# The Corticotropin-Releasing Hormone Challenge in Depressed Abused, Depressed Nonabused, and Normal Control Children

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*Hypothalamic–pituitary–adrenal (HPA) axis disturbances in depressed children with a history of abuse were examined. Thirteen depressed abused, 13 depressed nonabused, and 13 normal control children were given 1.0 μg/kg of human corticotropin-releasing hormone (CRH) intravenously. Blood samples for corticotropin (ACTH) and cortisol were obtained at nine intervals. When compared to depressed nonabused and normal control children, depressed abused children had significantly greater peak, total, and net ACTH secretion post-CRH. Increased ACTH secretion was only observed in depressed abused children experiencing ongoing chronic adversity (marital violence, emotional abuse, poverty, lack of supports). The pattern of findings of the depressed abused children experiencing ongoing adversity parallels the pattern of HPA axis dysregulation reported in animal studies of chronic stress. They add to a growing body of literature suggesting measures of past trauma and current adversity are important sources of variability in psychobiological correlates of major depression.* © *1997 Society of Biological Psychiatry*

**Key Words:** Child abuse, child depression, cortisol, corticotropin

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## Introduction

Although disturbances of the hypothalamic–pituitary–adrenal (HPA) axis are among the more robust and consistent biological findings reported in samples of adults with depression (e.g., Holsboer 1995; Stokes and Sikes 1987), disturbances of the HPA axis are relatively rare in children (Ryan et al 1994). Hypercortisolemia (Dahl et al 1989, 1991; Kutcher and Marton 1991; Puig-Antich et al 1989), dexamethasone nonsuppression (see Casat et al 1989; Dahl et al 1992 for a review), and blunting of corticotropin (ACTH) secretion after corticotropin-releasing hormone (CRH) infusion (Birmaher et al in press) are infrequently observed in depressed children.

For example, when the CRH challenge was administered to children with major depression (MDD) and normal controls, there were no differences between the two groups on any of the baseline or stimulation summary measures (Birmaher et al 1996). Depressed children with

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melancholia ($n$ = 3) had a nonsignificant trend toward elevated cortisol at baseline. In addition, melancholic ($n$ = 3) and inpatient ($n$ = 10) depressed children secreted significantly less ACTH throughout the CRH challenge. Change in ACTH secretion in response to CRH was comparable among all groups, however. These results are in contrast to studies with adults, which typically report elevated cortisol at baseline and blunted ACTH secretion post-CRH infusion in depressed patients when compared to normal controls (e.g., Holsboer et al 1987; Lesch et al 1988; Rupprecht et al 1989).

Recent research has highlighted the importance of experiential (e.g., trauma) factors in explaining heterogeneity in the psychobiological correlates of depression (Halbriech et al 1989; Williamson et al 1995a; Yehuda et al 1995). As abuse history data were available for 62% (21/34) of the MDD and 63% (14/22) of the normal control children who participated in the CRH study described above (Birmaher et al 1996), secondary analyses were performed on the data as a preliminary test of the hypothesis that HPA axis disturbances are most prominent in depressed children with a history of trauma (e.g., abuse). Five MDD children were identified with a history of sexual abuse. When compared to the depressed and normal control children without a history of abuse, the depressed children with a history of abuse had blunted ACTH secretion post-CRH infusion, and a trend toward elevated cortisol at baseline (Kaufman et al 1993).

Similar finding were reported in another study in which the CRH challenge was administered to sexually abused and normal control children (DeBellis et al 1994a). Sixty-two percent of the sexually abused children in this study met criteria for dysthymia. When compared to normal controls, sexually abused children were found to have a blunted ACTH response to CRH, and normal basal and post-CRH cortisol values. In addition to these preliminary reports documenting HPA axis dysregulation in abused children, three other studies have reported abnormalities in the pattern of cortisol secretion in clinically heterogenous samples of abused children (Hart et al 1996; Kaufman 1991; Putnam et al 1991). In one of these reports (Kaufman 1991), cortisol secretion abnormalities were found to be significantly more likely among abused children who met criteria for MDD than in abused children without depressive symptomatology.

These initial reports suggest that, in contrast to the relative lack of HPA axis disturbances observed in cohorts of nontraumatized depressed children, depressed children with a history of abuse are likely to have altered HPA axis function. To further test the hypothesis that disturbances of the HPA axis are most prominent in depressed children with a history of trauma (e.g., abuse), a cohort of depressed children with a history of abuse was recruited and administered the CRH challenge. It was hypothesized that the depressed abused children, when compared to depressed nonabused and normal control children, would have increased basal cortisol values, and blunted ACTH and normal cortisol response post-CRH infusion.

## Subjects

### *Referral*

Depressed children were recruited from the inpatient and outpatient clinics at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center. Normal control children were recruited through advertisement and personal contacts. The depressed nonabused and normal control children were recruited to participate in a larger study on the psychobiology of childhood depression (PO5 MH 41712, Program Director, Neal Ryan, MD), and the depressed abused children were recruited to participate in an interlocking study examining depressive disorders in maltreated children (5K21 MH 01022, Principal Investigator, Joan Kaufman, PhD). Informed consent to participate in the study was obtained in accordance with the University of Pittsburgh Institutional Review Board guidelines.

### *Clinical Assessment*

Diagnostic assessments of the depressed cohorts were completed by research assistants who administered the Present Episode (Chambers et al 1985) and Epidemiological (Orvaschel and Puig-Antich 1987) versions of the semistructured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS). The diagnosis of MDD was made using research diagnostic criteria (RDC; Spitzer et al 1978), with the presence of all positive symptoms confirmed by a child psychiatrist or psychologist. For normal controls, if an initial telephone screen of the family was promising, the child's lifetime history of psychiatric symptomatology was assessed using only the K-SADS-E (Orvashel and Puig-Antich 1987). All symptom ratings were made by interviewing the parent(s) first, then interviewing the child. All children who participated in the study were reinterviewed using a short version of the K-SADS at the time of the psychobiological studies to confirm the stability of depressive symptomatology.

