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AGE EFFECTS IN SERIAL HYPOTHALAMIC – PITUITARY – ADRENAL MONITORING

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SUMMARY

To evaluate age effects on hypothalamic – pituitary – adrenal (HPA) regulation in depressives, we studied 65 patients with major depressive disorder, endogenous subtype. With each patient serving as his or her own control, we compared weekly dexamethasone suppression test (DST) results among three age subgroups (< 40 years, $n = 18$; 40 – 70 years, $n = 40$; > 70 years, $n = 7$). The oldest patient group had higher mean post-dexamethasone plasma cortisol concentrations both before and after treatment, and more were DST nonsuppressors. Life table analyses revealed that elderly patients who were DST nonsuppressors had significantly slower patterns of normalization during treatment and that fewer elderly patients ever achieved normal suppression. The results indicate that age effects on HPA function may be confounded with other aspects of depression, such as severity, chronicity and number of previous episodes.

ANIMAL studies demonstrate that age is an important variable in hypothalamic – pituitary – adrenal (HPA) regulation (Timiras, 1983; Riegle, 1983). Consequently, clinical investigators studying HPA regulation in humans have been forced to consider that age might be an important source of variance. To date, the greatest emphasis has been placed on the study of possible age effects on the dexamethasone suppression test (DST) of depressive pathophysiology. The results have been somewhat conflicting.

Dilman *et al.* (1979) administered 0.5 mg dexamethasone and compared subsequent cortisol levels in older and younger subjects using a spectrophotometric assay. They found that the older group had higher levels. Asnis *et al.* (1981) noted positive correlations between age and post-dexamethasone plasma cortisol concentrations in depressed patients, but only when the patients were depressed. Lewis *et al.* (1984) identified a significant positive correlation between age and the 0800 h post-dexamethasone plasma cortisol concentration in depressives (using a 1.0 mg dose of dexamethasone) but found no significant age effects in normal controls. Stokes *et al.* (1984) used a 2.0 mg dose of dexamethasone and compared depressed patients 50 years or older with those younger than 50 years of age. They found significantly higher cortisol levels with increasing age in depressed patients, but only in the afternoon and at night. A higher percentage of their aged depressives were DST nonsuppressors, but there were no significant age-related DST differences in their healthy controls. Oxenkrug *et al.* (1983) administered dexamethasone (0.5 mg) to normal controls and found no age differences in basal cortisol levels, but there was a significant positive correlation between age and post-dexamethasone plasma cortisol levels ($r = 0.71$, $p < 0.001$). Other studies also have shown age differences in DST results (Davis *et al.*, 1984; Nelson *et al.*, 1984; Halbreich *et al.*, 1984).

In contrast, Tourigny-Rivard *et al.* (1981) found no significant age differences in post-dexamethasone plasma cortisol concentrations of normal subjects. And, Carroll *et al.* (1981) were unable to identify age differences in DST results in their large sample of depressed patients and non-depressed controls.

Several methodological issues must be considered when studying age effects on HPA activity. If sample sizes are small or age ranges are too skewed, age-related differences may be missed. Age may be confounded in depressed patients with such factors as severity, chronicity, clinical features, or duration of psychopharmacologic treatment. Age may differentially affect basal HPA activity, chronobiologic patterns, and feedback regulation; few studies have assessed these parameters simultaneously. As suggested previously, the dosage of dexamethasone may be an important confounding variable, with age differences important only for the lower dose of dexamethasone, perhaps because of differences in rates of dexamethasone metabolism. The ratio of men to women in the sample may confound results. In support of this, Halbreich *et al.* (1984) found that cortisol levels showed a significant linear correlation with age in normal women but not in normal men, whereas both depressed women and men showed significant linear increases of cortisol levels with age. Increasing age also is confounded with changes in ovarian function and menopausal status.

