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COMPARISON OF PLASMA CORTISOL AND CORTICOSTERONE IN THE DEXAMETHASONE SUPPRESSION TEST FOR MELANCHOLIA

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SUMMARY

The suppression of plasma corticosterone (B), measured by radioimmunoassay (RIA), was compared to simultaneous suppression of plasma cortisol (F), measured as total corticoids by a competitive protein binding (CPB) assay, in the overnight dexamethasone suppression test (DST). Baseline plasma B concentrations in 10 control subjects were 4.04 ± 1.07 ng/ml (X ± S.D.) at 0800 hr and 1.51 ± 0.68 ng/ml at 1600 hr. Post-dexamethasone 1600 hr B levels in the controls were 0.46 ± 0.29 ng/ml. An early escape of plasma B (> 1.2 ng/ml), like that of F (> 5 μg/dl), during the overnight 24 hr 1.0 mg dose DST was noted in patients with melancholia (endogenous depression).

Half-hourly catheter samples in a normal subject stimulated to escape from dexamethasone suppression showed that in general, plasma B concentrations parallel plasma F concentrations over a 12 hr period. Repeated weekly DSTs on two patients with different psychiatric diagnoses resulted in B : F correlations of 0.74 and 0.60. Overall agreement between B- and F-DST outcomes in all categories tested at 1600 and 2300 hr was 93%; the agreement in the melancholic and non-endogenous depressed groups was 100%.

Post-dexamethasone, both B and F were suppressed 55 – 60% below the criterion level in controls. In those patients who escaped from dexamethasone suppression, the percentage increase in plasma B above the criterion level was significantly greater (+55%) than the corresponding percentage change in plasma F. Most patients with borderline abnormal F-DSTs (3.5 – 4.9 μg/dl) exhibited clearly abnormal B-DSTs (> 1.2 ng/ml). We conclude that the use of dexamethasone suppression of plasma B (using 1.2 ng/ml as the abnormal criterion value) is an additional indicator of an abnormal DST in depressed patients.

Keywords—Cortisol; corticosterone; dexamethasone suppression test; hypothalamic – pituitary – adrenocortical system; melancholia; depression.

INTRODUCTION

PATIENTS with endogenous depression (melancholia) frequently have disinhibited activity of the hypothalamic – pituitary – adrenocortical (HPA) system. This disinhibition is seen most specifically in the dexamethasone suppression test (DST) of HPA function. Abnormal DST results may be useful in the diagnosis of melancholia (Carroll *et al.*, 1976a; 1976b; 1981; Brown *et al.*, 1979; Schlesser *et al.*, 1980; Carroll, 1982). When oral dexamethasone is given at 2300 – 2400 hr, normal subjects maintain plasma cortisol (F) suppression below 5 μg/dl for at least the next 24 hr. Patients with melancholia may suppress their plasma F concentrations temporarily, but they often fail to maintain

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plasma F suppression below 5 μg/dl for 24 hr. The abnormal escape of plasma F concentration usually occurs by 1600 hr and may be observed as early as 0800 hr (Carroll *et al.*, 1976a; 1976b; 1981; Carroll, 1982).

In melancholia the secretion rate of the 'minor' human glucocorticoid, corticosterone (B), is increased to a similar extent as that of cortisol (F) (Gibbons, 1966). Both F and B are produced in similar regions of the adrenal cortex, and both are modulated by the HPA system, i.e. regulated by ACTH (Krieger, 1979; Harding, 1979). Studies in humans (Oddie *et al.*, 1972; Nabors *et al.*, 1974; Matsumura, 1980) reported 70–90% suppression of both B and F 4–8 hr post-dexamethasone (Table I). More importantly, both these studies, and *in vitro* studies as well (Kahri *et al.*, 1979), revealed that the rate of B secretion or percentage increase in B levels is 2–3 times greater than that of F in response to adrenal stimulation by endogenous or exogenous ACTH.

We have investigated plasma B and F concentrations during the DST to determine whether plasma B concentrations give the same diagnostic information for melancholia as plasma F. Knowing the differential responses of plasma B and F to ACTH, we checked particularly to see if plasma B more accurately assessed those patients with borderline abnormal F-DST values (3.5–4.9 μg/dl) (Carroll *et al.*, 1981).

