

## Psychological and Endocrine Abnormalities in Refugees From East Germany: Part II. Serum Levels of Cortisol, Prolactin, Luteinizing Hormone, Follicle Stimulating Hormone, and Testosterone

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**Abstract.** We investigated afternoon serum levels of cortisol, prolactin, luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone in a group of 84 refugees who had fled from East to West Germany and suffered from psychiatric disorders within 6 weeks of their arrival in West Berlin. The mean hormone levels were compared with those of healthy control subjects. Cortisol levels were lower and LH levels were higher in the patients than in the control subjects, but only at trend levels of significance. No differences were found between the prolactin, FSH, or testosterone concentrations of the two groups. The patients with major depressive disorder (MDD) had a significantly higher mean cortisol level than the mean levels in the subgroups in whom posttraumatic stress disorder, dysthymia, and adjustment disorder were diagnosed. It can be concluded that the hypothalamic-pituitary-adrenal axis may "adapt" during severe long-term psychological stress and that long-term stress may be only one of the neurochemical mechanisms underlying the hypercortisolemia in patients with MDD.

**Key Words.** Affective disorder, posttraumatic stress disorder, cortisol, prolactin, luteinizing hormone, follicle stimulating hormone, testosterone, stress, migration.

The organism responds to both acute psychological and physical stress in numerous different ways, including activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to a release of adrenocorticotrophic hormone (ACTH) and cortisol. This has been demonstrated both in animal models and in humans (Rose, 1984; Murburg et al., 1990). In their recent review, Harbuz and Lightman (1992) concluded that (in animal models, at least) circulating levels of ACTH and corticosterone as a rule remain normal under conditions of chronic stress. While the response to the same stressful stimulus may be diminished, the HPA system may, however, be more sensitive to other acute stressors (e.g., see Levine, 1962; for a review, see Yehuda et al., 1991). Likewise, low urinary cortisol excretion has also been found in men after exposure to chronic stress—for example, in Vietnam soldiers (Bourne et al., 1968).

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These latter findings have been interpreted as a physiological adaptation to chronic stress (Mason, 1968). Voigt et al. (1990) demonstrated a decline in ACTH and cortisol responses with increasing experience to the same stressors in men. On the other hand, Rahe et al. (1990) showed that American hostages held in Iran for 444 days showed elevated plasma and saliva cortisol levels on arrival in Wiesbaden following their liberation. However, psychological testing of these hostages indicated that they were generally well defended, appearing to have endured their ordeal well.

Neuroendocrine findings in patients with posttraumatic stress disorder (PTSD) have been contradictory (for a review, see Yehuda et al., 1993*b*): On the one hand lower urinary levels of free cortisol have been found in PTSD patients than in patients with major depressive disorder (MDD) (Mason et al., 1986) and non-psychiatric control subjects (Yehuda et al., 1990). Furthermore, Yehuda et al. (1993*c*) reported normal baseline cortisol levels, but greater suppression in the dexamethasone suppression test (DST) in PTSD without depressive symptoms than in patients with MDD. Recently, Yehuda et al. (1993*a*) reported that patients with PTSD had the largest and those with MDD the smallest number of lymphocyte glucocorticoid receptors per cell. Furthermore, the mean 24-hour urinary cortisol excretion was significantly higher in patients with MDD than in subjects with PTSD. Finally, Halbreich et al. (1989) found that none of a group of 14 male Vietnam veterans with PTSD had elevated basal cortisol plasma concentrations or abnormal DST results. Note that all of these patients also had endogenous depression.

On the other hand, Pitman and Orr (1990) reported elevated 24-hour urinary cortisol excretion in patients with PTSD. Two questions thus arise: (1) Is the activity of the HPA axis really reduced in PTSD patients? (2) Does the activity of the HPA axis in PTSD patients with concomitant MDD differ from that in patients without MDD?

As we had been able to include large enough numbers of both patients diagnosed as having major depressive disorders and patients with PTSD in our study, it seemed worthwhile measuring cortisol levels in our sample of refugee patients.