Most prior clinical studies of age effects on HPA regulation have relied on cross-sectional assessments. Because HPA activity is characterized by secretory bursts, there is a higher likelihood of spurious findings when isolated cross-sectional samples are the only source of data, especially in small samples. A different strategy for addressing this problem is to use subjects as their own controls and monitor them serially, comparing different age subgroups. Using this strategy, we studied 65 depressed patients with weekly dexamethasone suppression tests comparing HPA activity and clinical patterns among young, middle-aged and elderly subjects. We found that elderly patients more commonly showed persistent post-dexamethasone plasma cortisol elevation and nonsuppression. They also had a slower course of good clinical response.

METHODS

Subjects and diagnostic procedures:

All 65 patients were hospitalized in the Clinical Studies Unit for Affective Disorders (CSU) between 1982 and 1984. Each underwent the CSU's standard diagnostic evaluation, consisting of a 10 – 14 day drug-free washout period, two or three unstructured clinical interviews (including evaluation by a senior staff psychiatrist), a structured interview by a different, trained member of our research team using the Schedule for Affective Disorders and Schizophrenia (Spitzer & Endicott, 1975), and a comprehensive physical examination and laboratory screening to rule out serious medical illnesses. Consensual diagnoses then were formulated using Research Diagnostic Criteria (RDC) (Spitzer *et al.*, 1977). Diagnosticians were blind to DST results. Self-report ratings of severity of depression were obtained from the Carroll Self-Rating Scale of Depression (Carroll *et al.*, 1981) and the Visual Analogue Line Scale (Aitken, 1969).

To minimize the variance introduced by diagnostic heterogeneity, we studied only patients who met RDC for major depressive disorder, endogenous subtype. Other inclusion criteria included: (1) weekly DSTs; (2) no technical exclusion criteria known to invalidate DSTs (Greden *et al.*, 1983), including serious medical illness, current alcoholism or drug abuse, pregnancy, and recent treatment with carbamazepine (Privitera *et al.*, 1982); (3) weekly 17-item Hamilton Rating Scales for Depression (HRSD) (Hamilton, 1960); and (4) informed consent to participate in these research activities.

All patients received treatments that were deemed clinically appropriate. Table 1 indicates the specific treatments for each age subgroup. There were no significant differences in the percentage of each subgroup receiving lithium, antidepressants, neuroleptics, or electroconvulsive therapy (ECT). Treatment adequacy was

monitored with standard techniques for each patient. Lithium intake was adjusted to produce lithium levels between 0.7 and 1.1 m-equiv/liter. Antidepressant levels were monitored whenever possible for patients receiving imipramine (IMI), desipramine (DMI), amitriptyline or nortriptyline. Patients that received other antidepressants did not have plasma level monitoring, but doses were adjusted clinically to accepted levels. Twenty-one of the 52 patients receiving antidepressants had plasma monitoring. There were no statistically significant differences in any of the antidepressant levels between the < 40 years age group and the 40 – 70 years age group, whether compared individually or summed (e.g. IMI + DMI for patients receiving imipramine). ECT was monitored with the leg calf and/or EEG techniques to insure adequate response. The mean number of ECT treatments in this sample was 9.3 ± 2.2 (S.D.).

TABLE I. PSYCHOPHARMACOLOGIC OR ECT TREATMENTS BY AGE GROUPS AND DRUG CATEGORIES (% IN PARENTHESES)

Treatments	Age groups (years)				
	< 40 (n = 18)	40 – 70 (n = 40)	> 70 (n = 7)	χ^2	p
Lithium	6 (33)	15 (38)	3 (43)	0.21	N.S.
Antidepressants	14 (78)	34 (85)	4 (57)	3.00	N.S.
Neuroleptics	4 (22)	4 (10)	0 (0)	2.80	N.S.
ECT	5 (28)	9 (22)	4 (57)	3.60	N.S.

