findings of low urinary free-cortisol levels in PTSD. Cortisol was measured in 16 male patients (9 inpatients, 7 outpatients) with PTSD and in 16 nonpsychiatric control subjects. The mean cortisol level in the PTSD group was significantly lower, and the range narrower, than that observed in control subjects. Low cortisol in PTSD did not seem to be related to the presence or absence of a major depressive disorder or to overall psychiatric symptomatology as assessed by the sum Brief Psychiatric Rating Scale score. In the outpatient group, there was a relationship between PTSD symptomatology and cortisol levels. The findings suggest a physiological adaptation of the hypothalamic-pituitary-adrenal axis to chronic stress.

REVIEWS

BOEHNLEIN, J.K. (1989). **The process of research in posttraumatic stress disorder.** *Perspectives in Biology and Medicine, 32,* 455-464.

BURGES WATSON, I.P., HOFFMAN, L., & WILSON, G.V. (1988). **The neuropsychiatry of post-traumatic stress disorder.** *British Journal of Psychiatry, 152,* 164-173.

DAVIDSON, J.R.T., & NEMEROFF, C.B. (1989). **Pharmacotherapy in posttraumatic stress disorder: Historical and clinical considerations and future directions.** *Psychopharmacology Bulletin, 25,* 422-425.

FRIEDMAN, M.J. (1988). **Toward rational pharmacotherapy for posttraumatic stress disorder: An interim report.** *American Journal of Psychiatry, 145,* 281-285.

KOLB, L.C. (1987). **A neuropsychological hypothesis explaining posttraumatic stress disorders.** *American Journal of Psychiatry, 144,* 989-995.

KOLB, L.C. (1988). **A critical survey of hypotheses regarding posttraumatic stress disorders in light of recent findings.** *Journal of Traumatic Stress, 1,* 291-304.

KOSTEN, T.R., & KRYSTAL, J. (1988). **Biological mechanisms in posttraumatic stress disorder: Relevance for substance abuse.** *Recent Developments in Alcoholism, 6,* 49-68.

KRYSTAL, J.H., KOSTEN, T.R., SOUTHWICK, S., MASON, J.W., PERRY, B.D., & GILLER, E.L. (1989). **Neurobiological aspects of PTSD: Review of clinical and preclinical studies.** *Behavior Therapy, 20,* 177-198.

VAN DER KOLK, B.A. (1987). **The drug treatment of posttraumatic stress disorder.** *Journal of Affective Disorders, 13,* 203-213.

VAN DER KOLK, B.A. (1988). **The trauma spectrum: The interaction of biological and social events in the genesis of the trauma response.** *Journal of Traumatic Stress, 1,* 273-290.

BOOKS

GILLER, E.L. (1990). **Biological assessment and treatment of posttraumatic stress disorder**. Washington, DC: American Psychiatric Press.

WOLF, M.E., & MOSNAIM, A.D. (1990). **Posttraumatic stress disorder: Etiology, phenomenology, and treatment.** Washington, DC: American Psychiatric Press.

ADDITIONAL CITATIONS
Annotated by the Editors

CROCQ, M., MACHER, J., DUVAL, F., BARROS-BECK, J., & VAN VALKENBURG, C. (1990). **The residual effect of cranial injury on post-traumatic stress symptoms over 40 years later.** *Biological Psychiatry, 27*:54A.

Studied the effects of cranial injury in French Alsatian men who had been drafted into the German Army during World War II, and then were captured and imprisoned by the Russians. Cranial injury was more closely associated than other wounds with PTSD symptoms, including intrusive recollections, intense anxiety upon exposure to stimuli associated with war or imprisonment, efforts to avoid thoughts or feelings associated with the trauma, frequent anger outbursts, and inability to have loving feelings. Non-cranial injuries were associated only with stimulus-provoked intense anxiety.

