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Review Article

The Dexamethasone Suppression Test

Fact and Artefact

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It is claimed that the dexamethasone suppression test (DST) can be used in the diagnosis of depression, on the grounds that a positive test occurs in about half of patients with depressive illness but in few patients with other diagnoses. It is also variously claimed that a positive test is associated with particular types or features of depressive illness, that it is an index of severity, and that it can be used to predict outcome. Many of these claims appear in the literature, fail to be reproduced by others, but nevertheless become incorporated into a persistent body of unsubstantiated professional folk lore. The aim of this paper is to evaluate these claims, and to establish what use the test does have in the diagnosis and management of a depressive illness.

I. The DST in Psychiatry

(i) Method

A low dose of dexamethasone suppresses pituitary ACTH production, leading to suppression of plasma corticol levels for 24–48 hours. In most of the studies reviewed here, the dose of dexamethasone was 1 mg, though in earlier studies 2 mg was used; a 1 mg dose gave a higher non-suppression rate than 2 mg in two studies (Carroll *et al,* 1981a; Brown *et al,* 1983), but not in a third (Haier & Keitner, 1982). The hypothalamic–pituitary axis is said to be most sensitive to dexamethasone given between 10 pm and midnight, though administration at 7 pm did not affect non-suppression in the study of Pepper *et al* (1983).

Non-suppression of cortisol is defined as a post-dexamethasone cortisol level above a cut-off point or criterion value; it should be noted that the choice of this value is made on pragmatic grounds. Carroll *et al* (1981a), in their standardisation paper, found that a level above 5 μg/100 ml provided the best separation between depressed and non-depressed patients. They used a competitive protein binding assay (CPBA) for plasma cortisol, while Stokes *et al* (1984), who used a radioimmunoassay (RIA), found that either 3 μg/100 ml or 4 μg/100 ml gave the best discrimination.

Plasma cortisol assay methods have been reviewed in detail by Meltzer & Fang (1983); they concluded that results from CPBA and RIA—the two commonest methods—are not necessarily comparable, as different RIA methods may over- or under-estimate cortisol levels, as measured by CPBA. They suggest that any study on the DST should show that the cortisol assay method used is sensitive in the concentration range of interest, and that it is accurate by comparison with a reference method.

Studies reviewed here have used criterion values of between 4 and 6 μg/100 ml; one author (Sachar *et al,* 1980) has used 3 μg/100 ml. The risk with a lower value is that more false positives will be collected, and with a higher value that fewer depressed patients will be identified. However, because of variations in the accuracy of plasma cortisol assay methods, it may be appropriate for a cut-off point other than 5 μg/100 ml to be used in some studies.

Although the timing and number of plasma cortisol levels can affect the sensitivity of the test, many workers have for practical reasons used only a 4 pm sampling time. Using several sampling times, Carroll *et al* (1981a) found that the addition of an 11 pm level raised the detection rate of positive tests from 78% to 98%. However, Peselow *et al* (1983a) found that a 4 pm-only sample identified 92% of all positive tests, while Goggans *et al* (1983) picked up only 64% of positive tests at 4 pm. Use of a single 4 pm sampling time may therefore under-estimate the number of positive tests by a variable amount. For simplicity, no distinction will be made in this review between studies which report only a 4 pm level and those using additional sampling times.

(ii) Findings in depressive illness compared to controls

Most studies use established diagnostic criteria to

TABLE I
The DST in depressive illness

Source	*Diagnostic criteria*	*% Non-suppressors*		*P**	*Comments*
		Depressed	*Controls*		
Amsterdam *et al*, 1982	RDC	26%	15%	NS	outpatients
Coppen *et al*, 1983	RDC	70%	11%	<0.001	inpatients, 3 pm levels
Meltzer *et al*, 1982	RDC	55%	7%	<0.05	inpatients
Peselow *et al*, 1983b	RDC	23%	4%	<0.01	outpatients
Schatzberg *et al*, 1983	DSM III	48%	3%	<0.001	inpatients
Stokes *et al*, 1984	RDC	31%	10%	<0.001	inpatients, 8.30 am levels
		36%	27%	NS	inpatients, 4 pm levels
Winokur *et al*, 1982	RDC	8%	8%	NS	outpatients†

