ANXIETY RESEARCH (U.K.), Volume 4: Pages 199-212.

THE BIOLOGICAL RESPONSE TO PSYCHIC TRAUMA: MECHANISMS AND TREATMENT OF INTRUSION AND NUMBING

BESSEL A. VAN DER KOLK and JOSE SAPORTA
Harvard Medical School

(Received 23 December 1991)

The recognition that trauma is qualitatively different from stress and results in lasting biological emergency responses following traumatic experiences may account for the biphasic trauma response, and the accompanying memory disturbances. The past decade has seen rapid advances in our understanding of the underlying biology of this "physioneurosis". In addition to classically conditioned physiological reactions, changes now have been demonstrated in startle response in people with post-traumatic stress disorder and in central nervous system catecholamine, serotonin, and endogenous opioid systems. This paper reviews the research data which have demonstrated changes in these systems and explores how these biological changes may be related to the characteristic hyper-reactivity, loss of neuromodulation, numbing of responsiveness, dissociative states, and memory disturbances seen in PTSD. There is growing evidence that trauma has different biological effects at different stages of primate human, development. This article relates these findings to the studies which have demonstrated clear linkages between childhood trauma, and a variety of psychiatric disorders, including borderline personality disorder, and a range of self-destructive behaviors.

KEY WORDS: Post-traumatic stress disorder, psychobiology, arousal, memory, self-destructive behavior., psychopharmacology

> They will fail to cope psychologically with their problems until they have a sense of security in their bodies. In loosing control over their bodily functions they are not the competent people they were before.
>
> (Kolb & Multipassi, 1982 p. 985).

BACKGROUND

The recognition that trauma is qualitatively different from stress and results in lasting biological change goes back to the dawn of contemporary psychiatry. A century ago, Pierre Janet (1889) taught that overwhelming experiences are accompanied by "vehement emotions" which interfere with proper information processing and appropriate action. He thought that this hyperarousal caused the characteristic

memory disturbances that accompany traumatization, by interfering with information processing on a verbal, symbolic level. Hyperarousal causes memories to be split off from consciousness and to be stored as visual images or bodily sensations. Fragments of these "visceral" memories return later as physiological reactions, emotional states, nightmares, flashbacks, or behavioral reenactments (van der Kolk & van der Hart, 1989).

Janet thought that the original excessive physiological response to trauma accounted for the continued emergency responses to subsequent stresses. He claimed that fear needs to be tamed for proper cognitive appraisal and for appropriate action: experiences which overwhelmed people's coping mechanisms set the stage (or to use Pavlov's later concept "condition" them) to react automatically with excessive emotional reactions to current experiences rooted in the past.

Freud adopted these views from Janet and also suggested that the fixation on the trauma is biologically based: "After severe shock . . . the dream life continually takes the patient back to the situation of his disaster from which he awakens with renewed terror . . . the patient has undergone a physical fixation to the trauma" (Freud, 1919, 1954, p. 207). The feature of hyperactivity to external stimuli was described by Freud in the clearest neuropsychiatric terms that he knew: "I think that one may venture . . . the traumatic neurosis as the result of an extensive rupture in the barrier against stimuli . . . we seek to understand the effect of the shock by considering the breaking through of the barrier with which the psychic organ is provided (p. 207).

Pavlov's investigations continued the tradition of explaining the trauma response as the result of lasting physiological alterations (Pavlov, 1926). He, and others employing his paradigm, coined the term "defensive reaction" for a cluster of innate reflexive responses to environmental threat. Many studies have shown how the response to potent environmental stimuli (unconditional stimuli-US) becomes a conditioned reaction. After repeated aversive stimulation, intrinsically non-threatening cues associated with the trauma (conditional stimuli-US) becomes a conditioned reaction. After repeated aversive stimulation, intrinsically non-threatening cues associated with trauma (conditional stimuli-CS) become capable of eliciting the defensive reaction by themselves (conditional response-CR). A rape victim may respond to conditioned stimuli, such as the approach by an unknown man as if she were about to be raped again, and experience panic. Pavlov also pointed out that "constitutional factors", i.e. individual differences in temperament, accounted for the variability in the human approach to traumatic stimuli.

Abraham Kardiner (1941) who first systematically defined post-traumatic stress for American audiences, noted that sufferers from PTSD continue to live in the emotional environment of the traumatic event, with enduring vigilance for and sensitivity to environmental threat. He described the five principal features of PTSD

as (1) persistance of startle response and irritability, (2) proclivity to explosive outbursts of aggression, (3) fixation on the trauma, (4) constriction of the general level of personality functioning, nad (5) atypical dream life. He suggested that the startle reaction probably was a conditioned reflex and considered it the central element of the post-traumatic stress reaction, relating it to the development of irritability and psychosomatic symptoms in these patients.

In War Stress and Neurotic Illness, Kardiner and Spiegal (1945) stated that a traumatic neurosis is a physical one, and that the physical sensation endures: "the nucleus of the neurosis is a physioneurosis. This is present on the battlefield and during the entire process of organization; it outlives every intermediary accommodative device, and persists in the chronic forms. The traumatic syndrome is ever present and unchanged" (p. 38).

In Men under Stress, Grinker and Spiegel (1945) describe physical symptoms in the acute post-traumatic state that seem to reflect neurochemical changes of the catecholamine system: they describe flexor changes in posture, hyperkinesis, "violently propulsive gait", tremor at rest, masklike faces, absence of associated movement while walking, cogwheel rigidity, gastric distress, urinary incontinence, mutism, and a violent startle reflex. Grinker and Spiegal noted the similarity of many of these symptoms and those of diseases of the extrapyramidal motor system. They seem to depict an extraordinary stimulation of biological systems, implicating ascending amine projections in particular. Contemporary studies, generally unaware of this earlier research, have continued to scientifically test these conceptions and they confirm that the stress hormones of people with PTSD continue to react in minor stimuli as emergencies.

