A Longitudinal Study of Plasma Cortisol and Depressive Symptomatology by Random Regression Analysis

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The authors utilized a random regression model to test the longitudinal relationship between depressive symptomatology and plasma cortisol levels obtained before and after the administration of dexamethasone in 62 affectively ill inpatients. This statistical model for longitudinal studies permits the inclusion of subjects with incomplete data as well as subjects measured at different time points. The most significant relationships were found between decreases in depressive symptoms and decreases in the 8:30 AM predexamethasone and the 4:00 PM postdexamethasone cortisol values. Patients were also classified as responders or nonresponders, and the rate of change in several plasma cortisol measures were separately analyzed for these two groups. No differences in the rate of change in plasma cortisol levels were found between responders and nonresponders. These results suggest that the decreases in cortisol production associated with clinical improvement may be partially explained by a regression toward the mean effect. Some of the possible explanations for these results are discussed.

Introduction

Several reports have examined the longitudinal or coincidental relationship between improvement in depression and both the decrease in plasma cortisol and normalization of the dexamethasone suppression test (DST). In general, they found that cortisol production decreases and the DST suppresses with clinical improvement (Sachar 1967; Rubinow et al 1984; Baumgartner et al 1986). However, previous attempts to analyze the longitudinal relationship between depression and plasma cortisol have primarily been descriptive, and when testing hypotheses have not done so in a nonrigorous fashion.

Emphasizing the need for a formal approach to this question is a recent report that decreases in plasma cortisol can occur even in patients who do not improve substantially. Examining data from published investigations, Gibbons et al (1987) reported that decreases in postdex 4:00 PM cortisol values occurred regardless of clinical response. Thus, when

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Received September 14, 1990; revised July 17, 1991.
Presented at the 143rd annual meeting of the American Psychiatric Association, New York, New York. May 14, 1990.

0006-3223/92/$05.00

patients were categorized as responders and nonresponders, the nonresponders were as likely to show a normalization of their postdex plasma cortisol levels as were the responders. This suggests that plasma cortisol values can be predicted to decrease from a higher baseline value to a lower subsequent treatment value independent of clinical response (at least as measured by the Hamilton Depression Rating Scale). Such a situation is illustrative of a regression toward the mean effect. The authors conclude that, because such an effect is characteristic of any relationship in which the correlation is less than perfect, the only scientifically rigorous test of the relationship between depression and plasma cortisol is to compare the normalization of cortisol independently in patients who respond, and in those who do not.

The statistical analysis of the longitudinal relationship between a behavioral variable and a biochemical variable (e.g., depressive symptomatology and plasma cortisol) is complicated by several factors. Two critical issues are that subjects may not be measured at the same number of timepoints, as missing data are almost inevitable, and also they may be measured at different timepoints during the course of the study. Thus, to statistically examine the longitudinal relationship between depression and plasma cortisol, one must allow for the possibility that each individual may have differing amounts of data and that the time structure of the data may vary among individuals.

Random regression models have recently been developed in the biological (Laird and Ware 1982), psychological (Bryk and Raudenbush 1987), and educational (Goldstein 1987; Bock 1989) literatures to examine longitudinal data of this type. They are also referred to as random effects models, hierarchical linear models, or multilevel models in the various literatures, and have significantly advanced the examination of such data. Specifically, the model allows for the presence of missing data, time-varying or invariant covariates, and subjects measured at different timepoints. Recent developments on the use of random regression models with longitudinal psychiatric data can be found in Gibbons et al (1988) and Hedeker et al (1989).

Basically, the focus in the random regression model remains on the individual rather than on the sample group to which the subject belongs. This is done by computing statistics for each individual which express how that particular subject is changing over time. These individual estimates are then used to compute the more common overall population parameters, and the process is repeated, iterating between the computation of the individual and population statistics, until convergence. Because this technique uses the available data for each individual to compute his/her individual statistics, subjects can be measured at a varying number of timepoints, or in fact, at different timepoints. The underlying assumption is that the individual statistics characterize how each person deviates from the estimated population change during the time-course of the study.

