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Pharmacoendocrinology of Major Depression* **

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Summary. Major depressives often have abnormalities in the secretion patterns of their anterior pituitary hormones and target endocrine gland hormones. There are changes in both basal hormone secretion and the responses of these hormones to perturbation tests. Considerable work has been done attempting to develop a clinical application for some of these changes as biological state markers of endogenous depression. Prominent among the changes is an overactivity of the hypothalamo-pituitary-adrenocortical (HPA) axis. The dexamethasone suppression test (DST), as a reflection of HPA axis activity, has been the most thoroughly investigated "biological test" in psychiatry to date. Considerably fewer studies have addressed more fundamental issues of HPA axis regulation in depression, such as the relationship between pre-DST cortisol hypersecretion and DST outcome. The next most widely investigated endocrine axis in depression has been the hypothalamo-pituitary-thyroid (HPT) axis. Most studies have dealt with the TSH response to exogenously administered thyrotropin releasing hormone. While blunted TSH responses have been found in depressives compared with normal controls, the frequency of blunted responses in other types of psychiatric patients has made this test marginally useful for differential diagnosis. The reported changes in other hormone axes, for example the blunted growth hormone response to several challenges noted in depressed patients, have not been investigated sufficiently thoroughly to support their general clinical use at present. Because the same putative central nervous system (CNS) neurotransmitters appear to be involved in both the modulation of affects and the regulation of the hypothalamic releasing and inhibiting factors, it is tempting to suggest that a common CNS neurotransmitter dysfunction underlies both the depressive state and the aforementioned altered endocrine dynamics. However, proposing this hypothesis has been considerably easier than demonstrating it.

Key words: Depression – Pituitary – Hormones – Neurotransmitters

It is widely acknowledged that depressive illness consists of a heterogeneous group of disorders which have different clinical symptom pictures and which respond to different treatment modalities. Many individuals suffer self-limiting depressions, but others may have episodes of major depression, characterized by a specific set of symptoms, a protracted course, often a family history of similar illness, and, for the endogenous (Kendell 1976) or melancholic (American Psychiatric Association 1980) subtype, generally a responsiveness only to somatic therapies. The signs and symptoms of endogenous or melancholic depression have been codified in the Research Diagnostic Criteria (Spitzer et al. 1978) and in the DSM-III and DSM-III-R (American Psychiatric Association 1980, 1987).

Major depressives, particularly those with endogenous features, often have abnormalities in the secretion patterns of their anterior pituitary hormones and target endocrine gland hormones (Rubin et al. 1973, 1979; Rubin and Kendler 1977; Carroll 1978; Checkley 1980; von Zerssen and Doerr 1980; Rubin and Poland 1982, 1983). There are changes in both the basal secretion levels of several hormones and the responses of these hormones to various perturbation tests. This review highlights the more important of

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these changes and considers their potential clinical usefulness and their relevance to understanding the etiology of this type of depression.

Prominent among the abnormalities of neuroendocrine function in major depression is an overactivity of the hypothalamo-pituitary-adrenocortical (HPA) axis, as reflected by increased circulating corticotropin and cortisol concentrations (Sachar et al. 1973a; Carroll et al. 1976a; Pfohl et al. 1985), increased cerebrospinal fluid cortisol concentrations (Carroll et al. 1976b; Träskman et al. 1980), increased urinary free cortisol excretion (Carroll et al. 1976c, d), and cortisol resistance to dexamethasone suppression (Carroll 1972; 1985; Carroll et al. 1981; Holsboer 1983; Rubin and Poland 1984; Arana et al. 1985). Considerable work has been done in attempting to develop a clinical application for these hormone changes as biological state markers of endogenous depression; in this regard, the dexamethasone suppression test (DST) has been the most thoroughly investigated "biological test" in psychiatry to date. The potential clinical applications of the DST have included the differentiation of patients with endogenous or melancholie depression from those with other kinds of depressive disorders, the identification of probable affective disorder in patients with schizophreniform psychoses, the identification of endogenous depressives within an alcoholic population, the identification of patients at high risk for suicide, the selection of pharmacotherapeutic agents for the treatment of depression, serial monitoring for determining biological recovery from endogenous depression, and identification of early relapse of depressive illness (Targum 1983). Even though thousands of patients have been studied with the DST, it has been found to be reliable in only a few of the aforementioned clinical applications – as stated by the American Psychiatric Association Task Force on the DST (Glassman 1987), "...like many laboratory tests in clinical medicine, the DST does less than one might hope... a positive DST may reinforce a diagnosis of major affective disorder in certain ambiguous situations... patients who have an abnormal test following apparent clinical improvement may be at risk of clinical worsening ... beyond these suggestions, the task force found no incontrovertable role for the DST in current clinical practice..." One important methodologic issue is the way the DST has been performed: different doses of dexamethasone and different blood sampling schedules can contribute to differing values of sensitivity and specificity (Kraemer 1987). As with any test in medicine, users of the DST must be thoroughly familiar with its assumptions and limitations (Rubin and Poland 1984), as well as the specific situations in which it might be useful.

Considerably fewer studies have addressed more fundamental issues of HPA axis regulation in depression, such as the relationship between pre-DST cortisol hypersecretion and DST outcome. Because less-than-perfect relationships have been found between various pre-DST measures of cortisol and DST status, there has been some controversy as to where in the HPA axis the physiologic stimulus to cortisol hypersecretion occurs. For example, we studied HPA axis function in 40 primary definite endogenous depressives and 40 normal matched control subjects (Rubin et al. 1987a) and found that the 15 patients (38%) who were DST nonsuppressors had significantly higher pre-DST serum and urine cortisol levels than both their matched controls and the 25 suppressor patients. All cortisol measures were unimodally distributed across both groups of subjects. Circadian cortisol rhythms of similar magnitude occurred in both groups, and there was no significant phase advance of the circadian rhythm in the patients. Moreover, the cortisol measures before and after dexamethasone administration were positively correlated to a similar degree in the patients and the control subjects.