THE SYMPTOMATOLOGY OF PTSD

The phasic post-traumatic symptoms of hyperalertness, hyper-reactivity to stimuli and traumatic reexperiencing have been documented in a vast literature on combat trauma, crimes, such as rape (e.g., Burgess & Holstrom, 1974; Kilpatrick, Veronen, & Best, 1985), kidnapping (Terr, 1983), natural disasters (e.g., Shore, Tatum & Vollmer, 1986), accidents (e.g., Wilkinson, 1983) and imprisonment (Krystal, 1978). The human response to trauma is so constant across traumatic stimuli that it is safe to say that the central nervous system (CNS) seems to react to any overwhelming, threatening and uncontrollable experience in quite a consistent pattern. Regardless of these circumstances, traumatized people are prone to have intrusive memories of element of the trauma, to have a poor tolerance for arousal, to respond to stress in an all-or-nothing way, and to feel emotionally numb. All of these psychological phenonema must have a basis in biological functioning, some of these relationships between biological states are now ready to be explored. PTSD as defined in the DSM-III-R,

highlights those post-traumatic symptoms that are most clearly biologically based (for reviews see van der Kolk, 1987; Krystal et al., 1989); the secondary post-traumatic changes in identity and interpersonal relations are slated to be classified in the separate category of Disorders of Extreme Stress Not Otherwise Specified (DESNOS) in the DSM IV. Since there are good reasons to assume that the current PTSD hyperarousal are, biologically speaking, intimately related, we will discuss them jointly throughout this paper.

Autonomic Hyperactivity and Intrusive Reexperiencing

Kardiner (1941) coined the term "physioneurosis" to describe post-traumatic stress. He pointed out that while people with PTSD tend to deal with their environment by emotional constriction, their bodies continue to react to certain physical and emotional stimuli as if there were a continuing threat of annihilation. Starting with studies by Dobbs and Wilson (1960), conditioned autonomic arousal to combat stimuli has repeatedly been documented in veterans with PTDS. Using a variety of different techniques, Mallow, Fairbank, and Keane (1983) Kolb and Multipassi (1982), Blanchard, Kolb, Geradi, Ryan, and Pallmyer (1986) and Pitman, Orr, Forque, deJong, and Claiborn (1987), all have found significant conditioned reactions in response to stimuli reminscent of the original trauma, as measured by heartrate, bloodpressure and electromyogram. More recent studies have shown that both traumatized children (Ornitz, & Pynoos, 1989) and adults (Shalev et al., submitted) lack habituation to acoustic startle.

A relationship between autonomic arousal and intrusive recollections has long been postulated, and in recent years has started to be confirmed by the work of such investigators as Rainey and Southwick. Rainey et al. (1987) showed that the administration of lactate, which stimulates the physiological arousal system, elicited PTSD-like flashbacks in 7/7 subjects and panic attacks in 6 in 7 patients with PTSD, 6 of whom also met panic disorder criteria. Southwick and his colleagues demonstrated that yohimbine injections (which stimulate NE release from Locus Coeruleus) were able to induce somatosensory flashbacks in people with PTSD (Southwick et al., submitted). These studies further suggest common biological underpinnings of flashbacks and panic attacks in PTSD.

The reliability and specificity of the studies of physiological reactions to traumatic stimuli are beginning to raise the possibility that in the future a psychophysiologically based diagnostic test for PTSD will be available to help make the diagnosis. However, it is still unclear how specific the hyperarousal is as a conditioned response to traumatic stimuli alone. Clinical experience suggests that the increased autonomic arousal can be rather non-specific, and may occur in response to a variety of stimuli. In fact, some research suggests that habituation may follow repeated exposure to the traumatic stimulus itself, but associated events

continue to illicit hyperactivity (Strian & Klicpera, 1978). These findings can be used therapeutically in implosion therapy (Keane, Fairbanks, & Caddell 1989).

The loss of neuromodulation that is at the core of PTSD leads to intensification of emotional reactivity in general: traumatized people go immediately from stimulus to response without being able to make the intervening psychological assessment of the cause of their arousal, which causes them to overreact and intimidate others. Non-specific noises played into the rooms of sleeping people with post-traumatic stress may precipitate nightmares in which old traumatic occurrences are recreated in exact detail (Kramer, Schoen, & Kinney, 1984). Hyperorousal also interferes with psychotherapy, in preventing remembering and working through painful memories.

Numbing of Responsiveness

Numbing of responsiveness, which may be registered as depression, as anhedonia and amotivational states, as psychosomatic reactions, or in dissociative states, is tonic and part of the patients' baseline functioning. It interferes with the ability to explore, remember and symbolize which are essential to finding good meaning. Throughout the literature numbing is all too unquestioningly described as a psychological defense against remembering painful affects. Below, we will argue that numbing is a core, biologically based, symptom of PTSD.

DEVELOPMENTAL LEVEL AFFECTS THE PSYCHOBIOLOGICAL EFFECTS OF TRAUMA

While most studies on PTSD have been done on adults, particularly on war veterans, in recent years, a small prospective literature has emerged which calls attention to the differential effects of trauma at various age levels. Anxiety disorders, chronic hyperarousal, and reenactments have now been described with some regularity in acutely traumatized children (Bowlby, 1969; Eth & Pynoos, 1985, Stoddard, 1989; Terr; 1988). In addition to the reactions to discrete, one time, traumatic incidents documented in these studies, intrafamilial abuse must certainly be included among the most severe traumas encountered by human beings. This recognition opens up the boundaries between the current concept of PTSD and the what we have called "the trauma spectrum" (van der Kolk, 1988): other post-traumatic disorders ranging from those that result from brief traumatic exposure at an early age, such as phobias and panic, to Borderline Personality Disorder and Multiple Personality Disorder which are usually associated with chronic intrafamilial abuse (Herman, Perry, and van der Kolk, 1989). Specific neurobiological abnormalities are beginning to be identified along this spectrum: prospective studies by Putnam are showing neuroendrocrine disturbances in sexually abused girls compared with normals, while others (G. Gillette, personal communication, 1989) have demonstrated abnormalities of the hypothalamic-pituitary-throid axis in adult female psychiatric patients with childhood histories of incest. Non-brain damaged adult patients who mutilate themselves