*(from χ^2 tests on authors' data)
†cut off was mean control value + 2 SD.

characterise their patient population. The main diagnostic systems used are the Research Diagnostic Criteria (RDC) of Spitzer *et al* (1977) or the earlier but related criteria of Feighner *et al* (1972). Recently, the third edition of the Diagnostic and Statistical Manual for Mental Disorders (American Psychiatric Association, 1980) (DSM III) has been in use. Some European authors have used the International Classification of Diseases (ICD) (World Health Organisation, 1980). All these systems define a broad category of depressive illness. Occasional studies have used their own diagnostic criteria, similar to the established diagnostic systems.

Populations of patients selected according to such diagnostic criteria may therefore differ widely from study to study and from centre to centre, depending on which system is used and on how the criteria are applied. Feinberg *et al* (1979) point out that the use of the RDC as a 'checklist' is likely to generate a very heterogeneous group of patients, and the same consideration applies to other diagnostic systems, if criteria are used to supplant clinical diagnosis rather than to refine it; this may account for a large part of the variation in non-suppression rate for depressed patients (Carroll, 1980).

Seven studies have reported on the DST in depressed patients with control data for comparison (Table I); all but two found a significant excess of non-suppression in the depressed group, with rates tending to be higher in inpatient populations. One study of normal females (Hallstrom *et al*, 1983) found a non-suppression rate of 19%.

(iii) Findings in other psychiatric conditions

Non-suppression rates comparable to those reported in depressed patients have been found in mania (Graham *et al*, 1982), in schizo-affective disorder (Greden *et al*, 1981a; Meltzer *et al*, 1982), and in chronic schizophrenia by Castro *et al* (1983) and Dewan *et al* (1982), though not by Coppen *et al* (1983) or Stokes *et al* (1984). Confounding factors in the assessment of these reports include the presence of acute psychosis, which may affect plasma cortisol levels (Sachar *et al*, 1970) and concomitant depressive symptoms which are associated with non-suppression in manic patients (Evans & Nemeroff, 1983; Stokes *et al*, 1984).

Demented patients are frequently non-suppressors (Balldin *et al*, 1983; Raskind *et al*, 1982; Spar & Gerner, 1982), though again, an association with depression is suggested (Carnes *et al*, 1983; Katona & Aldridge, 1984).

In neurotic illnesses, non-suppression rates are no different from control rates for anxiety states (Coppen *et al*, 1983; Curtis *et al*, 1982; Lieberman *et al*, 1983; McIntyre *et al*, 1981; Sheehan *et al*, 1983) or for depressive neuroses in the studies of Carroll *et al* (1976b, 1981a). Insel *et al* (1982) found 38% of a small group of patients with obsessive–compulsive disorder to be non-suppressors; several of these had depressive symptoms, though none was judged to have a primary depressive illness.

(iv) Non-specific factors which might affect non-suppression

(a) *Stress of hospital admission.* Connolly *et al* (1968) found a high non-suppression rate in non-acute medical and surgical patients in a general hospital, while Kalin & Shelton (1984) reported that acute behavioural stress could partially over-ride

dexamethasone suppression of plasma cortisol in monkeys. Roy-Byrne *et al* (1984) found a higher non-suppression rate in psychiatric patients tested on 1–2 days after admission, than in patients tested on days 4–6, but this was not statistically significant. The differential between depressed and non-depressed inpatients is maintained in most studies, though admission could simply be experienced as more stressful by depressed patients. The non-suppression rate is generally lower in outpatients than inpatients (Amsterdam *et al*, 1982; Peselow *et al*, 1983b; Winokur *et al*, 1982). Outpatient studies tend to include fewer endogenous patients and less severely depressed patients, and to sample at only 4 pm, which may lower the detection rate. However, Carroll *et al* (1980a; 1981a) has found a high non-suppression rate in outpatients with melancholia, using 4 pm samples.