METHODS

Patients were studied at the Clinical Studies Unit, Department of Psychiatry, University of Michigan, where they received diagnostic evaluations as described previously (Carroll *et al.*, 1976a; 1976b; 1980; 1981). For the diagnosis of melancholia, we required agreement between the clinical assessment and the Research Diagnostic Criteria (RDC) (Spitzer & Endicott, 1975). All other diagnoses were made according to the RDC. The reliability of these diagnoses was high (kappa 0.80). Severity of depression was recorded by the Hamilton Rating Scale (HRS) (Hamilton, 1960), with a coefficient of variation among raters of 6%. The DST was performed as described by Carroll *et al.* (1981). An oral dose of dexamethasone (1.0 mg) was given at 2300 hr; blood samples obtained the following day at 1600 hr in 112 tests and at 2300 hr in 26 tests were selected for the simultaneous assay of B and F concentrations.

Ten normal, drug-free subjects with no current psychiatric disorder were tested with blood samples obtained at 0800 and 1600 hr pre-dexamethasone and 1600 hr post-dexamethasone. We studied a total of 25 patients from several diagnostic groups, as listed in Table II. We used repeated DSTs obtained over time from many individual patients. Thus, the focus of this study was the comparative suppression of F and B rather than the diagnostic sensitivity and specificity of the two steroids in a large group of patients.

For the study of borderline abnormal F-DST results, we searched our stored plasma samples for 8 cases in which the F concentration post-dexamethasone was between 3.5 and 5.0 μg/dl. Plasma samples had been kept at 0°C for six months to one year, with no detectable changes in either B or F concentrations over this time. For this study we used samples obtained in any previous DSTs, regardless of whether the time of collection was 0800, 1600, or 2300 hr (Table III). The following additional studies were performed: (1) a venous catheter study was carried out by measuring plasma concentrations of F and B at 30 min intervals for 12 hr in one normal subject. To elicit an escape of plasma F post-dexamethasone, L-DOPA (100 mg) was administered intravenously (Haskett *et al.*, unpublished results). (2) Longitudinal studies of serial DSTs at weekly intervals over four to seven months were run on two outpatients (J.L.B. and L.S.T.), and the corresponding 1600 hr plasma F and B concentrations were compared.

Determination of plasma F and B

Plasma F was measured as total corticoids by a modified competitive protein binding (CPB) method of Murphy (1967), with inter- and intraassay coefficients of variation of 11 and 4%, respectively. An ultra-micro scale Murphy CPB assay system was used, with 2.0% human serum as the source of corticosteroid binding globulin (CBG). The standard curve was run in triplicate at concentrations of 0, 0.5, 1.0, 2.0, 5.0, 10.0, 15.0 and 20.0 ng cortisol per 0.2 ml of ethanol. All solvents were redistilled in our laboratory, and the water was of HPLC quality. ^{3}H-Corticosterone was used as the radioactive ligand in the binding solution. The binding solution consisted of 5 ml of normal human serum, 1.0 ml of 1,2-^{3}H-corticosterone (10 μCi/ml and 50-60 Ci/mmol), 1.5 ml ethanol, and water to make a volume of 250 ml. Thus the working concentration of the tracer was

0.04 μCi/ml. Care was taken in preparing the binding solution so as not to precipitate the serum proteins when adding the ethanol and the tracer. The binding solution was incubated at 4°C for at least 24 hr prior to use and was stable for 10 days. Duplicate aliquots of a 1 : 2 ethanolic extract of patient's heparinized plasma were used for the first assay of every sample. The sample extracts and standards were taken to dryness under an air stream in a 45°C water bath. Quality control (QC) samples (treated as patient plasmas) were always included at low, intermediate and high concentrations (2.9, 5.1 and 10.2 μg/dl). In each assay no more than 141 tubes (stds, QC or patient samples) were included. One millilitre of binding solution was added to each assay tube. The tubes were mixed and incubated at 45°C for 10 min, then transferred to an ice-bath (4°C) for 20 min. Approximately 40 mg of predried florisil (magnesium silicate) then was added to each tube. The tubes were shaken for 2 min and then placed back into the ice bath for 10 min. The florisil absorbed all unbound cortisol, leaving the bound ligands in solution. The tubes next were centrifuged (2000 g, 2°C, 6 min) and 0.5 ml of clear supernatant was transferred to a scintillation vial. Extreme care was taken during this step, so as not to pipette any florisil from the bottom of the tube. Four millilitres PPO/POPOP scintillation cocktail was added to each vial. The vials were shaken and counted to 20,000 cpm or 7 min, whichever came first. Under these conditions, as stated by Murphy (1967), time to count is linear with respect to concentration. Quench correction was not necessary, due to the ethanol extraction and the extraction of the tracer into the scintillation cocktail.