This latter finding suggests that pre-DST HPA hyperactivity and cortisol nonsuppression on the DST are not independently physiologically regulated in endogenous depression, as has been suggested by others on the basis of only partial overlap between increased pre-DST circulating cortisol and a positive DST (Rubin et al. 1987a). Further evidence against this hypothesis is provided by the correspondence in depressed patients between ACTH and cortisol concentrations, both before and after dexamethasone (Pfohl et al. 1985; Mortola et al. 1987). The overall results of our study, and of other studies in aggregate, suggest that depressed patients, especially DST nonsuppressors, have a higher cortisol secretion than normal subjects, even occasionally in the cushingoid range, but they have preservation of the timing and amplitude of their cortisol circadian rhythm, in contrast to many patients with Cushing's syndrome. This may be one reason why depressed patients with cortisol hypersecretion manifest few, if any, physical and laboratory stigmata of Cushing's syndrome.

From a pharmacological standpoint, an important variable affecting DST outcome is the bioavailability of dexamethasone. Several studies have indicated that serum dexamethasone concentrations are lower in subjects who show DST nonsuppression compared with those who show suppression (Arana et al. 1984; Holsboer et al. 1984a, 1986; Johnson et al. 1984; Berger et al. 1985; Carr et al. 1986; Morris et al. 1986), indicating that a positive DST might not always be a reflection of heightened activity in the central nervous system but could be due to insufficient

circulating concentrations of dexamethasone. To determine the extent that pre-DST HPA activity and serum dexamethasone concentrations contributed to the outcome of the DST in our 40 endogenous depressives and 40 matched control subjects, we measured serum dexamethasone by radioimmunoassay and assessed the relative contributions of these two measures to the outcome of the DST by multivariate analysis (Poland et al. 1987). Both variables significantly influenced DST outcome, but the major factor contributing to the discrimination of cortisol escapers from suppressors was the pre-DST 24-h cortisol concentration, accounting for approximately two-thirds of the incidence of positive DSTs. Serum dexamethasone concentrations significantly influenced DST outcome only when they were below a certain threshold level, as has been suggested for the DST in the diagnosis of Cushing's syndrome (Meikle 1982).

Challenge studies with corticotropin releasing factor (CRF) have also revealed important information about HPA axis function in depression. Most of the studies have shown that there is a decreased ACTH response to CRF in depressed patients compared with control subjects, indicating some down-regulation of CRF receptors on the corticotrophs of the pituitary (Holsboer et al. 1984b; Gold and Chrousos 1985). This suggests increased endogenous CRF production. The cortisol response following CRF, on the other hand, has been for the most part similar between depressives and controls, even though the depressives had a blunted ACTH response, suggesting the possibility of up-regulation of ACTH receptors in the adrenal cortex. The adrenals of depressed patients have been reported to be larger than those of controls by computed tomography (Amsterdam et al. 1987a). All these data taken together provide consistent evidence for increased limbic-hypothalamic driving of the HPA axis in endogenous depression, resulting in some down-regulation of CRF receptors in the pituitary but increased circulating ACTH concentrations nevertheless. The increased ACTH secretion results in increased circulating cortisol concentrations at all times of the day and night, but, as mentioned, with preservation of the timing and amplitude of the normal cortisol circadian rhythm.

The next most widely studied endocrine axis in depression has been the hypothalamo-pituitary-thyroid (HPT) axis. There is a normal circadian rhythm of circulating thyroid stimulating hormone (TSH) concentrations, with highest levels occurring in the late evening, usually prior to the time of sleep onset, and lowest levels occurring about 12 h later, in the late morning (Morley 1981; Hershman and Pekary 1985). This rhythm may be blunted or absent in some, but not all, depressed patients (Weeke and Weeke 1978, 1980; Golstein et al. 1980; Kijne et al. 1982; Kjellman et al. 1984).

Most studies of serum and plasma TSH patterns in depression have dealt with the TSH response to exogenous (administered) thyrotropin releasing hormone (TRH). Many groups of investigators are consistent in the finding of a blunted TSH response to TRH in both unipolar and bipolar endogenous depressives, as well as in manic patients, alcoholics et al. (Hollister et al. 1977; Prange 1977; Kirkegaard 1981; Loosen and Prange 1982; Loosen 1985). These studies have been done with different doses of intravenous TRH, ranging between 100 μg and 500 μg, different post-TRH blood sampling times to determine the TSH response, and different criterion TSH concentrations for a blunted response. Thus, there is little wonder that the predictive value of the TRH test in comparison with normal control subjects has ranged between 20% and 100%, indicative of a large overlap of individual post-TRH TSH values between endogenous depressives and normal controls. There also has been considerable overlap of individual values between endogenous depressives and schizophrenic and alcoholic patients.

While many studies have attempted to develop a clinical application of the TSH response to TRH as a biologic state marker of endogenous depression, as with the DST, fewer studies have addressed more fundamental issues of HPT axis regulation, such as the relationship among serum TSH, T_3 and T_4 concentrations and the relationship of these measures of HPT activity to measures of HPA activity. In our 40 primary definite endogenous depressives and 40 normal control subjects, we also measured basal serum TSH, T_3, and T_4 concentrations, as well as TSH responses to TRH, and compared these measures of HPT activity with the measures of HPA axis activity also determined in these subjects (Rubin et al. 1987b). Compared with their matched controls, the patients showed significant reductions in mean nocturnal serum TSH and mean serum T_3 concentrations. However, these reductions were not large, being about 20% for TSH and 10% for T_3. Even though the mean TSH response to TRH in the depressives was only about two-thirds that of the controls, neither it nor the mean serum T_4 concentration was significantly different between the two groups of subjects.