Subgroups

The 65 subjects were divided into three age subgroups: less than 40 years of age (n = 18); 40 – 70 years of age (n = 40); and greater than 70 years of age (n = 7). Selected demographic and clinical characteristics for these three patient subgroups are provided in Table II. Thirty-three of the 65 patients have been considered in a prior report (Greden *et al.*, 1983).

Dexamethasone suppression tests

We used our previously standardized procedure for DSTs (Carroll *et al.*, 1981). We administered oral dexamethasone (1 mg) at 2330 h each week and collected plasma samples the following day at 1600 h and 2300 h. Plasma samples were assayed for cortisol by a modification of Murphy's (1967) competitive protein-binding (CPB) technique. We used maximum post-dexamethasone plasma cortisol concentrations as our continuous DST variable. For categorical classifications, patients were considered DST suppressors if both post-dexamethasone cortisol concentrations at 1600 h and 2300 h were less than 5 μg/dl. We classified them as nonsuppressors if either of these DST values were equal to or greater than 5 μg/dl. This referent value of 5 μg/dl was determined from our own comparisons of DST results from endogenous depressives, non-depressed psychiatric controls, and normal controls using our CPB assay; therefore, our referent value cannot be generalized to other settings. Local assay standardizations are essential.

The DST values that we used for categorizing patients as suppressors or nonsuppressors were those determined immediately before the initiation of antidepressant treatment. Subsequent DSTs then were performed weekly. If patients had nonsuppressive DSTs prior to treatment, but their discharge DST was < 5 μg/dl, they were included in the normalize category. Those patients whose subsequent DSTs continued to be nonsuppressive (≥ 5 μg/dl) until discharge from the hospital, despite apparent adequate treatment, were classified in the failure to normalize category.

Clinical ratings and outcome criteria

The 17-item HRSD was administered on the day of the DST. Raters were always blind to DST results. Patients were defined as responders if their HRSD following treatment was below 10 and had decreased by at least 50% from the pre-treatment score. A post-treatment HRSD greater than 10 resulted in classification as a nonresponder.

Data analysis

To improve normality of distribution and equality of variances, we log-transformed all DST results before conducting statistical analyses. The Chi-squared test was used for non-parametric comparisons among the three age subgroups, and analysis of variance (ANOVA) was used to compare parametric variables.

TABLE II. SELECTED CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF THE THREE SUBGROUPS

	Age subgroups			Test[a]
	< 40 (n = 18)	40 – 70 (n = 40)	> 70 (n = 7)	
Sex				
Female (%)	13 (72%)	30 (75%)	6 (86%)	χ^2 0.50, p = 0.78
Male (%)	5 (18%)	10 (25%)	1 (14%)	
Polarity				
Unipolar (%)	12 (67%)	30 (75%)	5 (71%)	χ^2 0.43, p = 0.81
Bipolar (%)	6 (33%)	10 (25%)	2 (29%)	
Presence of delusions	3 (15%)	7 (18%)	0 (0%)	F = 1.43, p = 0.49
Number of previous episodes of depression	1.8 ± 2.4	2.8 ± 2.8	4.0 ± 2.9	F = 1.76, p = 0.18
Length of hospital stay (days)	50.8 ± 22.9	61.1 ± 24.4	82.4 ± 34.7	F = 4.00, p = 0.02*
Pre-treatment absolute weight (kg)	64.5 ± 12.2	65.3 ± 12.5	51.0 ± 7.8	F = 3.65, p = 0.03*
Weight change since beginning of episode	−2.0 ± 6.6	−4.8 ± 7.9	−7.7 ± 8.4	F = 1.60, p = 0.21
Maximum post-dexamethasone plasma cortisol concentrations (μg/dl)				
Pre-treatment	6.6 ± 6.5	9.4 ± 9.1	13.8 ± 10.6	F = 1.63, p = 0.20
Post-treatment	2.6 ± 2.5	2.9 ± 2.9	9.5 ± 6.9	F = 7.20, p = 0.00*
Percentage with maximum post-dexamethasone plasma cortisol concentrations > 5.0 (μg/dl)				
Pre-treatment	50%	55%	71%	χ^2 = 0.94, p = 0.62
Post-treatment	17%	22%	71%	χ^2 = 8.54, p = 0.01*
Hamilton Depression Rating Scale Score				
Pre-treatment	20.4 ± 6.0	24.7 ± 5.4	25.6 ± 5.7	F = 4.21, p = 0.02*
Post-treatment	6.7 ± 6.2	7.0 ± 5.5	7.4 ± 5.5	F = 0.04, p = 0.96
Carroll Self-Rating Scale Score				
Pre-treatment	26.9 ± 7.9	32.3 ± 6.9	32.0 ± 6.0	F = 2.69, p = 0.08
Post-treatment	10.6 ± 11.5	12.1 ± 8.9	15.4 ± 7.7	F = 0.48, p = 0.62
Visual Analog Line Scale of Depression				
Pre-treatment	31.3 ± 16.8	18.6 ± 19.2	13.4 ± 10.8	F = 2.85, p = 0.07
Post-treatment	67.3 ± 20.2	66.7 ± 26.3	74.4 ± 16.2	F = 0.23, p = 0.80

