The Use of Psychoendocrine Strategies in Post-Traumatic Stress Disorder[1]

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An overview is presented of a pilot psychoendocrine study of PTSD inpatients in comparison with several subgroups of schizophrenic and affective disorder patients. Using a hormonal profile including cortisol, norepinephrine, epinephrine, testosterone, and thyroxine, it was found that the mean values for the PTSD group were at or near the extreme end of the range for every hormone measured, i.e., relatively low for cortisol and high for the remaining hormones. The possible clinical meaning of these findings is considered in the light of prior psychoendocrine research on chronic stress. The hormonal alterations in PTSD appear to be persistent and suggest the possibility of being linked largely to traits or character structure, perhaps particularly to cognitive variables related to defense and coping mechanisms, as reviewed in detail for each hormonal system. There appears to be a potential for a fruitful union between the traumatic stress and psychoendocrine fields and some future strategies for developing and strengthening such a union are suggested.

In reviewing the literature on post-traumatic stress disorder (PTSD) several years ago, we found extremely few biological studies in this field, even though there was a substantial and growing body of publications concerned with clinical and psychosocial aspects of this illness. It was evident that research in this field was still at a very early stage and many basic questions concerning the nature, pathogenesis, diagnosis, and clinical management of PTSD remained to be investigated in a more systematic and rigorous way (Green, Lindy, & Grace, 1985; Laufer, Brett, & Gallops, 1985). Since the precipitating factor in this disorder is clearly defined as exposure to a severely stressful life experience, it seemed to us particularly logical that research strategies from the field of psychoendocrinology, which has developed historically and conceptually in the context of stress theory, might be especially useful in contributing to further understanding of PTSD.

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A number of guiding principles have emerged from basic psychoendocrine research during the past 30 years which indicate how hormone levels may be helpful in the study of psychological and social aspects of stress. Some examples of these principles are: (a) many hormonal systems are keenly sensitive to both acute and chronic social and psychological influences; (b) the social environment can exert a "tonicity" effect upon basal hormonal levels in a continuing background fashion; (c) hormonal levels can undergo phasic adaptations in relation to prolonged, severe stress exposure; (d) hormonal levels are related not only to emotional or state changes, but also to trait and cognitive variables, including the style, organization, and effectiveness of defensive and coping mechanisms; (e) there is a bidirectional relationship between the brain and hormones, the latter being capable of reflecting as well as modulating psychological mechanisms; and (f) different hormones are linked in a specific way with different and distinctive sets of psychological dimensions (Mason, 1968a, 1975a). Such principles suggest a variety of ways that psychoendocrine approaches might be applicable to the objective and systematic investigation of some of the key conceptual and clinical issues needing resolution in the traumatic stress field. Yet, except for the work of Baum and his colleagues (Schaeffer & Baum, 1984), there appeared so far to be very little awareness of the possible benefits of linking these two fields.

It should be emphasized that psychoendocrinology has not developed historically and conceptually as a primarily biological field, but rather as one with the purpose of complementing psychosocial approaches by providing concepts and experimental methods to assist in the extremely difficult task of investigating psychological mechanisms in relation to stress and the social environment (Mason, 1975b). It was from this perspective that we began several years ago to broaden an ongoing exploratory survey of multiple hormonal systems in schizophrenia and affective disorders to include a pilot sample of patients with PTSD. Because of our concern that the several stages of illness through which psychiatric patients move as they recompensate may have distinctive biological correlates (Sachar, Mason, Kolmer, & Artiss, 1963; Docherty, van Kammen, Siris, & Marder, 1978), the design of our study was longitudinal.

Both hormonal and clinical evaluation of male Veterans Administration (VA) inpatients began soon after hospital admission and continued at 2-week intervals thereafter until discharge. The following diagnostic subgroups were included: PTSD ($n = 9$); major depressive disorder, endogenous depression ($n = 8$); bipolar I disorder, manic ($n = 8$); paranoid schizophrenia ($n = 9$); and undifferentiated schizophrenia ($n = 7$). In order to measure a broad profile of stress-responsive hormones (Mason, 1968a), we collected 24-hour urine samples for measurement of cortisol, norepinephrine, and epinephrine along with 9 a.m. serum samples for measurement of testosterone, free thyroxine, and

total thyroxine. At the time of each biological sampling, clinical state was assessed with the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962). The diagnosis of PTSD was made using DSM III-R criteria (American Psychiatric Association, 1988) and Research Diagnostic Criteria (RDC) were used for the other diagnoses (Spitzer, Endicott, & Robins, 1978), on the basis of information obtained with the Schedule for Affective Disorders and Schizophrenia (SADS) interview (Endicott & Spitzer, 1978). The number of sample collections averaged four per patient. Measures were taken to minimize the role of such potential confounding variables as medications and physical activity. All hormonal determinations were done by radioimmunoassay, except for the catecholamines which were measured by radioenzymatic assay, as reported in the papers to be reviewed.

The purposes of this paper are to present an overview of the main findings reported so far from this initial exploratory psychoendocrine survey of PTSD, to discuss the clinical implications of the findings in the light of prior basic psychoendocrine research on stress, and to suggest some promising lines for future psychoendocrine research on PTSD based upon our preliminary findings.

The Hormonal Profile in PTSD

Figure 1 presents a comparison of the profile of mean hormonal values during hospitalization in PTSD versus the other four diagnostic subgroups with major psychiatric disorders. Note the striking tendency for the PTSD group, depicted by the solid square symbols, to have extreme values for every hormone measured, being at or near the *high* extreme for norepinephrine, epinephrine, testosterone, free thyroxine, and total thyroxine, while at the *low* extreme for cortisol.

There are a number of interesting and provocative features in the organization of this profile:

1. It indicates that PTSD is associated with a rather intense degree of sustained regulatory adaptation in a broad range of major hormonal systems, equaling or exceeding that associated with the severe psychopathology of major affective disorders and schizophrenia.

2. There are some unusual features in the interhormonal relationships, especially in view of its categorization as a stress-related syndrome. While elevations in norepinephrine and epinephrine levels are widely seen in response to acute stressful experiences, they are characteristically associated with concurrent elevation of cortisol and lowering of testosterone levels, rather than the lowered cortisol and elevated testosterone, as shown in Figure 1. The implications of this unusual hormonal pattern with regard to the

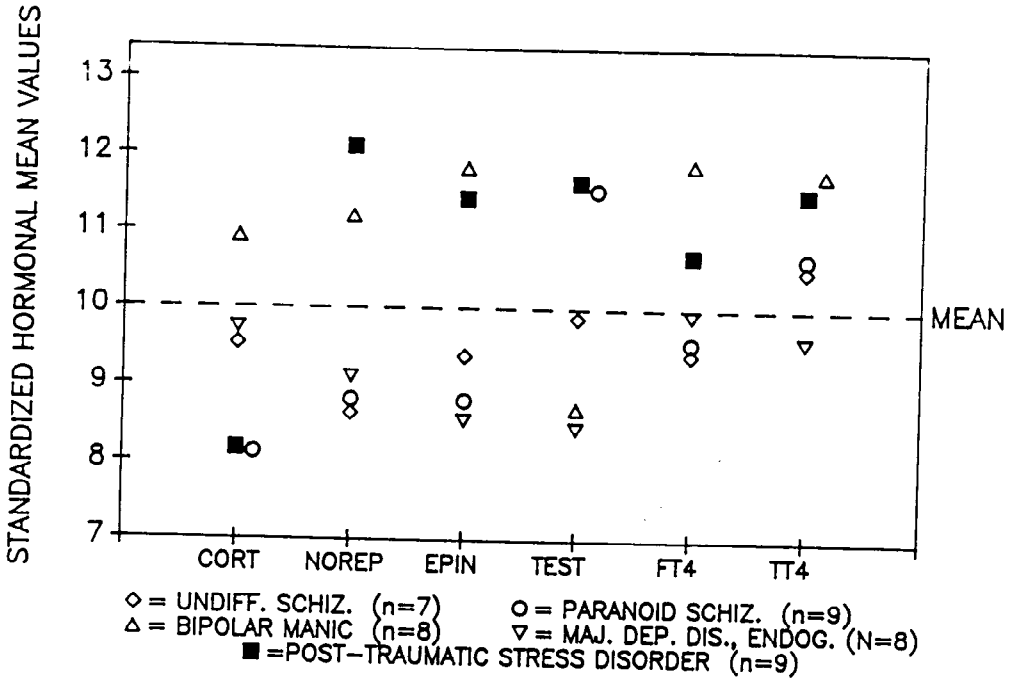

Figure 1. Comparison of the mean hormonal profile in PTSD with other diagnostic groups.

chronic stress factors in PTSD and the role of the distinctive set of psychological mechanisms linked to each of the hormones will be discussed later.