The elements of altered HPT axis function noted in our depressed patients have been found to a greater or lesser degree in two conditions of clinical hypothyroidism. The first is hypothalamic (tertiary) hypothyroidism, which is postulated to be caused by reduced TRH production in the hypothalamus as well as the production of TSH with reduced biologic activity (Morley 1981; Hershman and Pekary 1985; Caron

et al. 1986). The result is low to normal circulating TSH concentrations, with an absent nocturnal TSH surge; blunted or normal TSH responses to TRH; and reduced circulating T_3 and T_4 concentrations. The second condition is that of the low T_3 or "euthyroid sick" syndrome, in which the peripheral conversion of T_4 to T_3 is reduced and serum reverse T_3 is elevated, because its metabolic clearance is diminished (Cavalieri and Rapoport 1977; Wartofsky and Burman 1982; Chopra 1983). In this condition there may or may not be a net hypothyroid effect. The laboratory findings in both these conditions of clinical hypothyroidism, however, have not been described with any reproducibility in patients with endogenous depression. Reduced nocturnal TSH secretion also can occur secondary to sleep deprivation (Parker et al. 1987), and sleep disturbance is often a part of the depressive syndrome. Thus the state of the HPT axis in depressed patients, even the fundamental question of whether it is dysregulated or not, remains very much an open question.

Based on the finding of blunted TSH responses to TRH in patients with Cushing's syndrome (Morley 1981; Hershman and Pekary 1985), Kendler and Davis (1977) suggested that the blunted TSH response to TRH in depression might be secondary to the increased HPA activity that, as mentioned above, occurs in about 50% of patients with major depression. Prior studies of this relationship have been discrepant in their findings, some reporting significant inverse correlations between HPT and HPA activity, but others reporting no such association (Loosen et al. 1978a, b; Kirkegaard and Carroll 1980; Asnis et al. 1981; Extein et al. 1981; Loosen et al. 1983; Rush et al. 1983; Larsen et al. 1985; Dam et al. 1986). In both groups of our subjects, both depressives and controls, the correlations between the HPT and HPA axis measures were all of low order, with only a few representing more than 10% shared variance. Similarly, a χ^2 test of TRH test status (blunted, normal) versus DST status (escaper, suppressor) for the 40 patients was clearly nonsignificant. Thus, the measures of HPT and HPA activity were quite independent in both the patients and their controls. While the results of our study and of other studies in aggregate do not support the hypothesis that a blunted TSH response to TRH is determined by increased HPA activity, it should be pointed out that this conclusion is based on across-subjects data. Longitudinal studies of the same patients before and after treatment will be necessary to elucidate any relationship with certainty.

A third pituitary hormone which has received attention in depressive illness is prolactin. The reported abnormalities of prolactin release in depressives have included alterations in the amount of prolactin secreted and its circadian pattern (Halbreich et al. 1979; Linkowski et al. 1980; Mendlewicz et al. 1980; Mai et al. 1985), both increased and decreased prolactin responses to TRH stimulation (Maeda et al. 1975; Linkowski et al. 1980; Witschy et al. 1984), and decreased prolactin responses to several other challenges, including hypoglycemia, opiates, tryptophan, and fenfluramine (Extein et al. 1980; Grof et al. 1982; Judd et al. 1982; Winokur et al. 1982; Heninger et al. 1984; Robertson et al. 1984; Siever et al. 1984; Amsterdam et al. 1987b). Nonsuppression of prolactin following dexamethasone administration also has been reported (Meltzer et al. 1982; Klein et al. 1984). In contrast, other studies have reported no differences between depressives and control subjects in the amount of prolactin secreted, its circadian pattern, or in prolactin responses to TRH and other challenges (Sachar et al. 1973b; Næije et al. 1978; Coppen et al. 1980; Langer et al. 1980; Kirkegaard et al. 1981; Winokur et al. 1982; Amsterdam et al. 1983b; Kjellman et al. 1985; Zis et al. 1985, 1986).

In our aforementioned 40 endogenous depressives and 40 matched normal controls, we also determined basal serum prolactin concentrations and prolactin responses to TRH and dexamethasone (Rubin et al. 1989). Compared with their matched controls, the patients showed no difference in basal nocturnal prolactin concentrations, a marginally significant 20%–25% increase in the prolactin response to TRH, and no difference in the prolactin response to dexamethasone. The prolactin measures also were unrelated to pre- and post-dexamethasone cortisol concentrations and to the TSH responses to TRH in both the depressives and the controls. Thus, in contrast to the hypothalamo-pituitary-adrenal cortical and thyroid axis abnormalities frequently found in endogenous depressives, our findings suggest that prolactin secretion in these patients is relatively normal.

There also are reported abnormalities in the secretion patterns of other hormones in depression. As a last example, there is a suggestion that the normal slow-wave sleep-related nocturnal secretion of growth hormone may be blunted in depressed patients; this may be related to the fragmented sleep architecture of these patients (Schilkrut et al. 1975). Because growth hormone secretion is enhanced by a variety of stimuli, growth hormone provocation tests in depression have been performed with a number of compounds, including L-dopa, insulin hypoglycemia, 5-hydroxytryptophan, amphetamine, the α-adrenergic agonist clonidine, and the tricyclic antidepressant desmethylimipramine. While the growth hormone response to L-dopa typically has been normal in depression and the response to insulin hypoglycemia depends on a number of factors (Sachar et al. 1973b; Koslow

et al. 1982), stimuli such as clonidine and desipramine have revealed a blunted growth hormone response (Rubin and Kendler 1977; Carroll 1978; Rubin et al. 1979; Checkley 1980; Rubin and Poland 1983). Taken together, the data suggest that the defect resulting in the blunted growth hormone response in depression is at the hypothalamic and not at the pituitary level, although some investigators have reported an inappropriate growth hormone response to TRH in depression.