(b) *A history of treatment with antidepressant or other psychotropic drugs.* Carroll *et al* (1976b) did not find this to affect non-suppression rates, and Holsboer *et al* (1982) showed non-suppression persisting through the first few weeks of antidepressant and neuroleptic treatment. Langer *et al* (1979) and Tosca *et al* (1982) have suggested that benzodiazepines can lower plasma cortisol and thereby increase the suppression rate, but there is insufficient detail in these reports to decide the question. Greden *et al* (1983) have shown that the test returns to normal before clinical improvement. Overall, therefore, previous treatment would be likely to increase the false negative rate, rather than produce false positive results.

(c) *Age.* A positive correlation of non-suppression with age has been reported (Asnis *et al*, 1981a; Brown & Qualls, 1981; Coryell *et al*, 1982a), but was not found by Carroll *et al* (1981a); Tourigny-Rivard *et al* (1981) found no increase in non-suppression in elderly controls. The association with age may be an artefact of the later age of onset of depressive illness, compared to reactive depression.

(d) *Metabolism of dexamethasone.* Significantly lower plasma dexamethasone levels were found in depressed non-suppressors after 17 hours by Holsboer *et al* (1984), but not by Carroll *et al* (1980b), who concluded that there was no increase in dexamethasone clearance in their endogenously depressed patients. Increased clearance, secondary to hepatic enzyme induction, may account for the non-suppression seen in alcoholics and for false positive results in patients on high dose oestrogens (Hallstrom *et al*, 1983).

(e) *Weight loss.* Patients with anorexia nervosa who have stable low body weight are frequently non-suppressors (Doerr *et al*, 1981; Fichter *et al*, 1982; Gerner & Gwirtsman, 1981). So are bulimics (Hudson *et al*, 1983; Gwirtsman *et al*, 1983) who have normal body weight, so that it may be in part the metabolic aspects of eating disturbances which give rise to non-suppression. Active loss of weight in normal or obese subjects (Berger *et al*, 1983; Doerr *et al*, 1981; Edelstein *et al*, 1983) produces non-suppression. Targum (1983a) and Berger *et al* (1983) have reported an association of non-suppression with weight loss in depressed patients, but Coppen *et al* (1984) did not find this.

II. The DST and Clinical Picture in Depressive Illness

A. Endogenous depression

There is a certain appeal in the notion that an abnormal DST might be an index of hypothalamic dysfunction, linked to the syndrome of 'endogenous depression', where this is loosely conceived as a severe illness with vegetative symptoms likely to respond to physical methods of treatment. Although the term 'endogenous' is correctly used to refer to states which are not reactive to, in the sense of being caused by, external events, it is the wider usage which finds expression in the diagnostic systems in current use.

(i) Definitions of endogenous depression

The endogenous sub-type of the RDC major depressive disorder and the DSM III criteria for melancholia both confine themselves to symptoms of the present illness. The main emphasis is placed on features of depressed mood such as lack of reactivity and diurnal variation, with subsidiary emphasis on the presence of guilt, of vegetative symptoms such as weight loss, and psychomotor change. This definition of endogenous depression remains neutral with respect to the question of precipitation and *excludes* considerations of pre-morbid adjustment and past history. It constitutes a symptom picture considered by Spitzer *et al* (1977) to be associated with a good response to physical treatment.

