Neuroendocrine Predictors of Electroconvulsive Therapy Outcome[a]

Dexamethasone Suppression Test and Prolactin

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There is much interest in biological markers in mental illness for diagnosis and classification, treatment selection, and prediction of outcome. This interest is not a new development, for many markers have been studied in the past quarter century. In the 1950s, we were interested in the blood pressure response to epinephrine and methacholine ("Funkenstein test"), which was used to select patients with good outcome in electroconvulsive therapy (ECT) and lobotomy. The fast frequency EEG response to amobarbital, the "sedation threshold," was used to separate patients with high degrees of anxiety and panic from those who were depressed and demented. Then various monoamine measures were studied, and in the past decade, neuroendocrine tests, particularly measures of cortisol, thyroid stimulating hormone (TSH), and prolactin, have captured our interest.

While the literature is complex, a few themes emerge that are relevant to the convulsive therapy process. Neuroendocrine dysregulation is a frequent finding in patients with severe mood disorders, particularly those with melancholia. So much so, that many authors consider a blunted TSH response to thyrotropin releasing hormone (TRH), elevated plasma cortisol levels with failure to suppress after dexamethasone, and impaired growth hormone response to insulin, apomorphine, or clonidine as markers of endogenous mood disorders. The measures normalize with clinical improvement, either in response to treatment or even when the illness abates spontaneously, as mood disorders often do.

In this report, I would like to review two aspects of neuroendocrine studies which have received much recent attention—the evidence for the dexamethasone suppression test (DST) as a predictor of clinical outcome, and prolactin release as an index of the centrencephalic activity of treatments.

DST AS PREDICTOR OF CLINICAL OUTCOME

Cortisol dysregulation characterizes the active phase of many psychiatric patients, particularly those who are severely depressed with melancholia. The changes in cortisol measures with clinical course have come under extensive study, and both Carroll[9] and Baldessarini and Arana[6] have summarized these findings. Carroll writes: "As patients improve with treatment their DST responses gradually approach normal values. When

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the test results convert to normal before significant clinical change is evident, this is usually a good prognostic sign that the patient will eventually respond."[9] He summarizes seven studies of DST conversion in relation to clinical response. All cases had abnormal DSTs on admission. Of 102 patients, 35 still had abnormal DST tests on discharge, and of these, 83% had a poor outcome even though treatment was continued in most cases. In two studies, suicides were recorded among the patients with persistently abnormal DSTs. In contrast, 90% of the patients whose DSTs normalized had a good short-term response to treatment and were free of relapse for up to six months. (See TABLE 1.)

Baldessarini and Arana reach a similar conclusion. They summarize the data of 13 reports in patients with severe depression.[6] Of 136 depressed patients who were DST nonsuppressors at initial assessment, 88 (65%) became cortisol suppressors to dexamethasone either during their treatment course or at follow-up (several weeks to six months). They write: "Among depressed patients whose DST normalized, only 17/88 (19.3%) had a poor clinical outcome. In contrast, 38/48 (79.2%) of the patients who persisted as DST(+) cortisol non-suppressors were found to have a poor clinical

TABLE 1. DST Normalization and Clinical Outcome[a]

	DST Normalized		DST Not Normalized	
	Poor Outcome	Good Outcome	Poor Outcome	Good Outcome
Carroll 1972	—	—	7	0
Greden, 1980	2	8	4	0
Papakostas, 1981	0	5	3	1
Holsboer, 1982	0	16	4	0
Targum, 1982	3	16	3	3
Yerevanian, 1983	0	4	10	0
Nemeroff, 1983	2	11	5	2
TOTALS	7	60	36	6

Chi squared p = 0.0001

[a]Data from Reference 9.

outcome with recrudescence of symptoms, rehospitalization or, in several cases, attempted or successful suicides ($X^2y = 44$; 1 df, $p = 0.0001$)."[6] (See TABLE 2.)

ECT has been a feature in only a few of these studies, since most patients have been treated with tricyclic antidepressants. Yet, some reports exist. Albala *et al.* studied the effects of ECT in 6 unipolar depressed patients with abnormal DSTs on admission to the hospital.[2] Five of 6 converted, and these had a satisfactory clinical outcome; in 1 patient, the test did not normalize and this subject had a poor clinical outcome. In another report from this group, Greden *et al.* compared the clinical results in 10 unipolar or bipolar depressed patients who had an abnormal DST on admission and a normal test on discharge with 4 patients whose abnormal DST on admission had not normalized at discharge.[16] On all measures, those patients whose DST failed to normalize showed substantially less improvement. Four patients were treated with ECT; in 3 the tests normalized, and the response was evaluated as favorable. In 1 patient, the DST did not normalize, and she was readmitted within six weeks, treated with ECT again, and this time the DST normalized. (Further outcome was not reported.)

