danger, however, that Addison's disease may be neglected as a diagnostic possibility, especially when pigmentation is not a feature on presentation, as in this case.

The pathophysiology of hyponatraemia in adrenal insufficiency is imperfectly understood.[2-4] There is little doubt, however, that it includes disordered secretion of antidiuretic hormone.[5] That this is not solely due to the response of the hormone to volume depletion was shown by the persistence of antidiuretic hormone secretion in the face of hyponatraemia in volume repleted adrenalectomised rats.[6] Ahmed *et al* postulated a direct effect of cortisol deficiency on the hypothalamus which served to potentiate the response to other stimuli.[2] In a sense, therefore, Addison's disease may be considered as merely another cause of "inappropriate" secretion of antidiuretic hormone, although the clinical importance of differentiating them is plainly critical. There have been no systematic studies of antidiuretic hormone concentrations in Addison's disease since the development of a precise immunoassay. The one other reported case was remarkably similar to ours in many respects, including the clinical presentation, tuberculous aetiology, degree of hyponatraemia, and magnitude of the rise in antidiuretic hormone concentration.[7] As this is only the second such case to be reported it is impossible to say whether tuberculous Addison's disease is more likely to result in this metabolic disturbance than is autoimmune adrenalitis. Ectopic production of antidiuretic hormone has been shown in lung affected by chronic caseous tuberculosis, and it is therefore possible that Addison's disease and ectopic production of antidiuretic hormone coexisted in these patients. Such ectopic hormone production, however, has never been shown in miliary disease. Although we failed to grow the acid fast bacillus, the radiological and pathological evidence and the rapid improvement in clinical state and markers of inflammation secure the primary diagnosis.

The patient described by Lever and Stansfield caused some alarm by suffering a relapse of hyponatraemia with raised antidiuretic hormone concentrations despite receiving replacement steroids. The authors were unable to account for this. Our experience and that of others, however, indicates that conventional replacement doses of steroids may not be adequate while the patient is taking rifampicin.[8] It is quite likely that the explanation for the relapse of hyponatraemia was simply inadequate steroid replacement. Although formal testing of adrenal function was not possible at presentation because of the prior administration of steroids, in retrospect it is possible to discern some clues to the presence of adrenal insufficiency. The slightly low blood pressure and the normal potassium and urea concentrations in the face of severe hypo-osmolality should perhaps have raised suspicion. Serum for cortisol estimation should have been reserved before hydrocortisone was given, despite the emergency nature of the treatment.

Further studies of antidiuretic hormone secretion in Addison's disease are necessary, but it remains vital to understand that in the investigation of hyponatraemia the finding of a raised antidiuretic hormone concentration does not exclude Addison's disease but may, in fact, represent a salient metabolic feature of this disease.

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## References

1 Irvine WJ, Toft AD. Diagnosing adrenocortical insufficiency. *Practitioner* 1977;**218**:539-45.
2 Ahmed ABJ, George BC, Gonzalez-Anvert C, Dingman JF. Increased plasma arginine vasopressin in clinical adrenocortical insufficiency and its inhibition by corticosteroids. *J Clin Invest* 1967;**46**:111-23.
3 Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of anti-diuretic hormone. *Am J Med* 1967;**42**:790-806.
4 Kleeman CR, Czaczkes JW, Cutler R. Mechanisms of impaired water excretion in adrenal and pituitary insufficiency: IV. Anti-diuretic hormone in primary and secondary adrenal insufficiency. *J Clin Invest* 1964;**43**:1641-8.
5 Linas SL, Berl T, Robertson GL. Role of vasopressin in the impaired water excretion of glucocorticoid deficiency. *Kidney Int* 1980;**18**:58-67.
6 Mandell IN, De Fronzo RA, Robertson GL, Forrest JN. Role of plasma arginine vasopressin in the impaired water diuresis of isolated glucocorticoid deficiency in the rat. *Kidney Int* 1980;**17**:186-95.
7 Lever EG, Stansfield SA. Addison's disease, psychosis, and the syndrome of inappropriate secretion of anti-diuretic hormone. *Br J Psychiatry* 1983;**143**:406-10.
8 Elansary EH, Earis JE. Rifampicin and adrenal crisis. *Br Med J* 1983;**286**:1861-2.