Prolactin has been found to be elevated after several forms of acute stress and is often considered to be a "stress-responsive" hormone. However, several studies have failed to find changes in prolactin levels, particularly after acute or chronic psychological stress (for review, see Baumgartner et al., 1988). We therefore also measured prolactin concentrations in the refugees. Finally, as far as we know, no one has yet investigated the influence of chronic psychological stress on the hormones of the hypothalamic-pituitary-gonadal (HPG) axis. Kreuz et al. (1972) reported subnormal plasma levels of testosterone in the early stressful part of a course at an officer candidate school. On the other hand, both declines (Tanaka et al., 1986) and rises (Sutton et al., 1973) in testosterone concentrations have been reported after physical exercise. In particular, there is an ongoing debate as to whether plasma levels of testosterone fall during stress in the presence of normal or high circulating LH values (for a discussion, see Tanaka et al., 1986). The complexity of the situation is highlighted by a study by Hellhammer et al. (1985) in which they observed an increase in salivary testosterone levels in 20 young adult men during presentation of a film with erotic and sexual stimulation, while declines in testosterone levels were observed during a movie showing dental surgery. We therefore decided also to investigate the hormones of the HPG axis—namely LH, FSH, and testosterone.

## Methods

The sociodemographic data and criteria for inclusion in the study are given in Part I of this study (Bauer et al., 1994). The afternoon serum hormone concentrations of cortisol and prolactin were measured in all 84 patients (43 women, 41 men) and all 20 healthy controls (5 women, 15 men). Assays for LH, FSH, and testosterone were done for the male patients and male controls only, as the female patients were in different phases of the menstrual cycle. Details of the blood sampling procedure are given in Part I (Bauer et al., 1994). The hormones were determined in duplicate with commercial kits. Cortisol and testosterone were measured with radioimmunoassay (RIA) kits from Diagnostic Products and prolactin with RIA kits from Serono Diagnostica. We used the Maya clone kits produced by Serono Diagnostica to determine LH and FSH. Details of the sensitivities of the kits and the interassay coefficients of variation measured by our laboratory have been published in previous reports (Baumgartner et al., 1986a, 1988, 1990). All hormone levels were measured in the same assay for both patients and controls. For the statistical methods, see Part I (Bauer et al., 1994).

## Results

Fig. 1 and Table 1 present the cortisol concentrations of 84 patients and 20 healthy control subjects. The mean cortisol level was lower in the patients than in the control subjects, but not significantly so ( $p = 0.07$ , Table 1).

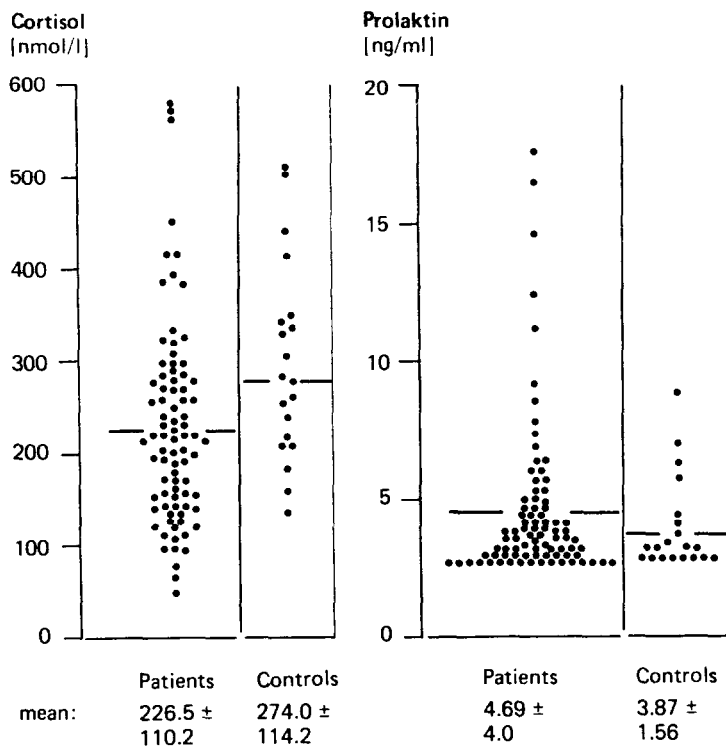
Analysis of variance showed significant group effects for the cortisol values only. Individual ranking by the Newman-Keuls test revealed that patients with MDD had significantly higher mean cortisol concentrations than those in the groups with PTSD, dysthymia, and adjustment disorders (Table 2). The cortisol concentrations of the PTSD patients were somewhat lower than those seen in healthy control subjects, but the difference was not statistically significant ( $p = 0.06$ ).