This review suggests that disturbances in the secretion patterns of several polypeptide and steroid hormones from a regular part of the syndrome of major depression. Because the same putative central nervous system (CNS) neurotransmitters appear to be involved in both the modulation of affects and the regulation of the hypothalamic releasing and inhibiting factors, it is tempting to suggest that a common CNS neurotransmitter dysfunction underlies both the depressive state and the altered endocrine dynamics. However, proposing this hypothesis has been considerably easier than demonstrating it.

For example, the norepinephrine deficiency hypothesis of depression was proposed in 1965 (Schildkraut 1965; Bunney and Davis 1965). Noradrenergic neurotransmission in the hypothalamus has been considered to be inhibitory to CRF secretion and thus to ACTH and cortisol secretion (VanLoon 1973; Weiner and Ganong 1978). It is logical to propose that depressives with hyperactivity of the HPA axis may represent those having a deficiency of norepinephrine function in the CNS underlying their affective disorder, and it would further logically follow that such patients should respond to antidepressants which enhance CNS noradrenergic neurotransmission better than they would respond to antidepressants which affect primarily serotonin or other neurotransmitters.

Unfortunately, in clinical practice this has not proved to be the case; reports which have suggested a differential response to antidepressants in DST-positive and DST-negative patients (Brown et al. 1980; Brown and Qualls 1981; Cobbin et al. 1981; Fraser 1983; Arato et al. 1984; Beckmann et al. 1984) have been countered by a number of other reports indicating that there is no difference in antidepressant response between DST-positive and DST-negative depressives (Greden et al. 1981; Nelson et al. 1982; Amsterdam et al. 1983a; Peselow et al. 1983; Gitlin et al. 1984; Simon et al. 1987; Steardo et al. 1987). One complicating factor is that antidepressants which may have selective effects on particular neurotransmitters in laboratory test situations have much more widespread effects in treated patients. For example, desmethylimipramine (a fairly specific presynaptic norepinephrine reuptake inhibitor), zimeldine (a specific serotonin reuptake inhibitor), and clorgyline (a monoamine oxidase-A inhibitor), when given to patients for several weeks, all reduced both MHPG (a norepinephrine metabolite) and 5-HIAA (a serotonin metabolite) in the cerebrospinal fluid (Potter et al. 1985). Because of the intricate functional interrelationships among many neurotransmitter systems in the CNS, there is little wonder that measures of HPA axis hyperactivity thus far have not been able to predict which depressed patient will respond to which antidepressant.

The same complexity obtains for endocrine axes other than the HPA axis; another example is the regulation of prolactin secretion. The current view is that dopamine is prolactin-inhibiting factor (PIF), or at least the main one (Ben-Jonathan 1985; Tuomisto and Männistö 1985). A physiologic prolactin releasing factor (PRF) has not yet been completely identified (Hyde et al. 1987). Serotonin and opioid peptides and opiates are stimulatory to prolactin secretion, but by an apparently indirect route, namely modulation of the PIF and (putative) PRF neurons. The relatively normal basal and TRH-stimulated secretion of prolactin in endogenous depression suggests that the dopaminergic neurons which exert their tonic inhibitory influence on prolactin secretion are functioning normally and that pituitary prolactin reserve is normal. On the other hand, the blunted prolactin responses to opiates and serotonin agonists reported in several studies, as mentioned above, imply reduced responses of the dopaminergic (PIF) and PRF neurons to these stimuli, perhaps resulting from subtle alterations in the function of CNS serotonergic and opioidergic systems in depressive illness.

The use of neuroendocrine abnormalities in depressive illness to help elucidate neurotransmitter dysfunction in this illness thus has been a frustrating endeavor (Rubin 1985). In addition to methodologic differences among studies, which undoubtedly have led to many of the discrepant findings reported in the scientific literature, there are several major considerations which further complicate the issue. First, it is very likely that major depression, even endogenous depression, is not indicative of the same CNS neurotransmitter abnormality in every patient; furthermore, at present there is no supreme diagnostic algorithm for determining the presence of endogenous depression (Rubin et al. 1987c). Second, as mentioned above, the neuroendocrine regulation of each of the anterior and posterior pituitary hormones is complex, resulting from an interplay among many different neurotransmitter systems in the CNS. Third, the pharmacologic probes that have been available thus far to perturb both the affective state and the secretion of various hormones (e.g. the antidepressants in

current use) have relatively nonspecific effects in the intact, functioning patient. And fourth, we still have no reliable animal models of depression. We must thus continue to adduce carefully collected evidence, from other biologic studies of depressive illness as well as from neuroendocrine studies, to clarify the roles of various neurotransmitters in the etiology of affective disturbances and the neuroendocrine changes which accompany them.

References

American Psychiatric Association (1980) Diagnostic and statistical manual of mental disorders (3rd edn) DSM-III. American Psychiatric Press, Washington, DC

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders (3rd edn, revised). American Psychiatric Press, Washington, DC

Amsterdam JD, Winokur A, Bryant S, Larkin J, Rickels K (1983a) The dexamethasone suppression test as a predictor of antidepressant response. Psychopharmacology 80:43–45

Amsterdam JD, Winokur A, Lucki I, Caroff S, Snyder P, Rickels K (1983b) A neuroendocrine test battery in bipolar patients and healthy subjects. Arch Gen Psychiatry 40: 515–521

Amsterdam JD, Marinelli DL, Arger P, Winokur A (1987a) Assessment of adrenal gland volume by computed tomography in depressed patients and healthy volunteers: a pilot study. Psychiatry Res 21:189–197

Amsterdam JD, Schweizer E, Winokur A (1987b) Multiple hormonal responses to insulin-induced hypoglycemia in normal volunteers. Am J Psychiatry 144:170–175