invariably seem to have a history of severe childhood trauma, and their behavior has been associated with abnormalities of the endogenous opioid and catecholamine systems (Bach-y-Rita, 1974), van der Kolk, Greenberg, Orr, & Pitman, 1989). Research in the last decade has shown that many children who have been victims of intrafamilial abuse have chronic problems with hyperarousal, and aggression against others and themselves (Green, 1980; Cicchetti & Rosen, 1984; van der Kolk, Perry & Herman, 1991).

The biological effects of developmental trauma has best been studied in young non-human primates, who in many ways resemble young human beings. Forty years of primate research has firmly established that early disruption of the social attachment bond reduces the long term capacity to cope with subsequent social disruptions and to modulate physiological arousal. These studies have demonstrated that trauma early in the life cycle has long term effects on the neurochemical response to stress, including the magnitude of the catecholamine response, the duration and extent of the cortisol response, as well as a number of other biological systems, such as the serotonin and endogenous opioid systems (Kraemer et al., 1984, Reite & Field, 1987, van der Kolk, 1987).

TRAUMA AND THE LIMBIC SYSTEM

The limbic system plays an important role in guiding the emotions that stimulate the behavior necessary for self-preservation and survival of the species. It is responsible for such complex behaviors as feeding, fighting, fleeing and reproduction, and it also assigns free-floating feeling of significance, truth and meaning to experience (MacLean, 1985). Destruction of parts of the limbic system abolishes social behavior, including play, cooperation, mating, and care of the young. The apparent similarities between some aspects of Temporal Lobe Epilepsy (TLE), PTSD and some long term sequelae of childhood trauma continues to challenge us to further explore the effects of trauma on the limbic system. During this past decade, the relationships between environmental trauma and the organization and function of the limbic system are slowly beginning to be understood, in part because of the work on non-human primates, which has conclusively shown that disruption of early attachment directly affects the maturation of the limbic system (Kling & Steklis, 1976). The limbic system also is the primary area of the CNS where memories are processed, and the most likely place to find an explanation for the memory disturbances which follow trauma. The hippocampus, which records in memory the spatial and temporal dimensions of experiences, dose not fully mature until the third or fourth year of life. However, the system that subserves memories related to the quality (feel and sound) of experience (which is located in the amygdala) matures much earlier (O'Keefe & Nadel, 1978; Jacobs & Nadel, 1985). Thus, in the first few years of life only the quality of events, but not their context can be remembered. Even after that, the hippocampal

localization system remains vulnerable to disruption: severe or prolonged stress can disrupt hippocampal functioning, creating context-free fearful associations which are hard to locate in space and time. This results in amnesia for the specifics of traumatic experiences, but not the feelings associated with them. (Sapolsky, Krey, & McEwen, 1984). These experiences then may be encoded on a sensorimotor level without proper localization in space or time. They therefore cannot be easily tranlated into the symbolic language necessary for linguistic retrieval.

A third trauma related function of the limbic system involves the issue of kindling. Intermittent stimulation of the limbic system with an electrical current that was initially too small to produce overt behavioral effects can eventually sensitize limbic neuronal circuits and lower neuronal firing thresholds: repeated stimulation of the amygdala causes long-term alterations in neuronal excitability (for a review, see van der Kolk, 1987). It is possible that similar kindling phenomena occur when people are repeatedly traumatized, or when one traumatic event is followed by intrusive reexperiences. Thus, trauma may lead to lasting neurobiological and behavioral (characterological) changes mediated by alterations in the temporal lobe. Kindling may also account for the frequent finding of soft neurological signs in trauma victims, especially in child victims of physical or sexual abuse (van der Kolk, 1987). Open studies claim that carbamezapine is an effective treatment for the intrusive symptoms of PTSD (Lipper et al., 1986) which lends some support for a role of the limbic system in codifying post traumatic reactions.

THE NEUROMODULATION OF AROUSAL NORADRENERGIC VERSUS SEROTONERGIC PATHWAYS.

The Locus Coeruleus (LC) is at the anatomical core of the physiological arousal mechanism in the Central Nervous System (CNS). It is the principal source of noradrenaline (NE) in the CNS, the neurotransmitted responsible for delivering messages to the rest of the brain about the need to prepare for emergencies. These noradrenergic connections prepare the hypothalamic mechanisms which control defensive reactions to be ready for action. Another noradrenergic bundle connects the LC with the septo-campal system, the part of the limbic system involved in the evaluation of the incoming stimuli. This noradrenergic bundle does not carry specific information, only the general message: this in important (Gray, 1982). Impulses reaching the septo-hippocampal system influence the interpretation of incoming information. Several naturally occurring or exogenous biochemical agents influence noradrenergic activity: endogenous opiates inhibit the firing of the LC (Bird & Kuhar, 1977), while such pharmacological agents as clonidine and the beta adrenergic blockers produce the same effect by: reducing noradrenergic activity in the the LC neurons. Antianxiety drung interferer with LC activity by increasing GABA-ergic inhibition on the cell bodies of the LC.