3. Some common features are shared between PTSD and two of the other diagnostic groups. The paranoid schizophrenic and PTSD groups have an almost identical subpattern of low cortisol and high testosterone levels, while the PTSD and bipolar manic groups share in a second subpattern of elevated norepinephrine, epinephrine, and thyroxine levels. Among other things, these subpatterns appear to provide an opportunity to gain insight into the clinical meaning of the hormonal profile in PTSD through a search for common psychological and symptom dimensions which PTSD shares selectively with these two other psychiatric disorders.

4. It is also particularly interesting that for virtually all the hormones, the PTSD group differs markedly from the major depressive disorder group, even though depressive symptoms are a prominent clinical feature of PTSD, and over half of our PTSD patients also met RDC criteria for major depressive disorder. This finding suggests some significant qualitative differences in the depressive syndromes associated with these two disorders.

5. While no single hormone provides a very powerful discrimination between PTSD and all the other diagnostic groups, increasingly more powerful differential diagnoses are provided as one moves from conventional uni-

variate analysis of each hormone separately to bivariate and multivariate analyses of the overall hormonal profile. We have reported, for example, that classification accuracy in the differential diagnosis of PTSD versus major depressive disorder moves from a maximum of about 60% with any single hormone, to 78% with the use of two hormones (the norepinephrine/cortisol ratio) (Mason, Giller, Kosten, & Harkness, 1988), to 95% when three or more hormones are used in stepwise discriminant analysis or multidimensional scaling procedures (Mason, Giller, Kosten, & Wahby, 1990). The purpose of the present paper, however, is not to focus on the diagnostic potential of this multidimensional psychoendocrine approach, but rather to consider the possible implications of our hormonal profile findings with regard to psychosocial and symptom factors in PTSD. Before proceeding with the clinical interpretation of our findings with each of the individual hormonal systems, however, we should move beyond the mean hormonl data shown in Figure 1 to summarize some longitudinal aspects of our data.

Hormonal Correlates of Clinical Change in PTSD

Figure 2 compares the total symptom levels (BPRS sum scores) and their change as clinical improvement occurs during hospitalization in all the diagnostic subgroups. Note that, although there are no significant differences in severity of illness as judged by total symptom scores at any point in time among the groups, the PTSD group shows the least symptomatic improvement with hospitalization (Mason, Giller, Kosten, & Yehuda, 1990).

A similar picture of constricted range of fluctuation in the PTSD group is evident in the changes over time in the various hormonal systems, as summarized in Figure 3 which compares the mean percentage changes (admission to discharge) in each group for all six hormones, as well as the total BPRS symptom score. In general, the PTSD and paranoid schizophrenic groups again share a common feature, in this case showing the most constricted range of hormonal fluctuations over time. Except for a tendency for thyroxine levels to decline in the PTSD group, all the other hormones remain relatively fixed, with perhaps a modest increase in testosterone and norepinephrine with symptomatic improvement.

Because of this rather constricted range of hormonal and clinical variation, this pilot inpatient sample permitted limited opportunity to study possible correlations between specific hormonal changes and specific symptom or psychological changes over time. Future studies should obtain similar measurements in outpatients and inpatients not simply at regular intervals, but also at points in their clinical courses where acute severe symptoms are being experienced in order to compare the hormonal levels at such points with those after clinical improvement. This approach would help maximize the oppor-

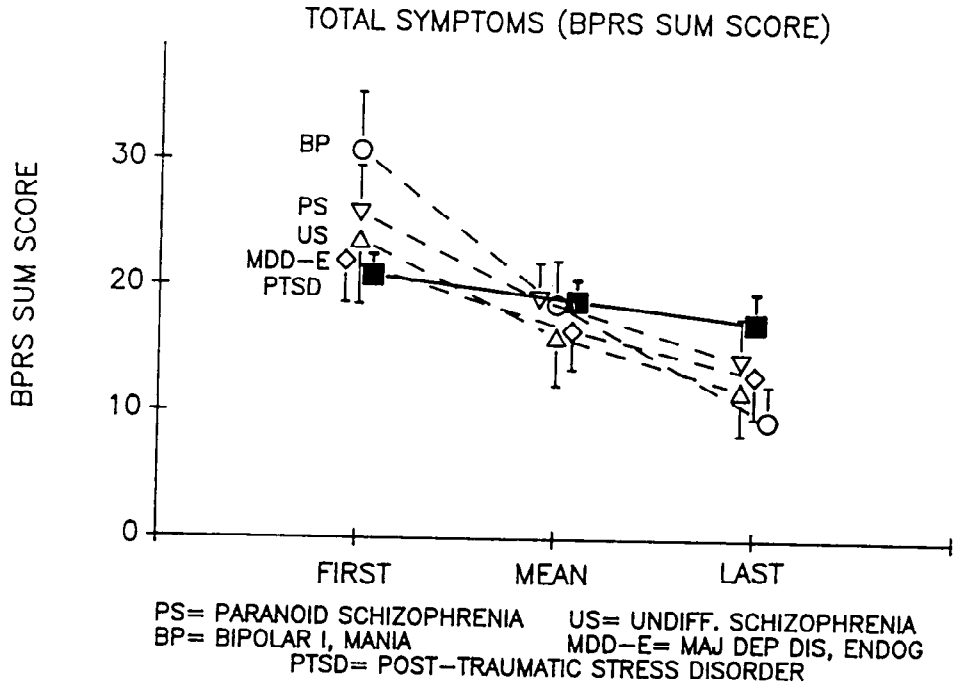

Figure 2. Change in BPRS sum score during hospitalization in PTSD inpatients in comparison with other diagnostic groups.

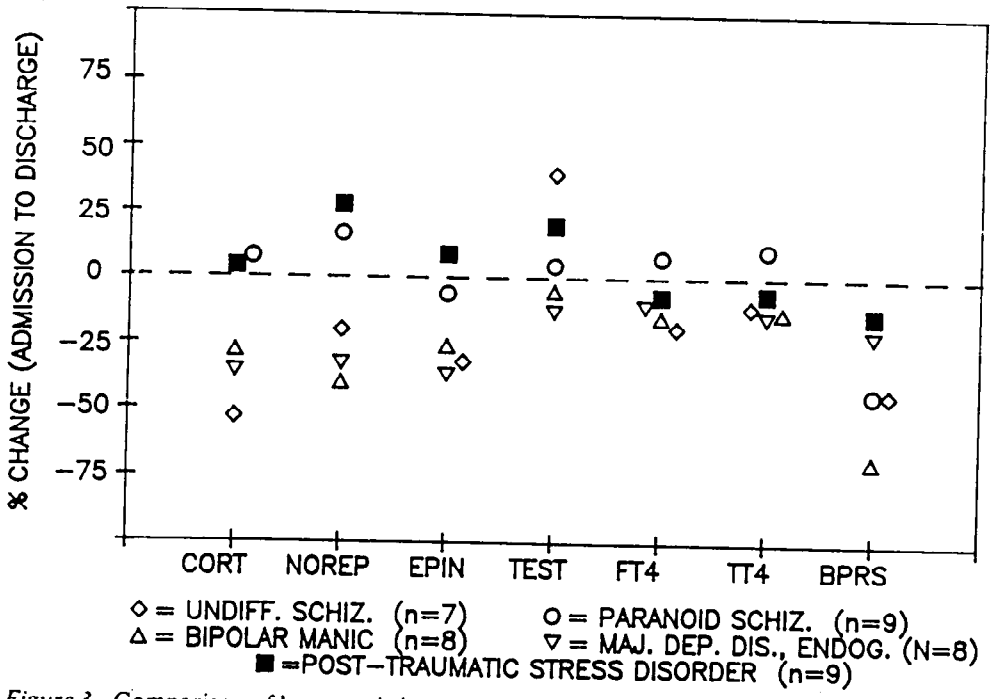

Figure 3. Comparison of hormonal changes (% change from admission to discharge sample) following clinical improvement between PTSD and other diagnostic groups.

tunity to discover the correlations between levels of the various individual hormones and the clinical and psychological measurements and to enlarge the core knowledge of such relationships which is essential for elucidating the clinical meaning of psychoendocrine findings.