Arana GW, Workman RJ, Baldessarini RJ (1984) Association between low plasma levels of dexamethasone and elevated levels of cortisol in psychiatric patients given dexamethasone. Am J Psychiatry 14:1619–1620

Arana GW, Baldessarini RJ, Ornsteen M (1985) The dexamethasone suppression test for diagnosis and prognosis in psychiatry: commentary and review. Arch Gen Psychiatry 42: 1193–1204

Arato M, Rihmer Z, Szadoczky E, Grof P (1984) Dexamethasone suppression test as a predictor of drug teatment response. Prog Neuropsychopharmacol Biol Psychiatry 8: 649–652

Asnis GM, Sachar EJ, Halbreich U, Nathan RS, Ostrow L, Solomon M, Halpern FS (1981) Endocrine responses to thyrotropin-releasing hormone in major depressive disorders. Psychiatry Res 5:205–215

Beckmann H, Holzmüller B, Fleckenstein P (1984) Clinical investigations into antidepressive mechanisms. II. Dexamethasone suppression test predicts response to nomifensine or amitriptyline. Acta Psychiatr Scand 70:342–353

Ben-Jonathan N (1985) Dopamine: a prolactin-inhibiting hormone. Endocrinol Rev 6:564–589

Berger M, Pirke KM, Krieg JC, Zerssen D von (1985) The effect of weight loss and of inappropriate plasma dexamethasone levels on the dexamethasone suppression test. Psychiatry Res 15:351–360

Brown WA, Qualls CB (1981) Pituitary-adrenal disinhibition in depression: marker of a subtype with characteristic clinical features and response to treatment? Psychiatry Res 4: 115–128

Brown WA, Haier RJ, Qualls CB (1980) Dexamethasone suppression test identifies subtypes of depression which respond to different antidepressants. Lancet I:928–929

Bunney WE Jr, Davis JM (1965) Norepinephrine in depressive reactions: a review. Arch Gen Psychiatry 13:483–494

Caron PJ, Nieman LK, Rose SR, Nisula BC (1986) Deficient nocturnal surge of thyrotropin in central hypothyroidism. J Clin Endocrinol Metab 62:960–964

Carr V, Morris H, Gilliland J (1986) The effect of serum dexamethasone concentrations in the dexamethasone suppression test. Biol Psychiatry 21:735–743

Carroll BJ (1972) Control of plasma cortisol levels in depression: studies with the dexamethasone suppression test. In: Davies B, Carroll BJ, Mowbray RM (eds) Depressive illness: some research studies. Thomas, Springfield, IL, pp 87–148

Carroll BJ (1978) Neuroendocrine function in affective disorders. In: Lipton MA DiMascio A, Killam KF (eds) Psychopharmacology: a generation of progress. Raven, New York, pp 487–497

Carroll BJ (1985) Dexamethasone suppression test: a review of contemporary confusion. J Clin Psychiatry 46:13–24

Carroll BJ, Curtis GC, Mendels J (1976a) Neuroendocrine regulation in depression. I. Limbic system-adrenocortical dysfunction. Arch Gen Psychiatry 33:1039–1044

Carroll BJ, Curtis GC, Mendels J (1976b) Cerebrospinal fluid and plasma free cortisol concentrations in depression. Psychol Med 6:235–244

Carroll BJ, Curtis GC, Davies BM, Mendels J, Sugerman AA (1976c) Urinary free cortisol excretion in depression. Psychol Med 6:43–50

Carroll BJ, Curtis GC, Mendels J (1976d) Neuroendocrine regulation in depression. II. Discrimination of depressed from non-depressed patients. Arch Gen Psychiatry 33:1051–1058

Carroll BJ, Feinberg M, Greden JF, Tarika J, Albala AA, Haskett RF, James NM, Kronfol Z, Lohr N, Steiner M, Vigne JP de, Young E (1981) A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. Arch Gen Psychiatry 38:15–22

Cavalieri RR, Rapoport B (1977) Impaired peripheral conversion of thyroxine to triiodothyronine. Annu Rev Med 28: 57–65

Checkley SA (1980) Neuroendocrine tests of monoamine function in man: a review of basic theory and its application to the study of depressive illness. Psychol Med 10:35–53

Chopra IJ (moderator) (1983) UCLA conference: thyroid function in nonthyroidal illnesses. Ann Intern Med 98: 946–957

Cobbin DM, Cairncross KD, Jurd S, Veltman DG, Pohlen GH (1981) Urinary MHPG levels and the dexamethasone test predict clinical response to the antidepressant drug mianserin. Neuroendocrinol Lett 5:133–138

Coppen A, Rama Rao VA, Bishop M, Abou-Saleh MT, Wood K (1980) Neuroendocrine studies in affective disorders. 1. Plasma prolactin response to thyrotropin-releasing hormone in affective disorders: effect of ECT. J Affective Disord 2:311–315

Dam H, Mellerup ET, Rafaelsen OJ (1986) The TRH stimulation test and the dexamethasone suppression test in depression. Psychiatry Res 17:309–316

Extein I, Pottash ALC, Gold MS, Sweeney DR, Martin DM, Goodwin FK (1980) Deficient prolactin response to morphine in depressed patients. Am J Psychiatry 137:845–846

Extein I, Pottash ALC, Gold MS (1981) Relationship of thyrotropin-releasing hormone test and dexamethasone sup-

pression test abnormalities in unipolar depression. Psychiatry Res 4:49–53

Fraser AR (1983) Choice of antidepressant based on the dexamethasone suppression test. Am J Psychiatry 140:786–787

Gitlin MJ, Gwirtsman H, Fairbanks L, Sternbach HA, Cedars PI, Gerner RH (1984) Dexamethasone suppression test and treatment response. J Clin Psychiatry 45:387–389