### *Abuse History*

Information about abuse was derived by completing the Psychosocial Schedule for School Aged Children (PSS; Kaufman et al 1993; Lukens et al 1983; Puig-Antich et al 1985a, 1985b). The PSS is a semistructured interview that

was designed to obtain information about functional impairment, family environment, and abuse history. Both parents and children were used as informants in collecting these data. Abuse history data and global ratings of the quality of children's relationships with their primary caregivers are examined in this report. Supplemental abuse history data were obtained by reviewing the children's medical records. This information was integrated with the information obtained using the PSS to obtain a "best estimate" of children's lifetime abuse experiences (Kaufman et al 1994). Child maltreatment history data were reviewed blind to information about children's CRH data.

### *Inclusion Criteria*

Inclusion criteria common for all subjects were: 1) 7–13 years of age; and 2) Tanner Stage I–II. Children in both depressed cohorts were required to meet RDC criteria for MDD, and children in the depressed abused cohort were additionally required to have a lifetime history of maltreatment (e.g., physical abuse, sexual abuse, and/or exposure to extreme marital violence). For the normal controls only, additional inclusion criteria included: 1) no lifetime history of any psychiatric disorder; and 2) low familial risk for affective illness. Inclusion in the normal control cohort was contingent on low family history of affective illness, because nonaffected offspring of depressed adults have been found to have some of the psychobiological findings typical of unipolar patients (Giles et al 1989). In this study, low familial risk for affective disorder was operationally defined as having no first-degree relative with a lifetime episode of any affective disorder or schizophrenia spectrum illness, no second-degree relative with a lifetime episode of recurrent, bipolar, or psychotic depression, schizoaffective disorder, or schizophrenia, and no more than 20% of second-degree relatives with a single episode of MDD. Lifetime psychiatric history of first- and second-degree relatives was determined using the K-SADS-E for relatives ages 6–18, and the Schedule for Affective Disorders–Lifetime (SADS-L; Spitzer and Endicott 1978) for relatives over 18 years old. Unavailable adult first- and second-degree relatives were assessed using the Family History–RDC (FH-RDC; Andreasen et al 1986) technique with the children's parent(s) serving as the informant(s).

### *Exclusion Criteria*

Exclusion criteria for all groups included: 1) significant medical illnesses; 2) medications (except Tylenol) within 2 weeks of the study; 3) inordinate fear of needles; 4) obesity (weight greater than 150% of ideal body weight) or severe growth failure (weight or height less than 3% of the National Health Statistic Curve); and 5) mental retardation (IQ $< 70$) or the presence of a specific learning disability. Additional exclusion criteria for the MDD cohorts only included: 1) concurrent DSM-III-R diagnosis of anorexia nervosa, bulimia nervosa, autism, schizoaffective disorder, or schizophrenia; and 2) MDD chronologically secondary to conduct disorder. All the children in the study were carefully screened for lifetime history of physical abuse, sexual abuse, and exposure to domestic violence. Only children with no lifetime history of maltreatment (e.g., physical abuse, sexual abuse, and/or exposure to domestic violence) were included in the nonabused depressed and normal control cohorts.

### *Sample*

The sample consisted of 39 children: 13 depressed abused (MDD-AB), 13 depressed nonabused (MDD-NA), and 13 normal control (NC-NA) children with no lifetime history of psychopathology or abuse. As discussed previously, the children in the MDD-NA and NC-NA groups were selected from a larger cohort of children participating in the program project "The Psychobiology of Childhood Depression." The children were selected to match as well as possible the depressed abused children on age, sex, and race distribution, with priority given first to matching subjects on age, then sex, then race. Two of the children included in the normal control nonabused cohort in this study were included in the prior report comparing the CRH response of depressed and normal control children (Birmaher et al 1996). The demographic characteristics of the sample included in this manuscript are depicted in Table 1. The mean age of the sample was about 9.5 years (range 7–13), two thirds (66%) of the children in the study were Caucasian, and approximately half were male (52%). There were no differences among the three groups in terms of age, race, or sex. The groups differed in terms of socioeconomic status (SES), however, with the depressed abused children having the lowest SES.

The depressed abused and depressed nonabused samples were comparable in terms of the proportion with: melancholia (MDD-AB: 5 vs. MDD-NA: 2); a prior episode of MDD (MDD-AB: 2 vs. MDD-NA: 1), and a history of inpatient hospitalization (MDD-AB: 4 vs. MDD-NA: 2; Fisher's Exact Test, ns for all comparisons). The duration (43.8 $\pm$ 45.3 weeks) and severity of the current depressive episode (33.7 $\pm$ 5.7 12-item K-SADS depression scale score) was also comparable for the MDD-AB and MDD-NA children. As expected, the depressed abused children were significantly more likely to meet criteria for posttraumatic stress disorder than the depressed nonabused children (8 vs. 0; Fisher's Exact

Table 1. Demographic Characteristics of Sample

| | MDD-AB ($n$ = 13) | MDD-NA ($n$ = 13) | NC-NA ($n$ = 13) | Statistic | $p$ value |
|---|---|---|---|---|---|
| Age (years) | 9.6 ± 1.4 | 9.9 ± 0.9 | 9.5 ± 1.2 | $F(2,36) = 0.29$ | ns |
| Race (black/white) | 5/8 | 4/9 | 3/10 | Fisher's Exact Test | ns |
| Sex (female/male) | 7/6 | 7/6 | 6/7 | $\chi^2$(df 26 2) = 0.2 | ns |
| Socioeconomic status | $26.0 \pm 14.4_a$ | $40.2 \pm 13.8_b$ | $51.2 \pm 9.7_c$ | $F(2,36) = 12.2$ | .001 |

MDD-AB, MDD abused; MDD-NA, MDD nonabused; NC-NA, normal controls nonabused. Means with different subscripts are significantly different from one another ($p < .05$), Newman–Keuls Multiple Comparison Test.

Test, $p < .001$), and somewhat more likely to meet criteria for comorbid dysthymia (6 vs. 2; Fisher's Exact Test, $p < .09$). There were no differences between the two groups in rates of other comorbid diagnoses. Overall 38% (10/26) of the depressed children met criteria for comorbid overanxious disorder, 31% (8/26) met criteria for oppositional defiant disorder, 23% (6/26) met criteria for attention-deficit hyperactivity disorder, 19% (5/26) met criteria for separation anxiety disorder, and 8% (2/26) met criteria for a simple phobia.