When the first determined patient value was > 3 and < 7 μg/dl, the sample was re-assayed with three varying sized aliquots of the ethanolic extraction to provide at least two separate and duplicate estimates on the steep portion of the binding curve. The mean of these four is reported. While this double-checking often is redundant, it improves the precision of the assay in this critical range.

The assay for plasma B was based on the most recent procedure and antiserum (B3-163) obtained from Endocrine Sciences (Tarzana, CA). The antiserum was used at a dilution of 1/64,500, and the standard curves ranged from 0 to 750 pg/tube. Interfering steroids (e.g. F and progesterone) were removed by extraction of the plasma (300 μl) into hexane : benzene (80 : 20, v/v) and then hexane : benzene (20 : 80, v/v). Triplicate tubes with either standards or plasma extracts were incubated at room temperature for 2.5 hr in a mixture containing 0.05 M borate buffer (pH 8.0), 1,2-(^{3}H)corticosterone, 60 Ci/mmol (New England Nuclear, No. NET-182), 10% bovine serum albumin (Schwarz/Mann, No. 751), 0.5% bovine gamma globulin (Schwarz/Mann, No. 3004), and antiserum. To determine non-specific binding to the assay tubes, triplicate tubes likewise were incubated in a similar buffer solution without antiserum. The two-step organic extraction procedure minimized nonspecific protein binding from the plasma samples. Saturated ammonium sulfate was added to separate the bound from the free B, and the free fraction then was extracted and counted. Final values were calculated with correction for the recovery of labelled B, which averaged 60.35% (S.E. 1.93%) through the entire method. The cross-reactivity of the antiserum to cortisol, progesterone and dexamethasone was 0.4, 0.6 and 0.05%, respectively. The extraction procedure removed 92.1% of the cortisol, 85% of the progesterone and 68% of the dexamethasone. Thus, in the assay system an original plasma F concentration of 100 ng/ml (10 μg/dl) would cause negligible displacement of tritiated corticosterone, equivalent to 0.03 ng/ml. The interfering effects of other steroids similarly were negligible. The inter- and intra-assay coefficients of variation were 19 and 8%, respectively, as determined by analysis of pooled human sera at concentrations above and below the 50% binding of the standard curve. The lower limit of sensitivity of the assay was 0.2 ng/ml. Due to the high interassay variation, patient samples were randomized into 10 different assays. All longitudinal and catheter studies were analyzed in single assays.

The half-lives of B and F in plasma during the 12 hr venous catheter study were determined as described by Carroll (1972).

Statistical analysis

Statistical comparisons between experimental groups were evaluated by Students *t*-test (two-tailed). Sensitivity and specificity results were calculated according to standard conditional probability principles (Vecchio, 1966; Galen & Gambino, 1975).

RESULTS

Normal subjects

The 0800 hr baseline plasma B values in the normal subjects (Table I) agreed well with previous studies in which morning B plasma concentrations ranged from 2.4 ng/ml (Kobayashi *et al.*, 1979) to 6.1 ng/ml (Matsumura, 1980). No sex difference in the plasma B or F concentrations was noted within controls or among the various experimental

groups (data not shown). The marked difference between the 0800 and 1600 hr baseline plasma B values agrees with the report of Nabors *et al.* (1974).

After dexamethasone there was a clear suppression of plasma B concentrations (Table I). Though measured at 1600 instead of 0800 hr, the post-dexamethasone plasma B values and the percentage suppression (70%) agree closely with other studies (Meikle *et al.*, 1974; Nabors *et al.*, 1974).