Glassman A (chairman) (1987) The dexamethasone suppression test: an overview of its current status in psychiatry. Am J Psychiatry 144:1253–1262

Gold PW, Chrousos GP (1985) Clinical studies with corticotropin releasing factor: implications for the diagnosis and pathophysiology of depression, Cushing's disease, and adrenal insufficiency. Psychoneuroendocrinology 10:401–419

Goldstein J, Van Cauter E, Linkowski P, Vanhælst L, Mendlewicz J (1980) Thyrotropin nyctohemeral pattern in primary depression: differences between unipolar and bipolar women. Life Sci 27:1695–1703

Greden JF, Kronfol Z, Gardner R, Feinberg M, Mukhopadhyay S, Albala AA, Carroll BJ (1981) Dexamethasone suppression test and selection of antidepressant medications. J Affective Disord 3:389–396

Grof E, Brown GM, Grof P (1982) Prolactin response to hypoglycemia in acute depression. Prog Neuropsychopharmacol Biol Psychiatry 6:487–490

Halbreich U, Grunhaus L, Ben-David M (1979) Twenty-four-hour rhythm of prolactin in depressive patients. Arch Gen Psychiatry 6:1183–1186

Heninger GR, Charney DS, Sternberg DE (1984) Serotonergic function in depression: prolactin response to intravenous tryptophan in depressed patients and healthy subjects. Arch Gen Psychiatry 41:398–402

Hershman JM, Pekary AE (1985) Regulation of thyrotropin secretion. In: Imura H (ed) The pituitary gland. Raven, New York, pp 149–188

Hollister LE, Davis KL, Berger PA (1977) Thyrotropin-releasing hormone and psychiatric disorders. In: Usdin E, Hamburg DA, Barchas JD (eds) Neuroregulators and psychiatric disorders. Oxford University Press, New York, pp 250–257

Holsboer F (1983) The dexamethasone suppression test in depressed patients: clinical and biochemical aspects. J Steroid Biochem 19:251–257

Holsboer F, Haack D, Gerken A, Vecsei P (1984a) Plasma dexamethasone concentrations and differential suppression response of cortisol and corticosterone in depressives and controls. Biol Psychiatry 19:281–291

Holsboer F, Müller OA, Doerr HG, Sippell WG, Stalla GK, Gerken A, Steiger AM, Boll E, Benkert O (1984b) ACTH and multisteroid responses to corticotropin-releasing factor in depressive illness: relationship to multisteroid responses after ACTH stimulation and dexamethasone suppression. Psychoneuroendocrinology 9:147–160

Holsboer F, Wiedemann K, Boll E (1986) Shortened dexamethasone half-life in depressed dexamethasone non-suppressors. Arch Gen Psychiatry 43:813–815

Hyde JF, Murai I, Ben Jonathan N (1987) The rat posterior pituitary contains a potent prolactin-releasing factor: studies with perifused anterior pituitary cells. Endocrinology 121:1531–1539

Johnson GF, Hunt G, Kerr K, Caterson I (1984) Dexamethasone suppression test (DST) and plasma dexamethasone levels in depressed patients. Psychiatry Res 13:305–313

Judd LL, Risch SC, Parker DC, Janowsky DS, Segal DS, Huey LY (1982) Blunted prolactin response: a neuroendocrine abnormality manifested by depressed patients. Arch Gen Psychiatry 39:1413–1416

Kendell RE (1976) The classification of depressions: a review of contemporary confusion. Br J Psychiatry 129:15–28

Kendler KS, Davis KL (1977) Elevated corticosteroids as a possible cause of abnormal neuroendocrine function in depressive illness. Commun Psychopharmacol 1:183–194

Kijne B, Aggernæs H, Fog-Møller F, Anderson HH, Nissen J, Kirkegaard C, Bjørum N (1982) Circadian variation of serum thyrotropin in endogenous depression. Psychiatry Res 6:277–282

Kirkegaard C (1981) The thyrotropin response to thyrotropin-releasing hormone in endogenous depression. Psychoneuroendocrinology 6:189–212

Kirkegaard C, Carroll BJ (1980) Dissociation of TSH and adrenocortical disturbances in endogenous depression. Psychiatry Res 3:253–264

Kirkegaard C, Eskildsen PC, Bjørum N (1981) Parallel changes of the responses of thyrotropin, growth hormone and prolactin to thyrotropin-releasing hormone in endogenous depression. Psychoneuroendocrinology 6:253–259

Kjellman BF, Beck-Friis J, Ljunggren J-G, Wetterberg L (1984) Twenty-four-hour serum levels of TSH in affective disorders. Acta Psychiatr Scand 69:491–502

Kjellman BF, Ljunggren J-G, Beck-Friis J, Wetterberg L (1985) Effect of TRH on TSH and prolactin levels in affective disorders. Psychiatry Res 14:353–363

Klein HE, Seibold B, Bender W, Nedopil N, Albus M, Schmauss M (1984) Postdexamethasone prolactin and cortisol: a biological state variable in depression. Acta Psychiatr Scand 70:239–247

Koslow SH, Stokes PE, Mendels J, Ramsey A, Casper R (1982) Insulin tolerance test: human growth hormone response and insulin resistance in primary unipolar depressed, bipolar depressed and control subjects. Psychol Med 12:45–55

Kraemer HC (1987) The methodological and statistical evaluation of medical tests: the dexamethasone suppression test in psychiatry. Psychoneuroendocrinology 12:411–427

Langer G, Schönbeck G, Koinig G, Reiter H, Schüssler M, Aschauer H, Lesch O (1980) Evidence for neuroendocrine involvement in the therapeutic effects of antidepressant drugs. In: Brambilla F, Racagni G, de Wied D (eds) Progress in psychoneuroendocrinology. Elsevier/North Holland, Amsterdam, pp 197–208