FRANK, J., KOSTEN, T., GILLER, E., DAN, E., & MCDOUGALL, C. (1990, May). **Phenelzine and imipramine in the treatment of PTSD.** *Paper presented at the American Psychiatric Association Meeting, New York City.*

Extended research (abstracted above) to a total of 60 outpatient combat veterans with PTSD who received phenelzine, imipramine, or placebo in an 8-week, randomized, double-blind trial. Both drugs were superior to placebo in improving global functioning and specific PTSD symptoms, but phenelzine was the most effective for intrusive symptoms such as nightmares, intrusive recollections, and flashbacks. Nonspecific improvement in depression or anxiety did not account for these findings. The authors state that these findings are more consistent with a neurotransmitter imbalance theory of PTSD than with theories of transmitter surplus or deficiency.

HALBREICH, U., OLYMPIA, J., GLOGOWSKI, J., CARSON, S., AXELROD, S., & YEH, C.M. (1988). **The importance of past psychological trauma and pathophysiological process as determinants of current biologic abnormalities.** [Letter to the editor]. *Archives of General Psychiatry, 45,* 293-294.

Assessed HPA function in depressed (MDD) patients with (n = 14) and without (n = 73) PTSD. Not a single patient with PTSD & MDD was a dexamethasone nonsuppressor compared with 26 patients with MDD alone. Basal plasma cortisol levels were significantly lower in the PTSD & MDD group than in the MDD group. The authors point out that traumatic exposure appears to have influenced the biology of the PTSD & MDD group even though it did not differ phenomenologically from the MDD group with respect to DSM-III diagnostic symptoms.

HAMNER, M., & DIAMOND, B. (1990, May). **Elevated plasma dopamine levels in PTSD.** *Paper presented at the American Psychiatric Association Meeting, New York City.*

Measured resting plasma dopamine and norepinephrine levels by HPLC with electrochemical detection in male Vietnam combat veterans meeting DSM-III-R criteria for PTSD, male veterans meeting DSM-III-R criteria for major depressive episode, and controls. Resting plasma dopamine was higher in PTSD patients than in the other groups. The authors conclude that their findings support the hypothesis that abnormalities of catecholamine function are present in PTSD.

HAMNER, M., DIAMOND, B., & HITRI, A. (1990, May). **Plasma catecholamine response to exercise in PTSD.** *Paper presented at the American Psychiatric Association Meeting, New York City.*

Compared the effects of a standard grade-incremented exercise treadmill test to maximal intensity on plasma catecholamines in 10 male veterans meeting DSM-III-R criteria for PTSD and in 8 age-matched controls. Exercise produced a significant increase in plasma NE levels in both groups, but plasma MHPG increased significantly only in the PTSD patients. The authors conclude that the comparable NE responses but differential MHPG responses suggest that altered catecholamine metabolism may be present in PTSD.

INMAN, D.J., SILVER, S.M., DOGHRAMJI, K. (1989). **Sleep disturbance in post-traumatic stress disorder: a comparison with non-PTSD insomnia.** *Journal of Traumatic Stress, 3,* 429-437.

Used a questionnaire to compare sleep disturbance between Vietnam combat veterans with PTSD and non-PTSD patients with insomnia. PTSD patients reported more agitation, nocturnal body movements, and repetitive nightmares that disrupted sleep. PTSD patients also showed more fatigue and anxiety when awake.

KAMINER, H., & LAVIE, P. (1989). **Dreaming and long term adjustment to severe trauma.** *Sleep Research, 18,* 146.

Evaluated the sleep of 23 Holocaust survivors (12 well-adjusted and 11 with PTSD symptoms) and 10 controls by polysomnograph for four nights. The PTSD group had poorer sleep but no difference in REM percent, REM latency, or percentages of stages 3/4 than the other two groups. The most significant finding, however, was a dramatic lack of dream recall in Holocaust survivors with "outstanding adjustment to post-war life" in contrast to the other two groups.

KRAMER, M., & KINNEY, L. (1988). **Sleep patterns in trauma victims with disturbed dreaming.** *Psychiatric Journal of the University of Ottawa, 13,* 12-16.