In terms of maltreatment history, the majority of the depressed abused children in the study experienced more than one type of abuse. Ten (77%) children had a history of sexual abuse; 5 (38%) had a history of physical abuse; and 10 had a history of emotional maltreatment. For the purposes of the present investigation and consistent with other research studies (Hart and Brassard 1991), emotional maltreatment was operationally defined to include: exposure to severe domestic violence, verbal rejection and hostile degradation, repeated ignoring of active attempts from the child to engage the parent, and terrorizing, including threatening to physically harm or abandon the child. Although none of the children in the depressed abused cohort were living with a perpetrator of past sexual or physical abuse, and none was known to be experiencing sexual or physical abuse at the time of the study, 7 (54%) were being subjected to ongoing emotional abuse. As stated previously, none of the depressed nonabused or the normal control children had a history of any type of maltreatment.

## Methods

The sleep/neuroendocrine laboratory where the tests were completed is furnished with many age-appropriate materials, including books, art supplies, board games, entertainment videos, and computer games. In the lab, children are given a lot of one-to-one attention from staff who have years of experience running biological studies with children, and the majority of children who participated in this and other studies in the lab rated the experience very positive (Townsend et al 1988; Nelson 1996).

The CRH challenge was administered on the second day of a larger, multitest psychobiological protocol. An intravenous catheter was inserted at the onset of the protocol, at 5 PM the evening prior to the CRH challenge. Other assessments obtained earlier in the protocol included: cortisol specimens after IV insertion and sleep electroencephalographic (EEG) recordings the night before the CRH challenge; a growth hormone releasing hormone challenge conducted at 9:00 AM; and reaction time (Matthews et al 1990) and mirror image tracing (Allen and Crowell 1989) tasks completed at 1:00 PM the day of the CRH challenge. These latter tasks and other similar behavioral stressors are associated with transient increases in heart rate and blood pressure (Allen and Crowell 1989; Matthews et al 1990), and minimal to no changes in cortisol secretion (Granger et al 1994).

The CRH challenge was administered at 5:30 PM, a time when the HPA axis is usually quiescent (Schulte et al 1985). A 1.0-μg/kg dose of human CRH was given as an intravenous infusion over a 2-min period. A physician was in attendance throughout the procedure. Blood samples for ACTH and cortisol were obtained through the indwelling catheter (placed the night before) at −30, −15, and 0 min pre-CRH infusion, and 15, 30, 60, 90, 120, and 150 min post-CRH infusion. Blood samples were collected in plastic tubes containing edetic acid (EDTA), then centrifuged immediately in a refrigerated centrifuge. Plasma was separated and stored at −80°C until assayed.

There were no significant side effects experienced by any of the children during the CRH challenge. Some children reported mild tingling in their arm over the 2-min period when the CRH was administered, and a few children had brief episodes of facial flushing, which was noted by the sleep laboratory personnel, but not the children themselves.

### *ACTH Assay*

ACTH plasma levels were determined from a 100-μL plasma sample using a slightly modified version of the double antibody $^{125}$I radioimmunoassay developed by Radioassay Systems Laboratory, Inc. This method is sensitive to 5 pg/mL for ACTH. The range of the coefficient of variation (CV) was 1.5–9.0%, with an upper limit

Table 2. CRH Challenge ACTH Values (pg/mL): MDD Abused versus MDD Nonabused versus Normal Control Children

| | MDD-AB (X ± SD) ($n$ = 13) | MDD-NA (X ± SD) ($n$ = 13) | NC-NA (X ± SD) ($n$ = 13) | Statistic | $p$ value |
|---|---|---|---|---|---|
| Baseline ACTH | $25.5 \pm 8.2_a$ | $21.1 \pm 7.5_a$ | $19.7 \pm 5.1_a$ | $F(2,36) = 0.63$ | ns |
| Total ACTH post-CRH | $51.5 \pm 26.4_a$ | $29.0 \pm 16.3_b$ | $31.5 \pm 10.0_b$ | $F^1(2,36) = 4.85$ | .01 |
| Peak ACTH post-CRH | $80.6 \pm 44.1_a$ | $41.0 \pm 24.1_b$ | $44.4 \pm 14.1_b$ | $F^1(2,36) = 6.00$ | .005 |
| Net ACTH response | $28.0 \pm 19.9_a$ | $7.8 \pm 13.2_b$ | $11.8 \pm 9.6_b$ | $F^1(2,36) = 5.27$ | .001 |

MDD-AB, MDD abused; MDD-NA, MDD nonabused; NC-NA, normal controls nonabused. Means with different subscripts are significantly different from one another, $p < .05$, Newman–Keuls Multiple Comparison Test. Raw scores are presented in the table, transformed scores were used to analyze the data.

of 11.0 pmol/L (50 pg/mL) for linearity. The ACTH samples were diluted and measured with reliability at 1.1–22.0 pmol/L (5–100 pg/mL). The interday variation for the assay ranged from 9.3% CV (mean of 11.8 pmol/L) to 19.9% CV (mean of 1.9 pmol/L). This assay detects both $I^{39}$ and $I^{24}$ molecular forms of human ACTH.

### *Cortisol Assay*

Cortisol plasma levels were determined from a 25-μL sample, which was assayed in duplicate using the Diagnostic Products Solid-Phase $^{125}I$ radioimmunoassay for cortisol (Coat-a Count, Diagnostic Products Corporation, Los Angeles, CA). This method is sensitive to 0.5 μg/dL of cortisol. Patient duplicates exceeding a 5.0% CV were reassayed. The intraassay coefficient of variation ranged from 1.3% to 2.7% with a mean of 1.9%. Interassay variation ranged from 11.7% at 3.76 μL/dL to 7.0% at 30.4 μL/dL. All specimens for each patient were analyzed in the same run on a batch basis.

## Statistical Analyses

There were no problems with missing data. The following summary values were used to characterize children's ACTH and cortisol responses to the CRH challenge: baseline, total post-CRH, peak post-CRH, and net response. The baseline values were computed by determining the mean of the three ACTH and cortisol specimens taken at −30, −15, and 0 min pre-CRH infusion. The total post-CRH scores were computed by determining the area under the curve (AUC) using the seven ACTH and cortisol specimens obtained between 0 and 150 min post-CRH infusion. The peak values represent the highest values post-CRH, and the net response scores were computed by subtracting the mean baseline values from the six post-CRH draws and calculating an AUC of the difference scores. AUCs were derived using the trapezoidal rule.