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# *For Debate . . .*

# Dexamethasone suppression test as a simple measure of stress?

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## Abstract

**Non-suppression of cortisol by dexamethasone has been described as a biological marker of a diagnostic subgroup of depressed patients. This paper presents the hypothesis that the degree of non-suppression is a variable that reflects the quantity of stress or distress experienced by the patient rather than relating to a specific diagnosis. Such a quantitative measure of stress would be valuable for research in general medicine as well as in psychiatry. Testing of this postulate should apply a more precise interpretation of endocrine principles than has been applied to the dexamethasone suppression test to date.**

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## Introduction

Serum cortisol concentrations may be raised by many factors causing stress or threats to homoeostasis.[1] Carroll claimed that though there is no consistent relation between corticosteroid concentrations and psychiatric conditions, a more dynamic test of the production of cortisol, the 1 mg dexamethasone suppression test, permits the delineation of a specific subgroup of depressed patients exhibiting melancholia.[2] The initial enthusiasm for this suggestion has been gradually tempered by caution.[3-5] The specificity of the dexamethasone suppression test has been questioned particularly in clinical circumstances in which diagnostic discrimination

is most required.[6,7] The presence of a high degree of non-suppression in diverse clinical conditions suggests that we should not speak of false positive results but should look more carefully for alternative explanations of this lack of suppression of cortisol by dexamethasone —for example, profiles of cortisol after administration of dexamethasone could be examined.[8]

## Stress and distress

Stress has been an elusive concept to define. We have followed the nomenclature of Selye[9] and Lazarus *et al*,[10] whereby stress is defined as the common biological response of the organism to a wide variety of endogenous or exogenous factors causing stress. Although factors causing stress and the response to them may be pleasant and wanted, we have limited our considerations to the components of distress. Some physical factors causing stress have been defined precisely[1] and the organism's response to these characterised by variables including effects on the hypothalamopituitary adrenal axis. The nature of the factors causing stress that engender physiological responses in psychiatric illness are less well known.

The severity of the specific stress associated with an illness might be related to the speed of onset of the illness, the degree of deviation from normality, the degree of subjective distress, the intensity or amount of treatment required, the degree or duration of residual disability, the disruption to life style, or to the person's perception of the condition. A simple global variable of severity, particularly one that is quantifiable, would remove some of the difficulties that have confronted researchers trying to relate previous events and patients' responses to them to the presence and degree of the illness.

We hypothesise that the dexamethasone suppression test may fulfil this purpose. Non-suppression of cortisol has been found with the dexamethasone suppression test in psychiatric patients with schizophrenia,[4,7] anorexia nervosa,[11] alcoholism,[12] dementia,[6] attacks of panic,[13] and mania.[14] We hypothesise that there is a dimension of non-specific distress (or stress) that may be a part of the clinical picture of any of these states and that the degree of this is reflected more sensitively in the results of a dexamethasone suppression test than in a single estimation of serum cortisol concentration. If this suppression test had been performed on patients with other physical illnesses a high degree of non-suppression might also have been found. Illnesses with rapid onset or that cause acute pain or threat to life would be expected to be associated with less suppression of cortisol than their opposites.

This dimension of stress would be moderately independent of diagnosis, though some disorders—for example, melancholia in psychiatry—would be associated with particularly high amounts of stress. The association of non-suppression of cortisol by dexamethasone with loss of weight,[15] sleeplessness,[16] suicidal intent,[17] severity of depression,[5,18] and starvation[11,19] is also consistent with its being a measure of the degree of disturbance.

## Pathophysiology

In discussing the dexamethasone suppression test (whether as a general phenomenon of stress or as a specific marker of depressive illness) researchers should consider the possible underlying pathophysiological variables.