Larsen JK, Bjørum N, Kirkegaard C, Aggernæs H, Krog-Meyer I, Lund-Laursen AM, Mikkelsen PL (1985) Dexamethasone suppression test, TRH test and Newcastle II depression rating in the diagnosis of depressive disorders. Acta Psychiatr Scand 71:499–505

Linkowski P, Brauman H, Mendlewicz J (1980) Prolactin secretion in women with unipolar and bipolar depression. Psychiatry Res 3:265–271

Loosen PT (1985) The TRH-induced TSH response in psychiatric patients: a possible neuroendocrine marker. Psychoneuroendocrinology 10:237–260

Loosen PT, Prange AJ Jr (1982) Serum thyrotropin response to thyrotropin-releasing hormone in psychiatric patients: a review. Am J Psychiatry 139:405–416

Loosen PT, Prange AJ Jr, Wilson IC (1978a) Influence of cortisol on TRH-induced TSH response in depression. Am J Psychiatry 135:244–246

Loosen PT, Prange AJ Jr, Wilson IC (1978b) The thyrotropin response to thyrotropin-releasing hormone in psychiatric patients: relation to serum cortisol. Prog Neuropsychopharmacol 2:479–486

Loosen PT, Kistler K, Prange AJ Jr (1983) Use of TSH response to TRH as an independent variable. Am J Psychiatry 140:700–703

Maeda K, Kato Y, Ohgo S, Chihara K, Yoshimoto Y, Yamaguchi N, Kuromaru S, Imura H (1975) Growth hormone and prolactin release after injection of thyrotropin-releasing hormone in patients with depression. J Clin Endocrinol Metab 40:501–505

Mai FM, Shaw BF, Jenner MR, Wielgosz G, Giles D (1985) Nocturnal prolactin secretion in depression. Br J Psychiatry 47:314–317

Meikle WA (1982) Dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone. Clin Endocrinol 16:401–408

Meltzer HY, Fang VS, Tricou BJ, Robertson A, Piyaka SK (1982) Effect of dexamethasone on plasma prolactin and cortisol levels in psychiatric patients. Am J Psychiatry 139: 763–768

Mendlewicz J, Van Cauter E, Linkowski P, L'Hermite M, Robyn C (1980) The 24-hour profile of prolactin in depression. Life Sci 27:2015–2024

Morley JE (1981) Neuroendocrine control of thyrotropin secretion. Endocrinol Rev 2:396–436

Morris H, Carr V, Gilliland J, Hopper M (1986) Dexamethasone concentrations and the dexamethasone suppression test in psychiatric disorders. Br J Psychiatry 148:66–69

Mortola JF, Liu JH, Gillin JC, Rasmussen DD, Yen SSC (1987) Pulsatile rhythms of adrenocorticotropin (ACTH) and cortisol in women with endogenous depression: evidence for increased ACTH pulse frequency. J Clin Endocrinol Metab 65:962–968

Næije R, Golstein J, Zegers de Beyl D, Linkowski P, Mendlewicz J, Copinschi G, Badawi M, Leclercq R, L'Hermite M, Vanhælst L (1978) Thyrotrophin, prolactin and growth hormone response to TRH in barbiturate coma and in depression. Clin Endocrinol 9:49–58

Nelson WH, Orr WW, Stevenson JM, Shane SR (1982) Hypothalamic-pituitary-adrenal axis activity and tricyclic response in major depression. Arch Gen Psychiatry 39:1033–1036

Parker DC, Rossman LG, Pekary AE, Hershman JM (1987) Effect of 64-hour sleep deprivation on the circadian waveform of thyrotropin (TSH): further evidence of sleep-related inhibition of TSH release. J Clin Endocrinol Metab 64:157–161

Peselow ED, Fieve RR, Goldring N, Wright R, Deutsch SI (1983) The DST and clinical symptoms in predicting response to tricyclic antidepressants. Psychopharmacol Bull 19:642–645

Pfohl B, Sherman B, Schlechte J, Stone R (1985) Pituitary/adrenal axis rhythm disturbances in psychiatric depression. Arch Gen Psychiatry 42:897–903

Poland RE, Rubin RT, Lesser IM, Lane LA, Hart PJ (1987) Neuroendocrine aspects of primary endogenous depression. II. Serum dexamethasone concentrations in relation to dexamethasone suppression test response. Arch Gen Psychiatry 44:790–795

Potter WZ, Scheinin M, Golden RN, Rudorfer MV, Cowdry RW, Calil HM, Ross RJ, Linnoila M (1985) Selective antidepressants and cerebrospinal fluid: lack of specificity on norepinephrine and serotonin metabolites. Arch Gen Psychiatry 42:1171–1177

Prange AJ Jr (1977) Patterns of pituitary responses to thyrotropin-releasing hormone in depressed patients: a review. In: Fann WE, Karacan I, Pokorny AD (eds) Phenomenology and treatment of depression. Spectrum, New York, pp 1–15

Robertson AG, Jackman H, Meltzer HY (1984) Prolactin response to morphine in depression. Psychiatry Res 11:353–364

Rubin RT (1985) The prospects for clinical psychoneuroendocrinology, or: has the curtain been drawn across the neuroendocrine window? Psychol Med 15:451–454

Rubin RT, Kendler KS (1977) Psychoneuroendocrinology: fundamental concepts and correlates in depression. In: Usdin G (ed) Depression: clinical, biological, and psychological perspectives. Brunner/Mazel, New York, pp 122–138

Rubin RT, Poland RE (1982) The chronoendocrinology of endogenous depression. In: Müller EE, MacLeod RM (eds) Neuroendocrine perspectives, vol 1. Elsevier, Amsterdam, pp 305–337