Prior to examining group differences on the summary scores, the Shapiro–Wilk's test for normality was performed on all summary measures. Log and other transformations were used to normalize the nonnormally distributed summary scores. Analyses of variance (ANOVAs) with Neuman–Keuls multiple comparison tests were then used to examine group differences on the normally distributed raw or log-transformed summary scores. Pearson correlations were used to examine the associations among the normally distributed raw or transformed ACTH and cortisol measures. $T$ tests were used to test the effects of sex and race, and correlational analyses were used to test the effects of age and SES on the summary measures.

## Results

### *ACTH Values*

Table 2 portrays the means and standard deviations of the ACTH summary scores, and results of tests for group differences on these measures. As depicted in Table 2, there were no differences in the mean ACTH values at baseline. The depressed abused children, however, had significantly greater total, peak, and net ACTH response post-CRH than the children in the other two groups ($p <$ .01, all comparisons). Overall the depressed abused children, when compared to the depressed nonabused and normal control children, had a significantly augmented ACTH response to the CRH challenge.

None of the following demographic factors were related to any of the ACTH summary scores: age, sex, or race. SES was related to each of the ACTH summary scores, with zero order correlations between SES and the ACTH summary scores ranging from −0.36 to −0.48 ($p < .05$, all comparisons). When stepwise multiple regression analyses were performed to simultaneously examine the effects of diagnostic/abuse status and SES, in all cases diagnostic status accounted for the greatest amount of variance. For example, in the stepwise multiple regression analyses predicting peak ACTH post-CRH values, diag-

Table 3. CRH Challenge Cortisol Values (μg/dL): MDD Abused versus MDD Nonabused versus Normal Control Children

| | MDD-AB (X ± SD) ($n$ = 13) | MDD-NA (X ± SD) ($n$ = 13) | NC-NA (X ± SD) ($n$ = 13) | Statistic | $p$ value |
|---|---|---|---|---|---|
| Baseline cortisol | 6.0 ± 2.4 | 7.0 ± 2.3 | 6.7 ± 2.7 | $F(2,36) = 0.54$ | ns |
| Total cortisol post-CRH | 11.5 ± 3.2 | 9.8 ± 4.6 | 11.2 ± 4.2 | $F(2,36) = 0.58$ | ns |
| Peak cortisol post-CRH[a] | 17.8 ± 4.9 | 14.7 ± 6.1 | 17.0 ± 5.1 | $F(2,36) = 0.74$ | ns |
| Net cortisol response | 5.5 ± 2.5 | 2.9 ± 4.3 | 4.5 ± 2.9 | $F(2,36) = 1.98$ | ns |

MDD-AB, MDD abused; MDD-NA, MDD nonabused; NC-NA, normal controls nonabused.
[a] Raw scores are presented in the table, transformed scores were used to analyze the data.

nostic/abuse status accounted for 41% of the variance. The addition of SES to the model contributed an extra 4% of variance, bringing the total model $R^2$ to .45 [$F(2,37) = 25.53$, $p < .0001$].

### *Cortisol Values*

Table 3 portrays the means and standard deviations of the cortisol summary scores, and results of tests for group differences on these measures. No group differences and no significant relationships with the demographic factors (age, sex, race, or SES) were detected with any of the cortisol summary measures.

### *Examination of Outliers*

The depressed abused children in this study were expected to have *lower* ACTH post-CRH when compared to the depressed nonabused and normal control children. Instead, the depressed abused children in this study were found to have significantly *greater* ACTH secretion. Consequently, the ACTH values of the depressed abused children were examined for outliers. There was a bimodal distribution of peak ACTH values post-CRH within the depressed abused cohort, such that the group could be divided into "high ACTH responders" and "low ACTH responders." The minimum peak ACTH post-CRH secretion value within the high ACTH responder group was more than 2 standard deviations above the mean score of children included in the low ACTH responder group. In addition, there was no overlap in the distribution of peak ACTH scores of the depressed abused children in the high and low ACTH responder groups.

### *Exploratory Analyses*

Exploratory analyses were conducted within the depressed abused cohort comparing the high vs. low ACTH responders on demographic, clinical, abuse, and family characteristics. Analyses were also conducted comparing the depressed abused children who were currently living under conditions of chronic ongoing adversity to depressed abused children living in stable environments, as this was the one factor that emerged from the exploratory analyses that completely distinguished the high versus low ACTH responders.

### *Demographic Characteristics: High versus Low ACTH Responders*

The high ($n$ = 7) and low ($n$ = 6) ACTH responders within the depressed abused group did not differ in terms of the following demographic factors: age ($t_{12} = 0.79$, ns), sex (Fisher's Exact Test, ns), or race (Fisher's Exact Test, ns). They did differ in terms of SES, with the high responders found to have significantly lower SES than the depressed abused children in the low responder group ($t_{12} = 10.86$, $p < .01$). Six out of the 7 children in the high responder group were receiving Aid to Families with Dependent Children (AFDC), with family income substantially below the poverty line in all 7 cases.

### *Clinical Characteristics: High versus Low ACTH Responders*

In terms of clinical factors, there were no differences between the high and low responders in terms of proportion of melancholics (Fisher's Exact Test, ns), severity of depression ($t_{12} = 1.17$, ns), or duration of depression ($t_{12} = 0.10$, ns). There was a trend for proportionately more children in the high responder group to meet criteria for a comorbid posttraumatic stress disorder (6/7 vs. 2/6, Fisher's Exact Test, $p < .07$).