We present the results of a longitudinal study of plasma cortisol (obtained during the administration of a DST procedure) in a sample of depressed inpatients after a washout period, and during 8 weeks of clinical treatment. Though we hypothesized that decreases in plasma cortisol would be associated with symptomatic improvement, as has been reported in numerous descriptive studies, our objective was to test this relationship in a statistically rigorous manner, using random regression analysis.

Method

Sixty-two patients (28 women, 34 men) with a mean age of 44.7 years (SD = 15.6) were admitted to an inpatient research unit at the Illinois State Psychiatric Institute

(ISPI). After obtaining informed consent, subjects were maintained on a reduced tyramine diet, and underwent a mean hospital washout period of 13.1 days (SD = 5.7 days). All patients were free of significant medical disorders and had no recent history of substance abuse. Diagnostic and behavioral assessments were conducted by two-member, independent rating teams blind to the DST results. Diagnoses were obtained according to Research Diagnostic Criteria (RDC) and included 40 unipolar, 16 bipolar, and 6 schizoaffective depressed patients. Depressive symptoms were quantitated using the Hamilton Depression Rating Scale (HDRS), and interrater reliability on the total HDRS scores, as computed by the intraclass correlation coefficient for independent raters, was 0.95.

A standard DST as described by Carroll et al (1981) was administered at the end of the drug-free washout phase. On day 1, baseline plasma cortisol values (predex) were obtained at 8:30 AM and 11:00 PM and dexamethasone (1.0 mg p.o.) was given at 11:00 PM. On day 2, plasma cortisol levels (postdex) were drawn at 8:30 AM, 4:00 PM, and 11:00 PM. All samples were stored in a −20°C freezer within an hr of being drawn. Plasma cortisol levels were determined by radioimmunoassay obtained from the New England Nuclear Corp (Boston, MA); this assay can detect as little as 0.2 μg/dl. The within-assay coefficient of variation was 4% and the between-assay coefficient of variation was 6%.

After the washout period and completion of the baseline procedures, patients were treated clinically using psychotropics or electroconvulsive therapy (ECT), none of which are known to independently modify the results of the DST. Thus, patients received either one or a combination of the following treatments: antidepressants such as phenelzine, desipramine, imipramine, trazodone, amoxapine, fluoxetine, lithium, and neuroleptics such as trifluoperazine, molindone, and/or fluphenazine. Treatment regimens were based entirely on clinical discretion.

The DST procedures were performed at varying time points for up to 8 weeks of treatment, with a minimum of 1 week between consecutive determinations. All patients participated in at least two DST procedures, one at baseline and one or more during treatment. Overall, 26 patients had two DSTs, 18 had three, 8 had four, 7 had five, and 3 had six. The frequency and number of DSTs were determined by such factors as patient cooperation and length of hospital stay. HDRS ratings were performed concurrently with each DST sample procedure.

Data Analysis

The following random regression model was fit for the HDRS score of subject i on occasion t:

$$y_{it} = a + bt + ct^2 + a_i + b_i t + e_{it}$$

$$i = 1, 2, \ldots, n \text{ subjects} \qquad (1)$$

$$t = 0, 1, \ldots, n_i - 1 \text{ timepoints}$$

where

y_{it} is the HDRS score for subject i on occasion t,

a is the overall population mean HDRS baseline score,

b is the population linear trend over the 8-week period,

c is the population quadratic trend over the 8-week period,

a_i is subject i's deviation from the mean HDRS baseline score,

b_i is subject i's deviation from the mean linear trend,

e_{it} is an independent residual distributed normally with mean 0 and variance s^2.

In this model, we also assume that the distribution of individual intercepts (a_i) and slopes (b_i) in the population is bivariate normal.

Notice that this model represents the measurements of the HDRS as a function of time, both at the individual (a_i and b_i) and population (a, b, and c) levels. The intercept parameters indicate the starting point, the slope parameters indicate the degree of linear change over timepoints, and the quadratic parameter represents the curvilinear change over timepoints in the population. For these data, a quadratic trend model was necessary at the population level, as the average HDRS scores decrease over time in a curvilinear fashion (i.e., more dramatic improvement in the beginning of the study and a leveling off towards the end). However, there was not enough variability in this quadratic term in the sample to warrant its inclusion at the individual level. That is, two parameters (a_i and b_i) were sufficient to represent each individual's deviation from the overall population trend estimated from a, b, and c. Finally, note that the timepoints range from $t = 0$ (i.e., baseline) to $t = n_i - 1$, with the subscript i indicating that each subject may vary in terms of the number of occasions upon which their response was recorded.

