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GENERAL REVIEW

STEROIDS AND DEPRESSION

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Summary—Patients with endogenous depression (major affective disorder) frequently have high cortisol levels, but the diurnal rhythm is usually maintained and they do not develop the physical signs of Cushing's syndrome. On the other hand, depression is a frequent feature of Cushing's syndrome regardless of etiology, and it is often relieved when the cortisol levels are reduced, by whatever means. The mechanisms of the hypercortisolemia and resistance to dexamethasone suppression commonly found in endogenous depression are poorly understood; contrary to expectations, ACTH levels are not clearly elevated. There is a striking difference in the psychiatric features seen in endogenous hypercorticism compared to those seen after exogenous administration of glucocorticoids or ACTH. This suggests that either there are other stimulating or modifying factors besides ACTH or that the steroids stimulated by ACTH or other peptides differ from those in control subjects, i.e. there may be an alteration in the metabolism of steroids in depression. Little is known about the metabolic changes or the many steroids besides glucocorticoids produced by the hyperactive steroid-producing tissue. Preliminary studies suggest that major depression may be improved by steroid suppression. It is hypothesized that steroids themselves may be important in causing and perpetuating depression.

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Abbreviations: ATHF, allotetrahydrocortisol (5α); CBG, corticosteroid-binding globulin, transcortin; CPB, competitive protein-binding assay; CRH, corticotropin-releasing hormone; CT, computerized tomography; DOC, 11-desoxycorticosterone; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised; DST, dexamethasone suppression test; ECT, electroconvulsive therapy; GABA, γ-aminobutyric acid; GCR, glucocorticoid receptors; GH, growth hormone; hCRH, human CRH; HPA, hypothalamic–pituitary–adrenal; 17-OHCS, 17-hydroxycorticoids; 17-KGS, 17-ketogenic steroids; 17-KS, 17-ketosteroids; oCRH, ovine CRH; RIA, radioimmunoassay; RTA, radiotransinassay; S, 11-desoxycortisol; THE, tetrahydrocortisone; THF, tetrahydrocortisol; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; UFC, urinary "free" cortisol (i.e. unconjugated); VIP, vasointestinal peptide.

1. INTRODUCTION

Patients with endogenous depression (major affective disorder) frequently have high cortisol levels, but the diurnal rhythm is usually maintained and they do not develop the physical signs of Cushing's syndrome. On the other hand, depression is a frequent feature of Cushing's syndrome regardless of etiology, and it is often relieved when the cortisol levels are reduced, by whatever means. The mechanism of the hypercortisolemia in endogenous depression is poorly understood since, contrary to expectations, ACTH levels are not clearly elevated. However, many depressed patients have resistance to dexamethasone. There is a striking difference in the psychiatric effects of endogenous hypercorticism compared to those of exogenously administered glucocorticoids or ACTH. The evidence for these puzzling observations is reviewed and possible explanations are considered.

1.1. Clinical problem of endogenous depression (major affective disorder)

Depression (major affective disorder as defined by DSM-III-R criteria [1]) is an important problem is psychiatry. The lifetime prevalence of a major depressive episode is 4–9% with a female–male ratio of 2:1 [2]. The preponderance of depression in women has not been explained and depression is frequently exascerbated during the premenstruum. In depressed men, Rubin *et al.* [3] found that the hypopituitary–pituitary–gonadal axis function is essentially normal; corresponding studies in depressed women are lacking. Untreated, episodes of depression last from 6 months to many years. About 17% last more than 2 years. It has been estimated [4, 5] that a considerable number (10–28%) of depressed patients do not respond to any form of treatment including psychotherapy, electroconvulsive therapy (ECT), antidepressants and although no longer used, even lobotomy. The incidences of some of the associated symptoms are listed in Table 1 [6, 7].

1.2. Association of high cortisol levels with depression

Although it has been known since the early 1960s that depression is often associated with high cortisol levels, the reason for this is still not understood. Cortisol hypersecretion has been demonstrated using various measures, including

Table 1. Frequency of psychiatric symptoms in patients with Cushing's syndrome and patients with major depression

Symptom:	Cushing's syndrome (%)	Major depression (%)	
No. of patients:	35	54	95
Ref.:	[24]	[7]	[6]
Depressed mood, feeling sad	74	93	93
Increased fatigue	100	57	NR[a]
Decreased energy	97	NR	75
Decreased libido	69	50	50
Irritability	86	67	NR
Crying	63	50	NR
Restlessness	60	59	46
Anxiety, apprehensiveness	66	30	NR
Impaired memory	83	NR	NR
Impaired concentration	66	93	76
Early insomnia	29	59	64
Middle insomnia	69	46	67
Late insomnia	57	61	58
Social withdrawal	46	NR	NR
Hopelessness	43	61	95
Guilt	37	28	31
Increased appetite or weight gain	34	7	NR
Decreased appetite	20	87	52
Slowing thoughts	11	69	NR
Thought blocking	17	NR	NR
Speeding thoughts	14	NR	NR
Elation-hyperactivity	11	NR	NR
Perceptual distortions, delusions	11	11	NR
Paranoid thoughts	9	7	9
Suicidal attempts	10	11	NR

[a]NR: not recorded.

mean 24 h 17-hydroxycorticoids (17-OHCS), 24 h urinary "free" cortisol (UFC), cortisol production rates, serial morning cortisol samples, 24 h integrated plasma samples, and CSF levels [8–16].

1.3. Association of high cortisol levels with suicide

Some 40–50% of all suicides are committed by depressed patients; more than 70% of depressed people experience suicidal thoughts. Suicide is the second most common cause of death among North Americans aged 15–20 years. A possible link between high cortisol levels (as measured by 24 h 17-OHCS) in urine was first suggested in 1965 by Bunney and Fawcett [17]; they found that of 143 depressed patients, 9 with near-fatal or fatal suicide tries had a higher mean 17-OHCS excretion than the remainder. Ostroff *et al.* [18] found a similar increase in 24 h UFC.

In a study of plasma cortisol measured 4 times a day in a group of psychiatric patients considered to be at high risk for suicide, Krieger [19] found a higher level in the 13 patients who committed suicide within 2 years of testing compared with the 39 who did not commit suicide. This subject has recently been reviewed by two groups [20, 21]. Eight of 13 studies using the dexamethasone suppression test (DST) (see Section 3.4) as an indicator of suicide risk also showed a higher rate of non-suppression among those who committed lethal or near-lethal suicide attempts.

1.4. Psychiatric features seen in Cushing's syndrome

About one-third of patients with Cushing's syndrome have significant psychiatric morbidity, and two-thirds are depressed; approx. 10% attempt suicide [22–25] (Table 1). Mania and euphoria may also occur but are much less common. The psychiatric features seen in Cushing's syndrome are quite similar to those seen in major depression. Table 1 compares some of these with those reported in two series of depressed patients. The mechanism bringing about these changes is unknown. The changes are similar in both primary and secondary adrenal disease, so appear to be related to the cortisol level rather than to the ACTH level. Trethowen and Cobb [23] found the most severe mental symptoms, in 25 cases of Cushing's syndrome, to occur in 2 cases of adrenal adenoma and 2 cases of adrenal hyperplasia. However, Carroll [26] found a higher proportion of patients with Cushing's disease (2/3 of 78) had significant depression than those with adrenal tumors (1/4). In a small series, Cohen [27] found 5 of 8 patients with adrenal tumors, and 20 of 21 patients with Cushing's disease had some evidence of psychiatric disorder. Jeffcoate *et al.* [28] studied 38 patients with Cushing's syndrome: 22 were depressed,

4 had other psychiatric problems and 13 had no psychiatric problems; of those who were depressed, 5 had adrenal tumors, 5 had ectopic ACTH, 11 had Cushing's disease and 1 was alcohol-induced. The depression in many cases resolved with treatment (see Section 8).

1.5. Lack of physical signs of Cushing's syndrome in endogenous depression

Despite the high cortisol levels in association with major depression, there are no physical signs of Cushing's syndrome (e.g. hypertension, purple striae, truncal obesity, buffalo hump and florid facies); nor are there any of the biochemical abnormalities (e.g. electrolyte changes) frequently associated with Cushing's syndrome. This is true no matter how high the plasma cortisol levels are. However, UFC levels are not usually as high in depression as in Cushing's syndrome, possibly because the high morning blood cortisol levels are usually not sustained throughout the day.