Of all the other hormones (Fig. 2), only LH showed a trend toward elevated concentrations in the patients ( $p = 0.08$ , see Table 1), whereas the prolactin, FSH, and testosterone levels were normal. No significant differences were found between any of the hormone levels of the patients previously imprisoned and those of the patients without a history of imprisonment.

Surprisingly, we found significant positive correlations between the thyroid stimulating hormone (TSH), thyroxine, free thyroxine, triiodothyronine, and reverse triiodothyronine values and the cortisol levels in the patients (all  $p$ 's  $< 0.05$ ). None of these correlations were significant in the control group. The correlations between the prolactin concentrations and the TSH, thyroid hormones, and cortisol levels were not significant in either the patients or the healthy control subjects.

We also found no significant correlations between the different hormone levels and the length of the period between the decision to leave East Germany and the actual time of departure, which we considered to be an appropriate value for the duration of the stress experienced by the patients (see Part I). Likewise, no significant correlations were found between the rating scores of the different rating scales (see **Methods**, Part I; Bauer et al., 1994) and any of the hormone concentrations. The hormone values were not correlated to the ages and the gender of the patients.

**Fig. 1. Cortisol and prolactin concentrations in 84 patients and 20 healthy control subjects.**



The bars indicate the mean levels.

**Table 1. Hormone concentrations of patients and healthy control subjects**

Hormones	Patients		Control subjects		<i>p</i>
	Mean	SD	Mean	SD	
Cortisol	226.5	110.2	274.0	114.2	NS (0.07)
Prolactin	4.69	4.00	3.87	1.56	NS
Luteinizing hormone	5.79	3.73	4.00	1.73	NS (0.08)
Follicle stimulating hormone	1.51	1.37	1.07	1.34	NS
Testosterone	5.61	1.89	5.47	1.55	NS

Note. For units of measurement, see text and Figs. 1 and 2.

**Table 2. Mean cortisol, prolactin, testosterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH) concentrations in all patients, in five different diagnostic subgroups, and in the subgroup of former political prisoners**