TABLE I. PLASMA CORTICOSTERONE CONCENTRATIONS IN NORMAL SUBJECTS PRE- AND POST-DEXAMETHASONE

Reference	Baseline X ± S.D.	(*n*)*	Time†	Post-dexamethasone‡ X ± S.D.	(*n*)*	Time†
Current	4.04 ± 1.07	(6)	0800	Not determined		
Study	1.51 ± 0.68	(10)	1600	0.46 ± 0.29	(10)	1600
Oddie *et al.* (1972)	4.20 ± 0.90	(17)	0900	Not determined		
Kobayashi *et al.* (1979)	2.40 ± 4.02	(20)	0930	Not determined		
Meikle *et al.* (1974)	4.76 ± 3.00	(11)	0800	0.47 ± 0.15	(11)	0800
Nabors *et al.* (1974)	5.25 ± 2.50	(30)	0800	0.46 ± 0.16	(11)	0800
Matsumura (1980)	6.10 ± 2.70	(9)	0900	1.80 ± 0.50	(9)	0400

*Values are expressed in ng/ml ± S.D.
†Indicates time of blood sampling.
‡Dexamethasone (1.0 mg) was given orally to subjects in all studies at 2300 hr of the preceding night.

12-Hour catheter study

Plasma concentrations of F and B post-dexamethasone were measured at 30 min intervals for 12 hr in a normal subject who had received dexamethasone (1 mg) the previous day at 2300 hr (Fig. 1). L-DOPA (100 mg) was administered intravenously over 15 mins to elicit an escape of plasma F (Haskett, *et al.*, unpublished results). There was a marked similarity in the concurrent secretion of B and F after L-DOPA. Between 1415 and 1615 hr, the percentage escapes of F and B compared to their suppressed baselines (1000 to 1400 hr) were 380 and 500%, respectively. In addition to this differential escape, the plasma half-lives of clearance following the secretory episodes differed, as determined on the five points between 1515 and 1630 hr, being 50.2 and 33.5 min for F and B, respectively.

Patient groups

We compared the plasma B and F results in a total of 112 DSTs. In all tests the 1600 hr post-dexamethasone blood sample was obtained. In 26 tests we also obtained the 2300 hr post-dexamethasone sample. Thus, we compared the B and F suppression response in a total of 138 post-dexamethasone blood samples (Table II). Using the plasma F result, the criterion value of an abnormal DST result was > 5 μg/dl. For the plasma B result we set a criterion value > 1.2 ng/ml, as suggested by Meikle *et al.* (1974).

Overall, the DST results by the two criteria agreed in 128 of 138 comparisons (93%). Eight of the 10 disagreements occurred in patients with rapidly cycling bipolar affective disorder. In the two other disagreements (one schizo-affective and one non-endogenous depression), the F-DST result was borderline abnormal (see below). At the 1600 hr sampling time there was 100% agreement for normal subjects, melancholic patients, non-

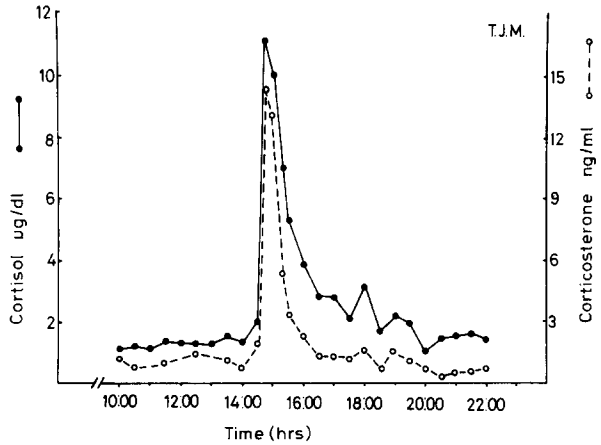

FIG. 1. Plasma F (– –) and B (O– –O) levels from 30 min catheter samples in a normal subject. Dexamethasone (1.0 mg) was given orally at 2330 hr the preceding night, and L-DOPA (100 mg i.v.) was given at 1425 – 1440 hr. The B – F correlation coefficient was 0.90.