[a]Non-parametric analyses by the Chi-squared test.
Parametric analyses by analysis of variance (ANOVA).

Our predominant analytic approach was the use of life tables. Life tables (Keller *et al.*, 1982) have been used widely to analyze longitudinal data in nonpsychiatric medical research, particularly in studies of risks of mortality from cancer. In these applications, when a patient dies, he or she is dropped from the sample, and the life table portrays the cumulative percentage of survivors. We calculated three different outcome measures: (1) the cumulative percent that failed to achieve normalization of the DST during treatment (cumulative % failure to normalize); (2) the cumulative percent who failed to achieve clinical euthymia, i.e., an HRSD score < 10 (cumulative % nonresponse), and (3) the cumulative percent with clinical nonresponse or failure to normalize their DST, i.e., those who failed to "recover" in either the clinical or the neuroendocrine paradigms. The life table approach enables use of length-of-episode data that cross-sectional methods cannot use, thereby accounting for a potentially-important variable in understanding HPA dysregulation. The use of length-of-episode data results in a continuous description of the pattern of events during the entire treatment phase.

We formulated the following hypotheses: (1) elderly depressives who were DST nonsuppressors prior to treatment would show a higher cumulative percentage of failure to normalize; (2) elderly depressives would show a higher cumulative percentage of failure to achieve clinical euthymia; (3) when both DST and clinical criteria were combined, elderly patients would show a higher cumulative percentage of failure to normalize the DST or clinical nonresponse, compared to the other age groups.

We tested these hypotheses by comparing the three outcome measures among the three age groups with both the Mantel – Cox and the Breslow tests. These tests differ in the way the observations are weighted. The Breslow test gives greater weight to early observations and is less sensitive to late events which occur when few patients remain in the active sample.

RESULTS

Clinical and demographic comparisons

Table II indicates that there were no significant differences among the three age subgroups in sex ratio, polarity (unipolar vs bipolar), presence or absence of delusions, or number of previous episodes of depression (although the elderly subgroup reported more episodes). The elderly patients were significantly more depressed prior to treatment (HRSD scores differed significantly, while Carroll Self-Rating Scales for depression and 100 mm visual analogue line scales approached significance) (Table II).

Pre-treatment DST comparisons

There was a steady increase in the average pre-treatment mean post-dexamethasone plasma cortisol concentration with increasing age, although differences among the three groups failed to reach significance (Table II). With the dichotomous criterion (i.e. suppressors vs nonsuppressors), 71% of the elderly patients were nonsuppressors, compared to 55% of the middle-aged group and 50% of the younger patients.