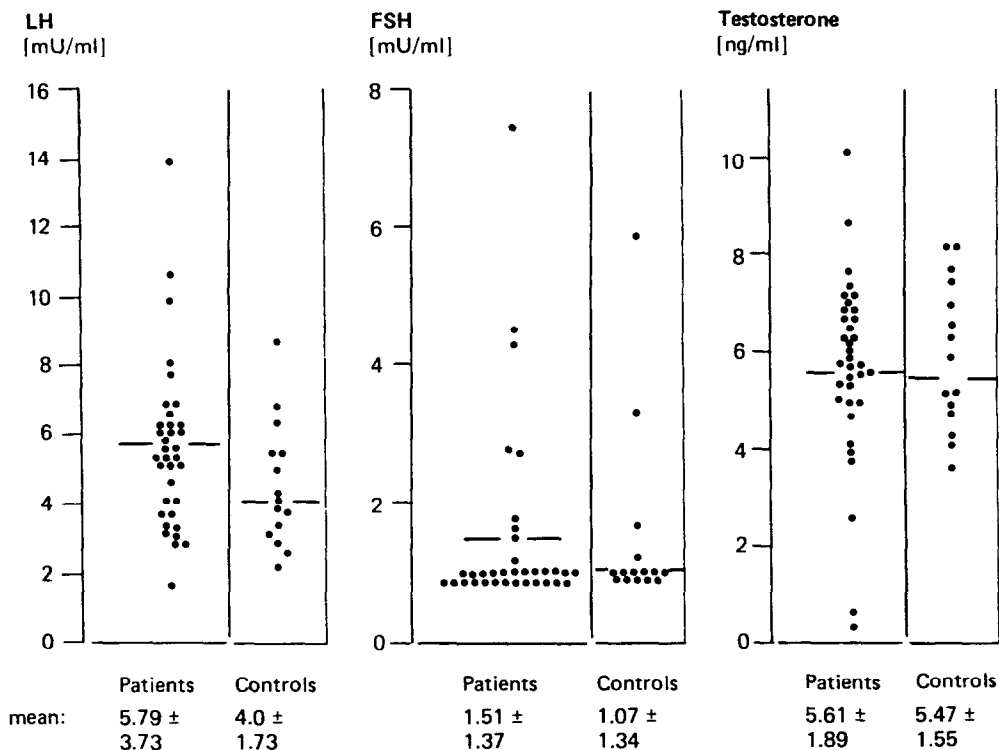
	All patients (n = 84)	Major depressive disorders (n = 18)	PTSD (n = 12)	Anxiety disorders (n = 11)	Dysthymia (n = 10)	Adjustment disorders (n = 33)	Previously imprisoned patients (n = 23)
Cortisol							
Mean	226.5	291.5 <sup>1</sup>	201.2	242.4	202.0	200.0	228.1
SD	110.2	134.9	92.5	132.0	58.2	90.5	100.1
Prolactin							
Mean	4.69	4.10	3.37	5.39	4.41	4.35	3.89
SD	4.00	1.60	0.95	4.44	2.27	2.81	2.03
		Major depressive disorders (n = 8)	PTSD (n = 9)	Anxiety disorders (n = 5) <sup>2</sup>	Dysthymia (n = 2) <sup>2</sup>	Adjustment disorders (n = 11)	Previously imprisoned patients (n = 14)
Male patients (n = 35)							
Testosterone							
Mean	5.61	6.91	5.62	5.82	4.90	5.09	6.00
SD	1.89	1.69	0.63	0.89	1.70	1.88	2.02
Luteinizing hormone							
Mean	5.79	7.30	4.60	5.80	6.50	5.12	5.27
SD	3.73	6.82	1.78	2.40	3.30	2.13	2.63
Follicle stimulating hormone							
Mean	1.51	1.38	1.00	2.62	2.75	1.26	1.32
SD	1.37	0.66	0.05	2.47	1.75	0.82	0.99

Note. For units of measurement, see Figs. 1 and 2. PTSD = posttraumatic stress disorder.

1.  $p < 0.05$  compared to the groups with PTSD, dysthymia, and adjustment disorders.

2. Not included in analysis of variance calculations.

**Fig. 2. Luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone concentrations in 41 male patients and in 15 healthy male control subjects**



The bars indicate the mean levels.

## Discussion

In this part of the study, the levels of three pituitary and two peripheral hormones from different endocrine axes were measured in refugees who had fled from East to West Germany and compared with those of a healthy control group. The mean cortisol concentrations of our patients were normal, although a nonsignificant trend toward a decline was noted. This result is in agreement with those of all studies that found an adaptation of the HPA axis during repeated or chronic stress in humans (e.g., Bourne et al., 1968; Voigt et al., 1990; for reviews, see Yehuda et al., 1991; Harbuz and Lightman, 1992). It is also known from animal studies that elevated ACTH and corticosterone levels after an acute stressor may gradually normalize during several weeks' repeated exposure to the same stressor and may adapt after acute exposure to the same stressor. The possibility that factors such as a subsensitivity of the pituitary corticotropin releasing factor (CRF) receptors (e.g., Odio and Brodish, 1990) may underlie this adjustment of the HPA axis has been discussed.