Clinical Implications of the Hormonal Profile in PTSD

Cortisol

The relatively low mean 24-hour urinary free-cortisol level in the PTSD patients (Mason, Giller, Kosten, Ostroff, & Podd, 1986; Yehuda et al., in press) certainly represents our most unexpected and puzzling finding, since this hormone has been so often reported to be elevated in relation to stress, anxiety, and depression, which are prominent features in PTSD. It is widely recognized that the hypothalamic-pituitary-adrenal cortical system is very responsive to psychosocial stimuli and represents a sensitive indicator of arousal at a rather undifferentiated level, in contrast to being linked to a single specific affect (Mason, 1975a). Terms such as distress, involvement, or arousal have been used to describe the excitatory state believed to be associated with cortisol release, although the precise psychological parameter or set of parameters remain to be conclusively identified. A somewhat neglected fact of adrenal stress physiology, however, is that under certain conditions of chronic psychological stress, cortisol levels become persistently and substantially lowered, apparently due to the adaptive operation of central suppressive mechanisms, as opposed to glandular exhaustion.

We have recently summarized a series of such observations in both monkeys and normal human subjects, including combat soldiers in Vietnam, demonstrating this phenomenon, which appears most likely to represent a secondary overcompensatory lowering of cortisol levels in chronic stress (Mason, Giller, Kosten, & Yehuda, 1990). Figure 4 presents an example from some longitudinal experiments in Rhesus monkeys with a repeated conditioned avoidance procedure simulating some aspects of military stress situations. This experiment reveals the progressive general lowering of cortisol levels in a monkey over a 6-week period to about 60% below the prestress baseline value and the persistence of this effect for the remainder of a 65-week study period involving weekly repetitions of 72-hour avoidance sessions. Note also the great constriction of the range of cortisol fluctuations between the baseline and avoidance periods from the 6th week on. The main evidence supporting the view that this lowering of cortisol is on the basis of active suppression rather than exhaustion is that, under such chronic stress conditions, the superimposed administration of ACTH or of a different and more

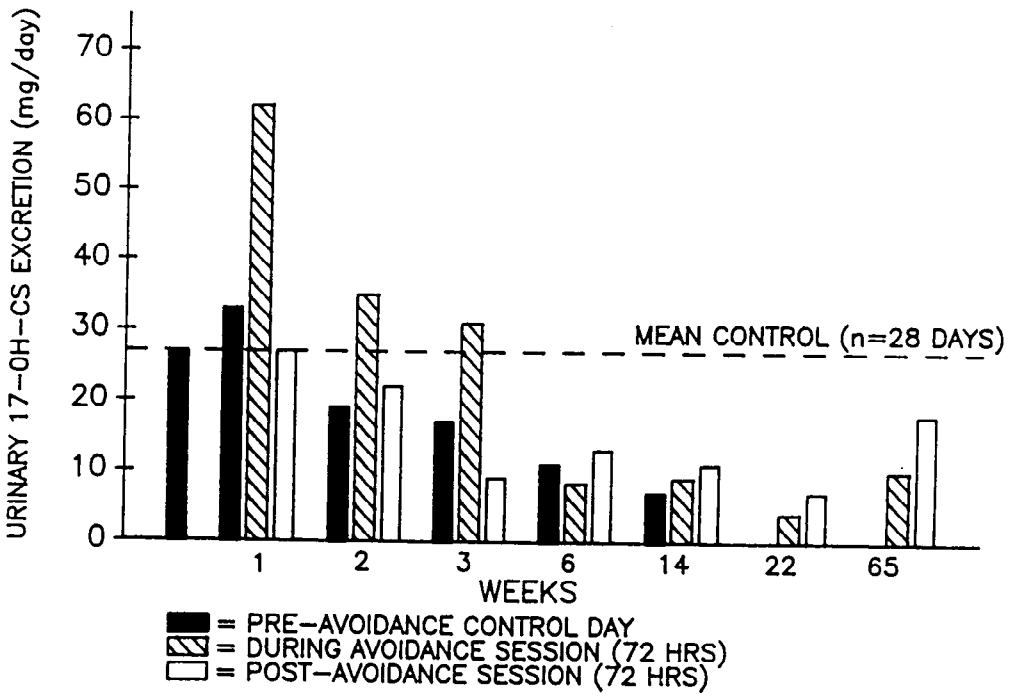

Figure 4. Lowering of urinary corticosteroid levels in a monkey during prolonged exposure to weekly 72-hour avoidance sessions.

intense emotional stimulus will produce a very substantial cortisol elevation against such a low cortisol baseline (Mason, Giller, Kosten, & Yehuda, 1990).

Unexpectedly low cortisol levels were also observed in two different groups of combat soldiers in Vietnam, as compared to a group of soldiers in training at Ft. Dix, N.J. (Rose, et al., 1969; Bourne, Rose, & Mason, 1967, 1968). Of particular interest was a longitudinal study of a green beret "A" team which revealed lower cortisol levels in enlisted men on the day of a threatened attack by a large Viet Cong force, apparently in connection with the intensified use of certain coping mechanisms and defenses enabling them to avoid active involvement in the developing situation (Bourne et al., 1968; Mason, Giller, Kosten, & Yehuda, 1990). More conclusive evidence of the suppressive influence of coping mechanisms and psychological defenses upon cortisol levels emerged from a predictive study of the parents of leukemic children. In this study a strong correlation was observed between cortisol levels and the style and effectiveness of psychological defenses in both fathers and mothers during the progression of the fatal illness of their child (Wolff, Friedman, Hofer, & Mason, 1964). The use of the psychological defense of denial was particularly likely to be associated with low mean basal cortisol levels in this study of chronic stress in normal human subjects (Friedman, Mason, & Hamburg,

1963). Finally, an early longitudinal psychoendocrine study of young soldiers with acute schizophrenic reactions also suggested that the projective and delusional mechanisms which are a prominent feature in paranoid schizophrenics may be associated with relatively low and stable cortisol levels (Sachar et al., 1963).

It appears important, therefore, that we conceptualize the cortisol system as one that reflects not simply stress arousal mechanisms, but rather the dynamic balance between opposing arousal and anti-arousal psychological mechanisms. This perspective presents an interesting challenge, then, to identify the balance of such mechanisms operating in PTSD, particularly those coping or defensive mechanisms that may be linked to the persistently low cortisol levels in our PTSD group. One possibility, for example, is that the mechanisms underlying the avoidance criteria for PTSD in DSM-III-R, such as the numbing or restricted range of affect, the feelings of detachment or estrangement from others, the avoidance of situations and stimuli reminiscent of the traumatic exposure (American Psychiatric Association, 1988), or the primitive defenses in PTSD impressive to some observers (DeFazio, 1978) may bear a close relationship to the denial mechanisms previously found to be linked to low cortisol levels in the parents of leukemic children (Friedman et al., 1963; Wolff et al., 1964).