### *Abuse and Family Characteristics: High versus Low ACTH Responders*

A comparable proportion of high and low ACTH responders had a history of physical and sexual abuse. All the

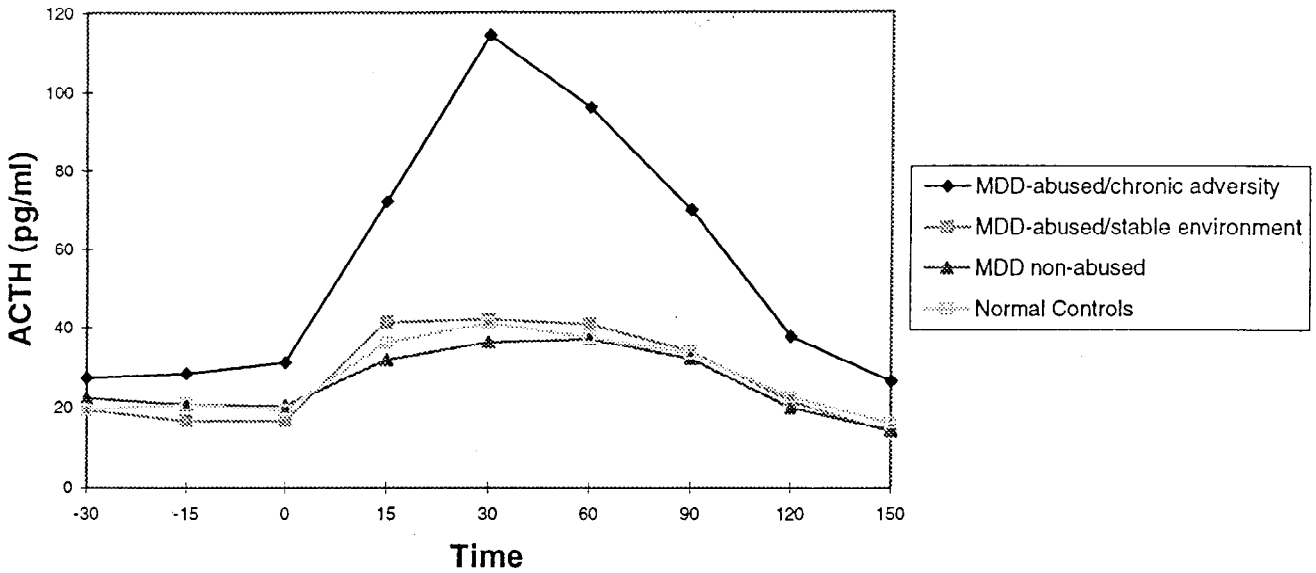


Figure 1. Results of the exploratory analyses conducted comparing the ACTH values of the depressed abused children living under conditions of chronic ongoing adversity ($n$ = 7), depressed abused children currently living in stable environments ($n$ = = 6), depressed nonabused children ($n$ = 13), and normal control nonabused children ($n$ = 13).

children in the high responder group, however, were currently living in homes in which there was active emotional maltreatment. Three of the children were living in families where there was extreme ongoing domestic violence, 1 child and his family was being repeatedly stalked and threatened by his estranged father, and 3 of the children's ongoing placement in the care of their natural parents was in jeopardy due to extreme emotional abuse (e.g., verbal rejection and hostile degradation, repeated ignoring of active attempts from the child to engage the parent, and terrorizing, including threatening to physically harm or abandon the child). None of the children in the low ACTH responder group were living in homes characterized by ongoing emotional maltreatment (7/7 vs. 0/6, Fisher's Exact Test, $p < .0003$). In addition, on the global rating of the quality of the child's relationship with their primary caregiver obtained on the Psychosocial Schedule, the children in the high responder group were found to have significantly less positive relationships with their primary caregivers than the children in the low responder group ($t_{12} = 2.5, p < .03$).

In summary, the experiences of the children in the high ACTH responder group can best be characterized as *chronic ongoing adversity*. All the children in this group were victims of ongoing severe emotional maltreatment, they were living in conditions of poverty, and their relationships with their primary caregivers were characterized as unsupportive.

### *Chronic Ongoing Adversity versus Current Stable Environment*

Exploratory analyses were conducted comparing the CRH data of the depressed abused children living under conditions of chronic ongoing adversity (MDD-AB/CA; $n$ = 7), depressed abused children currently living in stable environments (MDD-AB/SE; $n$ = 6), the depressed nonabused children (MDD-NA; $n$ = 13), and normal control nonabused children (NC-NA; $n$ = 13). The results of these analyses are depicted in Figures 1 and 2. The depressed abused children living under conditions of chronic ongoing adversity were found to have significantly *greater* baseline ACTH [MDD-AB/CA: 29.0 ± 6.0; MDD-AB/SE: 17.2 ± 5.3; MDD-NA: 21.1 ± 7.5; NC-NA: 19.7 ± 5.1, $F(3,35) = 4.13, p < .01$], and greater total [MDD-AB/CA: 68.4 ± 23.1; MDD-AB/SE: 31.8 ± 12.9; MDD-NA: 29.0 ± 16.3; NC-NA: 31.5 ± 10.0; $F(3,35) = 7.13; p < .001$], peak [MDD-AB/CA: 111.5 ± 35.2; MDD-AB/SE: 44.5 ± 16.9; MDD-NA: 41.0 ± 24.1; NC-NA: 44.4 ± 14.1; $F(3,35) = 10.54$; $p < .001$], and net [MDD-AB/CA: 39.5 ± 19.4; MDD-AB/SE: 14.6 ± 10.1; MDD-NA: 7.8 ± 13.2; NC-NA: 11.8 ± 9.6; $F(3,35) = 6.20$; $p < .002$] ACTH secretion post-CRH than the depressed abused children currently living in stable environments, the depressed nonabused, and the normal control children. There were no significant differences observed among the latter three groups on ACTH scores, and all four groups showed comparable cortisol response to the CRH challenge.