1.6. Other endocrine abnormalities observed in patients with depression

Decreased response of thyroid-stimulating hormone (TSH) to thyroid-releasing hormone (TRH), decreased growth hormone (GH) response to hypoglycemia, and low LH have been found in some patients with major depression, although less consistently than cortisol hypersecretion. These changes are also observed in Cushing's syndrome and are considered to be due to excess corticoids [22]. In depression they may be present in the absence of evidence of hypercortisolemia. Although these alterations are usually considered to be evidence of neurotransmitter defects in major depression, Kendler and Davis [29] have considered the possibility that these abnormalities may be consequences of increased adrenocortical function. In one study of depressed patients a good correlation was observed between the low GH response to hypoglycemia and the hypersecretion of corticoids [30]. In patients after treatment, a low response continued in those patients with persisting elevations of corticoids [31].

1.7. Hypercortisolism in other psychiatric disorders

Elevated cortisol levels have also been found in anorexia nervosa and bulimia [32–35], in some cases of Alzheimer's disease [36], and in psychogenically induced amenorrhea [37]. The mechanism of the hypercortisolemia in these conditions is also poorly understood and is also not accompanied by any signs of Cushing's syndrome. In anorexia nervosa many of the other features of the hypercortisolemia (e.g. resistance to dexamethasone) are similar to those in depression.

2. EVIDENCE OF HYPERACTIVITY OF THE ADRENAL CORTEX IN DEPRESSION

2.1. Cortisol assays

The hypercorticism of depression has been assessed mainly using assays of cortisol. The methods used to assay cortisol are numerous and have included assays of 17-OHCS and of 17-ketogenic steroids (17-KGS), fluorometric assays and various kinds of competitive protein-binding (CPB) assays: radiotransinassay (RTA) employing indigenous proteins of various species and RIA using antibodies raised to cortisol conjugates. None of these methods is entirely specific for cortisol.

17-OHCS determinations measure the steroids having a 17,21-dihydroxyacetone side-chain [38]. These include cortisol, 11-desoxycortisol, cortisone, and their ring A-reduced derivatives. They account for only one-quarter to one-half the total metabolites of cortisol. They may be altered by obesity, liver disease, hyper- or hypo-thyroidism and by many drugs, so that such interference must be carefully excluded.

The 17-ketosteroids (17-KS) measure compounds with a 17-ketone group, such as androstenedione and dehydroepiandrosterone. The 17-KGS measure steroids having a side-chain at C_{17} which can be converted into 17KS, these include all the 17-OHCS plus any other steroids with a side-chain and a 17-OH group. They are measured as the difference between 17-KS before and after bismuthate oxidation, which oxidizes the side-chain. The difference between the "native" and derived ketosteroids includes cortisol, 21-desoxycortisol, 11-desoxycortisol, cortisone, 17-hydroxyprogesterone, 17-hydroxypregnenolone, and their 20-dihydro and ring A-reduced derivatives. Thus, they measure many other steroids besides cortisol and its metabolites. They are also subject to the same alterations noted for 17-OHCS.

Fluorometric assays, which measure 11-hydroxylated steroids (mainly cortisol and corticosterone) have also been used but give higher

values since they also measure corticosterone and possibly other steroids [39].

CPB methods [40, 41] differ from the chemical methods in that specificity depends on the affinity of a particular ligand–protein interaction. Some make use of the naturally occurring high affinity binding of corticosteroid-binding globulin, transcortin (CBG) in the blood of various species, usually human, dog or horse, to provide the binding protein (RTA) while RIAs employ antibodies raised to cortisol conjugated to antigenic substances, usually at the C_{21} or C_3 positions. Although the term CPB, can be applied to any assay employing a protein of high affinity and specificity (receptor, antibody or transin), it is often used to refer particularly to assays employing indigenous serum proteins such as CBG.

While the CPB methods have the advantages of much greater sensitivity and specificity compared to the chemical methods, they vary greatly from one to another with respect to specificity, depending on the protein used and any additional purification employed. The indigenous CBGs vary from species to species, but are constant for any particular species, while the antibodies vary much more, according to the site of conjugation, the particular animal used to raise the antibody, and from time to time in the same animal.

While the absolute values for cortisol in plasma (excepting fetal plasma) using the various methods are in reasonably good agreement, with values for 17-OHCS and fluorometric assays running somewhat higher, those for urinary unconjugated ("free") cortisol are not. The true normal mean value as determined after extensive chromatography is about 20 μg/day (56 nmol/day); the mean value using the more specific RTAs (dog and horse) is about 35 μg/day, while that for RIAs varies from 35 to 70 μg/day [42]. Thus only about half or less of the material measured in normal subjects is actually cortisol. Nevertheless, provided that the urine corticoids are extracted into a solvent first, and that the normal range is established for the particular method used, clinically useful data can be obtained [42, 43].

Another factor which must be considered in assessing the validity of cortisol assays [and of those of ACTH and corticotropin-releasing hormone (CRH)] is the influence of stresses such as fever, even of low grade, or that of the first few days of hospitalization, which may elevate the levels.

2.2. Total plasma and urinary cortisol levels

While mean total plasma and urinary cortisol levels have been shown to be elevated in half or more depressed patients by most authors using all the available methods [8–16], high levels *per se* do not prove that the cortisol reaching the tissues is excessive. One must consider the various factors which are involved in determining the levels; the serum protein-binding, production, rate, metabolic clearance rate and the number and affinity of receptors.

2.3. Plasma unbound cortisol levels

Few studies have investigated plasma unbound ("free") cortisol levels or those of the specific corticosteroid-binding transport protein CBG in depression. Carroll *et al.* [14] found increased unbound plasma levels in depressed patients while Schechte and Coffman [44] found no significant difference in either unbound levels or transcortin levels. If the CBG level and plasma unbound cortisol levels are normal, how can we account for the high total cortisol levels?

More recently, Charles *et al.* [45] found a good correlation between total and unbound cortisol both in endogenous and non-endogenous depressed groups. Average levels in the endogenous group were more than twice as high as those in the non-endogenous group. Unfortunately, in neither study was there a healthy control group. These studies cannot be regarded as definitive.

2.4. Salivary cortisol levels in depression

Salivary hormone levels are usually considered to be proportional to those of unbound plasma levels. They have the advantages that they are non-invasive, non-stressing, and can be collected frequently and by the patients themselves, even in children. In healthy subjects [46] and in those with Cushing's syndrome [47] they appear to parallel serum unbound cortisol levels. Similar results have been found in depressed non-suppressors but the ratios of saliva/serum varied more widely. Poland and Rubin [48] studied levels in control subjects and in patients with major depression; for the DST, their cutoff of 50 ng/ml (136 nmol/l) in serum corresponded to a cut-off of 0.5 ng/ml (1.4 nmol/l) in saliva. On the other hand, Hanada *et al.* [49], using a cut-off in serum of 50 ng/ml, found a cut-off in saliva of 3.0 ng/ml (8.2 nmol/l), a value 6 times higher. Both used RIA methods. Charles *et al.* [45] have

defined a cut-off of 0.7 ng/ml (1.9 nmol/l) in saliva, in close agreement with the former group.

2.5. Urinary "free" cortisol (UFC) levels

Urinary unconjugated ("free") corticoid levels in urine are considered to reflect the integrated unbound plasma cortisol levels and have been shown to be useful in distinguishing the hyper-corticism of Cushing's disease [43]. However, as noted above, none of the routinely available methods measures true cortisol levels; we have shown, using chromatography on Sephadex LH-20, that other substances account for much of the material measured [42].

Levels of UFC in depressed patients have generally shown good agreement with plasma cortisol levels, but in no study has chromatography been used to define what is being measured. Stokes *et al.* [50], in a multicenter study, showed that the mean ± SEM UFC in all depressed patients (130 ± 11 μg/day; 360 ± 31 nmol/day) was about twice that found in healthy subjects (70 ± 6 μg/day; 194 ± 17 nmol/day). This 2-fold difference is much lower than that found in many cases of Cushing's syndrome. Using human CBG as the binding protein in a RTA assay, we found a mean in healthy subjects of 48 ± 7 μg/day (133 ± 19 nmol/day); levels in adrenal hyperplasia ranged from 130 to 900 (360–2500 nmol/day), with most values between 150 and 400, while patients with adrenal tumours and ectopic ACTH syndrome had levels usually from 1000 to 10,000 μg/day (2800–28,000 nmol/day); acutely ill subjects had a 4-fold increase in UFC [43].