Another possibility, in view of some of the close similarities in hormonal organization between the paranoid schizophrenic and PTSD groups in our pilot study, is that the low cortisol levels in PTSD may be linked to what might be called the "paranoid adaptations" reflected by such features as mistrust, hypervigilance, hostility, cynicism, or even nihilism, which are commonly observed in Vietnam combat veterans with PTSD (Hendin, 1984; Glover, 1984). Since different PTSD patients show such paranoid features to varying degrees, an opportunity is provided in future studies to search for correlations between cortisol levels and measurements of paranoid behavior. Our pilot experience indicated that this will require relatively sophisticated clinical methodology, since simple ratings of overt behavior can be quite misleading with paranoid symptoms and should at the least be accompanied by ratings involving inference and the global clinical judgment of an experienced observer. The observation that some persons prone to PTSD are compulsively "good" and extremely conscientious (Smith, 1985), along with the need for the soldier to find an idealized and acceptable way of restructuring his character into a combat personality (Brende, 1983), might well help explain the frequent recourse to the paranoid stance in Vietnam veterans with PTSD, especially in view of the widespread condemnation of the Vietnam conflict. One other interesting possibility relates to the characterological features observed in PTSD which bear a notable similarity to those typically seen in borderline patients, such as self-defeating, risk-taking behavior, shifting idealization and devaluation in interpersonal relationships, outbursts of uncon-

trollable anger, identity diffusion and feelings of meaninglessness, affective instability, and abandonment depression (Brende, 1983). We are not aware of any psychoendocrine studies in borderline patients as yet, but because of some anecdotal evidence in our pilot study suggesting that they may also have relatively low cortisol levels, this may be a good comparison group to include in future explorations of the psychological mechanisms linked to the low cortisol levels in PTSD.

Finally, it should be mentioned that, while the mean cortisol level of 33 ug/day in our PTSD group is at the low extreme of our group mean values, some individual PTSD patients showed higher values ranging up to 70 ug/day on certain days, particularly in the hospital admission period. Using admission and discharge sample days only on each patient, we found a strong positive correlation between cortisol and the activation factor (excitement plus tension) of the BPRS (Mason, Giller, Kosten, & Yehuda, 1990). While we have a preliminary impression that increased intrusive symptoms may have been linked to the higher cortisol values, further investigation is clearly needed in order to determine the nature of the acute disturbances associated with cortisol increase in PTSD patients.

Norepinephrine

The relatively high mean 24-hour urinary norepinephrine (NE) level of 76 ug/day observed in our PTSD group (Kosten, Mason, Giller, Ostroff, & Harkness, 1987) was not unexpected in view of previous reports of increased sympathetic nervous system activity in psychophysiological studies of this disorder (Blanchard, Kolb, Pallmeyer, & Gerardi, 1982; Brende, 1982; Malloy, Fairbank, & Keane, 1983). Less is known of the psychological mechanisms linked to the NE system than is known for the cortisol system, but basic psychoendocrine research has produced some interesting leads to pursue. The study of conditioned emotional stress procedures in the monkey indicated that NE elevations occurred in a wide range of conditions involving the threat or anticipation of an aversive stimulus and the need for alertness and appropriate coping behavior (Mason, Mangan, Brady, Conrad, & Rioch, 1961; Mason, Brady, & Tolson, 1966). Early human stress studies yielded some indirect evidence of an apparent relationship between anger and high NE levels (Ax, 1953) and a hypothesis that NE might be selectively related to "anger-out" (aggressive, hostile, active display) and epinephrine (E) to "anger-in" (self-critical, fearful, passive display) in a characterological way (Funkenstein, 1956). Although the latter formulation has been the basis of some controversy, it more recently has received some support from several lines of investigation. In an exploratory survey of male psychiatric patients, Kadish found a strong tendency for high urinary NE levels and NE/E ratios to be related to preoccupation with angry feelings or fantasies, especially those

associated with feeling cheated or unappreciated by others (Kadish, Mason, & Giller, 1983). In studies of psychopathy, it has been found that maximum security prisoners who exhibited a high degree of assaultiveness, aggressiveness, and violent behavior maintained an unusually high NE/E ratio when retested over periods ranging up to 25 months (Woodman, 1979a). On the other hand, studies have shown the urinary NE/E ratio to be relatively low in suicidal patients, in whom one might postulate anger to be largely directed "inwardly" (Ostroff et al., 1982). One of the special methodological problems in testing the direction of anger hypothesis for norepinephrine lies in the extraordinary difficulty of making a reliable assessment of subjective anger in its many disguised or covert forms. Ekkers (1975) has noted that, in early work on aggression and norepinephrine, it was only in those studies using the projective thematic apperception test (TAT), as opposed to ratings, that significant and interpretable results were obtained. This appears to be one of many examples indicating the need in the psychoendocrine and stress fields for finding a sensible methodological balance between the reliability of objective and quantitative rating procedures versus the validity of integrative evaluations of interacting psychodynamic factors, as assessed by projective tests or by the global clinical evaluation of experienced clinical observers.

More recent work on the psychological correlates of norepinephrine secretion has been conducted by Frankenhaeuser and her coworkers, who favor the view that such factors as involvement in self-paced, attention-demanding work or feelings of alertness and action proneness may be of principal importance in the elevation of NE levels (Frankenhaeuser & Rissler, 1970; Lundberg & Frankenhaeuser, 1980). A possibly related suggestion emerging from studies of military aircraft pilots in training is that higher NE levels are associated with acquisition of competence and control (Krahenbuhl et al., 1980). Clearly there is a need for further systematic and resourceful investigation directed toward identifying more fully the specific psychological correlates of norepinephrine elevations, particularly on a chronic or trait basis.

With regard to interpreting the meaning of our findings in PTSD, several of the above leads appear to be potentially applicable and worthy of further exploration. However, consideration should perhaps first be given to the possible confounding factor of muscular exertion, especially since the PTSD and bipolar manic (BP) groups share some common elements of hyperactivity as well as NE elevations. As reported previously, the magnitude of the 24-hour urinary NE elevations seen in both the PTSD and BP groups greatly exceeds that observed in normal human subjects involved in sustained heavy muscular work (Kosten et al., 1987). Furthermore, the consensus of our clinical observers was that the increased activity of our PTSD patients involved not so much heavy muscular exertion as seeking ways of keeping occupied and mentally busy. The latter may well fit with the above formula-

tion of elevated NE levels in association with intense involvement in attention-demanding activities requiring alertness and action proneness. Certainly, it would be useful to search further for some specific psychological mechanisms which PTSD and BP patients have in common as correlates of NE elevation, since the physical mechanism of muscular activity alone cannot account for our findings.

The irritability and outbursts of anger commonly seen in PTSD patients, particularly toward those in authority, might plausibly fit with the Funkenstein hypothesis of high NE levels in association with a style of "anger-out." With regard to the notion of NE elevations being linked to the perception of competence and control, this trait has not been emphasized in the PTSD literature, but it might fit with some formulations suggesting the possibly important role of narcissistic defenses with an omnipotence theme in combat stress reactions (Shaw, 1983; Brende, 1983). Finally, it will be interesting to see if our finding of a modest inverse relationship in the PTSD group between NE levels and total clinical symptoms (a 28% increase in NE in the face of a 14% decline in BPRS sum during hospitalization) can be confirmed in additional longitudinal studies. It is possible that this finding may point to a relationship primarily between NE levels and some enduring cognitive characteristics of the PTSD patient, with the lower admission value representing a transitory decrease in the effectiveness of coping or defense mechanisms associated with the development of acute symptoms.