The function of the septo-hippocampal system is to evaluate the rough meaning of incoming stimuli, and whether they are associated with reward, punishment, novelty, or non-reward. The hippocampus thus is thought to be the evaluation center involved in behavioral inhibition, obsessional thinking, exploratory behavior, scanning and construction of a spatial map (O'Keefe & Nadel, 1978). It fulfills the crucial function of storing and categorizing information. When categorization is complete, the hippocampus disengages from active control of behavior. External stress increases corticosterone production which decreases the firing rate of the hippocampuse (Pfaff, Silva, & Weiss, 1971). Lesions of the hippocampus lead to motor paralysis because of excessive interference from competing responses.

The signal that punishment is imminent activates two related mechanisms, one of which inhibits ongoing behavior, while the other increases the level of arousal. The behavioral facilitating system (BFS) (which is mediated by NE fibers emanating from the LC) activates the CNS structures necessary for emergency responses. The BFS is activated when specific goal-oriented aggressive attack patterns require motivated motor support (Dupre & Spoont, 1989). The opposing system, that of behavioral inhibition (BIS) is mediated by the septo-hippocampal system, primed by ascending serotonergic and cholingergic mechanisms. The crucial role of the septo hippocampal system is to activate a descending inhibatory pathway which prevents initiation of emergency responses until it is clear that they are needed. Numerous studies have shown that serotonergic antagonists also cause increased aggression in response to stress, and hyper-reactivity to stimuli. (Sheard & Davis, 1976). The suppression of behavior by punishment is reversed by serotonin receptor blockers (e.g., Cook & Sepinwall, 1975). The ascending serotonergic pathways are thought to signal the septo-hippocampus to distinguish punishment from reward. The introduction of the serotonin reuptake blockers fluvoxamine, fluoxetine and gepirone demonstrated how these agents reversed the continued emergency responses and repetitive behaviors following stress in animals, allowing a better understanding about the degree to which decreased serotonin seems to play a role in these behaviors. Current clinical trials of these drugs in people with PTSD suggest that they are by far the most effective biological treatments of PTSD currently available. This makes us believe that in traumatized individuals decreased serotonin decreases the influence of the Behavioral Inhibition System, thereby disposing the septo-hippocampal system to interpret ordinary stressors as recurrents of traumatic experiences. Thus we postulate that lowered serotonin activity in PTSD is responsible for the continuation of emergency responses to minor stresses long after the actual trauma has ceased.

THE STRESS RESPONSE AND THE PSYCHOBIOLOGY OF PTSD

Arousal

The body responds to increased physical or psychological demands by releasing norepinephrine from the Locus Coerulus and adrenorcorticotrophin (ACTH) from the anterior pituitary. The precise interactions between the various stress hormones is extremely complex, and still is poorly understood, but both norepinephrine and epinephrine play a role in stimulating the release of CRF (Axelrod & Neisine, 1984). The Hypothalamus regulates ACTH release by the secretion of corticotrophin releasing factor (CRF). The hypothalamus also secretes throxin releasing hormone (TRH) which activates the secretion of Thyroid Stimulating Hormone (TSH) from the pituitary. CRF, as well as vasopressin, activates the release of ACTH and beta endorphin and stimulate adenylate cyclase activity and the formation of cyclic AMP. Peripherally, the body's stress response consists of the secretion of norepinephrine by the sympathetic nerves and of epinephine by the adrenal medulla, while, stimulated by ACTH, the adrenal cortex secretes glucocorticoids. These hormones help the body mobilize the energy necessary to deal with stressors, ranging from increased glucose release to enhanced immune function. In a well functioning organism stress produces rapid and pronounced hormonal responses. However persistent stress blunts this effective stress response and induces desensitization: after prolonged stress, CRF secretion produces less cylic AMP formation and ACTH release because of down regulation of CRF receptors (Axelrod & Neisine, 1984).

It therefore is not surprising that, in a study of the psychobiology of PTSD, stress hormones have figured most prominently, and that abnormalities of these systems are often found in patients with PTSD. Kosten, Mason, Giller, Ostroff, and Harkness (1987) found increased 24 hour norepinephrine and epinephrine secretions in veterans with PTSD compared with patients other psychiatric diagnoses. Mason, Giller & Kosten (1988) found low 24 hour urinary cortisol levels in Vietnam veterans with PTSD. In a different study, PTSD subjects showed blunted ACTH response to CRH stimulation: Smith et al. (1989) found that the severity of PTSD was directly related to baseline cortisol level. This supports the notion that there is chronically increased levels of cortisol in patients with PTSD. However, Smith et al. also suggested the alternative explanation of decreased pituitary function secondary to persistent elevations of endogenous CRH due to chronic HYPAC axis activity at the level of the hypothalamus.

Changes in receptor activity have been found in PTSD which are consistent with down regulation secondary to chronic exposure to elevated levels of circulating catecholamines: Perry and associates (Perry, Giller, & Southwick, 1987) have demonstrated a 40% decrease in the muber of platelet alpha2 adrenergic receptors in 25 patients with PTSD. Lerer, Ebstein, Shestatsky, Shemesh, and Greenberg (1987) recently reported evidence of desensitization of adenylate cyclase coupled adrenergic receptors on lymphocytes and platelets with PTSD.

However, persistent activation of stress response is not only a function of the stress hormones themselves, but also of the capacity of the organism to modulate arousal. We discussed before how serotonergic input into the septal-hippocamus decreases the relative strength of the noradrenergic input, allowing modulation of the emergency responses. The serotonin reuptake blockers fluvoxamine, fluextine and gepirone seem to have a dramatic beneficial effect on the capacity to modulate arousal and decrease Post-traumatic repetitions of images, behaviors, or somatic states. The clinical trials with these drugs suggest that they are by far the most effective biological treatments of PTSD currently available.