The sleep pattern of dream-disturbed Vietnam combat veterans was compared with that of combat veterans whose PTSD was not marked by disturbed dreaming. Both groups slept poorly, but the dream-disturbed group exhibited a longer REM latency and more spontaneous awakenings during non-REM sleep.

KUDLER, H.S., DAVIDSON, J.R.T., STEIN, R., & ERICKSON, L. (1989). **Measuring results of treatment of PTSD.** [Letter to the editor] *American Journal of Psychiatry, 146,* 1645-1646.

Marked two important points about published double-blind trials with TCAs and MAOIs. First, there is a need for a well-validated observer-rated scale in PTSD research. Second, it appears that 8 weeks should be the minimum assessment period for drug trials in PTSD.

MASON, J.W., GILLER, E.L., KOSTEN, T.R., & WAHBY, V.S. (1990). **Serum testosterone levels in post-traumatic stress disorder inpatients.** *Journal of Traumatic Stress, 3,* 449-457.

Serum testosterone was measured at 2-week intervals during the course of hospitalization of 34 psychiatric patients with either PTSD, depression, bipolar disorder, or paranoid schizophrenia. A group of healthy controls was also included. PTSD patients had consistently higher testosterone levels than depressed or bipolar patients.

MCDOUGLE, C., SOUTHWICK, S., ST. JAMES, R., & CHARNEY, D. (1990, May). **An open trial of fluoxetine.** *Paper presented at the American Psychiatric Association*

Meeting, New York City.
Reported an open trial of fluoxetine in male Vietnam veterans with PTSD. Thirteen of 20 patients responded to treatment, with reduction of avoidance symptoms in particular contributing to global improvement in responders. The authors note that a controlled comparison with placebo is necessary.

PERRY, B. (1990, May). **Adrenergic receptors in child and adolescent PTSD.** *Paper presented at the American Psychiatric Association Meeting, New York City.*
Examined the effects of traumatic stressors on the development of the autonomic nervous system in abused children and adolescents using measures of heart rate, blood pressure, and platelet alpha-2 adrenergic receptor/effector systems. The results indicated higher baseline heart rate and blood pressure and down-regulated alpha-2 receptors in these abused children and adolescents.

PITMAN, R.K., & ORR, S.P. (1990). **Twenty-four hour urinary cortisol and catecholamine excretion in combat-related posttraumatic stress disorder.** *Biological Psychiatry, 27,* 245-247.
Measured 24-hour urinary catecholamines and free cortisol levels in 13 combat veterans with PTSD and in 10 healthy controls. No differences were found. This study failed to replicate findings from other laboratories showing decreased cortisol excretion, elevated catecholamine excretion, and increased catecholamine/cortisol ratio.

PITMAN, R.K., ORR, S.P., FORGUE, D.F., ALTMAN, B., DE JONG, J.B., & HERZ, L.R. (1990). **Psychophysiologic responses to combat imagery of Vietnam veterans with posttraumatic stress disorder versus other anxiety disorders.** *Journal of Abnormal Psychology, 99,* 49-54.
Used psychophysiologic techniques to assess responses to imagery of stressful past experiences among Vietnam combat veterans with PTSD ($n = 7$) or with non-PTSD anxiety disorders ($n = 7$). A discriminant function derived from a previous study correctly identified 5/7 PTSD veterans as physiologic responders and all 7 of the anxious subjects as nonresponders.

RAHE, R.H., KARSON, S., HOWARD, N.S., RUBIN, R.T., & POLAND, R.E. (1990). **Psychological and physiological assessments on American hostages freed from captivity in Iran.** *Psychosomatic Medicine, 52,* 1-16.
Performed medical, psychological, physiological, and neuroendocrine evaluations on 52 Americans who had been held hostage in Iran for 444 days within 5 days of their release. Psychological testing suggested that the hostages coped well with their ordeal. In contrast, plasma and saliva cortisol, urinary catecholamines, and saliva testosterone were all highly elevated. No hostages were diagnosed for the presence or absence of PTSD.