Epinephrine

At first there may be a tendency to view the elevated mean 24-hour urinary epinephrine level of 22.7 ug/day in our PTSD group (Kosten et al., 1987) as simply representing a second part of a unitary "catecholamine" adjustment together with norepinephrine. However, although epinephrine (E) and norepinephrine (NE) are very similar biochemically and both have their source in the sympathetic-adrenal medullary system, it appears increasingly that they can often be dissociated from one another in response to stress and are, in part at least, linked to independent psychological mechanisms (Kosten et al., 1987). Early basic studies in the monkey indicated rather clearly that, although there were many situations in which both hormones were released together, E was more selectively regulated than NE and appeared to be especially increased in situations involving elements of uncertainty, ambiguity, and perhaps uncontrollability (Mason et al., 1961). This finding appeared to fit with the idea of a rather specific link between E and fear or anxiety (Ax, 1953; Mason, 1968a) and with such observations as relatively high E levels in the adrenals of African mammals that typically resort to flight rather than combat when threatened (Goodall, 1951). Some evidence was also

found for linking trait anxiety to high E levels in human studies using the projective TAT test (Ekkers, 1975). More recent work has raised questions about a unitary fear or anxiety hypothesis for E and has indicated, for example, that positive affective or motivational elements such as interest, effort, or joyful excitement may be reflected in elevated E levels (Frankenhaeuser & Lundberg, 1985). The trait of achievement orientation has also been suggested as a particularly relevant determinant of E levels under stress conditions in men (Rauste-von Wright, von Wright, & Frankenhaeuser, 1981).

The Funkenstein hypothesis of "anger-in" as a correlate of elevated E levels has received less attention that the "anger-out" hypothesis for NE regulation, but some subsequent findings appear to lend support for pursuing this concept further. In a study of adolescent boys, Ekkers (1975) found intrapunitive subjects to have indications of higher E levels and lower NE levels than aggressive subjects. As mentioned earlier, elevated E levels and a low NE/E ratio have been reported as correlates of suicidality in psychiatric patients (Ostroff et al., 1982). Of the various psychological parameters mentioned above, the relationship of E to self-blame or guilt, which some observers believe commonly underlies the covering aggressive behavior in PTSD, may be especially deserving of further investigation. It may also be appropriate to look more closely in PTSD patients for a relationship between E levels and the sense of overwhelming helplessness, uncertainty, and fear of death instilled through the combat experience (Shaw, 1983) and which may continue as a threatening background for present experience.

Testosterone

The mean serum testosterone level of 578 ng% in our PTSD group is relatively high, not only in comparison with the other diagnostic subgroups of psychiatric patients, but also in comparison with a group of normal subjects in our laboratory (Mason, Giller, Kosten, & Wahby, 1990). As with the finding of low cortisol levels, the finding of high testosterone levels in PTSD is surprising, since the direction of change is the opposite of that which would have been predicted in view of the fact that much prior stress research has shown lowering of testosterone or androgen levels in such stressful experiences as conditioned avoidance and chair restraint in the monkey, final college examinations or hospital admission in normal young men, and basic training and Vietnam combat duty in soldiers (Mason, Giller, & Ostroff, 1984). In general, it has been assumed that in these situations such states as fear or anxiety exert an inhibitory influence on testosterone levels, but observations have been reported indicating that traits are also important. Subjects who are classified as high in trait anxiety, hostility, and depression have significantly

lower testosterone levels than do those rated low in these trait parameters (Francis, 1981).

There is also evidence that certain psychosocial factors can be associated with elevation of testosterone levels. Marked testosterone increases have been reported, for example, in individual subjects who showed a puzzling absence of any overt sign or subjective awareness of anger when they were exposed to stressful experiences which might be expected to provoke a strong anger reaction in most people, in other words, in relation to episodes probably associated with repressed anger (Mason et al., 1984). The great methodological problems involved in the valid assessment of anger, however, have made the above lead difficult to pursue. Along a different line, a particularly interesting finding in psychoendocrine studies of free-ranging male monkeys in social colonies has been the high testosterone levels associated with victory and the low testosterone levels associated with defeat in combat, which adjustments may then persist over long periods of time (Rose, Bernstein, & Gordon, 1975; Rose, 1984). A similar effect has been observed in young male tennis players, with victors in decisive triumphs showing elevations and the losers showing decreases in serum testosterone levels one hour after the matches (Mazur & Lamb, 1980). The winners of competitive college wrestling matches have also been found to show greater increases in testosterone levels than losers (Elias, 1981). These observations suggest the possibility that testosterone is closely linked to a "mastery-failure" axis, with successful attempts to achieve or maintain status by one's own efforts associated with high testosterone levels, and defeat or failure associated with low testosterone levels (Mason, Giller, & Kosten, 1988).

Although there is some controversy about the relationship between aggression and testosterone in the human, a number of studies involving such groups as normal young men (Olweus, Mattson, Schalling, & Low, 1980), prison inmates (Kreuz & Rose, 1972; Dabbs, Frady, Carr, & Beach, 1987), and college hockey players (Scaramella & Brown, 1978) have provided strong support for an association between aggressive and violent behavior with high testosterone levels. Mazur (1985) has suggested, however, that the essential parameter may not be aggressive behavior with an intent to simply inflict injury, but rather may be dominance behavior with an intent to achieve high status over another, since it has been observed that socially dominant but unaggressive prisoners also have relatively high testosterone levels (Ehrenkrantz, Bliss, & Sheard, 1974). It also is important to bear in mind that the link between testosterone and dominance appears to be bidirectional. Psychosocial influences related, for example, to victory or defeat may raise or lower testosterone levels, whereas high testosterone levels may, in turn, promote assertive or mastery-oriented behavior and low testosterone levels sustain a submissive and defeat-oriented attitude (Mazur, 1985). In addition to aggres-

sion and dominance, high testosterone levels have been found to be related to impulsivity, disinhibitory sensation seeking (Daitzman & Zuckerman, 1980), and persistence (Andrew & Rogers, 1972), which may also have relevance to the role of testosterone in PTSD.

From a clinical standpoint, the apparent link between testosterone and paranoid mechanisms suggested by the high testosterone levels in paranoid schizophrenics seems of special interest. Although little work has been previously reported in this area, a significant association between testosterone and paranoid symptoms is also suggested by the onset of paranoid reactions following androgen administration in some psychiatric patients or secondary to certain adrenal cortical adenomata (Batt & Reiss, 1958) and in imipramine-treated depressed men receiving methyltestosterone administration (Prange, Wilson, Bresse, & Lipton, 1976). A positive relationship between the Suspicion Scale of the Buss-Durkee Hostility Inventory and mean testosterone levels in young men has also been reported (Monti, Brown, & Corriveau, 1977). Although paranoid features are not emphasized in the current diagnostic criteria for PTSD, the mistrust, inclination to react violently to any hostility, and other paranoid adaptations of many Vietnam combat veterans with PTSD have been considered of special clinical significance by some observers (Glover, 1984; Hendin, 1984). A relationship between testosterone and paranoid mechanisms appears to be quite compatible with the "mastery-failure" hypothesis, in that projective and delusional processes tend to minimize perception of personal failure and promote illusions of mastery or superior status, if at the cost of breaking with reality. In any event, it appears likely that the possible relationship between high testosterone and paranoid adaptations in PTSD deserves further examination.

Thyroxine

The relatively high mean serum levels of 1.58 ng% for free thyroxine and 9.59 ug% for total thyroxine in our PTSD patients are interesting in relation to the clinical psychoendocrine literature dating back at least to Parry's classical case report in 1825 of the onset of hyperthyroidism following an unusual accident associated with severe fright but little physical injury (Mason, 1968b). Subsequently the frequent occurrence of extraordinarily stressful events just prior to the onset of thyrotoxicosis has been repeatedly and widely confirmed by many clinical investigators (Mason, 1968b). Bram (1927), for example, found "a clear history of psychic trauma as the exciting cause" in 85% of 3,343 cases of exopthalmic goiters, involving exposure to severe, life-threatening crises, such as fires, earthquakes, shipwrecks, combat, narrow escapes from accidents, impending surgery or parturition, and most of all, sudden object loss. In a manner perhaps similar to PTSD, the precipitat-

ing condition appears to be traumatic stress that only affects a subgroup of those who are exposed, so that the question is raised of possible predisposing or risk factors associated with increased vulnerability in certain individuals. Although the search for particular personality or psychodynamic factors linked to susceptibility to hyperthyroidism has produced a substantial literature with a number of interesting leads (Gibson, 1962), the precise psychoendocrine mechanisms underlying the pathogenesis remain to be conclusively identified. It should also be pointed out that, apart from the observations relating traumatic stress and thyrotoxicosis, basic psychoendocrine research has shown that thyroxine levels are elevated in response to a wide variety of stressful psychological stimuli (Mason, 1975c).