The cortisol levels we found in our PTSD patients are consistent with those reported by Mason et al. (1986), Halbreich et al. (1989), and Yehuda et al. (1990), who all found normal or even depressed HPA axis activity in this disorder. This contrasts with the results of a study by Pitman and Orr (1990), who reported elevated urinary cortisol levels in PTSD. Furthermore, Halbreich et al. (1989) and Yehuda et al. (1993c) reported that the basal cortisol levels of PTSD patients with MDD did not differ from those of healthy control subjects. Our design is not completely comparable to theirs, as we were unable to divide our small PTSD group ( $n = 12$ ) into PTSD patients with and without endogenous depression. However, like Halbreich et al. (1989), we found that patients with MDD had significantly higher basal cortisol levels than patients with PTSD. Likewise, Mason et al. (1986) reported significantly lower urinary levels of free cortisol in PTSD than in MDD.

On the other hand, MDD has been associated with hypercortisolemia (e.g., Sachar, 1967), nonsuppression in the dexamethasone suppression test (e.g., Carroll, 1982), and a blunted ACTH response to CRF (e.g., Gold et al., 1986). It remains unclear, however, whether hypercortisolemia in MDD results from mechanisms specific for depression, stress factors, or other "intervening variables" (e.g., weight loss or hospitalization) or from a combination of several of these factors (for a discussion, see Baumgartner et al., 1986b). As all patients in the present study (irrespective of their psychiatric diagnosis) were suffering from a similar kind of prolonged stress, it is likely that chronic stress, per se, is not responsible for the hypercortisolemia seen in MDD. Moreover, as all the patients who did not have MDD did have not only some depressive symptoms, but also a lower mean cortisol level, it can be concluded that hypercortisolemia in MDD is more likely to be induced by a disease-specific pathochemical mechanism than by the "nonspecific" stress factors mentioned above. On the basis of their findings in affective disorders, Gold's group developed an interesting hypothesis on the pathogenesis of "depressive disorder," namely that "the clinical and biochemical manifestations of major depression represent an activation of the major effects of the generalized stress response that have escaped their usual counter regulatory elements" (Johnson et al., 1992). It therefore seems noteworthy that the cortisol levels of chronically stressed people seem to adapt, whereas those of patients with MDD were elevated, which is consistent with the above-mentioned hypothesis. However, the parameters of the hypothalamic-pituitary-thyroid (HPT) axis (see Part I; Bauer et al., 1994) also showed a marked fall after chronic stress in patients with MDD, indicating that the "stress response" of this axis is normal in depressed patients.

The LH values were elevated in the patient group, but not significantly so. No significant differences were found between the serum levels of FSH, testosterone, or prolactin of the patients and those of the control subjects. Reduced plasma testosterone levels have been described in army officer candidates during stressful parts of their training (Kreuz et al., 1972). Diminished urinary excretion of testosterone has been observed in Vietnam soldiers under threat of attack (Rose, 1969). However, the pattern of LH and FSH concentrations has not been found to parallel the fall in testosterone levels (Carstensen et al., 1973). There is also evidence that plasma levels of testosterone can rise during potentially stressful events (Sutton

et al., 1973; Rahe et al., 1990; Voigt et al., 1990). Our results indicate that all these previously described effects of stress on the HPG axis reflect more or less acute stress responses. In contrast, the functional integrity of the HPG axis seems to be preserved during chronic and severe psychological stress.

Various studies in animals (Neill, 1970; Telner et al., 1982; Kant et al., 1983) and humans have shown elevated prolactin plasma levels after exposure to stress. Conversely, no changes in prolactin concentrations were found in a number of other studies—for example, in phobic patients during severe anxiety caused by flooding treatment (Nesse et al., 1980) or in medical students before, during, and after a major examination (Baumgartner et al., 1988). The normal prolactin values in the present study provide further support for the interpretation that this hormone is not seriously affected by chronic mental stress.