The Newcastle Scale (Carney *et al*, 1965) incorporates a slightly different sub-set of features, but still embraces the wider concept of endogenous

TABLE II
The DST in endogenous depression

Source	*Diagnostic criteria*	*% Non-suppressors*		*P**	*Comments*
		Endogenous	*Non-Endogenous*		
Ames *et al*, 1984	Newcastle	39%	30%	NS	
Berger *et al*, 1982	ICD-8	25%	21%	NS	1.5 mg dexamethasone
Brown & Shuey, 1980	RDC	66%	16%	<0.025	2 mg dexamethasone
Carroll *et al*, 1976b	'Endogenomorphic'	48%	2%	<0.000001	non-endogenous group includes other psychiatric diagnoses
Carroll *et al*, 1980a	Clinical diagnosis	40%	2%	<0.0001	
	RDC prob. & defin.	42%	0%		
Coppen *et al*, 1983	Newcastle	81%	49%	<0.001	dexamethasone given at 8 pm sample at 3 pm
Coryell *et al*, 1982b	DSM-III	27%	40%	NS	some 9 am only tests
Evans *et al*, 1983	DSM-III	67%	63%	NS	
Feinberg & Carroll, 1982	Discriminant index	43%	11%	<0.05	20% of 'uncertain' cases were non-suppressors
Giles & Rush, 1982	RDC	44%	4%	<0.001	outpatients
Holden, 1983	Newcastle	73%	11%	<0.001	
Jaffe *et al*, 1983	DSM-III	42%	0%	<0.023	outpatients
Kasper & Beckman, 1983	ICD 9	52%	20%	<0.01	8 am sample only
	Newcastle	51%	23%	<0.05	
McIntyre *et al*, 1981	Newcastle	51%	4%	<0.001	no cut-off value given
Meltzer *et al*, 1982	RDC	30%	67%	NS	
Meltzer *et al*, 1983	RDC	36%	55%	NS	
Peselow *et al*, 1983b	RDC	25%	19%	NS	outpatients
Rabkin *et al*, 1983	RDC	18%	14%	NS	included minor depressive disorder
Rush *et al*, 1982	RDC	41%	5%	<0.0003	outpatients
Stokes *et al*, 1984	RDC	28%	47%	NS	8.30 am sample only
	DSM-III	24%	35%	NS	Multi-centre trial

*χ^2 on authors' data

depression. Like the American criteria, it gives weight to weight loss, depressive psychomotor activity, and guilt, but in addition, gives positive weight to adequacy of premorbid personality, to the occurrence of a previous episode, and also to nihilistic delusions. The absence of precipitation is not a factor, though weight is given to the absence of psychological stress adequate to account for the perpetuation of symptoms. Negative weight is given to the presence of anxiety and to the tendency to blame others.

The concept of 'endogenomorphic' depression (Klein, 1974) has influenced American diagnostic practice. The central feature here, regardless of whether or not precipitants are present, is a pervasive loss of the ability to experience or anticipate pleasure, from which the effects on appetite and libido follow. This 'anhedonia' was strongly emphasised by Carroll *et al* (1980a) in their clinical diagnosis of endogenous depression. Criteria here were psychotic features, guilt, psychomotor change, and past psychiatric and family history. Less weight was given to vegetative symptoms and lesser degrees of cognitive and affective disturbance, and none to psychogenesis, anxiety, and inadequate personality, as these were regarded as occupying a separate dimension of neurotic features. In a later study, this group (Feinberg & Carroll, 1982) devised a discriminant index for endogenous depression, modelled on the Newcastle Index, with which it showed some overlap. Thus, in their later work, this group seem to be moving closer to the British concept of endogenous depression.