RAUSCH, J., BUTLER, R., BRAFF, D., JENKINS, M., SPROCK, J., & GEYER, M. (1990). **Empirical confirmation of an exaggerated startle response in PTSD.** *Biological Psychiatry, 27*:165A.
Compared Vietnam combat veterans with and without PTSD on eyeblink EMG amplitude to acoustic and tactile stimuli. Groups were divided into responders and nonresponders based on whether they demonstrated any eyeblink response to the stimuli. PTSD responders showed greater eyeblink amplitude than control responders at intermediate intensities of acoustic stimulation.

ROSEN, J., REYNOLDS, C., HOUK, P., YEAGER, A., & HURWITZ, L. (1990, May). **Sleep in survivors of the Nazi Holocaust.** *Paper presented at the American Psychiatric Association Meeting, New York City.*
Presented a comparison of self-reported sleep behavior in elderly survivors of the Nazi Holocaust, elderly depressed patients, and controls. Survivors had more sleep problems than controls but fewer than depressives. Survivors had more reported awakenings due to bad dreams than either of the other groups. The authors conclude that impaired sleep and frequent nightmares are significant problems for some Holocaust survivors.

ROSS, R., BALL, W., DINGES, D., KRIBBS, N., MORRISON, A., & SILVER, S. (1990, May). **REM sleep disturbance as the hallmark of PTSD.** *Paper presented at the American Psychiatric Association Meeting, New York City.*
Reported a comparison of sleep architecture in Vietnam veterans with PTSD and normal control veterans. The PTSD group had a higher percentage of REM sleep, longer REM sleep period duration, higher REM density, and greater variance of REM latency. The authors suggest that PTSD might involve a problem in the timely recruitment of CNS processes that define REM sleep and in specific events within REM sleep.

SOUTHWICK, S., KRYSTAL, J., & CHARNEY, D. (1990, May). **Yohimbine in PTSD.** *Paper presented at the American Psychiatric Association Meeting, New York City.*
Used a challenge paradigm to evaluate 13 male Vietnam veterans meeting SCID DSM-III-R criteria for PTSD and 7 healthy controls, who received either the adrenergic alpha-2 antagonist yohimbine or placebo in a randomized balanced design under double-blind conditions on two separate days. Of the PTSD patients, 62% experienced a panic attack and 31% had a flashback on yohimbine, but none had a panic attack and 8% had a flashback on placebo; no panic attacks or flashbacks were observed in controls under either condition. Forty-six percent of the PTSD patients met criteria for comorbid panic disorder. The authors conclude that because the response of PTSD patients to yohimbine closely resembles the response seen in panic disorder patients, PTSD and panic may share common biological abnormalities.

WOLF, M., LIPPER, S., & MOSNAIM, A. (1990). **Carbamazepine and the kindling hypothesis of PTSD.** *Biological Psychiatry, 27*:165A-166A.
Conducted an open trial of carbamazepine in two groups of veterans with PTSD. In one group, carbamazepine provided symptomatic relief of poor impulse control, violent behavior, and angry outbursts. In the other group, assessed with different measures, carbamazepine decreased nightmares, flashbacks, and intrusive recollections. The authors propose that confirmation of findings under double-blind conditions may provide support for the kindling hypothesis of PTSD.

YEHUDA, R., PERRY, B., SOUTHWICK, S., & GILLER, E. (1990, May). **Platelet alpha2-receptor binding in PTSD, generalized anxiety disorder, and major depressive disorder.** *Paper presented at the American Psychiatric Association Meeting, New York City.*
Reported platelet alpha-2 adrenergic binding in PTSD, generalized anxiety disorder, major depression, and controls. Patients with PTSD had significantly fewer alpha-2 adrenergic binding sites than patients with either MDD or GAD and normal controls. Patients with MDD or GAD did not differ from each other but had more binding sites than either patients with PTSD or normals.