Serial DST comparisons

To test hypothesis No. 1, we used the life table approach and analyzed weekly serial DST results only for patients who were nonsuppressors prior to treatment. As shown in Fig. 1, a higher cumulative % of elderly subjects failed to normalize over time, despite treatment. Indeed, at discharge, only 40% of the elderly nonsuppressors had normalized, compared to 90 and 100% of the other two subgroups. These patterns differed significantly (Breslow, $p < 0.01$; Mantel-Cox, $p < 0.01$).

To test hypothesis No. 2, we used the end point of clinical euthymia, defined as HRSD < 10. As illustrated in Fig. 2, elderly patients had a poorer (i.e., slower) pattern of clinical response. After 6 weeks of treatment, 70% of the elderly subgroup still had not responded, compared to 45% of the middle-aged and 28% of the younger patients. Analyses of the overall life table trends supported our hypothesis (Breslow, $p < 0.01$; Mantel-Cox, $p < 0.08$).

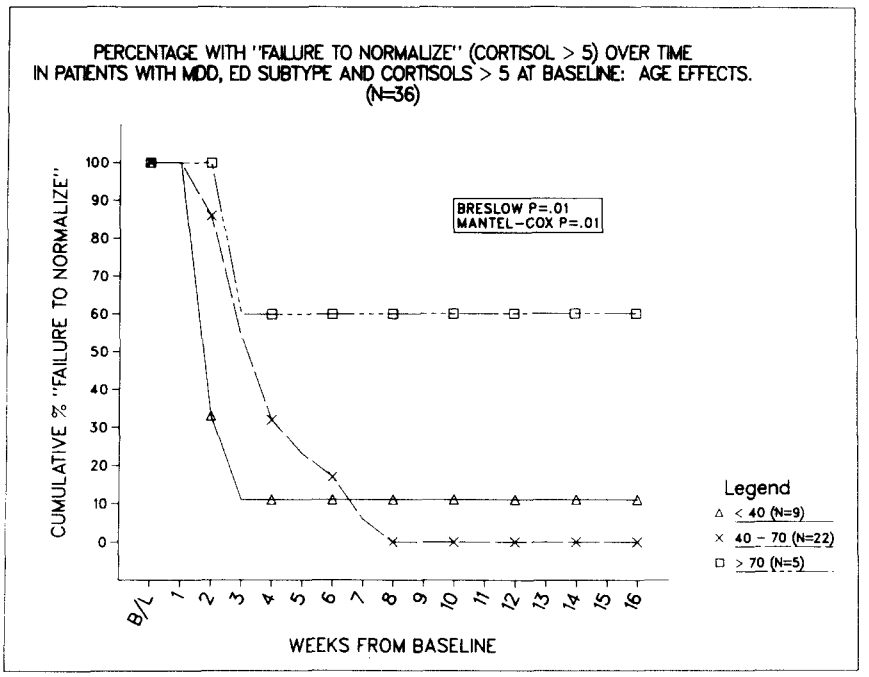

Fig. 1. Life table of all patients with nonsuppressive DSTs (>5 μg/dl) prior to treatment, divided into three age subgroups. When a subject's nonsuppressive DST "normalized" (<5 μg/dl), he or she was dropped from the sample. Aged depressives had significantly slower rates of DST normalization, and many aged subjects never achieved normalization.

Our third hypothesis stemmed from the fact that the ideal theoretical outcome in pre-treatment DST nonsuppressors is the attainment of both clinical euthymia and DST normalization. Figure 3 portrays the life table chart when clinical and HPA measures were combined. Consistent with the first two hypotheses, a higher percentage of the elderly patients either failed to normalize or failed to respond clinically (Breslow, $p < 0.00$; Mantel-Cox, $p < 0.01$). Thus, life table analyses supported all three hypotheses.

At discharge, the elderly subjects still had a mean post-dexamethasone plasma cortisol concentration of 9.5 ± 6.9, and 71% were still nonsuppressors. Both values were significantly greater than those for the other subgroups (Table II).