It has been long recognized that both hyperthyroidism and hypothyroidism are associated with changes in affective and cognitive functioning and with clinical symptoms similar to those of psychiatric disorders (Hayward & Woods, 1931; Whybrow & Hurwitz, 1976). In general, clinical studies have revealed that hyperthyroidism is often associated with anxiety, tension, and irritability, while hypothyroid patients often have depressive symptoms, but these relationships are not consistent in all patients. Psychometric studies have indicated that the most apparent impairment in thyroid disorders is in cognitive mechanisms, rather broadly involving the processes of attention, vigilance, abstraction, memory and intellectual function, sometimes with delusional and hallucinatory phenomena (Whybrow, Prange & Treadway, 1969; Levander & Rosenquist, 1979). Yet, although such observations of psychological changes in patients with thyroid disorders are useful, there is a great need in addition for basic experimental work on the links between thyroxine and psychological mechanisms in normal human subjects. Less is known at present of the specific psychological mechanisms related to thyroxine than is known concerning any of the other hormones included in our profile.

Perhaps because of the historical emphasis on glandular disorders of the thyroid in psychiatry and on a search for undiagnosed thyroid pathology in psychiatric patients, clinical psychiatric studies have so far also not yielded much information concerning the specific psychological mechanisms linked to thyroid regulation (Mason, Kennedy, Kosten, & Giller, 1989). Our pilot finding that the PTSD and bipolar manic groups share the common feature of higher thyroxine levels than the other diagnostic groups on hospital admission suggests the possibility that a future search for some common psychological characteristics shared by these two disorders may shed light on the clinical psychiatric meaning of thyroxine levels. The observation in an earlier study of a strong but complex relationship between thyroxine levels and clinical recovery in psychiatric patients with a broad range of diagnoses (Southwick, Mason, Giller, & Kosten, 1989) provides additional

interest for pursuing further study of the thyroid system in PTSD and related disorders.

It may be important, however, to make a distinction between the "primary" action of thyroxine upon specific psychological mechanisms versus the "secondary" clinical symptoms which may in turn develop once thyroxine levels are elevated. As a hypothetical example, if an effect of a rise in thyroxine level was to promote enhanced vigilance, the impact of such a rise might be quite different in a bipolar manic patient as compared to one with endogenous depression, in terms of the symptom pattern likely to be promoted by an increased level of vigilance. In any event, it is clear that future studies of the thyroid system need to include a broader and more sophisticated range of psychological measurements, including consideration of enduring character features and cognitive mechanisms as well as affective processes and clinical symptoms, if we are to develop a deeper understanding of the meaning of thyroxine levels in psychiatric disorders. It also should be recognized that the endocrine physiology of the thyroid system is complex and requires that we move to enlarge our battery of hormonal measures beyond free and total thyroxine to include thyrotropin, triiodothyronine, and thyroid binding globulin in order to interpret more accurately the mechanisms underlying hormonal changes. In spite of the special difficulties presented, however, there is much to indicate a very significant role for thyroxine in psychiatric illnesses and to emphasize the importance of including the thyroid system in future clinical psychoendocrine studies of PTSD and related psychiatric disorders.

Concluding Comment

As we seek some generalizations and guiding principles from this survey of our pilot psychoendocrine study of PTSD, some limitations in the work should first be emphasized. Because of the small number of patients in each diagnostic subgroup, it is clear that our data must be regarded as preliminary and in need of further evaluation with larger samples, preferably from regionally diverse populations of psychiatric patients. The study involved only male combat veterans, and the findings obviously cannot be extended directly to women or to those suffering from exposure to forms of traumatic stress other than combat without further investigations. Our study also involved only inpatients willing to be admitted to a VA hospital and may represent a subgroup that is clinically different in some respects from PTSD patients seen in psychiatric outpatient clinics, in community outreach centers, in medical or neurological clinics, or from those refusing medical attention. This possibility remains to be evaluated in future psychoendocrine studies, as does a fuller comparison of PTSD patients with other relevant groups, including normal control subjects, Vietnam combat veterans without PTSD, and psychiatric

patients with anxiety disorders. Because of increasing concern about relationships between PTSD and character pathology (Brende, 1983; Green, Lindy, & Grace, 1985), it may also be important to include borderline patients as a comparison group. There is also a need for more psychoendocrine observations in PTSD patients at points in time when there are severe acute disturbances in clinical state, in order to study more fully the interaction between state and trait factors in this disorder and to determine to what degree the constricted range of clinical and hormonal change in our inpatient sample is typical in PTSD.

Bearing in mind these limitations, the striking nature of the hormonal findings in this pilot sample of PTSD inpatients seems sufficiently compelling to warrant some tentative suggestions about the potential usefulness of psychoendocrine strategies in PTSD, the kind of clinical issues which they may help clarify, and the methodological refinements which may increase the conclusiveness of findings in the next stage of investigation. The main rationale for venturing an overview at such an early stage in this work is for a bridging purpose, to help investigators with a primarily psychological or social orientation in the traumatic stress field to envision the possible ways that psychoendocrine collaboration might offer concepts and tools that could provide new leverage for their own research approaches.

One of the first conclusions suggested by our data is that the hormonal changes in PTSD are broad ranging, substantial, enduring, and indicate that there are chronic alterations in either excitatory or inhibitory regulatory activity in every hormonal system we studied. We presume, incidentally, that these regulatory influences have a psychological basis, although this assumption will require continuing experimental evaluation. Furthermore, the overall hormonal pattern in PTSD is distinctive and clearly opens the way for exploration of simple descriptive approaches to improved differential diagnosis of PTSD, using multidimensional methods which promise up to 95% correct classification accuracy in our unpublished pilot work. Another important potential at the descriptive level for the hormonal profile is the possibility that it may prove useful in the differentiation of subtypes of PTSD, as suggested particularly by our preliminary experience with multidimensional scaling using a profile of five hormones. Such a contribution would have not just theoretical value, but could facilitate work on this disorder in a general, practical way by providing an objective basis for reducing the heterogeneity of PTSD patient samples for clinical and research purposes.

In addition to diagnosis and subtyping strategies, it appears that the altered hormonal profile may also have more long-term applications to the study of the nature and pathogenesis of PTSD and related clinical issues. In pursuing this application, attention is focused on the meaning of the changes in each hormonal system, and especially on the nature of the excitatory or inhibitory

psychological mechanisms which may be producing the hormonal change, and then, in turn, on the modulating effect that the altered hormonal level may have upon psychological mechanisms. Hopefully, the above survey of our hormonal findings and the suggestions concerning their possible interpretation has conveyed the concept that the hormonal measures are not regarded in our approach as independent biological measures providing an alternative or substitute for psychosocial investigation of the pathogenesis and nature of traumatic stress disorders, but rather as providing tools to assist the psychosocial investigator in this task.