(ii) Findings in endogenous depression

Using one or more of these sets of criteria for

endogenous depression, 20 studies have compared the non-suppression rates in endogenous and non-endogenous patients. Results are given in Table II: 12 studies found a significant increase in non-suppression rate among endogenous patients. The Newcastle Scale shows the best differentiation from non-endogenous patients, in that four out of five studies using the Newcastle Scale found a significant difference between endogenous and non-endogenous patients. This compared with three studies by Carroll's group, all of which found a significant difference, although non-suppression rates among non-endogenous patients were lower than in the studies using the Newcastle Scale. In contrast, only four out of nine studies using the RDC for the endogenous sub-type found a significant difference, and one out of four studies using DSM III criteria for melancholia. One study using ICD 8 found no difference, whereas one using ICD 9 did find a difference. Studies which have used more than one set of criteria find good agreement between them, suggesting that within centres, there is a fairly consistent view of what endogenous depression is, so that the same patients tend to be classified as endogenous by different sets of criteria. Another important reason for differences between groups is the nature of the base population: if mildly depressed outpatients are used, there is likely to be a different population of endogenous patients than if severely depressed inpatients, refractory to treatment and referred to a tertiary centre, are studied. Although use of uniform diagnostic criteria clearly does not ensure comparability of patient populations between centres, nevertheless some criteria for endogenous depression do identify a population of patients showing a higher rate of non-suppression than non-endogenous patients. The criteria employed by the Newcastle Scale and by Carroll's group seem more successful at identifying such patients than the present-state criteria of the RDC, DSM III, and ICD.

It is interesting to consider whether this higher non-suppression rate in endogenous depression might be due to a link with a particular symptom or symptoms. There are reports of an association of non-suppression with agitation and retardation, weight loss and 'endogeneity' (Agren & Wide, 1982), with sleep disturbance, libido and cognitive symptoms (Reus, 1982) and with the Hamilton Rating Scale Factor 4, 'somatic complaints' (Kasper & Beckmann, 1983). Coppen *et al* (1983) found post-dexamethasone cortisol to be significantly correlated with Newcastle score, when the Hamilton score was partialled out. All these studies included non-endogenous patients, however. Three studies which looked at endogenous patients only found no relationship between specific endogenous symptoms and non-suppression (Aggernaes *et al*, 1983; Asnis *et al*, 1982; Nelson *et al*, 1982). Only one paper (Kasper & Beckmann, 1983) acknowledges the need for correction of the significance level (alpha-correction) when multiple comparisons are made, and the significance levels reported in the other papers would almost all fail to survive alpha-correction. There is no evidence so far to support the existence of an association between dexamethasone non-suppression and specific symptoms of depression, therefore.

(iii) Severity of depression and the DST

One reason for the association of non-suppression with endogenous depression could be that endogenous patients are more severely depressed. Of five studies which report such a relationship, three have not distinguished between endogenous and non-endogenous patients in their sample, rendering it difficult to disentangle 'endogeneity' and severity (Brown *et al*, 1979; Davis *et al*, 1981; Holsboer *et al*, 1980). Two studies (Aggernaes *et al*, 1983; Kasper & Beckmann, 1983) found a relationship when endogenous patients only were studied. One group failed to replicate their original finding of an association (Carroll *et al*, 1968; Carroll & Davies, 1970).

In contrast, four studies find no relationship between non-suppression and severity. Giles & Rush (1982) found no association in either endogenous or non-endogenous patients. Targum *et al* (1983) found no difference in DST results between more or less severely depressed patients, and neither did Coppen *et al* (1983), using partial correlation to control for the effects of the Newcastle score on plasma cortisol. Comparing melancholic and non-melancholic patients, Carroll *et al* (1981a) found no difference in severity of depression.

Carroll *et al* (1976a) have suggested that more severely depressed patients escape from suppression earlier in the day. In patients followed with serial tests, both Holsboer *et al* (1982) and Greden *et al* (1983) found a relationship of post-dexamethasone plasma cortisol levels and Hamilton scores. When the relationship is sought within patients over time, removing the variance due to individual differences, the evidence so far does suggest a relationship between cortisol level and severity, therefore.

B. Other classifications of depressive illness

Failure to detect any association between non-suppression and individual symptoms might arise

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partly from an irreducible difficulty in measuring symptoms, coloured as these may be even within endogenous depression by the patient's personality and by the clinical picture as a whole. Study of other clinical sub-groups of depression might be more sensitive in detecting links between non-suppression and clusters of symptoms *in re naturae*.