Numbing

While the numbing in responsiveness in PTSD has generally been conceptualized only in psychological terms, as a defense against reliving memories of the trauma, our recent research may shed some light on the biological components of this aspect of PTSD. Stress induced analgesia (SIA) has been described in experimental animals following a variety of inescapable stressors as electric shock, fighting, starvation and cold water swim. (Kelly, 1982; for a review see van der Kolk, 1987). In these severely stressed animals, opiate withdrawal symptoms can be produced equally by termination of the stressful stimulus or by naxolone injections. Thus, severe, chronic stress in animals results in a physiological state which resembles dependence on high levels of exogenous opioids (Terman, Shavit, Lewis, Cannon, & Liebeskind, 1984; Maier & Seligman, 1976).

Stimulated by the finding that fear activates the secretion of endogenous opioid peptides and that SIA can be become conditioned to subsequent stressors, and to previously neutral events associated with the noxious stimuli, we tested the hypothesis that in people with PTSD, re-exposure to a stimulus resembling the original trauma will cause an endogenous opioid response that can be indirectly measured as naxolone reversible anesthesia (van der Kolk et al., 1989; Pitman, van der Kolk, Orr, & Greensburg, 1990). We found that two decades after the original trauma, people with PTSD developed opioid-mediated analgesia in response to a stimulus resembling the traumatic stressor, which we correlated with a secretion of endogenous opioids equivalent to 8 mg. of morphine. This change in pain response was the most significant factor differentiating the PTSD from the control groups' response to a traumatic stimulus. Self-reports of emotional responses to the combat videotape in the placebo condition indicated a relative blunting of emotional response to the traumatic stimulus and we interpreted this finding to indicate that opioid-mediated SIA may be involved in psychic numbing. Survivors of severee trauma have repeated described a triad of physical analgesia, psychic numbing and depersonalization. Our finding of SIA in PTSD may also be relevant to the phenomenon of self-mutilation. Patients who engage is such self-destructive behavior or neglect invariably have a history of severe childhood trauma and, in response to even relatively minor emotional stressors, they may experience physical

analgesia, dissociative reactions and emotional numbing, which can be abolished b (1) an act of self-mutilation or (2) the administration of naloxone (Richardson & Zaleski, 1983; Sandman, Barron, Crinella, & Donnelly, 1987) Whether the analgesia, dissociative reactions, and emotional numbing reported in these patients are all functions of a conditioned endogenous opioid response to a traumatic stressor remains a subject for further investigation.

Memory disturbances in PTSD. One of the hallmarks of PTSD is the intrusive reexperiencing of elements of the trauma in nightmares, flashbacks, or somatic reactions. These traumatic memories seem to be triggered by autonomic arousal (Rainey et al., 1987) and are thought to be due to the hyperpotentiation of memory pathways and mediated by noradrenergic pathways originating the locus coeruleus (LC) (van der Kolk, Greenberg, Boyd, & Krystal, 1985). The innervation of the structures of the brain subserving memory functions originate in the LC from which noradrenergic projections go to the limbic system, cerebral cortex, and to a lesser degree the hypothalamus (Grant & Redmond, 1981). The LC also facilitates memory retrieval by means of the noradrenergic tracts in the hippocampus and amygdala (Delaney, Tussi, & Gold, 1983). We (van der Kolk et al., 1985) and Pitman (1989) have hypothesized that a long term augmentation of the LC pathways following trauma underlies the repetitive intrusive relieving of the trauma, particularly after renewed stress. Since autonomic arousal is mediated by the LC it is plausible that not only flashbacks, but also traumatic nightmares accur following autonomic nervous system activation, mediated by the potentiated pathways from the LC to the hippocampus and amygdala. This also could account for the eidectic (picure-like), rather than oneiric (dream-like) quality of traumatic nightmares (van der Kolk et al., 1984) Further evidence for the existence of such long-term potentiation of memory in patients with PTSD comes from the recent experimental work by Southwick et al. (submitted).

Sleep studies. Patients with PTSD have been found to have chronically disturbed sleep which appears to be related to chronic hypearousal. Both Kaminer and Lavie (1988) and van Kammen, Christiansen,, van Kammen, and Reynolds (1990) found increased sleep latency, more awakening, less total sleep time and less REM time. Several researchers have found PTSD patients to be exquisitely sensitive to non-specific auditory stimuli during sleep; the resulting autonomic arousal seems to precipitate nightmares about traumatic experiences, a finding that appears to analogous to that of Soutwick et al. We (van der Kolk et al., 1984) found that post-traumatic nightmares occur during any stage of the sleep cycle; that most tend to occur during 2 and 3 a.m. during Stage II or III sleep, possibly during a transition to REM sleep. When they occur during Stage II or III, patient report exact living experiences of traumatic material, while, during REM, they are more likely anxiety dreams.

Psychosomatic reactions. Numerous studies for the past one hundred years have established a causal relation between the inhibition of expression of traumatic

experience and psychophysiological impairment. These studies have demonstrated a marked increase in symptoms of the respiratory, digestive, cardiovascular and endocrine systems in people with PTSD (Janet, 1989; Krystal, 1978). Recent studies have indicated that learning to express the memories and feelings related to the traumatic event can restore some of the psychophysiological and immunological competence to people with trauma histories (Pennebaker & Susman, 1988).