2.6. Circadian rhythm of cortisol in depression

The circadian rhythm, measured in plasma, urine and saliva, is usually maintained in depressed patients, with a general shift of the levels upwards [22, 51]. This is in contrast to patients with Cushing's syndrome, where the circadian rhythm is usually lost. Sherman *et al.* [52] have studied the diurnal changes in depressed patients before and after dexamethasone and have shown that in depressed subjects considerable variations may occur in non-suppressed plasma levels.

2.7. Cortisol levels in CSF

Since there is relatively little protein present, cortisol levels in CSF are also considered to represent "free" (i.e. unbound) cortisol, and are presumed to reflect the cortisol reaching the brain. Because of the high lipid content of the brain, and the great solubility of steroids in lipids, cortisol and other steroids pass readily into brain tissue; there is no blood–brain barrier for them. We have shown that cortisol passes quickly from the blood into the CSF and vice versa and that CSF levels correlate closely with blood levels [53]. Carroll *et al.* [14] showed that mean CSF levels in 35 unipolar depressed patients (12.2 ng/ml, 34 nmol/l), 4 bipolar depressed patients (14.2 ng/ml, 39 nmol/l), and depressed patients before ECT (13.3 ng/ml, 34 nmol/l) were all higher than those of the control groups: neurotically depressed patients (5.8 ng/ml, 16 nmol/l), bipolar manic patients (8.2 ng/ml, 23 nmol/l) and patients who had recovered from ECT (8.3 ng/ml, 23 nmol/l). They have refuted the work of others who claimed to have found no differences.

2.8. CRH levels in depression

Higher than normal levels of CRH in CSF of depressed patients have been reported [54, 55], but did not appear to relate to plasma cortisol levels before or after dexamethasone.

Nemeroff *et al.* [56] have shown a 23% reduction in the number of CRH binding sites in the frontal cortex of suicide victims compared with controls. They interpret this as evidence of chronic hypersecretion of CRH in depression. They reason that if CRH is chronically hypersecreted in depressed patients, then, due to down-regulation, a reduced number of CRH receptor binding sites should be present in suicidal patients.

The current hypothesis to account for the biochemical findings in major depression is that there is a disinhibition of the hypothalamic–pituitary–adrenal (HPA) axis (see Section 10). Roy *et al.* [54] have suggested that CRH excess may be responsible for the symptom complex of depressive illness. However, this would not account for the similarity in the psychiatric symptoms (including impairment of cognition and memory) of major depression and of all types of Cushing's syndrome, where CRH levels are considered to be low.

2.9. ACTH and β-endorphin levels in depression

Also, if the HPA axis disturbance in depression were simply a disinhibition, then one would expect to find elevated ACTH levels in depressed patients. These have not been clearly demonstrable, some studies having shown hypersecretion [57–59] while more often normal

or low values have been found [60–64]. Recently, Mortola *et al.* [65] have found an increase in ACTH pulse frequency in depressed women compared with controls; however mean 24 h ACTH levels were similar in the two groups. Possibly the discrepancies are due to differences in specificity of the RIA methods used. If peptides, other than ACTH are being produced in excess, they might cross-react in some assays, giving falsely high values for ACTH in some but not other assays (see Section 9).

Zis [66] has postulated that impaired opioid inhibition is responsible for the HPA dysfunction observed in depression and has reviewed the evidence for this. Plasma ACTH and cortisol decrease in response to opioid agonists and opioid peptides such as β-endorphin, and increase in response to naloxone. However, while opioids do seem to have an inhibitory effect on the HPA axis, the site and mechanisms of their possible regulation are not yet clear.

Galard *et al.* [67] have compared plasma β-endorphin levels in 14 patients with endogenous and 17 with non-endogenous depression before and after dexamethasone suppression. The endogenously depressed patients had significantly lower levels of β-endorphin and significantly higher levels of cortisol than the non-endogenous group before dexamethasone.

Poland *et al.* [68] compared ACTH levels in normal men using RIA and bioassay (dispersed rat adrenal cells) methods. They found a consistently close correlation ($r = 0.93$) between bioactive ACTH and cortisol concentrations but a more variable relationship (average $r = 0.69$) between cortisol levels and immunoassayable ACTH. They suggest that plasma ACTH levels by RIA may not be an accurate reflection of ACTH-like (i.e. adrenocortical stimulating) activity of plasma. Since virtually all the currently accepted studies of ACTH described here are based on RIA data, this is a very important observation.

If the hypercortisolemia is not due to ACTH excess, then what causes it? Other pituitary hormones such as αMSH, β-endorphin and vasopressin are possible regulators but their relationship is still not clear, or there may be as yet undiscovered peptides from the pituitary or elsewhere which stimulate the adrenal in depression. Another possibility is that some factor increases the responsiveness of the adrenal cortex to normal amounts of ACTH (see Section 3.1). Alternatively, if a factor normally decreasing the activity of the adrenal cortex, such as the newly discovered corticostatic peptides [69], were decreased, there might be an increased sensitivity of the adrenal to ACTH.

2.10. Cortisol stimulation by extrapituitary hormones

Blalock's group have suggested that human mononuclear leucocytes can produce immunoreactive ACTH in response to typhoid antigen [70]. Whitcomb *et al.* [71] have shown that human monocytes increase cortisol production by adrenocortical cells in culture; stimulation is not affected by CRH.

Recently some forms of Cushing's syndrome due to primary adrenocortical micronodular adenomatosis have been attributed to circulating adrenal-stimulating immunoglobulins [72].

2.11. Effects of psychotropic medications on regulation of the HPA axis

In addition to ensuring that the hormonal methods used in assessing the HPA axis are not subject to interference by drugs, one must also consider the possibility that psychotropic drugs may themselves distort the regulation of the HPA axis. Meador-Woodruff and Greden [73] have considered this possibility but have concluded that such alterations are minimal except when the drugs alter the severity of the underlying pathophysiology. They also suggest that after long-term administration, there may be an elevation of the hormones due to withdrawal.

3. DYNAMIC STUDIES OF THE ACTIVITY OF THE HPA AXIS IN DEPRESSION

3.1. Response of cortisol to ACTH stimulation in depression

Adrenal hypertrophy is associated with an exaggerated response to exogenous ACTH. Amsterdam *et al.* [74] and Jaeckle *et al.* [75] found that the response to 250 μg ACTH 1–24 (Cosyntropin) was greater in depressed patients than in controls and that the peak levels occurred earlier. In the latter study, non-suppressors showed a greater response than did suppressors [75].

In 11 patients with major depression, Amsterdam *et al.* [76] found that the cortisol response to 250 μg ACTH before treatment was higher than that after recovery. They attributed this hyperreactivity to an increase in adrenal volume (see Section 6). However the dose used was

supraphysiological; and when the same dose of exogenous ACTH was injected i.m., Sclare and Grant [77] found no difference between the depressed and control groups. Similarly when the same dose was infused over a long period by Carpenter and Bunney [78], there was no difference. When Fang *et al.* [60] reduced the dose of ACTH to 0.05 μg/kg body wt and suppressed endogenous ACTH secretion using dexamethasone, the change in plasma cortisol levels was similar although the depressed patients had higher baseline levels.

More recently, Amsterdam *et al.* [79] studied the response to ACTH (0.05 and 0.2 μg/kg body wt) at 16:00 h in depressed patients and controls. They found that 6 control subjects and 5 non-melancholic depressed patients had higher mean cumulative cortisol responses at the higher dose, while melancholic patients had an intermediate response at both doses. However, the mean responses among the groups at each dose did not differ significantly.

3.2. Response of cortisol levels to insulin hypoglycemia

Insulin hypoglycemia is a stress which results in a rise in ACTH and cortisol levels. Usually a level of blood sugar below 45 mg/dl (2.5 mmol/l) is low enough to cause a response. Carroll [80] found a decreased responsiveness to hypoglycemia in 16 unipolar depressed patients with a greater response in the same patients after recovery. This defect was not found in bipolar patients [81]. A similar flat response is found in Cushing's disease, presumably because endogenous CRH is suppressed.