(i) Primary and secondary depression

A number of authors (e.g. Brown *et al*, 1979; Charles *et al*, 1981; Coryell *et al*, 1982b) have found a low non-suppression rate in 'secondary depression'. Clearly, much depends on the composition of this secondary depression group, which under some circumstances might contain a high proportion of neurotic patients with depressive symptoms, who would be likely to be suppressors.

(ii) The unipolar–bipolar classification

As used in the American literature, this classification includes non-endogenous patients. Although some papers give low non-suppression rates for bipolar patients (Meltzer *et al*, 1982; Papakostas *et al*, 1981; Rothschild *et al*, 1982; Schatzberg *et al*, 1983), others have shown no difference from unipolar patients (Mendelwicz *et al*, 1982; Stokes *et al*, 1984; Targum, 1983b); two studies (Asnis *et al*, 1982; Schlesser *et al*, 1980) found a higher rate in bipolar patients. The numbers of bipolar patients are small (less than 10) in many of these studies. This classification does not help to identify non-suppressors, therefore.

(iii) Psychotic depression

A higher non-suppression rate in psychotic depression has been found by some authors (Asnis *et al*, 1982; Caroff *et al*, 1983; Mendelwicz *et al*, 1982; Rudorfer *et al*, 1982; Schatzberg *et al*, 1983), but not by Coryell *et al* (1982a and b) or Evans *et al* (1983). This apparent association might be explained by the presence in the psychotic group of more endogenous and more severely depressed patients, who would be more likely to be non-suppressors, the non-psychotic group containing the more mild reactive depressions. Three studies looked exclusively at endogenous depression, but two (Asnis *et al*, 1982; Caroff *et al*, 1983) included patients with secondary depression. Rudorfer *et al* (1982) looked at endogenous patients with primary depression only. High plasma cortisol levels were considered by Sachar *et al* (1970) to be linked to psychotic decompensation in depressed patients. However, the evidence does not so far support a straightforward association of non-suppression and psychotic depression.

(iv) Family history

Unfortunately, the question whether non-suppression is associated with a positive family history in the depressed patient has become entangled with attempts to validate the problematic typology of Winokur *et al* (1978). Several studies show a higher non-suppression rate in the familial pure depression disease (FPDD) sub-type (Schlesser *et al*, 1980, 1981; Targum *et al*, 1982; Coryell *et al*, 1983; Rush *et al*, 1982), although there is lack of agreement on the rate of non-suppression in the sporadic depressive disease (SDD) and depression spectrum disease (DSD) sub-types. Some smaller series have failed to find any difference between the sub-types, possibly because of the small numbers in each sub-group (Amsterdam *et al*, 1982; Asnis *et al*, 1982; Carroll *et al*, 1980c; Kasper & Beckmann, 1983), while Rudorfer *et al* (1982) found the highest non-suppression rate in the SDD group. An association with positive family history is suggested by the evidence, but is not unequivocally supported.

C. Relationship to outcome

(i) Relationship to clinical course

A number of studies claim to find persistent non-suppression in patients who do not improve. However, the number of unimproved patients in these studies is small compared to the number of those who improve, which may reflect some under-reporting of unimproved patients. Five studies looked at change in DST with clinical improvement (Albala *et al*, 1981; Brown & Shuey, 1980; Coryell *et al*, 1983; Greden *et al*, 1983; Papakostas *et al*, 1981). In total, nine out of 16 'non-normalisers', but five out of 36 'normalisers' were unimproved ($\chi^2 = 11.79$, $P < 0.001$ for the pooled data). This suggests an association between the presence of symptoms and the presence of non-suppression, but no more than this.