IMPLICATIONS FOR THE PSYCHOPHARMACOLOGICAL TREATMENT OF PTSD

While giving voice to both the traumatic events and the affects related to them is generally considered the most effective treatment of PTSD, verbal therapies cannot proceed as long as the patient is unable to tolerate the feelings associated with the trauma and continues to experience subsequent emotionally stimulating event as an unmodified recurrence of the trauma. It often is necessary to supplement psychotherapy with medications which decrease autonomic arousal, or increase neuromodulation. Clinical studies of war veterans have show that the autonomic nervous system is centrally involved in many of the symptoms of PTSD, including startle reactions, irritability, nightmares and flashbacks ad explosive outbursts of aggression. It is therefore predictable that those medications which affect autonomic arousal would prove helpful in relieving the symptoms of PTSD. Autonomic arousal can be reduced at different levels in the central nervous system: although inhibition of noradrenergic activity, (clonidine and the beta adrenergic blockers), by increasing the inhibitory effect of the gaba-ergic system with gaba-ergic agonists (the benzodiazepines) and through enhancing the serotonergic inhibition system with agents such as Lithium and the serotonin uptake blockers, monomine oxidase inhibitors (Hogben & Cornfield, 1981; Frank, Kosken, Giller, & Dan, 1988), lithium carbonate (van der Kolk, 1983), beta adrenergic blockers and clonidine (Kolb, Burris, & Griffiths, 1984), carbamezapine (Lipper et al., 1986) and antipsychotic agents. However, no carefully controlled studies documenting the differential effects of various psychotropic medications on the symptoms of PTSD exist at this time. The only psychotropic medications whose efficacy in PTSD sympomatology have been evaluated in double blind studies are tricyclic antidepressants and MAO inhibitors Bleich, Siegel, Garb, Kettler, & Lerer, 1987; Davidson, Kudler, Smith, Mahorney, & Lipper, in press; Frank et al., 1988). These studies indicate that tricyclic antidepressants are effective in treating affective disorders in patients with PTSD, but do no little for core PTSD symptomatology, including psychological numbing. Tricyclic antidepressants generally thought to be most effective in treating nightmares, depression, sleep disorders and startle reactions, but were less able to relieve numbing. Hogben and Cornfield (1981) found MAO inhibitors effective in the treatment in PTSD, but that anecdotal study has not consisently held up to subsequent investigation (e.g., Shetaksy, Greenberg, & Lerer, 1989). Current studies in our laboratory indicate that the serotonin reuptake blocker fluoxetine is markedly

effective in treating both the intrusive and the numbing symptoms seen in patients with PTSD.

CONCLUSIONS

A rapidly expanding knowledge of the effects of traumatization on the functioning of the Central Nervous System, the dawning awareness that memory functions are central in understanding the nature of PTSD, combined with the availability of animal models for PTSD, makes the psychobiology of trauma one of the most promising areas in psychiatry. As long as the most effective therapy of PTSD has not been firmly established, a greater understanding of the biochemical and physiological correlates of traumatization should provide important clues about appropriate intervention. A variety of psychopharmacological agents that affect the physiological arousal system, including clonidine, benzodiazepines, monoamine oxidase inhibitors, and tricylic antidepressants decrease the long term effects of inescapable shock in animals, and seem to have varying degrees of use in the pharmacotherapy of PTSD. The recent discovery that serotonin reuptake inhibitors seem to act by quite a different mechanism and may be extremely effective in reducing both the intrusive and the numbing effects of PTSD needs to be carefully documented and understood. Further exploration during the coming decades of how trauma affects neuroendocrine emergency systems, neuromodulation, and memory should provide us with a much greater understanding about the interplay between soma and psyche in coping with potentially overwhelming experiences.

References

Axelrod, J., & Neisine (1984). Stress hormones, their interaction and regulation. *Science*, **224**, 452-459.

Bach-y-Rita, G. (1974). Habitual violence and self-mutilation. *American Journal of Psychiatry*, **131**(9), 1018-1020.

Bird, S.J., & Kuhar, M.J. (1977). Iontophoretic application of opiates to the locus coeruleas. *Brain Research*, **122**, 523-533.

Blanchard, B.E., Kolb, L.C., Gerardi, R.J., Ryan, P. & Pallmeyer, T.P. (1986) Cardiac response to relevant stimuli as an adjunctive tool for diagnosing post-traumatic stress disorder in Vietnam veterans. *Behavior Therapy*, **17**, 592-606.

Bleich, A., Siegel B., Garb, B., Kottler, A., & Lerer, B. (1987). PTDS following combat exposure: Clinical; features and pharmacological management. *British Journal of Psychiatry*, **149**, 365-369.

Bowlby, J. (1968) *Attachment and loss, Volume I. Attachment.* New York: Basic Books.

Burgess, A.W., & Holstrom, L. (1974). Rape trauma syndrome. *American Journal of Psychiatry*, **131**, 981-986.

Burstein, A. (1985). Post-traumatic flashbacks, dream disturbances and mental imagery. *Journal of Clinical Psychiatry*, **46**, 374-378.

Cichetti, D., & Rosen, K.S. (1984). Theoretical and empirical considerations in the investigation of the relationship between affect and cognition in an atypical population of infants. In C. Izard, J. Kagan, & R. Zajanc (Eds.), *Emotions, cognition and behavior* (pp.). New York: Cambridge University Press.

Cook, L., & Sepinwall, J. (1975). Behavioral analysis of the effect and mechanism of action of the