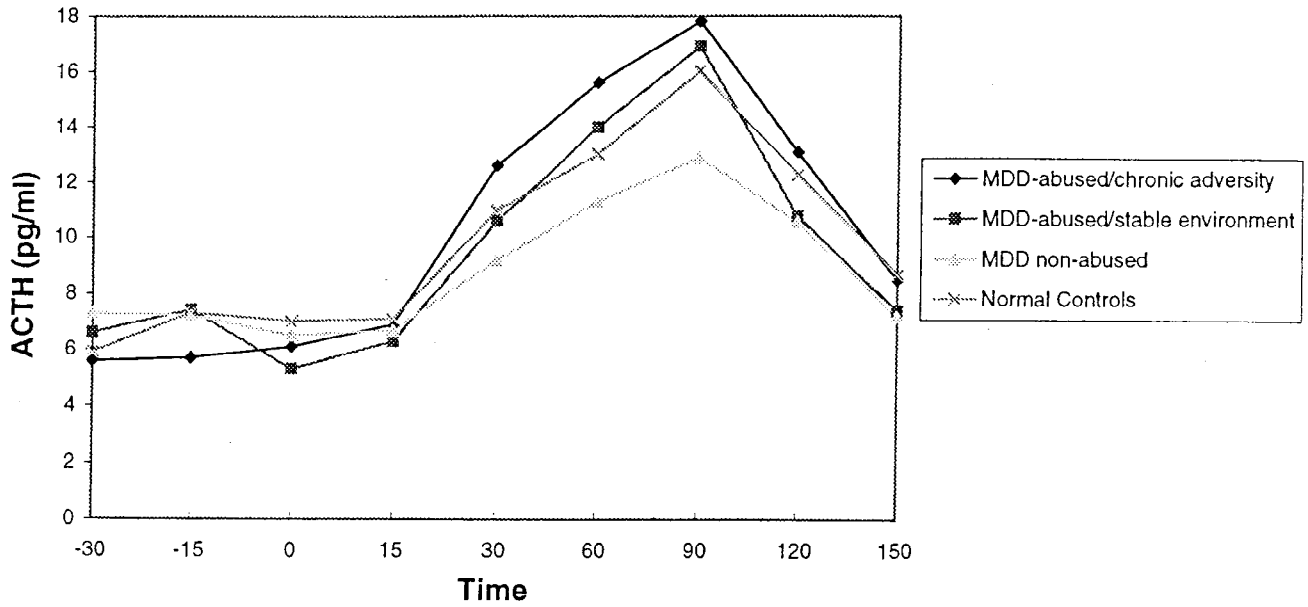


Figure 2. Results of the exploratory analyses conducted comparing the cortisol values of the depressed abused children living under conditions of chronic ongoing adversity ($n$ = 7), depressed abused children currently living in stable environments ($n$ = 6), depressed nonabused children ($n$ = 13), and normal control nonabused children ($n$ = 13).

## Discussion

The response of the depressed abused children to the CRH challenge was opposite initial predictions. Based on prior examinations of the HPA axis in abused children (DeBellis et al 1994a; Kaufman et al 1993), the depressed abused children were expected to have blunted ACTH secretion post-CRH infusion. Instead, the depressed abused children in this study were found to have significantly *augmented* ACTH secretion. This finding was limited to the depressed abused children living under conditions of chronic ongoing adversity (e.g., emotional abuse, poverty, marital violence, lack of social supports). The ACTH response of the depressed abused children living in currently stable home environments was comparable to the ACTH responses of the depressed nonabused and normal control children.

The abused children in the two CRH studies that reported blunted ACTH secretion post-CRH were also living in relatively stable environments at the time of investigation (DeBellis et al 1994a; Kaufman et al 1993). Preliminary findings from this group and other investigators suggest that variability in the psychobiological correlates of abuse are related to: age at onset of abuse (Galvin et al 1995); history of out-of-home placements (Kaufman 1991); current stressors and social supports (Kaufman 1991); family history of psychopathology (Kaufman et al 1995); and clinical picture at time of assessment (DeBellis et al 1994b; Hart et al 1996; Kaufman 1991; Perry et al 1995; Rogeness 1991). Consistent with this latter point was the finding from this study of a nonsignificant trend suggesting that depressed children with comorbid posttraumatic stress disorder (PTSD) were more likely than children without comorbid PTSD to exhibit HPA axis dysregulation. Considerable more work is needed to understand the interplay among developmental, clinical, and psychosocial factors that mediate the psychobiological effects of trauma (Kaufman 1996; Van der Kolk and Fisler 1994).

Although the standardized effect sizes (range: 1.61–2.43) of the significant findings in this report suggest the results are quite robust, there are a number of limitations to this study. The findings were serendipitous and not based on a priori hypotheses; the sample was relatively small; and the children in the study participated in multiple psychobiological tests, which may have influenced the results of the CRH challenge. Although all groups of children participated in the same multimeasure psychobiological protocol, the CRH results may not be representative of the effects that would have been seen if the children were not subjected to prior experimental manipulations. Replication of the findings will be necessary prior to generalizing the results of the study.

The CRH challenge responses of the depressed abused children living under conditions of chronic ongoing adversity, however, are consistent with the HPA axis changes reported in animal studies on the effects of chronic stress (e.g., Daniels-Severs et al 1973; Hauger et al 1988; LeMevel et al 1979; Marti et al 1994; Uehara et al

1989; Vernikos et al 1982). These studies have repeatedly shown that initial exposure to a stressor is associated with a marked rise in cortisol and ACTH secretion. With ongoing exposure to the stressor, animals adapt and cortisol and ACTH levels return to baseline; however, with exposure to a novel stressor or in response to exogenous CRH administration, chronically stressed animals have a significantly *augmented* ACTH response. The ability of the pituitary to respond to novel stimuli is not only preserved during adaptation, it is enhanced. Cortisol responses under these conditions have been found to be either normal or somewhat elevated.

The HPA axis has multiple mechanisms of feedback and control (see Akil and Morano 1995; DeSouza and Grigonades 1995 for reviews). Basic studies have identified the following mechanisms to account for the enhanced ACTH response to CRH observed in chronically stressed animals: 1) a reduction in hippocampal glucocorticoid receptor number such that the inhibition normally exerted on the HPA axis by the hippocampus is decreased (Young et al 1990); 2) enhanced monoaminergic activity that facilitates the activity of the HPA axis (Marti et al 1994); 3) reduced effectiveness of the fast feedback glucocorticoid inhibition mechanism, which normally inhibits the production of ACTH when there is a rapid rise in steroid levels (Young et al 1990); 4) abnormal glucocorticoid feedback at the anterior pituitary (e.g., positive feedback), such that glucocorticoids have a stimulatory rather than an inhibitory effect on ACTH secretion (Young and Akil 1988); and 5) increased proportion of arginine vasopressin released from the paraventricular nucleus (PVN) of the hypothalamus, a peptide which is colocalized and released with CRH from the PVN and potentiates the effects of CRH on the pituitary (Hauger et al 1988). Although the relevance of these mechanisms in explaining the observed findings is purely speculative, they highlight the complexity of the control systems that regulate the HPA axis, and the need for further research in this area.