TABLE II. AGREEMENT OF CORTICOSTERONE AND CORTISOL DST RESULTS*

Group (*n*)	1600 hr Agreements/tests	(% Agreement)	2300 hr Agreements/tests	(% Agreement)
Normal subjects (10)	10/10	(100%)	—	—
Melancholia (5)	32/32	(100%)	8/8	(100%)
Rapid cycling bipolar patients (4)	40/48†	(83%)	1/1	(100%)
Mixed manic-depressive (4)	8/8	(100%)	4/4	(100%)
Non-endogenous depression (4)	5/5	(100%)	4/5‡	(80%)
Schizoaffective (4)	4/5‡	(80%)	4/4	(100%)
Borderline personality disorder (4)	4/4	(100%)	4/4	(100%)
Overall (25)	103/112	(92%)	25/26	(96%)
Total	128/138 (93%)			

*DST plasma B results (abnormal B-DST > 1.2 ng/ml) were compared to corresponding plasma F results (abnormal > 5 μg/dl).

†The disagreements were six, normal B-DST, abnormal F-DST; two, normal F-DST, abnormal B-DST.

‡The disagreement was normal F-DST, abnormal B-DST.

endogenous depressives, mixed manic-depressives, and patients with borderline personality disorder.

Borderline abnormal F-DSTs

From previously reported studies of the F-DST (Carroll *et al.*, 1981; Fig. 3) the plasma F range of 3.5 – 4.9 μg/dl can be considered as borderline or transitional between definitely normal and definitely abnormal results. Table III lists the results of all post-dexamethasone samples (n = 8) in which the F values were borderline abnormal. In seven of these eight cases, the B concentrations clearly were elevated. Additionally, in the cases where the 0800 hr B value indicated an abnormal DST and F was borderline abnormal (Patients Nos. 1, 2, 6 and 7), the subsequent 1600 hr F values also indicated an abnormal DST (> 5 μg/dl) (data not shown).

TABLE III. PLASMA CORTISOL AND CORTICOSTERONE CONCENTRATIONS IN SIX PATIENTS WITH BORDERLINE ABNORMAL DSTs*

Patient No.	Sex	Time	Plasma cortisol (μg/dl)	Plasma corticosterone† (ng/ml)
1	F	0800	3.65	1.95
2	M	0800	3.71	1.55
3	F	1600	4.50	2.92
4	M	2300	3.88	1.94
5	F	1600	4.78	1.51
6	F	0800	4.51	1.92
7	M	0800	4.50	1.46
8	F	1600	4.80	1.14

*Post-dexamethasone (1 mg at 2300 the preceding night) plasma F concentrations of 3.5 – 4.9 μg/dl constitute a borderline abnormal DST.

†Normal post-dexamethasone plasma B is less than 1.2 ng/ml (Meikle *et al.*, 1974).

Longitudinal outpatient studies

Two patients were studied with repeated DSTs over four and seven months, respectively (Figs. 2 and 3). The Pearson product-moment correlation between the 1600 hr post-dexamethasone plasma B and F concentrations for the 18 tests in JLB (Fig. 2) was 0.74 and for the 17 tests in LST (Fig. 3) it was 0.60.

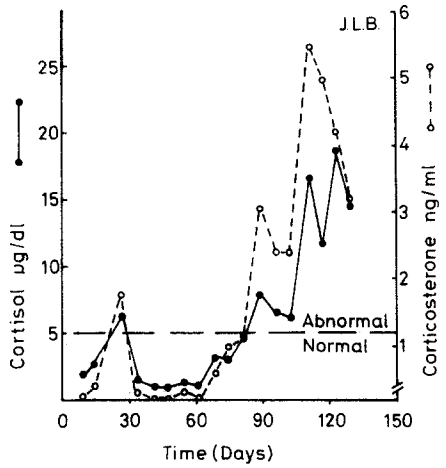

FIG. 2. Plasma F(– –) and B(O– –O) 1600 hr levels from repeated weekly outpatient DSTs on a melancholic outpatient. The overall B – F correlation was 0.74, and the agreement of the B : F DST outcome was 100% (18/18).