benzodiazepines. In E Costa & P. Greengard (Eds.), *Mechanisms of action of the benzodiazepines* (pp.), New York: Raven Press.
Davidson, J.R.T. Kudler, H.S., Smith, R.D., Mahorney, S.L., & Lipper, S.L. (in press). Amitriptyline and placebo in the treatment of post-traumatic stress disorder. *Archives General Psychiatry*.
Davidson, J.R.T., & Nemeroff, C.B. (1989) Pharmacotherapy in PTDS: Historical and clinical considerations and future directions. *Psychopharmacology Bulletin*, **25**, 422-425.
Delaney, R., Tussi, D., & Gold, P.E. (1983) Long term potentiation as a neurophysiological analog of memory. *Pharmacology, Biochemistry and Behavior*, **18**; 137-139.
Dobbs, D., & Wilson, W.P. (1960). Observations on the persistence of traumatic war neurosis. *Journal Mental & Nervous Disease*, **21**, 40-46.
Dupue, R.A., & Spoont, M.R. (1989). Conceptualizing a serotonin trait: A behavioral model of constraint. *Annals New York Academy of Sciences*, **12**, 47-62.
Eth, S., & Pynoos, R.S. (1985). Developmental perspective on psychic trauma in childhood. In C.R. Figley (Ed.), *Trauma and its wake* (pp.). New York: Brunner/Mazel.
Frank, J.B., Kosten, T.R., Giller, E.L., & Dan, E. (1988). A randomized clinical trial of phenelzine and imipramine in PTSD. *American Journal of Psychiatry*, **145**, 1289-1291.
Freud, S. (1954). *Introduction to psychoanalysis and the war neuroses Standard Edition*, Vol. 17 (pp.) (Strachey, Trans. and Ed.). London: Hogarth Press (Original work published 1919).
Grant, S.J., & Redmond, D.E. Jr. (1981). The neuroanatomy and pharmacology of the nucleus locus coeruleus. In H. Lal & S. Fieldings (Eds.), *Pharmacology of clonidine* (pp.). New York: Liss.
Gray, J. (1982) *The neuropsychology of anxiety. An inquiry into the functions of the septo-hippocampal system*. Oxford: Clarendon Press.
Green, A.H. (1980). *Child Maltreatment*. New York: Aronson.
Grinker, R.R. & Speigel, J.J. (1945). *Men under stress.* New York: McGraw-Hill.
Herman, J.L., Perry, J.C., & van der Kolk, B.A. (1989). Childhood trauma in borderline personality disorder. *American Journal of Psychiatry*, **146**, 390-395.
Hogben, G.L., & Cornfield, R.B. (1981). Treatment of war neuroses with phenelzine. *Archives General Psychiatry*, **38**, 440-445.
Jacobs, W.J., & Nadel, L. (1985). Stress-induced recovery of fears and phobias. *Psychological Review*, **92**, 512-531.
Janet, P. (1889). *L'Automatisme Psychologique* [The psychological automatism]. Paris: Alcan.
Kaminer, H., & Lavie, P. (1988). Dreaming and long term adjustment to severe trauma. *Sleep Research*, **18**, 146.
Kardiner, A. (1941). *The traumatic neuroses of war.* New York: Hoeber.
Kardiner, A., & Speigel, H. (1945). *War stress and neurotic illness*. New York: Hoeber.
Keane, T.M., Fairbank, J.A., & Caddell, J.M. (1989). Implosive (flooding) therapy reduces symptoms of PTSD in Vietnam combat veterans. *Behavior Therapy*, **16**, 419-423.
Kelly, D.D. (1982). The role of endorphins in stress-induced analgesia. *Annals New York Academy of Sciences*, **398**, 260-271.
Kilpatrick, D.G., Veronen, L.J., & Best, C.L. (1985) Factors predicting psychological distress in rape victims. In C. Figley (Ed.), *Trauma and its wake* (pp. 113-141). New York: Brunner/Mazel.
Kling, A., & Steklis, H.D. (1976). A neural substrate for affliative behavior in non-human primates. *Brain Behavioral Evolution*, **13**, 216-238.
Kolb, L.C., Burris, B.C. & Griffiths, S. (1984). Propranolol and clonidine in the treatment of post-traumatic stress disorders of war. In B.A. van der Kolk (Ed.), *Post-traumatic stress disorder: Psychological and biological sequelae* (pp.). Washington, D.C.: American Psychiatric Press.
Kolb, L.C., & Multipassi, L.R. (1984). The conditioned emotional response: A subclass of chronic and delayed post-traumatic stress disorder. *Psychiatric Annals*, **12**, 13-20.
Kosten, T.R., Mason, J.W., Giller, E.L., Ostroff, R.B., & Harkness, L. (1987). Sustained urinary norepinephrine and epinephrine elevation in PTSD. *Psychoneuroendocrinology*, **12**, 13-20.
Kramer, M., Schoen, L.S. & Kinney, L. (1984). The dream experience in dream disturbed Vietnam