3.3. Response of ACTH to CRH stimulation

When ovine CRH (óCRH) was used to stimulate ACTH production in normal, Cushing's disease and depressed subjects, Gold *et al.* [82] found an increased response in Cushing's disease but a decreased response in major depression. A similar decrease was found in anorexia nervosa [35]. These data suggest a down-regulation of the corticotrophs in the latter two conditions due to the feedback of persistently elevated cortisol levels. Holsboer *et al.* [83] and Amsterdam *et al.* [84] also found a blunted response to CRH in depressed patients. Depressed patients who had recovered had normal responses [82]. Similarly, patients with anorexia nervosa also had a reduced response to CRH which normalized with weight gain [35]. Human CRH (hCRH) has also been used by Holsboer *et al.* [85] but was found to be less effective than the ovine peptide and differences between depressed patients and controls were not apparent. Similarly, Nieman *et al.* [86] compared the use of hCRH and oCRH in 15 patients with Cushing's disease and concluded that oCRH is more effective as a diagnostic tool.

Von Bardeleben and Holsboer [87] showed that in 14 depressed patients pre-treated with dexamethasone (1.5 mg orally at 23:00 h) hCRH caused increases of ACTH and cortisol the following day, whereas in 14 control subjects it did not. This response disappeared when the patients recovered. The authors interpreted these results as evidence that in depression the action of hCRH is enhanced by a factor that is less sensitive to dexamethasone suppression and postulated that this factor is vasopressin.

Rupprecht *et al.* [88] showed that in depressed patients, there was a significantly lower ACTH release after hCRH administration than in control subjects. However, the β-endorphin and cortisol responses were similar. They were unable to account for this.

Holsboer *et al.* [89] found a positive correlation ($r = 0.65$, $P \leqslant 0.001$) between ACTH response to CRH and TSH response to TRH in depressed patients.

3.4. Suppressibility of cortisol levels by dexamethasone

Carroll *et al.* [90, 91] suggested that resistance to cortisol suppression by dexamethasone might be a useful diagnostic tool in depression. 1 mg dexamethasone is given at bedtime, and serum cortisol levels are drawn at 8:00 and 16:00 h, and sometimes 20:00 h the next day. If any of these exceed 5 μg/dl (136 nmol/l) the test is considered to be positive and the patient is termed a non-suppressor.

In depression, there is a high proportion of non-suppressors. Since the DST was considered to be possibly the first biochemical marker for depression, it was taken up with great enthusiasm and a flood of papers ensued. The response to dexamethasone has been very extensively studied by many investigators using many different cortisol methods and several different regimens of dexamethasone. These have been summarized recently by Arana *et al.* [92] (Table 2). Younger depressed patients tend to have a lower incidence of non-suppression [93]. Although there are variations from one group to another there is reasonably good agreement that about 50% of depressed patients have demon-

Table 2. Rates of suppression-negative responses in various psychiatric populations

	No. of subjects	Non-suppressors (%)
Major depression		
All adult	4411	43
Young (< 18 yr)	205	34
Elderly (> 60 yr)	183	64
Familial	265	47
Sporadic	379	38
Bipolar	110	38
Melancholic or endogenous	583	50
Psychotic	150	67
Mixed bipolar (manic–depressive)	41	78
Other psychiatric disorders		
Anxiety disorders (incl. panic and phobias)	74	8
Schizophrenia	260	13
Minor depression (dysthymic disorder or endogenous)	238	23
Acute or typical psychoses	69	34
Dementia	174	41
Mania	137	41
Grief reaction	Not stated	10
Controls		
Normal	1130	7
Normal + non-psychiatric patients	1269	8

Modified from Arana G. W. and Mossman D.: The dexamethasone suppression test and depression. In *Endocrinology of Neuropsychiatric Disorders* (Edited by W. A. Brown). W. B. Saunders, Philadelphia (1988) p. 27. *Endocr. Metab. Clins N. Am.* **17**, No. 1.

strable resistance to dexamethasone. Usually, but not invariably in such patients, urinary, salivary and plasma cortisol levels are increased over normal. Conversely, patients with a normal response to dexamethasone may have elevated cortisol levels. As with plasma cortisol levels, a lifting of the depression is associated with a normalization of the DST [93–98] (see Section 8).

There appears to be some relationship between severity of depression and non-suppressibility, thus the rank order of non-suppression is striking: normal patients (7–8%), grief reaction (10%), minor depression (23%), major depression (44%), melancholia (50%) and psychotic affective disorders (69%) (Table 2).

Because of the variations in proportion of depressed patients with abnormal DSTs in different studies, Meltzer and Fang [99] have considered the importance of the particular cortisol methods used and have recommended that each laboratory should establish its own normal range. Time of sampling has also been considered [100].

Some concern regarding possible differences in absorption and metabolism of dexamethasone among individuals have been expressed, although Morris *et al.* [101] found no significant difference in half-life between suppressors (39 h) and non-suppressors (34 h). In several studies where dexamethasone levels were measured during the DST, lower levels were consistently found in suppressors [82]. For this reason it has been recommended that levels of both dexamethasone and cortisol should be measured to give a dexamethasone suppression index [102]. However, this has been recently disputed [103].

Others have suggested that determinations of other steroids might be helpful. Corticosterone levels have been observed to respond similarly to those of cortisol [104] but there seems to be little advantage in their measurement. Because there is a tendency for cortisol and corticosterone (11-hydroxylated steroids) to predominate over their precursors, Demey-Ponsart *et al.* [105] have suggested using the ratio of 18-hydroxydesoxycorticosterone/free (i.e. unbound) plasma cortisol instead of total plasma cortisol. However, this would be a great deal of work and would probably not be very helpful in individual cases since the error would be larger.

4. GLUCOCORTICOID RECEPTORS (GCR)

4.1. GCR in endogenous depression and other diseases

Studies of lymphocyte GCR in depressed patients are about 30% lower than those of normal subjects [106–109] while those of patients with Cushing's syndrome and Addison's disease are unchanged [107]. No reason has been advanced for this observation.

Gormley *et al.* [106] considered the possibility that the receptors might be occupied by endogenous steroid, however since they had shown that the tracer used, [^{3}H]triamcinolone, could completely displace an equivalent amount of corticosterone from rat thymocytes under

similar conditions, they felt that this was unlikely. However they used only a single point saturation assay and did not do any Scatchard analyses. Kontula *et al.* [110] also found a reduced level of GCR in patients with anorexia nervosa.

Junker [111] studied the number and affinity of GCR in mononuclear leukocytes of groups of men and women of various ages, at various times of day and at various seasons and found no differences. Five pregnant women in the last trimester had a slight increase in receptor number and a slight decrease in affinity but overall the author felt that the results indicate a remarkable invariability of GCR, and did not support the idea that excess glucocorticoids down-regulate their own receptor number or affinity.

Elevated levels of corticosterone in rats were observed by Sapolsky *et al.* [112] to cause a decrease in GCR in the hippocampus, but not in other brain regions or in the hypothalamus or pituitary.

4.2. Primary cortisol resistance

Some of the features seen in depression are shared by humans [113–115] or animals with primary cortisol resistance. There is hypercortisolemia, an absence of Cushing's syndrome, decreased suppression in response to dexamethasone, and decreased or altered GCR binding in lymphocytes and fibroblasts.

4.3. Specificity of GCR

There appear to be at least two types of GCR in rat brain and these are particularly prominent in the hippocampus [116, 117]. One has high affinity for the synthetic glucocorticoid RU 26988 and a low affinity for aldosterone, while the other has low affinity for RU 26988 but high affinity for aldosterone and corticosterone. If steroids which bind strongly to GCR (but are not GCR agonists) are produced in depression, it might be expected that cortisol would occupy only a fraction of the GCR sites, thus decreasing glucocorticoid effects and, depending on the kinetics, apparent GCR number. Such an effect on hippocampal and/or hypothalamic receptors might also account for the increased CRH level. In Cushing's disease where the cortisol production is much greater, the other steroids would not compete effectively for GCR, so that CRH would be depressed. The normal ACTH levels in depressed patients, in the face of increased CRH levels, may be due to a combination of non-agonist steroids and high cortisol levels competing for pituitary GCR controlling negative feedback.