PILOTS: AN UPDATE

PILOTS, a bibliographical database covering Published International Literature On Traumatic Stress, is produced at the headquarters of the National Center for Post-Traumatic Stress Disorder. It will provide detailed subject indexing of the world's literature on PTSD, without disciplinary, linguistic, or geographical limitations, and will offer both current and retrospective coverage.

The announcement of our plans for PILOTS in the last *PTSD Research Quarterly* aroused considerable excitement; we have already been asked to perform several searches of the database, even though it contains at this point only a fraction of the known PTSD literature. We are therefore pleased to announce that we have made arrangements to add the PILOTS database to the health science offerings of BRS Information Technologies. Any registered BRS user will have access to PILOTS as well as to EMBASE, MEDLINE, PsycINFO, and scores of other databases in medicine, business, science, the humanities, and the social sciences.

The BRS Search Service offers both command- and menu-driven searching. Its powerful software offers librarians and other expert searchers great flexibility in developing search strategies and displaying the results. PILOTS will also be available through BRS Colleague, a simplified system developed for health professionals, and BRS After Dark, a low-cost evening and weekend service aimed at students and faculty members on limited budgets.

PILOTS will be a subfile of the Combined Health Information Database (CHID), a cooperative project of several federal agencies. CHID subfiles cover specialized fields in the health sciences, such as AIDS, Alzheimer's disease, diabetes, and health education. CHID is used heavily by health professionals; a recent survey of database users indicated that it is a leading source of information on medical research and consumer health issues. We feel that by joining forces with CHID we shall bring PILOTS to the attention of users beyond the PTSD field.

We plan to have PILOTS available on BRS beginning with CHID's quarterly update for April 1991. While the database will not be complete by that time, it will include substantially all of the following:

1. Current literature on PTSD as listed in *Current Contents* (Clinical Medicine, Life Sciences, and Social and Behavioral Sciences editions) since January 1990.
2. Articles in the *Journal of Traumatic Stress*, beginning with its first issue (January 1988).
3. Clinical articles listed in Dr. Arthur Arnold's *Selected Bibliography IV: Post-Traumatic Stress Disorder with Special Attention to Vietnam Veterans* (September 1987).
4. English-language articles on PTSD indexed in MEDLINE (from 1966) and PsycINFO (since 1967).
5. English-language books on PTSD listed in the National Library of Medicine's CATLINE database.

While it is our intention to include foreign-language material in PILOTS, the above priorities reflect the need for our small staff to concentrate its efforts on the literature that will be of the most immediate use to English-speaking researchers and clinicians. We have identified papers in over 20 languages; though we can index those in French and German, we will need help in dealing with those in other languages, particularly Eastern European and Oriental. Therefore we are soliciting the help of volunteers from the PTSD community who would be willing to provide us with English-language translations of titles and English abstracts. We would also encourage authors of papers published in languages other than English to supply us with English translations if they can do so conveniently. (We would also like to receive translations into other languages of English-language papers where these are available.)

A final request: despite extensive searches of the PTSD literature, we are sure to miss some valuable publications, or discover them well after their appearance in print. Researchers and clinicians publishing papers on PTSD can help us, their colleagues, and themselves by sending reprints to us. (Even when preprints are sent, it would be a great help also to have a copy of the paper as it actually appears in print.) We would also like to receive copies of already-published papers. If it is not possible to send us a complete set, a bibliography of PTSD publications would be helpful.

Through CHID and BRS, PILOTS will be available to PTSD researchers, clinicians, and policymakers worldwide. And through PILOTS the published work of PTSD experts will benefit from a high level of impact and visibility, crossing geographic, linguistic, and disciplinary borders.

For information on BRS, contact:

BRS Information Technologies
8000 Westpark Drive
McLean, Virginia 22102
(800) 955-0906

Maxwell Online
Achilles House
Western Avenue
London W3 0UA
England
#(01) 992 3456

Maxwell Online
P.O. Box 544
Potts Point, New South Wales
Australia
#(008) 22 6474