In addition to the studies cited above documenting the short-term consequences of chronic stress on the HPA axis, several investigators have also demonstrated that exposure to stress early in life can promote changes in the HPA axis that persist into adulthood (Ladd et al 1996; Meaney et al 1991; Thoman et al 1968). In a recently published report (Ladd et al 1996), similar to the results of this study, adult male rats subjected to stress (e.g., maternal deprivation) during postnatal days 2–20 were found to have significantly increased basal ACTH concentrations when compared to nondeprived rats. The adult rats with a history of early deprivation also exhibited an augmented ACTH response to an acute stressor (e.g., foot shock) when compared to nondeprived stressed rats. There were no differences observed in adulthood between the early deprived and nondeprived groups in basal or stress-induced corticosterone concentrations. This study suggests that it may not be the chronicity of stress exposure, but rather the developmental timing of exposure that is critical in determining the long-term consequences of early adversity.

## Conclusions

Consistent with the work of others (Halbriech et al 1989; Williamson et al 1995b; Yehuda et al 1995) the analyses presented in this report highlight the importance of experiential (e.g., trauma) factors in explaining heterogeneity in the psychobiological correlates of depression. The data suggest that experiences of abuse, in combination with ongoing stressors and an absence of positive supports, promote significant dysregulation of the HPA axis system. More research is needed to understand how maturational, inherent, psychosocial, and psychobiological factors interact to confer vulnerability to depression in maltreated children throughout the life cycle.

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## References

Akil H, Morano M (1995): Stress. In Bloom F, Kupfer D (eds), *Psychopharmacology: The Fourth Generation of Progress*. New York: Raven Press, pp 705–718.

Allen M, Crowell M (1989): Patterns of autonomic response during laboratory stressors. *Psychophysiology* 26:603–614.

Andreasen N, Rice J, Endicott J, Reich T, Coryell W (1986): The family history method approach to diagnosis: How useful is it? *Arch Gen Psychiatry* 43:421–429.

Birmaher B, Dahl RE, Perel J, et al (1996): Corticotropin releasing hormone challenge in prepubertal major depression *Biol Psychiatry* 39:267–277.

Casat CD, Arana GD, Powel K (1989): The DST in children and adolescents with major depressive disorder. *Am J Psychiatry* 146:503–507.

Chambers W, Puig-Antich J, Hirsch M, et al (1985): The assessment of affective disorders in children and adolescents by semi-structured interview. *Arch Gen Psychiatry* 42:696–702.

Dahl R, Puig-Antich J, Ryan N, et al (1989): Cortisol secretion in adolescents with major depressive disorder. *Acta Psychiatr Scand* 80:18–26.

Dahl R, Ryan N, Birmaher B, et al (1991): EEG sleep measures in prepubertal depression. *Psychiatry Res* 38:201–214.

Dahl RE, Kaufman J, Ryan ND, et al (1992): The dexamethasone suppression test in children and adolescents: A review and a controlled study. *Biol Psychiatry* 32:109–126.

Daniels-Severs A, Goodwin A, Kal LC, Verniko-Danellis J (1973): Effects of chronic crowding and cold on the pituitary-adrenal system: Responsiveness to an acute stimulus during chronic stress. *Pharmacology* 9:348–356.

DeBellis MD, Chrousos GP, Dorn LD, et al (1994a): Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *J Clin Endocrinol Metab* 78:249–255.

DeBellis MD, Lefter L, Trickett P, Putnam F (1994b): Urinary catecholamine excretion in sexually abused girls. *J Am Acad Child Adolesc Psychiatry* 33:320–327.

DeSouza E, Grigonades D (1995): Corticotropin-releasing factor: Physiology, pharmacology, and role in central nervous system. In Bloom F, Kupfer D (eds), *Psychopharmacology: The Fourth Generation of Progress* New York: Raven Press, pp 505–518.

Galvin N, Teb Eyck R, Sheknar A, et al (1995): Serum dopamine beta hydroxylase and maltreatment in psychiatrically hospitalized boys. *Child Abuse Neglect* 19:821–832.

Giles D, Schlesser M, Rush A, Orsulak P, Fulton C, Roffwarg H (1989): Polysomnographic parameters in first-degree relatives of unipolar probands. *Psychiatry Res* 27:127–136.

Grander D, Weisz J, Kauneckis D (1994): Neuroendocrine reactivity, internalizing behavior problems, and control-related cognitions in clinic-referred children and adolescents. *J Abnorm Psychol* 103:267–276.

Halbriech U, Olympia J, Carson S, et al (1989): Hypothelamo-pituitary-adrenal activity in endogenously depressed post-traumatic stress disorder patients. *Psychoneuroendocrinology* 14:365–370.

Hart SN, Brassard MR (1991): Psychological maltreatment: A program achieved. *Dev Psychopathol* 3:61–70.

Hart J, Gunnar M, Cicchetti D (1996): Altered neuroendocrine activity in maltreated children related to symptoms of depression. *Dev Psychopathol* 8:201–214.

Hauger R, Millan M, Lorang Harwood J, Aguilera G (1988): Corticotropin-releasing factor receptors and pituitary adrenal response during immobilization stress. *Endocrinology* 123: 396–405.

Holsboer F (1995): Neuroendocrinology of mood disorders. In Bloom F, Kupfer D (eds), *Psychopharmacology*. New York: Raven Press, pp 957–969.

Holsboer F, Gerkin A, Stalla G, Muller A (1987): Blunted aldosterone and ACTH release after human RH administration in depressed patients. *Am J Psychiatry* 144:229–231.

Kaufman J (1991): Depressive disorders in maltreated children. *J Am Acad Child Adolesc Psychiatry* 30:257–265.

Kaufman J (1996): Child abuse. *Curr Opin Psychiatry* 9:251–256.

Kaufman J, Brent D, Birmaher B, et al (1993): Measures of family adversity, clinical symptomatology, and cortisol secretion in a sample of preadolescent depressed children. Paper presented at the Annual Meeting of the Society of Research in Child and Adolescent Psychopathology (SRCAP), Santa Fe, New Mexico.

Kaufman J, Jones B, Stieglitz E, Vitulano L, Mannarino A (1994): The use of multiple informants to assess children's maltreatment experiences. *J Fam Violence* 9:227–247.

Kaufman J, Ryan N, Birmaher B, et al (1995). L-5-HTP in maltreated depressed children. Presented at the 52nd Annual Meeting of the American Academy of Child and Adolescent Psychiatry, New Orleans, Louisiana.

Kutcher SP, Marton P (1991): Affective disorders in first-degree relatives of adolescent onset bipolar, unipolar and normal controls. *J Am Acad Child Adolesc Psychiatry* 30:75–78.

Ladd C, Owens M, Nemeroff C (1996): Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology* 137:1212–1218.