The findings were the same in our study.[25] In a sample of 50 hospitalized male veteran patients, we identified 14 with unipolar depression and melancholia who were

treated with ECT. Ten exhibited abnormal DSTs before treatment. With ECT, symptoms of depression were reduced in all patients. The DST tests normalized in 8. In follow-up to nine months after treatment, 6 of the 8 remained well, and 2 had relapsed. Of the 6 patients with abnormal DSTs at the end of treatment, 3 were discharged from the hospital, but 2 were readmitted and 1 died in suicide within two months of discharge; and 3 were not dischargeable from the hospital.

Coryell examined the DST response in 42 depressed patients treated with ECT and reported that 21 patients with an initially abnormal DST response had better outcomes according to global ratings at the end of treatment than did patients with initially normal DSTs.[12] But the outcome was not poor in either group, with only 3 patients with initially normal DSTs being rated as unimproved at discharge. In a six-month follow-up of these patients, Coryell and Zimmerman failed to find any differences among the suppressors and nonsuppressors.[13] Indeed, they reported that the 9 patients whose DSTs had converted at discharge from abnormal to normal were less likely to have a sustained remission than were the 6 patients whose DSTs remained abnormal.

In a study of 18 severely depressed psychiatric inpatients with a positive DST on admission, Nemeroff and Evans treated 6 with ECT.[22] In each the DST normalized, and each was rated as asymptomatic at follow-up. Of the 12 patients treated with medications alone, 5 were nonsuppressors at the end of treatment and all required either further inpatient care or were symptomatic within 2 weeks to 4 months. Of the

TABLE 2. Clinical Outcome and DST Status on Follow-up of Depression[a]

Study (ref.)	Year	Rate of Poor Clinical Outcome	
		DST Normalized	DST Remained or Again Became (+)
TOTALS (%)	(n = 13 reports, 136 subjects)	17/88[b] (19.3%)	38/48[b] (79.2%)

[a]Data from Reference 6.
[b]$p < 0.0001$ by chi squared.

suppressors, 2 were readmitted within 2 months, and 5 were rated as asymptomatic in follow-up to 13 months. The authors concluded that continued cortisol nonsuppression was associated with poor clinical response or high risk of relapse.

Ames *et al.* studied 90 patients with primary depressive illness and reported that among 13 patients treated with ECT, they found the same degree of improvement in the Hamilton scale for the 6 nonsuppressors and the 7 suppressors at the time of first testing.[3] These authors do not provide data as to outcome, but in their discussion they write: "It is our present practice to continue ECT in non-suppressors until normal suppression occurs. Further studies are needed to see whether this will help prevent the relapses that are common after ECT treatment."[3]

Similar results were reported by Yerevanian *et al.* who reported DST and clinical results in 14 patients with Research Diagnostic Criteria (RDC) diagnoses of major depressive disorders with nonsuppressing DSTs on admission.[30] Four of the patients received courses of ECT; of these, the DST tests normalized in 2 and they were doing very well on follow-up; 2 failed to normalize—1 was readmitted within two weeks and 1 was persistently anhedonic and unable to work. The findings among the drug-treated patients were similar with all nonnormalizers doing poorly on follow-up, and 3 committing suicide. Similar observations and conclusions were reached by Holsboer *et al.*,[18] Greden *et al.*,[17] and Katona and Aldridge.[19]

While the prognosis for good outcome after a course of ECT is unrelated to the state of the pretreatment DST, the failure of the DST to normalize in a depressed patient is a cause for clinical concern and the serious consideration of further treatment.

PROLACTIN RESPONSE TO ECT

Plasma prolactin levels are another neuroendocrine measure of interest. There is a sharp increase in plasma prolactin after a grand-mal seizure, with peak activity about 30 minutes after the seizure and a rapid fall to baseline levels within 1 to 2 hours. This finding is so characteristic, that Trimble suggested that this increase be used to differentiate an epileptic fit from hysteria.[29] Similar increases occur after complex partial seizures[26] and during each seizure in convulsive therapy, both in patients with schizophrenia[5,8,21] and in depressive disorders.[23,24] The increase is found despite basal high levels which occur with the administration of chlorpromazine[20] or neuroleptic medication;[7] and the increase is not influenced by benzodiazepines.[4,7]

The significance of the prolactin release for the ECT process remains unclear. Does the plasma prolactin increase reflect a nonspecific release of humoral substances secondary to the physical stress of a seizure? Or does the prolactin release reflect a specific aspect of the seizure, with significance for the convulsive therapy process? When these increases in prolactin with seizures were first described, many sought for the persistence of plasma prolactin levels during the course of ECT, paralleling the clinical course perhaps. But no relationship between the level or the amount of prolactin released in successive seizures and the clinical course was found. The amount of prolactin released after the fifth or sixth seizure seemed to be the same as after the first, with the same time course, and with the levels returning to baseline within one to two hours after the seizure.