Activation of the hypothalamopituitary adrenal axis by physical factors causing stress and the mechanism of the resulting feedback inhibition from raised cortisol concentrations have been reviewed in detail recently.[20] Some physiologically abnormal states such as hypoglycaemia and hypotension lead to suppression of the release of adrenocorticotrophic hormone when reapplied within a defined period. Others which are more commonly thought of as factors causing stress—for example, experimental incision of the skin, laparotomy, and electric shock—are followed by only partial inhibition. In these cases it has been postulated that the hypothalamus (or perhaps other higher centres) is fairly insensitive to the negative feedback effects of raised concentrations of glucocorticoids and provides an override of release of adrenocorticotrophic hormone and cortisol.[20] Not surprisingly, there are dosage effects: the greater the physical factor causing stress the greater the output of glucocorticoid. In addition, Keller-Wood *et al* discussed the loci of negative feedback effects and pointed out that the pituitary gland, in particular, has separate mechanisms subserving immediate (minutes), short term (hours), and long term (hours to days) feedback.[20] The drug dexamethasone may have greater access to[21] and an increased effect on[20,22] the pituitary gland than has the natural glucocorticoid.

The model for non-suppression of cortisol that we suggest here relates psychological stress to the known effects of physical factors causing stress on the hypothalamopituitary adrenal axis. We propose that in response to psychological or physical factors causing stress or in the presence of morbid distress production of cortisol is increased in parallel with the degree or quantity of that stress or distress. This effect may be subject to negative feedback (predominantly at the pituitary gland or higher centres), but such feedback would be only partially effective so that a subsequent challenge with dexamethasone would fail to reduce the plasma cortisol concentrations to the same extent as in normal subjects. Non-suppression of cortisol by dexamethasone is itself probably related to dose, with higher doses of dexamethasone leading to increased suppression,[5] and is probably also a measure of the balance between long term negative feedback effects from persistent increased secretion of cortisol and the override effects of the nature of the factor causing stress. We consider the effects of psychiatric and physical stress to be additive.

Analysis of data in relation to this hypothesis should consider the various forms of pulsatile and rhythmic release of cortisol in addition to negative feedback effects—for example, an increase in the secretion of cortisol might result from a raised basal secretion or from an increase in the pulse frequency of secretion or pulse height. There might be an altered interaction with pre-existing stimuli to pulsatile secretion such as occurs after eating, exercise, or stress.[23] There may be an alteration in the circadian rhythm with loss of the normal late evening trough or an alteration in the phase of other, longer rhythms of cortisol.[24]

Other studies have provided some support for these concepts. Kasper and Bechman specified an association of the dexamethasone suppression test with psychiatric stress in their discussion but did not provide further details of this.[18] Spar and LaRue and Klein *et al* commented that the most severely depressed of their patients were most likely to be non-suppressors.[25,5] Morris *et al* thought that suppression by dexamethasone probably depended on the dose.[26] Blumenfield *et al* described less suppression of cortisol by dexamethasone in air force recruits distressed by their training than in controls.[27] A significant correlation between the production of cortisol and "affective arousal" and "psychotic decompensation" was shown by Sachar *et al* in 1970.[28]

We had difficulty finding documented data to test our hypothesis, though some studies permitted comparison of cortisol concentrations and non-suppressibility with measures of severity.[11,17,19] For example, Holsboer *et al* studied mean plasma cortisol concentrations in serial samples taken at 20 minute intervals from 1400 to 1700.[8] This eliminated the imprecision associated with taking single samples of cortisol when secretion is pulsatile. By recalculating their data we derived the Kendall rank correlation coefficient ($\tau$)[29] and found a significant association ($\tau=0{\cdot}3$, $p=0{\cdot}03$) between the mean concentration of cortisol in 10 samples of plasma taken in the afternoon and the severity of the depression, as reflected by the Hamilton rating scale for depression. A weak association was seen between the Hamilton rating scale for depression and the concentration of cortisol at 1600 after suppression by dexamethasone ($\tau=0{\cdot}17$, $p=0{\cdot}087$). The strongest association, however, was between the cortisol concentration before suppression by dexamethasone and the concentration at 1600 after suppression ($\tau=0{\cdot}53$, $p=0{\cdot}00003$). No correlation was seen between the concentrations after suppression and the severity of depression when this association was taken into account (Kendall partial rank correlation coefficient, $\tau=0{\cdot}057$, p not calculable). These data suggest that depression can raise the basal concentration of cortisol at 1600 in a manner dependent on its severity and that the dexamethasone suppression test is only an indirect measurement of that effect.