LeMevel J, Abito S, Beraud G, Maniey J (1979): Temporal changes in plasma adrenocorticotropin concentration after repeated neurotropic stress in male and female rats. *Endocrinology* 105:812–817.

Lesch KP, Widerlov E, Ekman R, et al (1988): Delta sleep-inducing peptide response in human corticotropin-releasing hormone (CRH) in major depressive disorder. Comparison with CRH-induced corticotropin and cortisol secretion. *Biol Psychiatry* 24:162–172.

Lukens E, Puig-Antich J, Behn J, Goetz R, Tabrizi M, Davies M (1983): Reliability of the psychosocial schedule for school-age children. *J Am Acad Child Psychiatry* 22:29–39.

Marti O, Gavalda A, Gometz F, Aarmanio A (1994): Direct evidence of chronic stress-induced facilitation of the adrenocorticotropin response to a novel acute stressor. *Neuroendocrinology* 60:1–7.

Matthews K, Woodall K, Stoney C (1990): Changes in and stability of cardiovascular response to behavioral stress: Results from a four-year longitudinal study of children. *Child Dev* 61:1134–1144.

Meaney M, Mitchell J, Aitken D, et al (1991): The effects of neonatal handling on the development of adrenocortical response to stress: Implications for neuropathology and cognitive deficits later in life. *Psychoneuroendocrinology* 16:85–193.

Nelson B (1996): Children's ratings of their experience participating in psychobiological studies. Unpublished manuscript.

Orvaschel H, Puig-Antich J (1987): *Schedule for Affective Disorders and Schizophrenia for School-Age Children (6–18), Epidemiologic Version* (K-SADS-E Fourth Version) Fort Lauderdale Nova University.

Perry B, Vigilante D, Blakey T, Baker B, Withers A, Sturges C (1995): Continuous heart rate monitoring in maltreated children. Presented at the 52nd Annual Meeting of the American Academy of Child and Adolescent Psychiatry, New Orleans, Louisiana.

Puig-Antich J, Lukens E, Davies M, Goetz D, Brennan-Quattrock J, Todak G (1985a): Psychosocial functioning in prepubertal depressive disorders I. *Arch Gen Psychiatry* 42:500–507.

Puig-Antich J, Lukens E, Davies M, Goetz D, Brennan-Quattrock J, Todak G (1985b): Psychosocial functioning in pre-

pubertal depressive disorders II. *Arch Gen Psychiatry* 42: 511–517.

Puig-Antich J, Dahl R, Ryan N, et al (1989): Cortisol secretion in prepubertal children with major depressive disorder. *Arch Gen Psychiatry* 46:801–809.

Putnam FW, Trickett PK, Helmers K, Dorn L, Everett B (1991): Cortisol abnormalities in sexually abused girls. In *Proceedings of the 144th Annual Meeting of the American Psychiatric Association*, Washington: American Psychiatric Press, p 107.

Rogeness GA (1991): Psychosocial factors and amine systems. *Psychiatry Res* 37:215–217.

Rupprecht R, Lesch KP, Muller U, Beck G, Beckman H, Schulte HM (1989): Blunted adrenocorticotropin but normal beta-endorphin release after human corticotropin-releasing hormone administration in depression. *J Clin Endocrinol Metab* 69:600–603.

Ryan ND, Dahl RE, Birmaher B, et al (1994): Stimulatory tests of growth hormone secretion in prepubertal major depression: Depressed versus normal children. *J Am Acad Child Adolesc Psychiatry* 33:824–833.

Schulte HM, Chrousos GP, Oldefield EH, Gold PW, Cutler GB, Loriaux DL (1985): Ovine corticotropin-releasing factor administration in normal men. Pituitary and adrenal responses in the morning and evening. *Horm Res* 21:69–74.

Spitzer RL, Endicott J (1978): *Schedule for Affective Disorders and Schizophrenia (SADS)*, 3rd ed. New York: New York State Psychiatric Institute.

Spitzer R, Endicott J, Robins E (1978): Research diagnostic criteria: Rationale and reliability. *Arch Gen Psychiatry* 35: 773–782.

Stokes P, Sikes C (1987): Hypothalamic-pituitary-adrenal axis in affective disorders. In Meltzer H (ed), *Psychopharmacology: The Third Generation of Progress*. New York: Raven Press pp 589–607.

Thoman E, Levine S, Arnold W (1968): Effects of maternal deprivation and incubation rearing upon adrenocortical activity in the adult rat. *Dev Psychobiol* 1:1–21.

Townsend EM, Puig-Antich J, Nelson B, Krawiec V (1988): Well-being of children participating in psychobiological research: A pilot study. *J Am Acad Child Adolesc Psychiatry* 27:483–488.

Uehara A, Habara Y, Kuroshimo A, Sekiya C, Takasugi Y, Namiki M (1989): Increased ACTH response to corticotropin-releasing factor in cold-adapted rates in vivo. *Am J Psychiatry* 257:E336–E339.

Van der Kolk BA, Fisler RE (1994): Childhood abuse and neglect and loss of self-regulation. *Bull Menninger Clin* 58:145–168.

Vernikos J, Dallman M, Bonner C, Katzen A, Shinsako J (1982): Pituitary adrenal function in rats chronically exposed to cold. *Endocrinology* 110:413–420.

Williamson DE, Birmaher B, Anderson BP, Al-Shabbout M, Ryan ND (1995a): Stressful life events in depressed adolescents: The role of dependent events during the depressive episode. *J Am Acad Child Adolesc Psychiatry* 34:591–598.

Williamson DE, Dahl RE, Birmaher B, Goetz RR, Ryan ND (1995b): Stressful life events and EEG sleep in depressed and normal control adolescents. *Biol Psychiatry* 37:859–865.

Yehuda R, Boisoneau D, Lowy M, Giller E (1995): Dose-response changes in plasma cortisol-lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. *Arch Gen Psychiatry* 52:583–593.

Young EA, Akil H (1988): Paradoxical effect of corticosteroids on pituitary ACTH/B endorphin release in stressed animals. *Psychoneuroendocrinology* 13:317–323.

Young E, Watson S, Koten J, et al (1990): B-Lipotropin, B-endorphin response to low dose urine corticotropin releasing factor in endogenous depression. *Arch Gen Psychiatry* 47:449–457.