5. ADRENOCORTICAL METABOLISM IN DEPRESSION AND CUSHING'S SYNDROME

5.1. Excretion of urinary metabolites in depressed patients

The early assays for glucocorticoids in urine (i.e. 17-OHCS, 17-KS and 17-KGS) measured mainly metabolites (see Section 2). Kurland [118], in 1964, measured these three entities in depressed patients before and after treatment. He found increased levels of all three in untreated patients compared to recovered patients but only the 17-KGS were excreted in absolute amounts exceeding those of normal control subjects, and only the 17-KGS were significantly correlated with the severity of the depression. Unfortunately he did not provide his values for healthy controls. He considered the 17-KGS to be disproportionately elevated over the 17-OHCS, and postulated that this might be due to a block in the metabolism of 17-OHCS or the presence of an abnormal steroid(s) produced by the adrenal cortex. He noted that disproportionate increases in 17-KGS may occur also in congenital adrenal hyperplasia, and in Cushing's syndrome from various causes.

This study was criticized by Sachar, who reviewed the literature up to 1966 [119] and who also did a similar study [120]. Sachar complained that most authors had failed to consider the stress of hospitalization *per se* in their studies. In his study he found normal 17-OHCS and 17-KGS in depressed patients with no change on recovery; unlike Kurland, he found a good correlation between 17-OHCS and 17-KGS, which he attributed to a better method for 17-KGS. His method employed periodate oxidation which is specific for a C_{17},C_{20}-dihydroxy configuration while that used by Kurland used bismuthate, which oxidizes either the C_{17}-OH,C_{20}-ketone or the dihydroxy configuration. The periodate method would therefore not measure steroids such as C_{21}-desoxycortisol, which is produced in large amounts in congenital adrenal hyperplasia and has never been measured in depressed patients.

Later, Sachar *et al.* [121] reported cortisol production rates and the sum, but unfortunately not the individual values, of tetrahydrocortisone (THE), tetrahydrocortisol (THF) and 5α-tetra-

hydrocortisol (ATHF) in 16 depressed patients. They concluded that cortisol production did not correlate with severity of depression, but was lower in patients after recovery. Cortisol production rates correlated better with psychiatric scores than did measures of the metabolites.

In 1966, Rubin and Mandell [122] reviewed the literature regarding 17-OHCS data in pathological emotional states. They noted that the affective changes in major depression more closely resemble those of Cushing's syndrome than those associated with exogenous ACTH or glucocorticoid therapy (also see Section 7) and suggested the possibility that depression might be a central nervous system response to high circulating glucocorticoids.

However, depression has been known to occur in adrenalectomized patients maintained on fixed doses of steroids, and to respond to ECT, indicating that depression can occur in the absence of the adrenal glands [123]. Altered metabolism of the administered steroids and those of the gonads by the liver might, however, still offer an explanation.

In 1969, Mendels [124] fractionated the urinary 17-KS of 8 male depressed patients and found an elevation of the ratio of 11-oxy-17-KS/11-desoxy-KS to 1.2, which fell to normal (0.5) with recovery. This occurred due to a rise in 11-oxy-17-KS, since the 11-desoxy-KS were normal. He suggested that there is a disturbance in steroid metabolism involving either an alteration in cortisol metabolism and/or a change in adrenal androgen metabolism.

In 1971, Stancakova and Stancak [125] compared cortisol metabolites in 10 patients with depressive illness to those of 17 healthy control subjects. In contrast to most others, they found that the levels of unconjugated corticosteroids, 17-OHCS and 17-KGS (determined using periodate oxidation) were all lower in the depressed patients than in the controls, and fell still further on treatment with thioridazine.

5.2. Excretion of urinary metabolites in Cushing's syndrome

In 1963, Guignard-de Maeyer *et al.* [126] estimated THF, THE and ATHF in the urine of 12 patients with Cushing's disease: 10 showed a marked change in metabolism; the ratios of ATHF/THF and (ATHF + THF)/THF were decreased, indicating a decrease in 5α- compared to 5β-reduction, and also an increase in C_{11} oxidation. These changes were not observed in patients receiving short-term ACTH (1–12 days). A decreased ATHF/THE was observed in 3 patients on long-term ACTH therapy (63–98 days) but there was a large difference in the ratio of THF/THE, being 0.98 (range 0.56–1.5) in Cushing's disease and 3.0 (range 2.6–3.7) after long-term ACTH. Long-term glucocorticoid administration was not associated with any alterations in the proportions of cortisol metabolites excreted. These observations suggest that ACTH alone may not be responsible for the increased cortisol secretion in Cushing's disease. Whether similar abnormalities of metabolism are present in major depression is not known.

In 1982, Phillipou [127] claimed that patients with Cushing's syndrome could be diagnosed by their urinary steroid profiles. He attributed the alterations in the steroid profiles to a decrease in the liver enzymes associated with 5α-reductase and 11β-hydroxysteroid dehydrogenase activity, resulting in increases in 5β- and 11β-OH steroid metabolites. Using a capillary gas chromatography method, he found that the ratio of etiocholanolone (a 5β steroid) to androsterone (5α) in 7 patients with Cushing's syndrome was 3.75 ± 1.33, significantly ($P \leqslant 0.001$) higher than that of 14 normal controls (1.3 ± 0.39), 17 obese subjects (0.7 ± 0.28) or 26 hirsute subjects (1.0 ± 0.35). Similarly, the ratios of THF (5β) to ATHF (5α) were elevated in the patients with Cushing's syndrome; these included 4 with-Cushing's disease, 2 with ectopic ACTH overproduction and 1 with adrenal carcinoma. The ratio of THE/THF (11-keto/11-hydroxy) was decreased in the Cushing's patients (0.49 ± 0.24) compared to the other groups (controls, 1.85 ± 0.34; obese, 2.17 ± 0.45; and hirsute, 2.3 ± 0.54). The alteration in metabolism was attributed to changes in triiodothyronine secretion secondary to hypercortisolism; similar changes can occur in hypothyroidism [128]. Unfortunately, comparable steroid profile data in depressed patients are lacking, although the frequent occurrence of similar alterations in the response of TSH to TRH have been well documented (see Section 1.6).

5.3. Steroids other than cortisol

Although the suggestion was made by several authors that steroids other than cortisol (and corticosterone) might be implicated in the increased adrenocortical activity associated

with depression, very few studies have explored this possibility. Since, apart from aldosterone, the other known adrenal products and their metabolites were not considered to be of particular physiological significance, they have not been studied in depression to any extent. Also, with the development in the 1960s of more specific and sensitive assays for cortisol, there was less emphasis on the study of metabolites.

Gibbons [10] showed that the corticosterone secretion rate as well as that of cortisol is increased in depression.

Holsboer *et al.* [129] studied the levels of corticosterone, DOC, 11-desoxycortisol (cpd S), cortisol and cortisone in 6 depressed and 6 normal women before and after dexamethasone suppression. Mean levels of corticosterone, S, DOC and cortisone were lower than those of the controls but there was considerable overlap. However, the ratios of cortisol/S and corticosterone/DOC were significantly increased in the depressed patients. They interpreted this as evidence of an activation of adrenal 11β-hydroxylase in depression by increased amounts of ACTH. In a subsequent paper [83] they also measured ACTH levels and found elevated levels for 12 of 23 depressed patients, in all of whom cortisol levels had not been suppressed after dexamethasone.

Demey-Ponsart *et al.* [105] found low or normal levels of 18-hydroxy-11-desoxycorticosterone in depressed subjects.

6. NEURAL AND ANATOMICAL FEATURES OF ENDOGENOUS HYPERADRENOCORTICISM

6.1. Effects of hyperadrenocorticism on brain function

As noted in Table 1, deficits of cognition and memory are often observed in patients with Cushing's syndrome [24] or depression [6, 7]. A significant relationship between UFC and cognitive impairment in depression has been demonstrated by Rubinow *et al.* [130]. In their series of 28 depressed patients, 17 (61%) scored above 80 on the Halstead–Reitan Category Test, a sensitive measure of cognitive impairment, compared to only 1 in 31 control subjects; 9 of the 17 had UFC within the normal range. No exactly comparable data for patients with Cushing's syndrome are available but Starkman *et al.* [24] noted that 83% of their Cushing's patients had impaired memory and 66% had impaired concentration.