### **Interpretation of the Findings of Parts I and II**

We found pronounced declines in all parameters of the HPT axis, but no significant changes in the HPA and the HPG axis parameters or the prolactin values in our severely stressed sample. These results are unexpected, as cortisol, prolactin, and testosterone are considered to be “classical stress hormones” (see Rose, 1984), whereas not much evidence has yet been found for an involvement of the HPT axis parameters in stress response. In his review, Rose (1984) mentioned thyroid hormones only once and concluded that the literature on their relationship to stress “is not sufficiently developed to warrant review.” Our surprising results indicate that in severe, chronic, and mainly psychological stress extending over a period of years, the stress responses of the HPA axis, the HPG axis and probably also prolactin may “adapt,” whereas that of the HPT axis, which is minimal in acute stress situations, is only beginning to become evident at this point. The physiological relevance of such a temporally fixed sequence of stress responses is unclear at present. However, the significant positive correlations between cortisol, TSH, and all thyroid hormones suggest that the changes in the HPT axis and those in the HPA axis seen during chronic stress may be somehow linked, although the latter (decreases in cortisol levels) did not reach statistical significance. Although we calculated a large number of correlations, we did not correct our *p* values, as this study was conducted for the purpose of generating hypotheses. However, we consider these significant correlations to be valid, since all of the intercorrelations between the individual HPT axis measurements and the correlations between the HPT axis measurements and cortisol were significant, whereas none of the correlations between the HPG axis and prolactin on the one hand, and the HPG axis and cortisol on the other, were significant.

The following interactions between the HPT and HPA axis during chronic stress could be hypothesized: (1) Both the HPT axis and the HPA axis may be stimulated by norepinephrine (see Spira and Gordon, 1986; Al-Damluji et al., 1987). On the other hand, the involvement of catecholamines and CRF in the stress-induced activation of the HPA axis is well documented (e.g., Axelrod and Reisine, 1984; Bruhn et al., 1984). It therefore seems conceivable that chronically enhanced central noradrenergic activity during long-term stress may down-regulate thyrotropin releasing hormone as well as CRF receptors at the pituitary, resulting in decreased



secretory activity of both the HPT and the HPA axes. (2) Direct interactions between thyroid hormones and glucocorticoids have also been reported. Significant increases in ACTH and corticosterone levels have been observed in hyperthyroid rats and reduced levels of these hormones in hypothyroid rats (Sanchez-Franco et al., 1989). The same stimulating effects of hyperthyroidism in cortisol secretion have also been reported in humans (Gallagher et al., 1972). A recent study by Ceccatelli et al. (1992) demonstrated that thyroid hormones may enhance the transcription of CRF in certain areas of the hypothalamus. It is therefore theoretically conceivable that decreases in thyroid hormone secretion cause a reduction in the activity of the HPA axis as a secondary response. Since the pronounced activation of the HPA axis occurs earlier than the corresponding changes in the HPT axis, it is also conceivable that elevated cortisol levels may blunt TSH secretion. This has often been demonstrated both in Cushing's disease (e.g., Duick and Wahner, 1979) and following administration of glucocorticoids to healthy subjects (e.g., Re et al., 1976; Sowers et al., 1977).

A major aim of future studies should therefore be to investigate whether the marked abnormalities in thyroid hormone concentrations observed during chronic stress are somehow linked to stress-induced alterations in the HPA axis, and whether or not they are of physiological significance (e.g., in regard to the hyperthyroid-like symptoms seen in chronically stressed subjects). Finally, one shortcoming of our study requires comment, namely that we based our results on samples drawn at a single sampling time only. As not only TSH, but also prolactin, cortisol, and LH are secreted episodically, we cannot rule out the possibility that differences in the levels of these hormones would have been more pronounced or maybe even somewhat different if we had performed serial blood sampling. However, our measurements of the HPT axis parameters were so consistent (pronounced decreases in all parameters without any exception) that we feel that the results can be considered to have a certain validity.

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