Rubin RT, Poland RE (1983) Neuroendocrine function in depression. In: Angst J (ed) The origins of depression: current concepts and approaches. Springer, Berlin Heidelberg New York, pp 205–220

Rubin RT, Poland RE (1984) The dexamethasone suppression test in depression: advantages and limitations. In: Burrows GD, Norman TR, Maguire KP (eds) Biological psychiatry: recent studies. Libbey, London, pp 76–83

Rubin RT, Gouin PR, Poland RE (1973) Biogenic amine metabolism and neuroendocrine function in affective disorders. In: Fuente R de la, Weisman MN (eds) Psychiatry: Proceedings of the V World Congress of Psychiatry. Excerpta Medica, Princeton, NJ, pp 1036–1039

Rubin RT, Poland RE, Hays SE (1979) Psychoneuroendocrine research in endogenous depression: a review. In: Obiols J, Ballus C, Gonzales Monclus E, Pujol J (eds) Biological psychiatry today. Elsevier, Amsterdam, pp 684–688

Rubin RT, Poland RE, Lesser IM, Winston RA, Blodgett ALN (1987a) Neuroendocrine aspects of endogenous depression. I. Cortisol secretory dynamics in patients and matched control subjects. Arch Gen Psychiatry 44:329–336

Rubin RT, Poland RE, Lesser IM, Martin DJ (1987b) Neuroendocrine aspects of primary endogenous depression. IV. Pituitary-thyroid axis activity in patients and matched control subjects. Psychoneuroendocrinology 12:333–347

Rubin RT, Poland RE, Lesser IM, Martin DJ, Blodgett ALN, Winston RA (1987c) Neuroendocrine aspects of primary endogenous depression. III. Cortisol secretion in relation to diagnosis and symptom patterns. Psychol Med 17:609–619

Rubin RT, Poland RE, Lesser IM, Martin DJ (1989) Neuroendocrine aspects of primary endogenous depression. V. Serum prolactin measures in patients and matched control subjects. Biol Psychiatry (in press)

Rush AJ, Schlesser MA, Roffwarg HP, Giles DE, Orsulak PJ, Fairchild C (1983) Relationships among the TRH, REM latency, and dexamethasone suppression tests: preliminary findings. J Clin Psychiatry 44:23–29

Sachar EJ, Hellman L, Roffwarg HP, Halpern FS, Fukushima DK, Gallagher TF (1973a) Disrupted 24-hour patterns of cortisol secretion in psychotic depression. Arch Gen Psychiatry 28:19–24

Sachar EJ, Frantz AG, Altman N, Sassin J (1973b) Growth hormone and prolactin in unipolar and bipolar depressed patients: response to hypoglycemia and L-dopa. Am J Psychiatry 130:1362–1367

Schildkraut JJ (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 122:509–522

Schilkrut R, Chandra O, Osswald M, Rüther E, Baarfüsser B, Matussek N (1975) Growth hormone release during sleep

and with thermal stimulation in depressed patients. Neuropsychobiology 1:70–79

Siever LJ, Murphy DL, Slater S, Vega E de la, Lipper S (1984) Plasma prolactin changes following fenfluramine in depressed patients compared to controls: an evaluation of central serotonergic responsivity in depression. Life Sci 34:1029–1039

Simon JS, Evans DL, Nemeroff CB (1987) The dexamethasone suppression test and antidepressant response in major depression. J Psychiatry Res 21:313–317

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

Steardo L, Barone P, Monteleone P, Iovino M, Cardone G (1987) Is the dexamethasone suppression test predictive of response to specific antidepressant treatment in major depression? Acta Psychiatr Scand 76:129–133

Targum SD (1983) Neuroendocrine challenge studies in clinical psychiatry. Psychiatr Ann 13:385–395

Träskman L, Tybring G, Åsberg M, Bertillson L, Lantto O, Schalling D (1980) Cortisol in the CSF of depressed and suicidal patients. Arch Gen Psychiatry 37:761–767

Tuomisto J, Männistö P (1985) Neurotransmitter regulation of anterior pituitary hormones. Pharmacol Rev 37:249–332

VanLoon GR (1973) Brain catecholamines and ACTH secretion. In: Ganong WF, Martini L (eds) Frontiers in neuroendocrinology. Oxford University Press, New York, pp 209–247

Wartofsky L, Burman KD (1982) Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome." Endocrinol Rev 3:164–217

Weeke A, Weeke J (1978) Disturbed circadian variation of serum thyrotropin in patients with endogenous depression. Acta Psychiatr Scand 57:281–289

Weeke A, Weeke J (1980) The 24-hour pattern of serum TSH in patients with endogenous depression. Acta Psychiatr Scand 62:69–74

Weiner RI, Ganong WF (1978) Role of brain monoamines and histamine in regulation of anterior pituitary secretion. Physiol Rev 38:905–976

Winokur A, Amsterdam J, Caroff S, Snyder PJ, Brunswick D (1982) Variability of hormonal responses to a series of neuroendocrine challenges in depressed patients. Am J Psychiatry 139:39–44

Witschy JK, Schlesser MA, Fulton CL, Orsulak PJ, Giles DE, Fairchild C, Crowley G, Rush AJ (1984) TRH-induced prolactin release is blunted in females with endogenous unipolar major depression. Psychiatry Res 12:321–331

Zerssen D von, Doerr P (1980) The role of the hypothalamo-pituitary-adrenocortical system in psychiatric disorders. Adv Biol Psychiatry 5:85–106

Zis AP, Haskett RF, Albala AA, Carroll BJ, Lohr NE (1985) Prolactin response to morphine in depression. Biol Psychiatry 20:287–292

Zis AP, Albala AA, Haskett RF, Carroll BJ, Lohr NE (1986) Prolactin response to TRH in depression. J Psychiatr Res 20:77–82

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