6.2. Reversible cerebral cortical atrophy in hyperadrenal states

Kellner *et al.* [131] showed a significant correlation between ventricular dilatation (as measured by CT scan) and UFC levels in 10 affectively ill patients. Similarly, Schlegel *et al.* [132] found that in depressed patients, mean plasma cortisol was positively related to elevated ventricular/brain ratio. CT scan evidence of ventricular enlargement and cortical atrophy in patients with Cushing's syndrome, anorexia nervosa or in those receiving exogenous ACTH or corticosteroids, appears to be reversible [133–135].

6.3. Evidence of possible adrenal hypertrophy in depression

Using CT scans, Amsterdam *et al.* [136] have compared adrenal volumes of 16 depressed patients with those of 11 healthy controls and found that 8 of the patients but only 1 control had volumes in excess of the 95th percentile value for the controls; however, the difference between the 2 groups was not significant by t-test ($P \geqslant 0.05$).

6.4. Role of adrenal nerves in the regulation of adrenocortical function

Holzwarth *et al.* [137] have reviewed the literature pertaining to the role of adrenal nerves in the regulation of adrenocortical function and suggest that regulation of the adrenal cortex is controlled by autonomic as well as humoral factors. They studied the distribution of nerve plexuses in the adrenal cortex and found that vasointestinal peptide (VIP) and neuropeptide Y were the most prevalent neurotransmitters and neuropeptides present. Catecholamine and neuropeptide Y nerve fibers entered the adrenal along blood vessels, while those of the VIP plexus appeared to be intrinsic to the adrenal. These authors suggest that these plexuses might have effects on cellular processes as well as on blood supply. Neural factors, mainly catecholamines, have been shown to be important in compensatory adrenal growth after unilateral adrenalectomy, such growth was inhibited by sympathectomy. Using a peripheral capsule–glomerulosa preparation, they found that VIP and isoproterenol stimulated steroidogenesis, the effect on aldosterone production being greater than that on corticosterone. It seems possible that such factors might play a part in

the apparently increased responsiveness of the adrenal cortex in depression.

7. PSYCHIATRIC EFFECTS OF EXOGENOUS ACTH, GLUCOCORTICOIDS AND OTHER HORMONES

7.1. Psychiatric effects of exogenous ACTH and glucocorticoids in patients treated for various conditions

By contrast to states of endogenous cortisol hypersecretion, administration of excessive glucocorticoids or ACTH to subjects with normal adrenal function is usually followed by a mild elevation of mood, sometimes euphoria, although there may be irritability, increased motor activity and sleeplessness; a small percentage become psychotic [138–141]. Results with ACTH and cortisone were similar.

It is difficult to find precise data as to the incidence of particular symptoms, or to distinguish between the effects of ACTH and glucocorticoids. Goolker *et al.* [138] give an account of 80 cases of patients treated with either ACTH or cortisone (data for individual patients is not available). Of these, 43 cases (54%) showed no reaction or one consistent with relief of their somatic symptoms. The symptoms in the other 37 patients are listed in Table 3. No clear relationships existed between dosage, pretreatment psychological state, or the psychic outcome, so that psychic reactions were completely unpredictable. Overall, the incidence of mood elevation was 62%, a figure in keeping with those of others [139, 140].

While the incidence of euphoric states and generally improved mental state is high with exogenous steroid excess and low in states associated with endogenous hypercorticism, depression is relatively rare after exogenous steroids but very common with endogenous hypersecretion (Table 4). While deficits of memory and cognition are common in depression and in Cushing's syndrome [24, 130], there are reports of improved memory, improved ability to concentrate, acceleration of thinking and increased ability to do creative thinking following administration of ACTH or cortisone [141].

Table 3. Psychiatric symptoms in 80 patients treated with ACTH or cortisone (compiled from the data of Goolker and Schein [137])

	No. of patients	% Of patients with affective reactions
None	19	
Consistent with relief of symptoms	24	
Inappropriate cheerfulness	15	41
Inappropriate well-being	2	5
Euphoria (hypomania)	6	16
Alternating moods	16	54
Apathy	3	8
Depression	3	8
Psychotic	4	11

Table 4. Incidence (%) of psychiatric type in spontaneous and iatrogenic Cushing's syndrome

	Cushing's syndrome	
Ref:	Spontaneous [24]	Iatrogenic [137]
Depressed	74	8
Euphoric	11	62

The discrepancy between states of endogenous and exogenous hypercortisolism suggests that the depression so frequently observed in association with high endogenous cortisol levels may be due to associated factors rather than to cortisol itself, and that there may be a difference in the circulating steroids or their metabolites in endogenous and exogenous hypercorticism.

7.2. Psychiatric and neural effects of steroids under controlled conditions

Glucocorticoids are known to have a number of neural effects: they decrease hippocampal electrical activity [142]; increase the latency of synaptic neurotransmission; affect serotonin biosynthesis [143]; and increase norepinephrine uptake in the brain [144]. Dubrovsky *et al.* [145] have shown that i.v. injected desoxycorticosterone and some of its derivatives, also decrease brain excitability in the rat. Glucocorticoids affect certain kinds of learning behavior, usually in a positive way [146]; however, the doses of steroids used in some animal experiments have been very high, so that it is difficult to know whether these have any meaning physiologically. Cortisol receptors are present in large numbers in the hippocampus, a structure known to be implicated in learning and memory [116].

Persky *et al.* [147] explored the effect on anxiety tests in normal subjects when cortisol and corticosterone were administered by i.v. infusion over several hours to give levels about 10 times those of endogenous steroids. They found that corticosterone increased anxiety more than cortisol. Corticosterone levels were approximately doubled after giving cortisol. They suggested that corticosterone might play some role in the etiology of anxiety states.

The effects of estrogens and androgens on behavior are well recognized. However, many other endogenous steroids from both the adrenals and gonads may have profound effects on the brain. Examples are the anesthetic effects of progesterone (a steroid produced by all

steroid-producing tissues), DOC and their ring A-reduced metabolites; almost all of the latter have some anesthetic properties [148–149]. Some of these, such as the 5-dihydroprogesterones, are among the most potent anesthetics known and act within seconds of injection—too rapidly to be explained by a genomic mechanism. These observations are in keeping with the findings that various steroid hormones bind with affinity to synaptic membranes [150] and that progesterone metabolites modulate γ-aminobutyric acid (GABA) binding to synaptic membranes *in vitro* [151].

Anesthetic steroids are produced in normal subjects but are rapidly conjugated and excreted so that the levels in plasma are low; their physiological effects are unknown. In an attempt to determine whether these steroids might have effects on motor activity at low doses, we implanted ovariectomized rats with silastic capsules containing 5α-dihydroprogesterone, 5β-dihydroprogesterone or nil, and measured motor activity of pairs of treated and control rats [152]. As expected, 5β-dihydroprogesterone decreased motor activity; surprising, however, was the increased activity observed in the rats implanted with 5α-dihydroprogesterone. Whether the production or metabolism of these compounds is altered in depression has never been explored. However, they are probably increased in the luteal phase of the menstrual cycle and might account for the behavioral symptoms seen in the premenstrual syndrome [149].

Another progesterone metabolite, 3α-hydroxy-5α-pregnan-20-one, was shown to be a potent barbiturate-like modulator of the neurotransmitter GABA in the rat [151] and it has been suggested that it might therefore influence changes in mood [153].

Progesterone, DOC and other steroids have recently been found by Su *et al.* [154] to bind to σ receptors in mammalian brain and lymphoid tissue; they have suggested that σ receptors may play a role in the etiology of human psychosis.

Klangkalya *et al.* [155] have studied the specificity of steroid binding to the hypothalamic muscarinic receptor, a receptor for the neurotransmitter acetylcholine. In competition with tritiated quinonuclidinyl benzilate, it was found that tracer binding was inhibited by a variety of steroids, the most potent of which were 17-hydroxyprogesterone $\geqslant$ its 5β analogue, DOC $\geqslant$ its 5β analogue, progesterone and its 5β analogue, which had IC_{50} values in the range of 20–50 μM. Although the brain is known to take up and concentrate steroids [156], the very high concentrations required for inhibition in these studies make their physiologic relevance doubtful.