The above random regression model does not include any terms to assess the effect of plasma cortisol on HDRS scores across timepoints. To accomplish this, plasma cortisol was treated as a time-varying covariate of the HDRS scores and so a term (x_{it}) was included into the model that indicates the plasma cortisol value of subject 'i' at the timepoint 't'

$$y_{it} = a + bt + ct^2 + dx_{it} + a_i + b_i t + e_{it} \quad (2)$$

where the additional parameter d represents the effect of this time-varying covariate plasma cortisol on HDRS scores. To the extent that this parameter is statistically significant, it represents a significant association between cortisol values and HDRS scores measured across timepoints.

Because the distribution of cortisol values in our sample was skewed, log transformation was done prior to data analysis.

Results

Table 1 lists the results for the random regression model based on equation (1). The initial level of severity on the HDRS is estimated as 27.39 and the improvement is approximately four points per week on the HDRS in the beginning of the study; this improvement decreases to approximately one-third of a point per week at week 8. At study's end the estimated mean of the HDRS is 10.01, indicating moderate to good

Table 1. Random Regression Model Results: HDRS without Cortisol

Parameter	Estimate	SE	$p <$
Overall intercept a	27.39	1.39	0.001
Overall linear slope b	−4.08	0.69	0.001
Overall quadratic trend c	0.25	0.10	0.012
s_a^2	63.77	19.62	0.001
s_b^2	2.54	1.05	0.016
s_{ab}	−5.81	3.76	0.122
Error variance s^2	42.67	6.88	0.001

SE = standard error.

clinical improvement (i.e., a 63% improvement). The variance estimates indicate a fairly large amount of variability in the initial level of severity across individuals. ($\hat{s}_a^2 \sim 64$ or $\hat{s}_a \sim 8$), and perhaps, some suggestion that the initial level of severity is negatively associated with the linear improvement over the course of the study ($\hat{s}_{ab} = -5.81$, or expressed as a correlation, $\hat{r}_{ab} = -0.46$). This negative and marginally significant relationship would imply that subjects with more severe baseline depression levels improve more rapidly than subjects with less severe initial depression levels; this agrees with previous results from the longitudinal analysis of HDRS scores by Gibbons et al (1982).

Table 2 lists the results for the random regression model based on equation (2), and examines the relationship between 8:30 AM predexamethasone cortisol and HDRS scores across the treatment period. Adding the effect contributed by the cortisol level of the subject significantly improves the model fit to the data (change in $\chi^2 = 9.5$, df = 1, $p < 0.002$) over that provided by equation (1). The d parameter provides an estimate of the overall relationship between the 8:30 AM predex cortisol value and the HDRS score across all time points. In this instance, the relationship is significant and positive, indicating concomitant changes in plasma cortisol and depression measures within the sample ($z = 3.15$, $p < 0.002$).

Similar analyses were completed for cortisol measures obtained at the other time points (i.e., 11:00 PM predex; 8:30 AM, 4:00 PM, and 11:00 PM postdex), and d parameters were estimated. In all instances, there was always at least a marginally significant positive

Table 2. Random Regression Model Results: HDRS with 8:30 AM Predex Cortisol Level

Parameter	Estimate	SE	$p <$
Overall intercept a	13.73	4.55	0.003
Overall linear slope b	−3.61	0.68	0.001
Overall quadratic trend c	0.20	0.097	0.04
Cortisol effect d	4.64	1.48	0.002
s_a^2	61.04	18.48	0.001
s_b^2	2.75	1.06	0.009
s_{ab}	−5.86	3.64	0.11
Error variance s^2	38.95	6.32	0.001

SE = standard error.

The difference in the a-intercept is due to the inclusion of the cortisol effect into the model. It no longer represents the intercept in the original unit of measurement (of the HDRS). What it does represent is the intercept when the effect of cortisol has been covaried out. In this instance, it is significantly different from the zero intercept, but in itself, much like the estimated intercept in an ordinary multiple regression model, is of limited interpretative value.