We compared these results with similar data from 40 of our own depressed patients, using a single basal cortisol value at 1600, the Hamilton rating scale for depression, and the value at 1600 after suppression by dexamethasone. Although there was a correlation between the cortisol concentration at 1600 after suppression by dexamethasone and the Hamilton rating scale for depression ($\tau=0{\cdot}4$, $p=0{\cdot}00003$), there was not one between the basal (single point) concentration of 1600 and the Hamilton rating scale ($\tau=0{\cdot}07$, $p=0{\cdot}00003$).

A possible explanation for these findings is that the dexamethasone suppression test is a measure of the severity of depression itself or of the stress component of depression. This effect, however, is a secondary one, resulting from an increase in the cortisol concentrations in the afternoon. Pulsation of hormones introduces an error into the estimation of true cortisol concentrations from single random or timed specimens. Multiple samples obviate this problem. Suppression by dexamethasone presumably smooths the pulsation of hormones but cortisol concentrations are still proportional to the baseline mean value, exposing the relation that is lost in single non-suppressed samples.

## Conclusion

Acceptance of our hypothesis would require an examination of the basal secretion of cortisol with collection of urinary free cortisol or multiple plasma samples, plus an examination of rhythms of cortisol after treatment with dexamethasone, all in relation to

several clinical variables reflecting the degree of stress and distress in various psychiatric and physical disorders. Further analysis of the data on which many reports relating to the dexamethasone suppression test are based may provide support for this hypothesis, but definitive studies would need to be prospective and to compare results of dexamethasone suppression tests with the severity of disease. Many of the variables mentioned above such as loss of weight, degree of affective disturbances, and loss of sleep, would need to be included, in addition to measures of speed of onset, degree of deviation from previous state, perceived importance of the illness, and quantity of tissue damage, for example.

### References


1 Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. *Endocr Rev* 1984;5:25-44.
2 Carroll BJ. The dexamethasone suppression test for melancholia. *Br J Psychiatry* 1982;**140**:292-304.
3 Hirschfeld RM, Koslow SH, Kupfer DJ. The clinical utility of the dexamethasone suppression test in psychiatry. *JAMA* 1983;**250**:2172-5.
4 Berger M, Pirke K, Doerr P, Krieg J, von Zerssen D. The limited utility of the dexamethasone suppression test for the diagnostic process in psychiatry. *Br J Psychiatry* 1984;**145**:372-82.
5 Klein HE, Bender W, Mayr H, Niederschweiberer A, Schmauss J. The DST and its relationship to psychiatric diagnosis, symptoms and treatment outcome. *Br J Psychiatry* 1984;**145**:591-9.
6 McKeith IG. Clinical use of the dexamethasone suppression test in a psychogeriatric population. *Br J Psychiatry* 1984;**145**:389-93.
7 Mellsop GW, Cooke RR, Vijayasenan ME. The diagnostic distribution of non-suppressors. *Aust NZ J Psychiatry* 1985;**19**(No 2).
8 Holsboer R, Gerken A, Steiger A, Fass V. Mean 1400-1700 h plasma cortisol concentration and its relationship to the 1 mg—dexamethasone suppression response in depressives and controls. *Acta Psychiatr Scand* 1984;**69**:383-90.
9 Selye H. *Stress in health and disease*. London: Butterworths, 1976.
10 Lazarus RS, Baker RW, Broverman DM, Mayer J. Personality and psychological stress. *J Pers* 1957;25:559-77.
11 Doer P, Fichter M, Pirke KM, Lund R. Relationship between weight gain and hypothalamic pituitary adrenal function in patients with anorexia nervosa. *J Steroid Biochem* 1980;**13**:529-37.
12 Swartz CM, Dunner FJ. Dexamethasone suppression testing of alcoholics. *Arch Gen Psychiatry* 1982;**39**:1309-12.
13 Sheehan DV, Claycomb JB, Surman OS, Baer L, Coleman J, Gelles L. Panic attacks and the dexamethasone suppression test. *Am J Psychiatry* 1983;**140**:1063-4.
14 Graham P, Booth J, Boranga G, Galhenage S, Myers C, Teoh C, Cox L. The dexamethasone suppression test in mania. *J Affective Disord* 1982;**4**:201-11.
15 Edelstein CK, Roy-Byrne P, Fawzy FI, Dornfeld L. Effects of weight loss on dexamethasone suppression test. *Am J Psychiatry* 1983;**140**:338-41.
16 Mendlewicz J, Kerkhofs M, Hoffman G, Linkowski P. Dexamethasone suppression test and REM sleep in patients with major depressive disorders. *Br J Psychiatry* 1984;**145**:383-8.
17 Targum SD, Rosen L, Capodanno AE. The dexamethasone suppression test in suicidal patients with unipolar depression. *Am J Psychiatry* 1983;**140**:877-9.
18 Kasper S, Beckmann H. Dexamethasone suppression test in a pluridiagnostic approach: its relationship to psychopathological and clinical variables. *Acta Psychiatr Scand* 1983;**68**:31-7.
19 Smith SR, Bledsoe T, Chhetri MK. Cortisol metabolism and the pituitary adrenal axis in adults with protein calorie malfunctions. *J Clin Endocrinol Metab* 1975;**40**:43-52.
20 Keller-Wood ME, Dallman MF. Corticosteroid inhibition of ACTH secretion. *Endocr Rev* 1984;5:1-24.
21 de Kloet R, Wallach G, McEwen BS. Differences in corticosterone and dexamethasone binding to rat brain and pituitary. *Endocrinology* 1975;**96**:598-609.
22 McEwen BS, de Kloet R, Wallach G. Interactions in vivo and in vitro of corticoids and progesterone with cell nuclei and soluble macromolecules from rat brain regions and pituitary. *Brain Res* 1976;**105**:129-36.
23 Brandenberger G, Follenius M, Muzet A. Interactions between spontaneous and provoked cortisol secretory episodes in man. *J Clin Endocrinol Metab* 1984;**59**:406-11.
24 Simpson HW. A new perspective: chronobiochemistry. In: Marks V, Hales CN, eds. *Essays in medical biochemistry*. London: Biochemical Society, 1976;2:115-87.
25 Spar JE, LaRue A. Major depression in the elderly: DSM III criteria and the dexamethasone suppression test as predictors of treatment response. *Am J Psychiatry* 1983;**140**:844-7.
26 Morris HA, Gilliland JM, Berriman HE, *et al*. Assessment of the dexamethasone suppression test for endogenous depression. *Clin Biochem* 1983;4:82.
27 Blumenfield M, Rose LI, Richmond LH, Beering SC. Dexamethasone suppression in basic trainees under stress. *Arch Gen Psychiatry* 1970;**23**:299-304.
28 Sachar EJ, Hellman L, Fukushima DK, Gallagher TF. Cortisol production in depressive illness. *Arch Gen Psychiatry* 1970;**23**:289-98.
29 S Siegel. Nonparametric statistics for the behavioural sciences. Tokyo: McGraw-Hill Kogakusha, 1956.