Henkin [157] has shown that taste, olfaction, audition and proprioception are altered by steroids. Adrenalectomy causes a greatly increased perception of all of these along with a decreased recognition acuity. The increased sensory detection is not altered by mineralocorticoids but is reversed by giving replacement doses of glucocorticoids. A diurnal variation in sensory detection and perception can be seen in normal subjects under physiological circumstances, with increased perception at night.

Patients with Cushing's syndrome have decreased sensory detection acuity of all types and this is reversed by treatment. The opposite is seen in patients with Addison's disease.

7.3. Psychiatric and neural effects of ACTH and other peptides under controlled conditions

Studies of ACTH and related peptides in animals and man have indicated that ACTH and ACTH 4–10 improve learning and motivation [158]. Vasopressin and its analogs also enhance memory [159]. The dorsal hippocampus and/or amygdaloid complex must be intact for this to occur. Endorphins tend to have the opposite effects on memory but increase analgesia, and are sedative at high doses; they are thought to be the physiological mediators of the placebo effect.

8. STATE DEPENDENCE OF ADRENOCORTICAL FUNCTION AND DEPRESSION

8.1. Effect of antidepressants or ECT on adrenocortical function in major depression

In 1963, Gibbons and McHugh [8] followed plasma cortisol weekly in 17 depressed patients and found that in 13 cases recovery was accompanied by a decline in cortisol levels.

McClure [12] also noted that the hypercortisolemia associated with depression decreased to normal with response to treatment and suggested that plasma cortisol levels could be used as a guide to the progress of treatment and to its efficacy.

Similarly, there is ample evidence that nonsuppression of the DST during episodes of depression reverts to normal when the de-

pression is relieved. Greden *et al.* [160], who reviewed this topic in 1983, followed DSTs weekly in 31 hospitalized patients with major depressive disorder during and after treatment with antidepressants. The DST of non-suppressors gradually normalized in relation to clinical improvement, the drop in DST cortisol levels usually preceding or coinciding with good clinical outcome. Failure to normalize was associated with poor clinical response. Suppressors showed no changes in DST.

Carroll [80] noted that the decreased response to insulin hypoglycemia in depressed patients became normal on recovery after ECT.

8.2. Alteration of adrenocortical function in manic and depressive phases of bipolar affective disorder

In bipolar disorder, in which mania and depression alternate, the changes in cortisol levels correspond. Bunney *et al.* [161] showed this particularly well for a woman who underwent regular 48 h manic–depressive cycles. The 17-OHCS alternated regularly with the episodes of depression, being consistently low at times of mania. When, later, the cycles became less frequent, the manic periods continued to be associated with lower 17-OHCS, and the depressive periods with higher 17-OHCS. Unfortunately, the authors do not state their normal levels of 17-OHCS but the values appear to be probably at about the upper and lower limits of the normal range. A similar case was described by Rizzo *et al.* [162]. This has also been found to be true for the DST, with non-suppression occurring during the depressive phase and suppression during the manic phase [163].

8.3. Severity of depression related to DST

Kumar *et al.* [164], in 1986, studied 73 drug-free depressed in-patients. They found a significant relationship ($P = 0.02$) between the maximum post-dexamethasone plasma cortisol levels and the number of endogenous symptoms.

A similar study by Meador-Woodruff *et al.* [165], in 1987, indicated a significant relationship ($P \leqslant 0.02$ at 8:00 h, $P \leqslant 0.004$ at 16:00 h, $P \leqslant 0.009$ at 23:00 h) between severity of depression, as measured by the Hamilton Depression Scale, and cortisol levels following a 1 mg DST in 66 patients. In a smaller group of 44 patients in whom plasma β-endorphin was determined as well, the relationship to cortisol was again significant ($P \leqslant 0.02$), and that for β-endorphin was also significant ($P \leqslant 0.05$). In this latter study, known confounding factors such as age, recent weight loss, number of previous depressive episodes, psychosis, and polarity, were controlled for.

Miller and Nelson [6], in 1987, also studied the relationship between the DST and various factors; they found significant correlations only with initial insomnia, agitation, loss of sexual interest, and weight loss.

Arana and Mossman [92] recently reviewed the literature to see how useful the DST might be in monitoring progress of treatment. They noted that in some cases, the DST reverted to normal before there were appreciable changes in depression ratings following antidepressant therapy or ECT. They concluded that the DST may be only partially state-stable. When outcome several months after start of treatment was considered, the results of 13 reports involving 144 depressed patients suggested that only 19% of patients who converted to and maintained normal cortisol suppression had a poor clinical outcome, while 77% of those who continued to be, or again became, suppressor positive, had a poor or fatal outcome.

8.4. Effect of treatment on depression of Cushing's syndrome

Cohen *et al.* [27] described a high incidence of depression (86%) in Cushing's syndrome whether due to Cushing's disease (20 in 21 patients) or to tumors (5 in 8 patients). The depression was relieved when the patients were treated. He suggested that the depression of Cushing's syndrome might be due to a substance other than cortisol produced by the adrenal and that this substance might be important in the etiology of depression in general.

Jeffcoate *et al.* [28] have provided more details regarding the response of psychiatric symptoms of Cushing's syndrome to treatment (see Section 9).

8.5. Effect of recovery on hypercortisolemia of other disorders

In anorexia nervosa the hypercortisolemia and the reduced response of ACTH to CRH are reversed by weight gain [35]. The hypercortisolemia associated with malnutrition is also reversed by re-feeding.

When menses are resumed, the hypercortisolemia associated with hypothalamic amenorrhea also reverts to normal [37].

9. RESPONSE OF DEPRESSION TO STEROID SUPPRESSION

9.1. Effect of adrenal suppression on the depression associated with Cushing's syndrome and pseudo-Cushing's syndrome

Jeffcoate *et al.* [28] studied 38 patients with Cushing's syndrome due to a variety of causes (adrenal tumor, pituitary tumor, ectopic ACTH and alcohol-induced pseudo-Cushing's syndrome): 5 patients (13%) were markedly depressed, 4 (10%) were moderately depressed and 13 (32%) were mildly depressed. There was no relationship between ACTH and depression, i.e. depression occurred in patients with adrenal adenomas with low ACTH and also in pituitary Cushing's disease with high ACTH levels. The cortisol level was reduced by either medical (metyrapone, which blocks 11-hydroxylation [166]) or surgical adrenalectomy; or in the case of alcohol-induced pseudo-Cushing's, by alcohol withdrawal. Successful control of the plasma cortisol level led to relief of the depression in all 5 severely depressed patients, 4 of the 5 moderately depressed patients and in 6 of the mildly depressed. The authors concluded that metyrapone may be of considerable value in the management of the acute psychiatric states which may occur in Cushing's syndrome.

Sonino *et al.* [167] treated 6 patients with severe hypercortisolism due to Cushing's disease with a combination of metyrapone and aminoglutethimide (which blocks steroid biosynthesis, particularly at the cholesterol side-chain cleavage, and at the C_{11}, C_{21} and C_{18} hydroxylation steps [168–172]. Although aminoglutethimide suppresses estrogen production as well as cortisol production, menstrual cycles which had been disrupted in association with the Cushing's syndrome resumed after 4 weeks on therapy. A striking effect of the treatment in one patient was rapid regression of severe depression which had failed to respond to antidepressant therapy [173]. Depression abated after 4 weeks of metyrapone and aminoglutethimide therapy and menses resumed. After 1 year on metyrapone and aminoglutethimide she was doing well.

Kramlinger *et al.* [174] describe a case of a 51-year-old man in whom a major depressive episode, ultimately complicated by delirium, heralded the development of the physical signs of Cushing's syndrome. The affective disturbance and delirium resolved within 3 days after starting metyrapone.

Angeli *et al.* [175] noted regression of psychiatric symptoms when 5 women with Cushing's disease were treated with ketoconazole, an agent which has a pattern of inhibition similar to that of aminoglutethimide except that it inhibits androgens rather than estrogens [176–178].

Nieman *et al.* [179], in 1985, reported successful treatment with RU 486, a synthetic antagonist of progesterone and cortisol [180] of a 25-year-old man with Cushing's syndrome caused by ectopic secretion of ACTH. As well as the somatic features of Cushing's syndrome, his suicidal depression resolved.