Table 3. Comparison of Responders and Nonresponders

	Responders	Nonresponders
Age (years)	43.8 (±16.0)	42.47 (±14.1)
Sex	18 women, 17 men	8 women, 7 men
Days of washout	13.2 (±5.1)	13.0 (±4.6)
Affective Diagnoses		
Unipolar	21	9
Bipolar	10	4
Schizoaffective depressed	4	2
Subtype		
Psychotic	4	3
Endogenous	15	7
Agitated	7	5

No significant differences between these two groups.

relationship between the HDRS scores and the cortisol values. The cortisol measurements most significantly related to the HDRS scores were the 8:30 AM predex ($\hat{d} = 4.64$, $p < 0.002$) and the 4:00 PM postdex ($\hat{d} = 2.33$, $p < 0.005$) values. We also examined the possibility that the relationship between cortisol values and HDRS scores was changing over the time frame of the study (i.e., a stronger relationship between HDRS scores and cortisol values might be expected during the most symptomatic period). In all cases, these time-related effects were not even marginally significant. Thus, the observed relationship between depression levels and cortisol values was consistent across the time frame of the study.

Finally, we analyzed the model separately in responders and nonresponders in order to examine the possibility of a regression toward the mean effect. The emphasis was to identify a group of patients who were unequivocally nonresponsive. Patients who had at least one DST procedure and HDRS measure after 3 weeks of antidepressant treatment were reclassified according to their clinical response. Classification of responders and nonresponders was done initially by published clinical criteria (i.e., response equals a score less than 10, or a 50% decrease in the HDRS) (Greden et al 1983). Using these criteria, the nonresponders demonstrated a significant decrease in cortisol but also had appreciable clinical improvement (yet did not qualify as responders by the above criteria), which confounded the interpretation of the results. Thus, to identify an unequivocal group of nonresponders, the slope parameter (b_i) of the regression line of HDRS versus time for each individual patient was computed from the random regression analysis. A negative slope represents clinical improvement, and the slope parameter quantitates the degree of improvement. Responders, or the best 70% (i.e., those with the greatest negative slope) and the nonresponders, or the worst 30% (i.e., those with the least negative slope) were then analyzed separately. Demographic data for the two groups are presented in Table 3, and descriptive statistics for the 8 weeks of the study are presented in Table 4. The average duration of treatment was 5.1 weeks for nonresponders and 6.1 weeks for nonresponders (SD = 1.8 for both), a difference that was not statistically significant. This assured that the above change in cortisol estimates was computed over a similar time period for both the responders and nonresponders.

As Table 5 indicates for the responders, both the linear and quadratic trends over time in the HDRS scores were observed to be statistically significant ($p < 0.001$ and $p < 0.001$, respectively); responders had an initial level of severity of approximately 28 points,

Table 4. Descriptive Values for Responders and Nonresponders

	Baseline	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8
Sample size									
Responder	35	4	11	14	18	8	7	3	6
Nonresponder	15	3	6	3	8	3	4	2	6
Hamilton Ratings (±SD)									
Responder	28 (9)	32 (14)	19 (12)	12 (7)	9 (6)	14 (9)	8 (5)	10 (3)	8 (3)
Nonresponder	24 (9)	27 (8)	24 (10)	21 (10)	21 (9)	34 (16)	20 (7)	36 (21)	25 (8)
8:30 AM pre-dexamethasone cortisol (μg/ml) (±SD)									
Responder	19.9 (6)	26.4 (17)	16.5 (5)	15.2 (5)	16.7 (8)	16.9 (4)	16.3 (8)	15.4 (3)	16.7 (3)
Nonresponder	19.9 (7)	15.7 (10)	16.0 (7)	14.3 (4)	13.5 (5)	22.3 (4)	14.2 (4)	22.1 (16)	16.7 (6)
4:00 PM post-dexamethasone cortisol (μg/ml) (±SD)									
Responder	6.3 (5)	11.8 (13)	3.5 (4)	4.3 (3)	2.8 (2)	4.1 (5)	1.9 (1)	3.4 (3)	2.2 (2)
Nonresponder	7.1 (7)	2.1 (1)	3.1 (2)	1.2 (2)	2.2 (1)	6.3 (4)	3.2 (3)	9.1 (11)	4.8 (4)
Nonsuppressors/suppressors									
Responder	20/15	2/2	3/8	8/7	8/10	3/5	1/6	1/3	1/5
Nonresponder	8/7	0/3	3/3	0/3	0/8	2/1	1/3	1/1	3/3

which decreased by about 6 points per week initially, tapering down to a decrease of 0.5 points per week by the eighth week. By contrast, there were no significant time-related changes in the HDRS scores for the nonresponders. Taken together, this demonstrates an effective separation of these two groups.