Sources of variance

Pre-treatment absolute weight differed significantly among the subgroups, with elderly patients weighing considerably less than younger and middle-aged patients. Elderly patients also reported the greatest weight change since the beginning of episode, although weight loss differences failed to reach significance.

Additional analyses revealed weak correlations between post-dexamethasone cortisol levels and absolute weight ($r = -0.30$, $p < 0.01$) and HRSD total score for severity of depression ($r = 0.21$, $p < 0.10$). To assess further the effect of age on cortisol values, we performed a repeated measures analysis of covariance (ANCOVA), using absolute weight

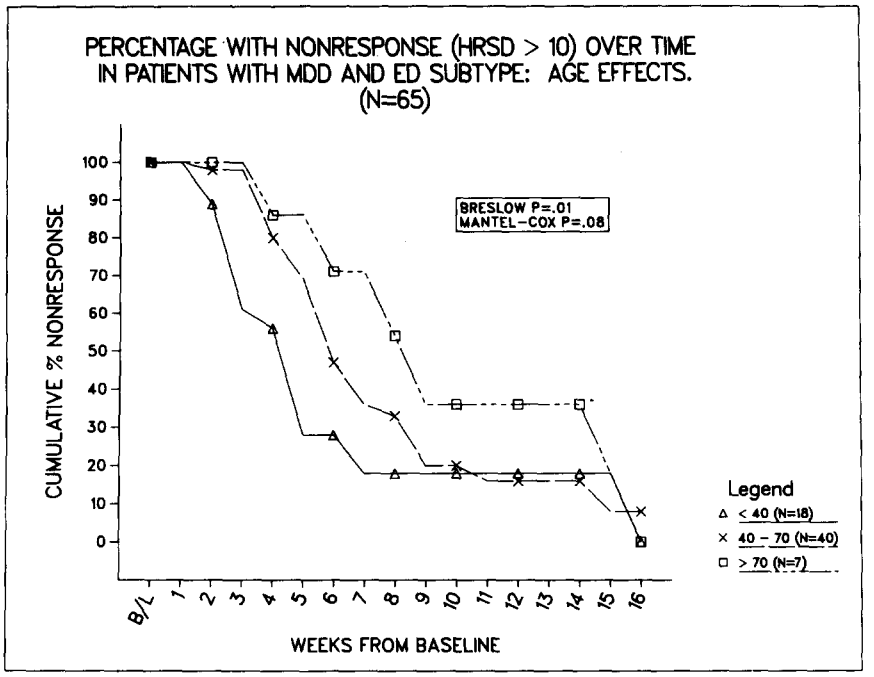

Fig. 2. Life table of all depressed patients, divided into three age subgroups. When a patient responded to treatment (HRSD < 10), he or she was dropped from the sample. Aged depressives had significantly slower rates of clinical response.

and severity scores as covariates. A 3 × 4 factorial design was used with age as the grouping factor, treatment phase (i.e. pre-treatment, 2 weeks of treatment, and discharge), as the within factor, and cortisol level as the dependent measure. Results indicated a main effect for age group [$F(2,52) = 3.44, p < 0.05$]. Covariates were significant in relation to the age grouping factor [$F(1,52) = 4.98, p < 0.05$]. By contrast, there was no significant main effect for treatment phase, and no age × treatment phase interaction. Covariates were not significant in relation to treatment phase.

DISCUSSION

The weekly DST data support a growing body of evidence suggesting that, in depressed patients, age is a significant variable affecting HPA determinations. A number of hypotheses can be generated to possibly explain the effects of increasing age on HPA values. First, higher DST values and persistent DST nonsuppression may be manifestations of chronicity and/or number of episodes, i.e., the more episodes of depression that one has and the longer they persist, the more significant and longstanding are the pathophysiological changes in the HPA axis. Because elderly patients usually have had more episodes, they may be expected to show more severe HPA disinhibition. In our study, this pattern was observed, although differences in the number of reported episodes did not reach significance.