Spontaneous remission of Cushing's syndrome is unusual but has been described in a few patients [181]; prolonged remission after stopping medical treatment of Cushing's syndrome has also been reported. Beardwell *et al.* [182], who have reviewed the latter, describe 2 cases of florid Cushing's syndrome with increased ACTH levels, where treatment with metyrapone led to prolonged remission. One of these patients was euphoric and became manic. On treatment his mental state improved rapidly. After 6 months the treatment was stopped and the patient remained well for at least 14 months. The other patient relapsed 6 months after stopping treatment. The paradoxical fall in the ACTH levels with metyrapone could not be explained. The authors suggested that glucocorticoids might be stimulating ACTH production.

9.2. Effect of steroid suppression on major affective disorder in the absence of Cushing's syndrome

In view of the large amount of literature attesting to state dependence of hypercorticism in major suppression and of the good response which has been observed in the depression of Cushing's syndrome after treatment, an obvious question is: what happens if the hypercorticism of major depression is suppressed? Since a significant number of depressed patients are resistant to conventional forms of therapy, it is surprising that no attempt has been made to answer this question. However, the author has been unable to find any reports of steroid suppression in the absence of Cushing's syndrome. She and her colleagues have studied the effects of 2 months of steroid suppression in 19 severely depressed patients resistant to antidepressant therapy, some of whom have been described [183–185].

In 5 cases, the response was dramatic, improvement occurring at 3 days to 2 weeks. All

commented early in the course of treatment that they were able to think much more clearly than they had for a long time. After the 2 months of treatment, these patients have remained well off all medications for 5–30 months. One of these patients had no evidence of hypercortisolemia, and had a negative DST.

Of the 17 who completed the 2 months of therapy, 66% responded (reduction of 50% or more in the Hamilton Depression Scale). One was given a course of ketoconazole therapy after aminoglutethimide and metyrapone proved ineffective; this was successful in part but the maximum dose used was not sufficient to lower the cortisol level into the normal range. Although her Hamilton Depression Scale ratings remained high (since the patient was a Cree Indian who spoke little English or French, there were some difficulties in communicating), her behavior was obviously much improved; whereas she had at the start of treatment remained in her room in bed most of the time, towards the end of treatment she took her meals with the other patients and participated in ward activities. She has maintained this improvement for more than a year and has been able to return to her community.

Of 7 patients who were DST-positive before treatment, 5 of the 6 who responded were DST-negative when tested 1 week or more following discontinuation of the therapy. The Cree patient who had not responded to aminoglutethimide and metyrapone had a positive DST 1 week after discontinuing these drugs but the DST had become negative 1 week after discontinuing ketoconazole.

Although the results are still preliminary, this study suggests that a period of adequate suppression can, at least in some cases, bring about a readjustment of the HPA axis, leading to a lasting remission. It also suggests that hypersecretion of steroids *per se* may be a factor in perpetuating the depression.

One interesting aspect of this study was that the ACTH levels in all the patients remained entirely in the normal range even during suppressive therapy and even when refractoriness to the drugs occurred. Under such circumstances one would have expected large increases in ACTH. The failure of this to occur provides evidence that some factor other than ACTH may be involved in the adrenal stimulation [186].

Because of these unexpectedly low ACTHs, the possibility was considered that perhaps the RIA used for ACTH might not be adequately specific to show up differences. Therefore, a second, ostensibly more specific, antibody was used to check 16 patient samples and the same group of 14 control samples [Murphy, unpublished data]. Contrary to expectation, the patient results using the "more specific" antiserum were higher ($P \leqslant 0.01$) than those obtained using the "less specific" antiserum. However, the control values by the more specific assay were significantly lower, as expected, than those using the "less specific" antiserum. When the mean values for the patients were compared to those for the controls, the patient values using the "more specific" assay were twice those of the controls, while those using the "less specific" assay were slightly, but not significantly, lower than those of the controls. These results suggest the presence of some other ACTH-like factor in the plasma of the depressed patients which cross-reacts with the "more specific" ACTH antibody, but not with the other.

10. THEORIES AS TO THE ETIOLOGY OF THE HYPERADRENOCORTICISM OF AFFECTIVE DISORDERS

10.1. Disinhibition of the HPA axis

The current concept of the altered HPA status in affective disorders is essentially that of Gold *et al.* [82]: a hypothalamic dysfunction characterized by hypersecretion of CRH, the normal pituitary cells are simultaneously stimulated by CRH and inhibited by the negative feedback of increased cortisol levels due to enhanced adrenal sensitivity, possibly on the basis of adrenocortical hyperplasia. More recently this group [79] have suggested that excessive cortisol secretion in depression may result from, dysregulation at several sites within the HPA axis, the alterations in regulatory mechanisms being due to a "limbic system-hypothalamic overdrive" of CRH. However, it is difficult to see why the hypercortisolemia or adrenal hyperplasia should be maintained for a prolonged period in the presence of normal ACTH levels. Nor does this concept explain the marked similarity of depressive symptomatology in many cases of Cushing's syndrome (Table 1) where CRH levels are thought to be low.

If one tries to relate the depression of affective disorder to that of Cushing's syndrome, one must recognize that biochemically the two states differ in at least four respects: ACTH level,

CRH level, glucocorticoid receptor number and response of ACTH to CRH (Table 5). Similar mental states have been observed whether the ACTH level is high as in Cushing's disease or very low as in an adrenal tumor.

10.2. An alternative hypothesis

An alternative hypothesis is that the common factor in these conditions is at the steroid level rather than centrally. One possibility is that steroid production of metabolites becomes deranged in these states and that it is the steroid derangement which gives rise to the depression.

Let us suppose that, in major depression and in Cushing's disease, an adrenocortical stimulating factor other than ACTH is produced (see Section 9), which affects steroid metabolism such that certain steroids, including cortisol, are produced to a greater extent than normally, and that these steroids affect brain function producing the affective and cognitive abnormalities seen. Such a steroid pattern might also be produced by some adrenal tumors or by abnormal metabolism of administered steroids, the latter accounting for the occurrence of major depression in adrenalectomized patients and the occasional occurrence of depression after exogenous glucocorticoid administration.

An alteration in steroid pattern might account for the striking differences in behavior seen after administration of glucocorticoids (or ACTH) compared with those seen in endogenous states of hyperadrenocorticism (Tables 3 and 4), depression predominating in the endogenous state and euphoria in the exogenous. Indeed there is some evidence that cortisol metabolism is altered in a different way in these two states (Section 5).

Table 5. Comparison of non-psychiatric features of major depression with those of Cushing's disease

	Depression	Cushing's disease
Sex incidence F/M[a]	2:1	2:1
Incidence of DST non-suppression (%)	43	>90
Incidence of hypercortisolemia (%)	55	100
Relative mean increase in UFC excretion	2 times	4–10 times
Salivary cortisol	Increased	Increased
Cortisol production rate	Increased	Increased
Metabolic clearance rate	?	Normal
State dependence	Yes	Yes
CBG	? Normal	Normal
Physical stigmata	Absent	Present
ACTH levels	Normal	High
CRH levels in CSF	Increased	Decreased
Response of ACTH to CRH	Decreased	Increased
Diurnal rhythm	Present	Absent
GCR	Decreased	Normal

[a]F/M, female:male; DST, dexamethasone test; CSF, cerebrospinal fliud; CBG, corticosteroid-binding globulin. Data from the text.

Although a great deal of attention has been paid to the hypercortisolemia of depression, very little attempt has been made to study the other steroids produced by the overactive adrenal cortex. Yet these are numerous and some of them are known to affect brain function and behavior [147–153]. Some of these are also produced by the ovary which might also be affected by a factor altering steroid metabolism; stimulation of steroids produced by the ovary as well as the adrenal might account for the sex difference favoring women, as well as the accentuation of affective problems in the luteal phase of the menstrual cycle when ovarian steroid levels are high.

The affective symptoms appear to be state dependent in both major depression and Cushing's syndrome. In the latter disorder, alleviation of the depression usually accompanies the reduction in glucocorticoid levels; preliminary data in patients with major depression suggest that steroid suppressive agents may also alleviate endogenous depression. Thus, although there can be little doubt that the primary etiologic factor in major depression originates centrally, its manifestations and persistence may be dependent, at least in part, upon the resulting steroid milieu reaching the brain.

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