Next we analyzed the weekly change in the cortisol values separately for responders and nonresponders to examine whether the changes in cortisol over time were consistent with the differential HDRS changes observed for these two groups. The results are presented in Table 6 for the 8:30 AM predex and the 4:00 PM postdex cortisol values, although similar results were obtained for the analysis of the other values as well. From this table, it is apparent that the average weekly decrease of 8:30 AM cortisol values is virtually identical for responders ($\hat{b} = -0.036$, $p < 0.03$) and nonresponders ($\hat{b} = -0.035$, $p < 0.03$). A test for the equality of regression lines is not rejected ($p < 0.61$), further supporting the observation that the 8:30 AM cortisol value time trends do not differ for the responders and nonresponders. For the analysis of the 4:00 PM postdex cortisol values, the time trends are again similar for the responders ($\hat{b} = -0.128$, $p < 0.001$) and nonresponders ($\hat{b} = -0.078$, $p < 0.007$), and the test for equality of regression lines is not rejected ($p < 0.18$). Thus, cortisol values are decreasing similarly across time, regardless of treatment response. Figures 1 and 2 illustrate the changes in log-

Table 5. Random Regression Model Results: HDRS Scores over Time by Response

	Responders (best 70%) $n = 35$			Nonresponders (worst 30%) $n = 15$		
Parameter	Estimate	SE	$p <$	Estimate	SE	$p <$
a	27.90	1.42	0.001	23.50	2.80	0.001
b	−6.05	0.78	0.001	−0.33	1.02	0.75
c	0.46	0.12	0.001	0.02	0.14	0.88
s_a^2	29.96	11.12	0.007	87.71	36.15	0.02
s^2	43.69	7.31	0.001	32.44	7.86	0.001

Table 6. Random Regression Model Results: Change in Cortisol Values over Time by Response

	Responders (n = 35)			Nonresponders (n = 15)		
Parameter	Estimate	SE	$p <$	Estimate	SE	$p <$
8:30 AM Predex cortisol						
a	2.892	0.07	0.001	2.849	0.10	0.001
b	−0.036	0.02	0.03	−0.035	0.02	0.03
s_a^2	0.009	0.02	0.64	0.094	0.05	0.04
s^2	0.185	0.03	0.001	0.091	0.02	0.001
4:00 PM Postdex cortisol						
a	1.434	0.13	0.001	1.319	0.24	0.001
b	−0.128	0.03	0.001	−0.078	0.03	0.007
s_a^2	0.267	0.10	0.008	0.627	0.27	0.018
s^2	0.414	0.07	0.001	0.291	0.07	0.001

transformed 8:30 AM predex cortisol values from baseline to the last week of treatment in individual responders and nonresponders.

To rule out the possibility that the decrease in plasma cortisol values in the nonresponders category was due to an overrepresentation of patients with higher cortisol excretion, we identified the number of high cortisol excretors in the responders as well as the nonresponders. Six out of the 15 nonresponders (40%) and 15 of the 35 responders (43%) had baseline 8:30 AM predex cortisol values higher than the total samples' median value of 20.5 μg/dl. A reanalysis of cortisol changes in these four groups (responder/high, responder/low, nonresponder/high, nonresponder/low) further substantiated the above findings. Decreases in cortisol were virtually identical in the responder/high and nonresponder/high groups, and also in the responder and nonresponder low groups although the decreases in the latter low groups were considerably smaller in magnitude.