In the Northwick Park ECT and sham-ECT study, prolactin (PRL), cortisol, growth hormone (GH), and TSH serum levels were measured before and 15 minutes after the first and the last treatments in 62 patients receiving either eight real or eight sham treatments. Prolactin levels increased in the patients with real seizures, with the degree of effect attenuated by about 30% by the end of the treatment course. Cortisol increased without attenuation in the series, and no changes were noted for growth hormone and TSH.[14] A similar decrease in the prolactin response to seizures with successive treatments is reported by Abrams and Swartz.[1]

Skrabenek *et al.* reported differences in time course of release for GH, follicle stimulating hormone (FSH), PRL, and luteinizing hormone (LH), but not for TRH and substance P, and concluded that the release of these substances was best interpreted as a nonspecific stress response.[27] But Whalley *et al.* found differences in release rates for three neuroendocrine substances (prolactin, nicotine-stimulated neurophysin, and estrogen-stimulated neurophysin) and concluded that hormone release was a specific effect of seizures.[31] Differential effects on neuroendocrine release were also reported by Christie *et al.* and Coppen *et al.*[10,11]

Balldin found elevations in serum prolactin at 15 minutes after ECT seizures in 35 of 37 patients.[7] The increase in serum prolactin was statistically related to the duration of the seizure but not to the duration of the stimulus. Swartz and Abrams report that postictal serum prolactin levels tend to be greater for seizures through bilateral electrode placements than after unilateral electrode placement, concluding that the differences reflected greater hypothalamic stimulating effects of bilateral seizures.[28] In another report, Abrams and Swartz find an inverse relationship between the mean

prolactin release for the first four treatments and outcome ratings, with the larger prolactin response associated with a slower treatment response.[1]

DISCUSSION

What can we make of these observations? These two indices of neuroendocrine function, cortisol regulation and prolactin release, are clearly of interest in the ECT process. The various findings reflect dramatic changes in the hypothalamic-pituitary neuroendocrine systems as a result of seizures.

Studies of cortisol seem to bear on clinical issues, particularly on the severity of the symptomatology and the resolution of the depressive illness. In our own practice, we are encouraged to repeat DST measures in our patients at biweekly intervals during a course of ECT, and failure of the test to normalize by the end of our course of treatment causes us considerable concern. But the studies are clearly incomplete, and we are left with many questions. Does the DST have prognostic significance, or is its merit chiefly as an index of the severity of the depressive disorder? Is normalization of the DST a valid end point to a course of therapy? If the DST does not normalize, should treatments continue? What is the significance, if any, of a normal DST at the initial evaluation for ECT treatment?

Prolactin levels seem unrelated to issues of mood or severity of depressive symptoms, but bear relationships to the seizure itself. Plasma prolactin level at 15 to 45 minutes after a seizure is an index to the intensity of the seizure. At the minimum, prolactin levels provide yet another index of a cerebral seizure. Further study may help us resolve the questions of therapeutic efficacy and equivalence among seizures induced by different currents or through different electrode placements. As with the studies of cortisol, the studies are incomplete and we are left with many questions. Is prolactin release a specific effect of seizures and their duration or is the release a nonspecific stress effect? Do the levels or do changes in the levels bear relations to the clinical outcome, or to the brain changes induced by the course of treatment? What is the relation of prolactin release to the release of other pituitary and hypothalamic peptides, and do measures of other peptides bear relations to clinical issues in the ECT process?

These studies help our understanding of the antidepressant activity of ECT. At the time that we were first studying the relationship between DST and TRH measures and the ECT process, much interest was being shown in the behavioral effects of peptides and peptide fragments, notably $ACTH_{4-10}$, $ACTH_{4-9}$, vasopressin, des-Tyr-gamma-endorphin, and beta-endorphin. These reports, and our experience with the DST and TRH tests, led Jan-Otto Ottosson and myself to suggest that neuroendocrine dysregulation may be a hallmark of syndromes responsive to convulsive therapy.[15] We proposed that the antidepressant efficacy of ECT depended on the release of peptides or other behaviorally active substances from centrencephalic (hypothalamic) stores. The recent experiences with cortisol and prolactin are encouraging, and further study of the pathophysiology and behavioral effects of brain peptides is clearly warranted, not only for an understanding of the ECT process, but of mood disorders as well.

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