In their systematic study of the course of 'normalisation' of the DST during antidepressant treatment, Greden *et al* (1983) found a gradual fall in post-dexamethasone plasma cortisol levels, which correlated with clinical improvement; return to normal suppression occurred before or during the week of improvement. Similar findings are reported by Holsboer *et al* (1982). There are case reports of

non-suppression in mixed manic-depressive states, returning to normo-suppression on recovery (Krishnan *et al*, 1983; Evans & Nemeroff, 1983), and of a return to normal suppression in bipolar patients who 'switch' into mania (Carroll *et al*, 1976a; Schaffer, 1982; Schlesser *et al*, 1980). Greden *et al* (1982), who reported weekly DSTs in three rapid-cycling bipolar patients, found that non-suppression occurred either within or during the week on either side of the depressive episodes.

Persistent non-suppression has been suggested to predict relapse. Several studies have reported a worse outcome after discharge in persistent non-suppressors, compared to patients who returned to normo-suppression (Greden *et al*, 1980; Papakostas *et al*, 1981; Targum, 1983b; Yerevanian *et al*, 1983), though a better course in persistent non-suppressors was found by Coryell & Zimmerman (1983). In total, there was a poor outcome in 21 out of 31 non-normalisers, compared to 17 out of 55 normalisers ($\chi^2 = 10$, $P < 0.01$ for the pooled data). From this, it does appear that persistent non-suppression is associated with later re-emergence of symptoms, but factors connected with discharge may crucially affect this. Relapse might be due to premature discharge, e.g. from a busy research unit or in cases where medical insurance covers only a limited hospital stay. Length of stay was only reported by Yerevanian *et al* (1983) and was short (23.7 ± 6.8 days). There is probably under-reporting of the fate of unimproved patients, which suggests that such patients are lost to follow-up through being transferred elsewhere. There is little information on other factors affecting relapse rate, such as the prescribing of maintenance antidepressants after ECT. Data on the outcome for suppressors, which would provide some control for these factors, are lacking.

(ii) Prediction of treatment response

Non-suppressors have been said to have both a good response (Brown *et al*, 1979, 1980) and a poor response (McLeod *et al*, 1970; McIntyre *et al*, 1981) to treatment. Treatment was uncontrolled in these studies, two of which included reactive or secondary depressions, which may have biased results. No difference between suppressors and non-suppressors was found with adequate doses of tricyclics (Amsterdam *et al*, 1983; Extein *et al*, 1982–3; Green & Kane, 1983) or with a variety of treatments (Ames *et al*, 1984).

A preferential response among non-suppressors to 'noradrenergic' antidepressants (desmethylimipramine, imipramine) and among suppressors to 'serotoninergic' antidepressants (amitriptyline, clomipramine) has been claimed (Brown *et al*, 1980), but larger studies have not confirmed this (Greden *et al*, 1981b; Nelson *et al*, 1982; Peselow & Fieve, 1982). A similar claim has been made by Beckmann *et al* (1984) for a preferential effect in non-suppressors of nomifensine, a 'dopaminergic' antidepressant.

Care is necessary in evaluating such claims, especially when the numbers of patients are small. Occasional positive findings may be explained by a good response to treatment of the endogenous patients in the sample, who will tend to be the non-suppressors.

(iii) Prediction of suicide

There is an apparent association of non-suppression and suicide, suggested by the reports of Greden *et al* (1980), Yerevanian *et al* (1983), and Papakostas *et al* (1981), who between them found five suicides among 18 non-normalisers, with no suicides among the normalisers. Carroll *et al* (1981b) reported that successful suicide was linked to abnormal DST results in their unit, but give insufficient detail for evaluation of this claim.

Targum *et al* (1983) found that among endogenously depressed patients, 14 out of 17 who had made a suicide attempt were non-suppressors, compared with nine of 32 non-suicidal patients ($\chi^2 = 11.02$, $P < 0.001$). The suicidal patients, however, were more severely depressed, and although non-suppression and severity were not found in this study to be linked, severity of depression may nevertheless (as discussed above) be a factor in determining non-suppression. The most economical explanation, therefore, is that since non-suppression and suicide are both linked to the presence and severity of depressive symptoms, both will tend to occur together; non-suppression is not strictly a predictor of suicide, but is associated with the continuation of a condition in which suicide is a risk.