veterans. In B.A. van der Kolk (Ed.), *Post-traumatic stress disorder: Biological and psychological sequelae* (pp.). Washington, D.C.: American Psychiatric Press.
Krystal, D. (1978). Trauma and affects. *The Psychoanalytic Study of the Child*, **33**, 81-116.
Krystal, J.H., Kosten, T.R., Southwick, S., Mason, D.W., Perry, B.D. & Giller, E.L. (1989). Neurobiological aspects of PTSD: Review of clinical and preclinical studies. *Behavior Therapy*, **20**, 177-198.
Lerer, B., Ebstein, R.P., Shestatsky, M., Shemesh, Z. & Greenberg, D. (1987) Cyclic AMP signal transduction in post-traumatic stress disorder. *American Journal of Psychiatry*, **144**, 1324-1327.
Lipper, S., Davidson, J.R.T., Grady, T.A., Edinger, J.D., Hammet, E.B., Mohorney, S.L. & Cavernar, J.O. (1986). Preliminary study of Carbamezapine in post-traumatic stress disorder. *Psychosomatics*, **27**, 847-854.
MacLean, P.D. (1985). Brain evolution relating to family, play, and the separation call. *Archives of General Psychiatry*, **42**, 505-517.
Maier, S.F. & Seligman, M.E.P. (1976). Learned helplessness: Theory and evidence. *Journal Experimental Psychology (General)*, **105**, 3-46.
Malloy, P.F., Fairbank, J.A. & Kean, T.M. (1983). Validation of a multimethod assessment of post-traumatic stress disorders in Vietnam veterans. *Journal of Consulting and Clinical Psychology*, **51**, 4-21.
O'Keefe, J. & Nadel, L. (1978). *The hippocampus as a cognitive map*. Oxford: Clarendon Press.
Ornitz, E.M. & Pynoos, R.S. (1989). Startle modulation in children with post-traumatic stress disorder. *American Journal of Psychiatry*, **146**, 866-870.
Pavlov, I.P. (1926) *Conditioned reflexes: An investigation of the physiological activity of the cerebral cortex* (G.V. Anrep, Trans. and Ed.). New York: Dover Publications.
Pennebaker, J.W. & Susman, J.R. (1988). Disclosure of traumas and psychosomatic processes. *Social Science and Medicine*, **26**, 327-332.
Perry, B.D., Giller, E.L. & Southwick, S.M. (1987). Altered plasma alpha-2 adrenergic receptor affinity states in PTSD. *American Journal of Psychiatry*, **144**, 1511-1512.
Pfaff, D.W., Silva, M.T. & Weiss, J.M. (1971). Telemetered recording of hormone effects on hippocampal neurons. *Science*, **172**, 394-395.
Pittman, R.K. (1989) Post-traumatic stress disorder, hormones, and memory. *Biological Psychiatry*, **26**, 221-223.
Pittman, R.K., Orr, S.P., Forque, D.F., de Jong, J. & Claiborn, J.M. (1987). Psychophysiologic assessment of post-traumatic stress disorder imagery in Vietnam combat veterans. *Archives General Psychiatry*, **44**, 970-75.
Pittman, R.K. van der Kolk, B.A., Orr, S.P. 7 Greenberg, M.S. (1990). Naloxone reversible stress induced analgesia in post-traumatic stress disorder. *Archives of General Psychiatry*, **47**, 541-547.
Rainey, J.M., Aleem, A., Ortiz, A., Yaragani, V., Pohl, R. & Berchow, R. (1987). Laboratory procedure for the inducement of flashbacks. *American Journal of Psychiatry*, **144**, 1317-1319.
Reite, M., Field, T. (Eds.). (1987). *The psychobiology of attachment and separation*. Orlando, FL: Academic Press.
Richardson, J.S. & Zaleski, W.A. (1983). Naloxone and self-mutilation. *Biological Psychiatry*, **18**, 99-101.
Sandman, C.A., Barron, J.L., Crinella, F.M. & Donnelly, J.F. (1987). Influence of naloxone on brain and behavior of a self-injurious woman. *Biological Psychiatry*, **22**, 899-906.
Sapolsky, R., Krey, L. & McEwen, B.S. (1984). Stress down-regulates corticosterone receptors in a site specific manner in the brain. *Endocrinology*, **114**, 287-292.
Shavel et al. (Manuscript submitted for publication).
Sheard, M.H. & Davis, M. (1976). Shock elicted fighting in rats: Importance of intershock interval upon effect of PCPA. *Brain Research*, **111**, 287-292.
Shetatsky, M., Greenberg, D. & Leter B. (1988). A controlled trial of phenelzine in post-traumatic stress disorder. *Psychiatry Research*, **24**, 149-155.
Shore, J.H., Tatum, E.L. & Vollmer, W.M. (1986). Psychiatric reactions to disaster: The Mount St.

Helens experience. *American Journal of Psychiatry*, **143**, 590-595.
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 post-traumatic stress disorder. *Biological Psychiatry*, **26**, 349-355.
Southwick et al. (Manuscript submitted for publication).
Stoddard, F. (1989). A diagnostic study of children and adolescents with severe burns. *The Journal of Trauma*, **29**, 471-477.
Strian, F. & Klipera, C. (1978). Die Bedeutung psychoautomer Reaktionen in der Entsthung und Persistenz von Angstzustanden [The significance of psychoautonomic reactions in the development and
persistence of states of anxiety]. *Nervenarzt*, **49**, 576-583.
Terman, G.W., Shavit, Y., Lewis, J.W., Cannon, J.T. & Liebeskind, J.C. (1984) Intrinsic mechanisms of pain inhibition: Activation by stress. *Science*, **26**, 1270-1277.
Terr, L. (1983). Chowchilla revisited: The effects of psychic trauma four years after a schoolbus kidnapping. *American Journal of Psychiatry*, **140**, 1543-1550.
Terr, L (1988). What happens to early memories of trauma? *Journal of the American Academy of Child and Adolescent Psychiatry*, **1**, 96-104.
van der Kolk, B. A. (1987). *Psychological Trauma*. Washington, D.C.: American Psychiatric Press.
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.
van der Kolk, B., Blitz, R., Burr, W. & Hartmann, E. (1984) Nightmares and trauma. *American Journal of Psychiatry*, **141**, 187-190.
van der Kolk, B.A., Greenberg, M.S., Boyd, H. & Krystal, J.H. (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., Greenberg, M.S., Orr, S.P. & Pittman, R.K. (1989). Endogenous opioids and stress induced analgesia in post-traumatic stress disorder. *Psychopharmacology Bulletin*, **25**, 108-112.
van der Kolk, B.A., Perry, J.C. & Herman, J.L. (1991). Childhood origins of self-destructive behavior. *American Journal of Psychiatry*, **148**, in press.
van der Kolk, B.A. & van der Hart, O. (1989). Piere Janet and the breakdown of adaption in psychological trauma. *American Journal of Psychiatry*, **146**, 1530-1540.
van Kammen, W.B., Christiansen, C., Van Kammen, D.P. & Reynolds. (1990). Sleep and the POW experience: Forty years later. In E.L. Giller (Ed.), *Biological assessment and treatment of PTSD* (pp.). Washington, D.C.: American Psychiatric Press.
Wilkinson, C.B. (1983). Aftermath of disaster, collapse of the Hyatt Regency Skywalks. *American Journal of Psychiatry*, **140**, 1134-1139.

Address correspondence to Bessel A. van der Kolk, M.D., The Trauma Clinic, Massachusetts General Hospital, Harvard Medical School, Erich Lindemann Mental Health Center, 25 Staniford Street, Boston, Mass., 02114, USA

Cite as:

- van der Kolk BA, Saporta J. The biological mechanisms and treatment of intrusion and numbing. *Anxiety Research* 1991; 4:199-212.