Patient JLB was a woman with bipolar II affective disorder who developed a severe depression each year in the spring and in the autumn. During the study shown in Fig. 2 and for four weeks before the study began she was taking lithium carbonate (1200 mg/day) and tranylcypromine (90 mg/day) continuously. A direct drug effect on the hormone concentrations therefore was considered unlikely, since both F and B changed in

parallel and lithium causes only a brief (< seven days) alteration in mineralocorticoid secretion. The study began in July 1981, as she was recovering from her spring depression. Eighteen consecutive DSTs with 1600 hr blood sampling were performed. A single abnormal result (by both B and F criteria) was observed in the first 11 tests. The next three consecutive abnormal tests that occurred just before and then after day 90 actually preceded the sudden onset of her next depression in mid-October, 1981. In these tests, as in the final four of the study when she was severely depressed, the plasma B elevation was proportionately much greater than the rise in plasma F values. Nevertheless, the 1600 hr DST results by both B and F criteria were in agreement for all 18 tests.

Patient LST was a woman with rapidly cycling bipolar affective disorder. The HRS scores in Fig. 3 illustrate seven brief episodes of depression during the seven months she was studied. When the HRS scores were low this patient was usually hypomanic, sometimes mildly manic. She was treated with lithium carbonate (2100 mg/day) from day 15 until the end of the study. The four normal F-DST results we observed occurred at times of low HRS depression ratings. Abnormal F-DST results during the first 120 days of the study occurred either with or just before a switch to high depression ratings (see Greden *et al.*, 1982). During the second half of the study, her recurrent depressive episodes were attenuated, but abnormal F-DST results continued.

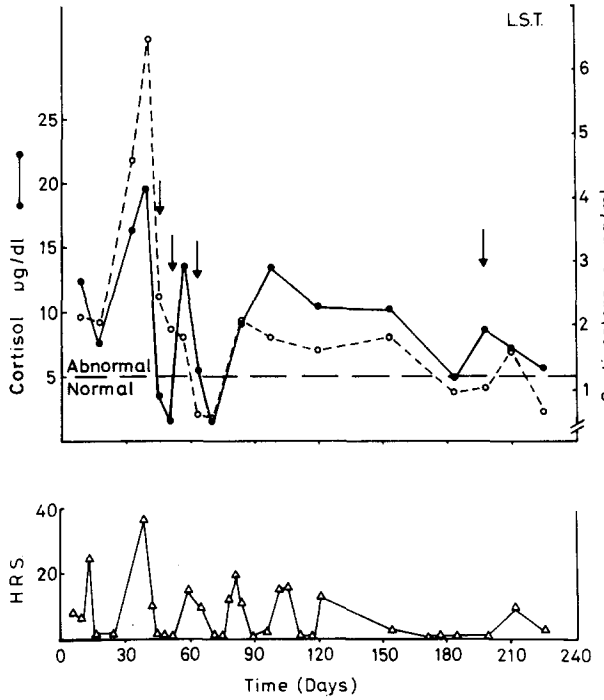

FIG. 3. Plasma F (– –) and B (O– –O) 1600 hr levels from repeated outpatient DSTs and the corresponding clinical phase data by Hamilton Rating Scale (HRS) on a rapid cycling patient. Arrows indicate disagreements of B- and F-DST results. The overall B – F correlation was 0.60, and the agreement of the B : F DST outcome was 77% (13/17).

In this patient, four of the 17 tests (indicated by arrows in Fig. 3) gave discordant results. In two instances, B was elevated but F was not, while the reverse pattern was seen in the other two tests. These discrepancies are included with the others in Table II (rapid cycling bipolar patients).

Comparison of B and F deviations from criterion values

The mean plasma B and F values found in normal and abnormal DSTs are shown in Fig. 4 in relation to the corresponding criterion values (B = 1.2 ng/ml; F = 5 μg/dl; n = 174). No significant differences were noted between B and F in normal DSTs, in which mean B and F levels were suppressed below the criterion values by 55 and 60%, respectively. In the abnormal tests, the magnitude of B increase (+210%) was significantly greater than the corresponding increase in F levels (+135%) ($p < 0.005$). This finding agrees with all other studies that report the differential relative responses of B and F to adrenal stimulation (Oddie *et al.*, 1972; Nabors *et al.*, 1974; Kahri *et al.*, 1979; Matsumura, 1980), and is in agreement with the results in Fig. 1.