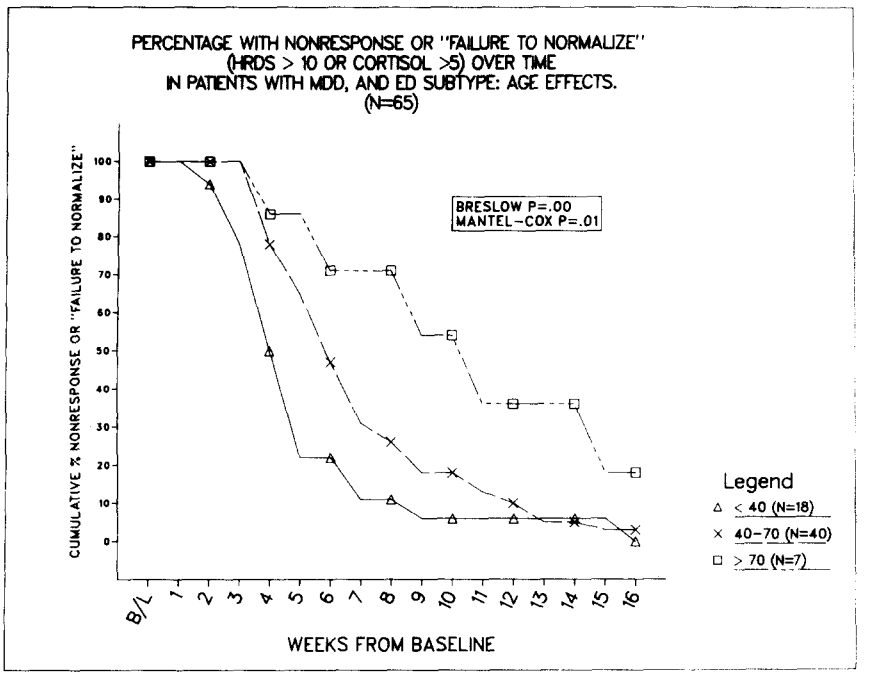

Fig. 3. Life table analysis of all patients, divided into three age subgroups. When patients achieved both clinical response (HRSD <10) and DST normalization (<5 μg/dl), they were dropped from the sample. The elderly subgroup had a significantly higher cumulative percentage of either nonresponse or failure to normalize. Younger patients achieved both criteria more rapidly.

Second, elderly persons may metabolize dexamethasone more rapidly, thus altering the proportional feedback response and producing higher cortisol levels and a higher proportion of nonsuppressors. Although there is no consistent support for this viewpoint, it must be considered and will require simultaneous measurement of plasma dexamethasone concentrations for verification.

Third, elderly persons may have a higher prevalence of subtypes of depression associated with DST nonsuppression. There is little support for this viewpoint, although aged patients are known to have more severe depressive symptomatology (Winokur *et al.*, 1980).

Fourth, it may be that there are normal age-related changes in the HPA axis (hypothalamus, pituitary, adrenal or some combination thereof) that produce disinhibition in elderly persons. Most studies, however, agree that age-related differences are less evident, or not present at all, in normal elderly subjects, and are most significant in depressives during an episode.

Fifth, it may be that the HPA manifestations found in aged persons may be an epiphenomenon associated with other aging changes in the central nervous system, such as in cholinergic or adrenergic neurotransmitter networks.

Studies of these and other possibilities should clarify the mechanisms that underlie apparent aging effects on HPA activity. If future studies find that age *per se* is altering

HPA regulation, rather than age-associated variables such as number or chronicity of depressive episodes, then additional steps will be required to improve the clinical use of the DST and other HPA tests in elderly persons. Specifically, it will be important to develop tables of normality that account for age. Such a task should not be too difficult; age-corrected tables are required for many laboratory tests in medicine. Meanwhile, to facilitate our understanding, investigators studying HPA activity in clinical settings should report age and the number and chronicity of episodes in patients and analyze the possible effects of these variables.

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