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# *Philosophical Medical Ethics*

## Autonomy and the principle of respect for autonomy

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One part of the moral defence of Dr Arthur was that doctors should not impose their views on parents; rather, their role was to provide good expert advice concerning the various available options and then to support the parents in their decision, whatever that was, provided that the parents were not incompetent to decide and not acting maliciously. The claim rests implicitly on the principle of respect for people's autonomy. In this article I shall outline what is meant by autonomy and the principle of respect for autonomy.

### A definition

Autonomy (literally, self rule) is, in summary, the capacity to think, decide, and act on the basis of such thought and decision freely and independently and without, as it says in the British passport, let or hindrance. (The word is sometimes used to mean other things as well, for example, moral reflection,[1] but moral reflection seems to be only one aspect of autonomy of thought and I therefore think it best to confine these concepts.) In the sphere of action it is important to distinguish between, on the one hand, freedom, liberty, license, or simply doing what one wants to do and, on the other hand, acting autonomously, which may also be doing what one wants to do but on the basis of thought or reasoning. Animals are not said to have autonomy but they may be perfectly free (at liberty), in what might be called the thin sense of freedom or liberty, if they are not constrained, for example, by cages, drugs, or having their wings pulled off by little boys.

Autonomy is a subclass of freedom or liberty, but not all freedom or liberty is autonomy. The concept of autonomy incorporates the exercise of what Aristotle called man's specific attribute, rationality.

### Three types of autonomy

Autonomy is sometimes subdivided into autonomy of action, autonomy of will, and autonomy of thought.

*Autonomy of thought* embraces the wide range of intellectual activities that are called "thinking for oneself," including making

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