Relating our present data to the prior psychoendocrine literature on stress has suggested a number of tentative hypotheses for future testing concerning the kinds of psychological mechanisms which may be associated with altered levels of specific hormones in PTSD. Included among the examples considered earlier are the possibilities of paranoid adaptations being linked to low cortisol and high testosterone levels, of anger directed outwardly or perhaps hypervigilance being linked to high norepinephrine levels, and of denial or closely related defense mechanisms being linked to low cortisol levels. It is interesting that most of the hypotheses emerging from our pilot study involve enduring character traits or styles rather than transient emotional states or acute symptoms, perhaps in keeping with the increasing recognition in modern psychoendocrine research that hormonal levels are much more strongly related to psychological trait factors than was originally suspected. The further testing of such hypotheses clearly will require valid and reliable methods for assessing these psychological variables, preferably including global clinical assessments which consider multiple interacting social and psychological factors in a dynamic and penetrating way. Substantial rigor and reliability can be attained in such assessments by the use of multiple observers, interobserver reliability, and by the powerful strategy of using predictive or prospective approaches once hypotheses are established by pilot observations (Wolff, Hofer, & Mason, 1964). The relationships between changes in psychological states and specific hormone levels also need further study. In this case, the use of laboratory settings involving exposure to appropriate stressful stimuli and of intensive longitudinal studies of selected patients by experienced and sensitive clinical observers may prove especially productive.

If specific hormones increasingly prove capable of providing valid and reliable indices closely linked to certain psychological dimensions, including cognitive as well as emotional processes, and especially those that often appear in subtle, disguised or covert forms, then the rigor and depth of traumatic stress investigation could be significantly strengthened. It is clear, however, that accurate knowledge of the relationships between specific hormones and specific psychological dimensions is a crucial foundation for this clinical psychoendocrine approach and that greater priority must be given in

the future to developing improved research strategies in this area. The union of traumatic stress research with psychoendocrine research seems to have a natural, deep logic in its favor and it seems quite likely that the continuation and strengthening of this union could very well prove to have significant mutual benefits for both fields.

References

American Psychiatric Association (1988). *DSM-III-R. Diagnostic and statistical manual of mental disorders, 3rd edition, revised.* Washington, DC.

Andrew, R. J., & Rogers, L. J. (1972) Testosterone, search behavior, and persistence. *Nature,* **237**, 343–346.

Ax, A. (1953). The physiological differentiation between fear and anger in humans. *Psychosomatic Medicine,* **15**, 433–442.

Batt, J. C., & Reiss, M. (1958). The changing concepts of the role of endocrine function and treatment in psychiatry. In M. Reiss (Ed.), *Psychoendocrinology* (pp. 41–51). Orlando, FL: Grune & Stratton.

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

Bourne, P. G., Rose, R. M., & Mason, J. W. (1967). Urinary 17-OHCS levels—data on seven helicopter medics in combat. *Archives of General Psychiatry,* **17**, 104–110.

Bourne, P. G., Rose, R. M., & Mason, J. W. (1968). 17-OHCS levels in combat—Special Forces "A" team under threat of attack. *Archives of General Psychiatry,* **19**, 135–140.

Bram, I. (1927). Psychic trauma in pathogenesis of exophthalmic goiter. *Endocrinology,* **11**, 106–116.

Brende, J. O. (1982). Electrodermal responses in post-traumatic syndromes. *Journal of Nervous and Mental Disorders,* **170**, 352–361.

Brende, J. O. (1983). A psychodynamic view of character pathology in Vietnam combat veterans. *Bulletin of the Menninger Clinic,* **47**, 193–216.

Dabbs, J. M., Frady, R. L., Carr, T. S., & Besch, N. F. (1987). Saliva testosterone and criminal violence in young adult prison inmates. *Psychosomatic Medicine,* **49**, 174–182.

Daitzmen, R., & Zuckerman, M. (1980). Disinhibitory sensation seeking, personality and gonadal hormones. *Personality and Individual Differences,* **1**, 103–110.

DeFazio, V. J. (1978). Dynamic perspective on the nature and effects of combat stress. In C. R. Figley (Ed.), *Stress disorders among Vietnam*

veterans: Theory, research, and treatment (pp. 23–42). New York: Brunner/Mazel.

Docherty, J. P., van Kammen, D. P., Siris, S. G., & Marder, S. R. (1978). Stages of onset of schizophrenic psychosis. *American Journal of Psychiatry*, **135**, 420–426.

Ehrenkrantz, J. E., Bliss, E., Sheard, M. (1974). Plasma testosterone: Correlation with aggressive behavior and social dominance in man. *Psychosomatic Medicine*, **36**, 469–475.

Ekkers, C. L. (1975). Catecholamine excretion, conscience function, and aggressive behavior. *Biological Psychology*, **3**, 15–30.

Elias, M. (1981). Serum cortisol, testosterone, and testosterone-binding globuin responses to competitive fighting in human males. *Aggressive Behavior*, **7**, 215–224.

Endicott, J., & Spitzer, R. L. (1978). A diagnostic interview: The Schedule for Affective Disorders and Schizophrenia. *Archives of General Psychiatry*, **35**, 837–844.

Francis, K. T. (1981). The relationship between high and low trait psychological stress, serum testosterone, and serum cortisol. *Experientia*, **37**, 1296–1297.

Frankenhaeuser, M., & Rissler, A. (1970). Effects of punishment on catecholamine release and efficiency of performance. *Psychopharmacologia*, **17**, 378–390.

Frankenhaeuser, M., & Lundsberg, U. (1985). Sympathetic-adrenal and pituitary-adrenal response to challenge. In P. Pichot, P. Berner, R. Wolf, & K. Thau (Eds.), *Psychiatry* (Vol. 2, pp. 699–704). London: Plenum.

Friedman, S. B., Mason, J. W., & Hamburg, D. A. (1963). Urinary 17-hydroxycorticosteroid levels in parents of children with neoplastic disease. *Psychosomatic Medicine*, **25**, 364–376.

Funkenstein, D. H. (1956). Norepinephrine-like and epinephrine-like substances in relation to human behavior. *Journal of Nervous and Mental Disease*, **124**, 56–68.

Gibson, J. G. (1962). Emotions and the thyroid gland: A critical appraisal. *Journal of Psychosomatic Research*, **6**, 93–116.

Glover, H. (1984). Themes of mistrust and the post-traumatic stress disorder in Vietnam veterans. *American Journal of Psychotherapy*, **38**, 445–452.

Goodall, McC. (1951). Studies of Adrenaline and noradrenaline in mammalian heart and suprarenals. *Acta Physiologica Scandinavia*, **24** (Suppl. 85).

Green, B. L., Lindy, J. D., & Grace, M. C. (1985). Posttraumatic stress disorder. Toward DSM-IV. *Journal of Nervous and Mental Disease*, **173**, 406–411.

Hayward, E. P., & Woods, A. H. (1931). Mental derangements in hypothyroidism. Their misleading effects in diagnosis. *Journal of the American Medical Association*, **97**, 164–165.

Hendin, H. (1984). Combat never ends: The paranoid adaptation to post-traumatic stress. *American Journal of Psychotherapy*, **38**, 121-131.

Kadish, W., Mason, J., & Giller, E. (1983). *Personality traits and the norepinephrine to epinephrine ratio.* Unpublished thesis, Yale Univ. School of Medicine.

Kosten, T. R., Mason, J. W., Giller, E. L., Ostroff, R. B., & Harkness, L. (1987). Sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder. *Psychoneuroendocrinology*, **12**, 13-20.

Krahenbuhl, G. S., Constable, S. H., Darst, P. W., Marett, J. R., Reid, G. B., & Reuther, L. C. (1980). Catecholamine excretion in A-10 pilots. *Aviation and Space Environmental Medicine*, **51**, 661-664.

Kreuz, L. E., Rose, R. M. (1972). Assessment of aggressive behavior and plasma testosterone in a young criminal population. *Psychosomatic Medicine*, **34**, 321-332.

Laufer, R. S., Brett, E., & Gallops, M. S. (1985). Symptom patterns associated with posttraumatic stress disorder among Vietnam veterans exposed to war trauma. *American Journal of Psychiatry*, **142**, 1304-1311.

Levander, S., & Rosenquist, U. (1979). Cerebral function in hypothyroid patients. *Neuropsychobiology*, **5**, 274-281.

Lundberg, U., & Frankenhaeuser, M. (1980). Pituitary-adrenal and sympathetic-adrenal correlates of distress and effort. *Journal of Psychosomatic Research*, **24**, 125-130.