Discussion

It is frequently asserted that the DST is a 'diagnostic test' or laboratory marker for endogenous depression. What this claim amounts to is that, allowing for methodological differences and variations in patient populations, most of the published data suggest that non-suppression is commoner in patients who meet criteria for endogenous depression. The reason for this is unclear; although post-dexamethasone plasma cortisol and severity are correlated in some studies, within endogenous patients, severity alone seems insufficient to account for the excess of non-suppression among them.

There is no good evidence to support an association of non-suppression with particular depressive symptoms, and the most robust association demonstrated so far is with the presence of illness. The association, so far as it exists, with such features of endogenous depression as psychotic symptoms, treatment response, and suicide is best seen as a consequence of prior association with endogenous depression.

How should the results reviewed in this paper be interpreted, therefore? Either non-suppression in depressive illness is a result of some physiological disturbance underlying endogenous depression, or it is a secondary feature of the illness.

Carroll (1982) has suggested that the dexamethasone test is comparable to serum acid phosphatase levels in carcinoma of the prostate, for instance, implying that the cause of the abnormal test reflects the cause of the disease. This analogy must not be taken too far or too literally, for it prematurely elevates the diagnosis of depressive illness from the syndromal to the clinicopathological category, but whether depressive illness can be said to belong to this latter category is precisely the question which is being explored by research in this field.

Indeed, there is not so far any evidence for a pathological process occurring in endogenous depression, for which non-suppression is a 'marker'. The test merely represents a statistical abnormality, related to the presence of illness, whose significance for the patient remains unclear. Non-suppression has been reported to occur in about 50% of depressed patients who 'hypersecrete' cortisol (Asnis *et al,* 1981b; Sachar *et al,* 1980; Stokes *et al,* 1984; Sherman *et al,* 1984). However, this degree of hypersecretion itself has no well-established pathological consequences for the individual, although depressed patients may rarely be described as Cushingoid, and it is not even clear whether hypersecretion is the parent abnormality to non-suppression.

There have been attempts to explain non-suppression as an indicator of under-function of cholinergic systems (Carroll *et al,* 1978) or of overfunction of noradrenergic systems (Jimerson *et al,* 1982) in the hypothalamus, and thus tie the test up to biochemical theories of depression. A review of this work is outside the scope of the present article, but it may be observed that current biochemical theories of depression, while intuitively appealing and intensely investigated, have yet to produce any well-supported predictions. Such theories remain speculative, and cannot offer much solid support for the notion of the DST as a marker of disturbed monoamine function.

There is no good reason so far, therefore, to justify the view that the DST is a marker for any underlying pathological process in depressive illness. The ability to measure precisely plasma hormone levels encourages the belief that neuroendocrine tests are thereby more fundamental and somehow nearer the putative neurophysiological abnormality than less precisely quantified behavioural or cognitive variables. Belmaker (1984) has pointed out the absurdity of taking what is just a peripheral variable as a biological marker for behaviour, and we do not talk for instance of early morning waking as a 'marker' for depressive illness.

What may be more informative, though not necessarily more fundamental, is the dynamic testing of the processes underlying neuroendocrine function. Perhaps we should regard abnormal plasma cortisol control as just another symptom, like sleep disturbance, but one which we are fortunate enough to be able to subject to a dynamic test with an easily measured end-point. Just as with other symptoms of endogenous depression, the question whether non-suppression is a manifestation of supposed underlying pathology or is a secondary phenomenon, remains undecided by the evidence so far. The way would then be clearer for a study of the weight which should be attached to this new symptom in the diagnosis of endogenous depression—an approach in fact suggested by Carroll (1980) but so far not adopted in any published study.

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