Finally, to examine changes in cortisol in each individual responder and nonresponder,

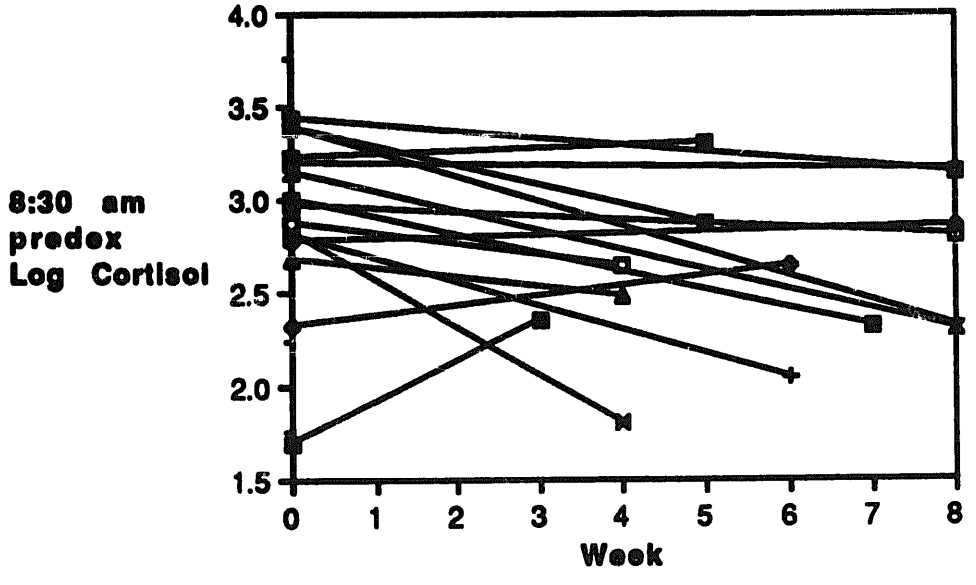

Figure 1. Log cortisol by time in 15 nonresponders.

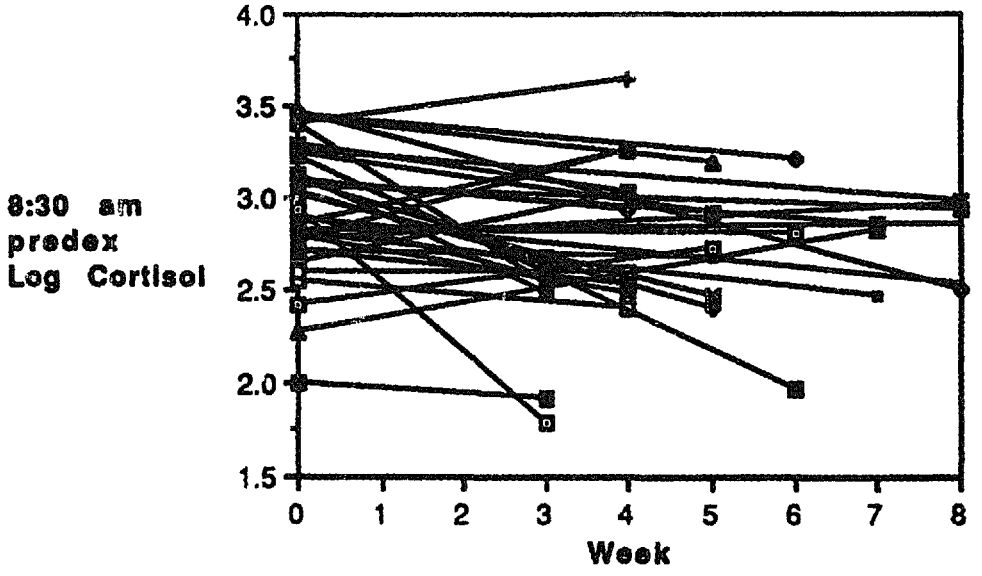

Figure 2. Log cortisol by time in 35 responders.

percent change in cortisol was computed using baseline and the last available cortisol value. There were 6 nonresponders (40%) and 7 responders (20%) with a 20%–40% decrease; 7 nonresponders (47%) and 21 responders (60%) with a 0%–20% decrease; and 2 nonresponders (13%) and 7 responders (20%) with no change or increase. A test for the homogeneity of proportions across these three categories for responders versus nonresponders was nonsignificant.

Discussion

At first glance, our analysis demonstrated a consistent longitudinal relationship between changes in several serially obtained plasma cortisol measures (predex and postdex) and HDRS scores. Results of the analysis for the 8:30 AM predex cortisol measure are summarized in Table 2 and are in agreement with the earlier literature.