Malloy, P. F., Fairbank, J. A., & Keane, T. M. (1985). Validation of a multimethod assessment of posttraumatic stress disorders in Vietnam veterans. *Journal of Consulting and Clinical Psychology*, **51**, 488-494.

Mason, J. W. (1968a). Organization of psychoendocrine mechanisms. *Psychosomatic Medicine*, **30**, 565-808.

Mason, J. W. (1968b). A review of psychoendocrine research on the pituitary-thyroid system. *Psychosomatic Medicine*, **30**, 666-681.

Mason, J. W. (1975a). Clinical psychophysiology: psychoendocrine mechanisms. In M. Reiser (Ed.), *American handbook of psychiatry* (Vol. IV, pp. 553-582). New York: Basic Books.

Mason, J. W. (1975b). Emotion as reflected in patterns of endocrine integration. In L. Levi (Ed.), *Emotions—their parameters and measurement* (pp. 143-181). New York: Raven Press.

Mason, J. W. (1975c). Psychologic stress and endocrine function. In E. Sachar (Ed.), *Topics in psychoendocrinology* (pp. 1-18). New York: Grune & Stratton.

Mason, J. W., Brady, J. V., & Tolson, W. W. (1966). Behavioral adaptations and endocrine activity—psychoendocrine differentiation of emotional states. In R. Levine (Ed.), *Endocrines and the Central Nervous System* (pp. 227-250). Baltimore: William & Wilkins.

Mason, J. W., Giller, E. L., & Kosten, T. R. (1988). Serum testosterone

differences between patients with schizophrenia and those with affective disorder. *Biological Psychiatry,* **23**, 357–366.

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

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

Mason, J. W., Giller, E. L., Kosten, T. R., & Wahby, V. S. (1990). Serum testosterone levels in post-traumatic stress disorder patients. *Journal of Traumatic Stress,* **3**, 449–457

Mason, J. W., Giller, E. L., Kosten, T. R., & Yehuda, R. (1990). Psychoendocrine approaches to the diagnosis and pathogenesis of posttraumatic stress disorder. In E. Giller (Ed.), *Biological assessment and treatment of PTSD* (pp. 65–86). Washington, DC: American Psychiatric Press, Inc.

Mason, J. W., Giller, E. L., & Ostroff, R. B. (1984). Relationships between psychological mechanisms and the pituitary-gonadal system. *Current Clinical Practice Series,* **26**, 215–228.

Mason, J. W. Kennedy, J. L., Kosten, T. R., & Giller, E. L. (1989). Serum thyroxine levels in schizophrenic and affective disorder diagnostic subgroups. *Journal of Nervous and Mental Disease,* **177**, 351–358.

Mason, J. W. Mangan, G. F., Brady, J. V., Conrad, D., & Rioch, D. (1961). Concurrent plasma epinephrine, norepinephrine, and 17-hydroxycorticosteroid levels during conditioned emotional disturbances in monkeys. *Psychosomatic Medicine,* **23**, 344–353.

Mazur, A. (1985). A biosocial model of status in face-to-face primate groups. *Social Forces,* **64**, 377–402.

Mazur, A., & Lamb, T. A. (1980). Testosterone, status, and mood in human males. *Hormones Behavior,* **14**, 236–246.

Monti, P. N., Brown, W. A., & Corriveau, D. P. (1977). Testosterone and components of aggressive and sexual behavior in man. *American Journal of Psychiatry,* **134**, 692–694.

Olweus, D., Mattson, A., Schalling, D., & Low, H. (1980). Testosterone, aggression, physical, and personality dimensions in normal adolescent males. *Psychosomatic Medicine,* **42**, 253–269.

Ostroff, R., Giller, E., Bonese, K., Ebersole, E. Harkness, L., & Mason, J. (1982). Neuroendocrine risk factors of suicidal behavior. *American Journal of Psychiatry,* **139**, 1323–1325.

Overall, J. E., & Gorham, D. R. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports,* **10**, 799–812.

Prange, A. J., Wilson, I. C., Bresse, G. R., & Lipton, M.A. (1976). Hormonal alteration of imipramine response: A review. In E. Sachar (Ed.), *Hor-*

mones, behavior, and psychopathology (pp. 41–67). New York: Raven Press.

Rauste-von Wright, M., von Wright, M., & Frankenhaeuser, M. (1981). Relationships between sex-related psychological characteristics during adolescence and catecholamine excretion during achievement stress. *Psychophysiology,* **18**, 362–370.

Rose, R. M., Bourne, P. G., Poe, R. O., Mougey, E. H., Collins, D. R., & Mason, J. W. (1969). Androgen responses to stress. II. Excretion of testosterone, epitestosterone, androsterone, and etiocholanolone during basic combat training and under threat of attack. *Psychosomatic Medicine,* **31**, 418–436.

Rose, R. M., Bernstein, I. S., & Gordon, T. P. (1975). Consequences of social conflict on plasma testosterone levels in Rhesus monkeys. *Psychosomatic Medicine,* **37**, 50–51.

Rose, R. M. (1984). Overview of endocrinology of stress. In G. Brown (Ed.), *Neuroendocrinology and psychiatric disorder* (pp. 95–122). New York: Raven Press.

Sachar, E. J., Mason, J. W., Kolmer, H. S., & Artiss, K. L. (1963). Psychoendocrine aspects of acute schizophrenic reactions. *Psychosomatic Medicine,* **25**, 510–537.

Scaramella, T. J., & Brown, W. A. (1978). Serum testosterone and aggressiveness in hockey players. *Psychosomatic Medicine,* **40**, 262–265.

Schaeffer, M. A., & Baum, A. (1984). Adrenal cortical response to stress at Three Mile Island. *Psychosomatic Medicine,* **46**, 227–237.

Shaw, J. A. (1983). Comments on the individual psychology of combat exhaustion. *Military Medicine,* **148**, 223–231.

Smith, C. H. (1985). Prognostic indicators in post traumatic stress disorder. *Alabama Medicine,* **55**, 50–54.

Southwick, S., Mason, J. W., Giller, E. L., & Kosten, T. R. (1989). Serum thyroxine change and clinical recovery in psychiatric inpatients. *Biological Psychiatry,* **25**, 773–782.

Spitzer, R. L., Endicott, J., & Robins, E. (1978). Research Diagnostic Criteria. *Archives of General Psychiatry,* **35**, 773–782.

Whybrow, P. C., Prange, A. J., & Treadway, C. R. (1969). Mental changes accompanying thyroid gland dysfunction. *Archives of General Psychiatry,* **20**, 48–63.

Whybrow, P. C., & Hurwitz, T. (1976). Psychological disturbances associated with endocrine disease and hormone therapy. In E. Sachar (Ed.), *Hormones, behavior, and psychpathology* (pp. 125–144). New York: Raven Press.

Wolff, C. T., Friedman, S. B., Hofer, M. A., & Mason, J. W. (1964). Relationship between psychological defenses and mean urinary 17-OHCS excretion

rates. I. A predictive study of parents of fatally ill children. *Psychosomatic Medicine*, **26**, 576–591.

Wolff, C. T., Hofer, M. A., & Mason, J. W. (1964). Relationship between psychological defenses and mean urinary 17-OHCS excretion rates. II. Methodological and theoretical considerations. *Psychosomatic Medicine*, **26**, 592–609.

Woodman, D. (1979a). Biochemistry of psychopathy. *Journal of Psychosomatic Research*, **23**, 343–360.

Woodman, D. (1979b). Evidence of a permanent imbalance in catecholamine secretions in violent social deviants. *Journal of Psychosomatic Research*, **23**, 155–157.

Yehuda, R., Southwick, S., Nussbaum, G., Wahby, V., Giller, E., & Mason, J. (in press). Low urinary cortisol excretion in patients with post-traumatic stress disorder. *Journal of Nervous and Mental Disorders*.