However, to further examine the relationship between plasma cortisol and changes in depression, we identified those patients who were clearly the most nonresponsive to treatment. Table 5 indicates that the average initial weekly decrease on the HDRS in these nonresponders was 0.3 points compared with 6.1 points for the rest of the sample. Despite this marked difference in the rate of clinical improvement, the weekly decreases in plasma cortisol values were surprisingly similar in the two samples (Figures 1 and 2). Thus, it would seem that the association between decreases in cortisol values and decreases in rating scores for depression may be partially explained by a regression toward the mean effect. Our present results, utilizing a different statistical method, support the earlier study of Gibbons et al (1987). Furthermore, a separate analysis of responders and nonresponders with high and low baseline cortisol values suggests that the rate of decrease in plasma cortisol is also a function of initial cortisol values.

There may be several reasons why cortisol decreased in our nonresponders. The first consideration would be the differential impact of moderating variables not formally controlled for in this design. For example, increased age, weight loss, and the stress of hospital admission have all been associated with increased cortisol secretion and rates of

nonsuppression (Sharma et al 1988; Gerken et al 1985; Coccaro et al 1984). If nonresponders had entered the study with higher levels on any of these variables, then their resolution during the inpatient period (i.e., normalization of the weight loss or reduction in initial stress related to admission or treatment) could have independently contributed to the decreasing cortisol levels. Although there was no difference in age between the responders and nonresponders in our study, weight was not systematically recorded at every timepoint, and could have influenced these results. Both groups had equivalent washout periods, which indicates that they had the same time period to recover from the stress of the admission process.

A second possibility is suggested by reports that decreases in cortisol may occur up to $3^1/_2$ weeks before any observable clinical response (Holsboer et al 1982). Perhaps our nonresponders might have converted to responders had we continued monitoring them beyond their last study timepoint (up to 8 weeks). However, the actual improvement during and up to 8 weeks was minimal (0.33 HDRS points/week), suggesting the lack of any trend towards improvement (see Table 6). Our selection of an exclusive group of nonresponders thus argues against a lag between cortisol and clinical response as being a major explanation for these findings.

Finally, cortisol secretion may be associated with certain abstract qualities of depression (or psychopathology in general). Ego disruption or intrapsychic conflict, paramount during the early part of a severe depressive episode, may resolve with treatment, or perhaps even the passage of time. As these abstract psychological constructs are not measured by the HDRS, it is difficult to assess their role in decreasing cortisol levels. Within the context of the HDRS, it might require measurement of transition from the more psychologically oriented symptoms (e.g., guilt, suicidal ideation, insight, helplessness, hopelessness, worthlessness) to more somatically oriented symptomatology (e.g., mood, insomnia, appetite). It is possible that this transition in symptomatology, which is not reflected in the total HDRS score, might better explain the cortisol changes in our apparent nonresponders.

In summary, if depression is related to increased production of cortisol due to abnormalities in the hypothalamic-pituitary-adrenocortical axis, then cortisol should decrease as the depression improves. An early study tracking cortisol across a treatment period with levels before and after treatment reported a 9.8% decrease in urinary cortisol excretion (Sachar 1967). However, the following confounding issues were evident, even in this early report: (1) 35% of those who recovered had higher cortisol excretion levels after treatment and recovery; (2) the decline of cortisol production with adaptation to hospital stress exceeded that due to actual clinical recovery; and (3) cortisol excretion at a given time was not strongly correlated with the severity of depression. To the above we may now add another potential confound: a regression toward the mean effect.

We thank Mrs. Patricia L. Mitchell for manuscript preparation and Barbara Brown for technical assistance. We also thank Dr. Robert Gibbons for his critique and suggestions. This work was partially supported by NIMH Grant MH-36169 to Dr. G.N. Pandey.

References

Baumgartner A, Graf K, Kurten I (1986): Serial dexamethasone suppression tests in psychiatric illness: Part II. A study in major depressive disorders. *Psychiatry Res* 18:25–43.

Bock RD (1989): Measurement of human variation: A two-stage model. In Bock RD (ed), *Multilevel Analysis of Educational Data*. New York: Academic Press.