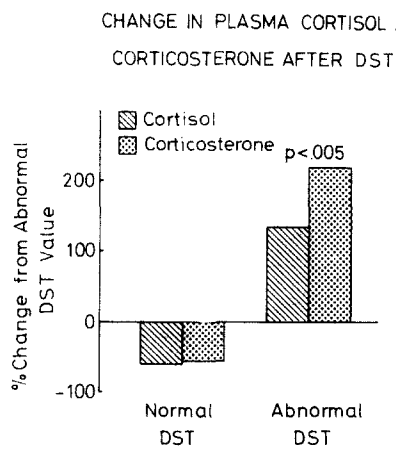

FIG. 4. These results are the cumulation of all normal (n = 76) and abnormal (n = 68) 0800, 1600 and 2300 hr samples (from 23 patients). Percent deviation from abnormal DST criterion value was determined by comparing individual samples with the corresponding F and B criteria values of 5 μg/dl and 1.2 ng/ml, respectively. DST percent deviation values were significantly different between B and F using a Student's t-test (two-tailed, df = 140, $P < 0.05$). There was no significant difference between the percent deviation in B and F in a normal DST.

DISCUSSION

There is a variety of techniques presently used to measure plasma concentrations of B. Reported values of 0800 hr plasma B in humans range from as low as 2.4 ng/ml (enzyme immunoassay, Kobayashi *et al.*, 1979) to as high as 6.1 ng/ml (radioimmunoassay, Matsumura, 1980). Plasma B levels reported here were determined using a single antibody radioimmunoassay with a two-step pre-extraction into benzene, sensitive down to 0.2 ng/ml, and lacking major interfering cross-reactions. Our data confirm other reports showing that (1) there was no sex difference in plasma B concentrations at any time; (2) dexamethasone suppressed plasma B concentrations by 70–90% (Meikle *et al.*, 1974;

Nabors *et al.*, 1974; Matsumura, 1980); (3) B was secreted in an episodic manner along with F (Nabors *et al.*, 1974); (4) the proportionate increase of plasma B was greater than that of plasma F over suppressed values in response to adrenal stimulation (Fig. 1) (Oddie *et al.*, 1972; Nabors *et al.*, 1974; Kahri *et al.*, 1979; Matsumura, 1980); and (5) the half-life of clearance of B from plasma is more rapid than that of F following a secretory episode (Fig. 1) (Brooks *et al.*, 1972; Nabors *et al.*, 1974). In addition, we have shown that baseline afternoon plasma B concentrations in normal subjects are lower than morning values (Table I).

The parallel secretion of B and F is shown in Fig. 1, where L-DOPA was administered to stimulate the HPA axis pharmacologically (Haskett *et al.*, unpublished results). Though the significance of this effect of L-DOPA is not to be addressed in this paper, this catheter study illustrates the parallel secretion and control of B and F secretion by ACTH. It also demonstrates the greater response of B to ACTH and the more rapid clearance of B after the secretory episode.

Meikle and associates (1974) reported that in patients with Cushing's Syndrome either a 50% decrease of the baseline B value or a criterion plasma B concentration of 1.2 ng/ml post-dexamethasone indicated non-suppression. The results in Table II show that by using the criterion value of 1.2 ng/ml, plasma B can be used to accurately identify depressed patients with abnormal DSTs. The DST results given by the plasma F and B criteria agreed in 93% of 138 comparisons (Table II). The apparent specificity of the B-DST in this small number of patients was 95%. This figure is based on the results in normal subjects and nonendogenous depressives, where 19 of 20 results were normal (Table II). The reported specificity of the F-DST in a much larger population is 96% (Carroll *et al.*, 1981). At the same time, the sensitivity of the B-DST may prove to be somewhat higher than that of the F-DST, since in seven of eight cases where the F result was borderline abnormal (3.5 – 5.0 μg/dl), the B result was definitely elevated.

Similarly, in the longitudinal studies of individual patients (Figs. 2 and 3), there was generally good agreement between the DST results by both the plasma F and the plasma B criteria. In subject JLB (Fig. 2) the results agreed in all 18 tests. In the rapidly cycling bipolar patient (Fig. 3) the DST results disagreed in four of 17 tests. This group of patients contributed almost all the disagreements noted in Table II. In fact, if this group were to be excluded, then the B-DST : F-DST agreement in the other groups of patients in Table II would be 98% (87 of 89 tests). We do not know why the rapidly cycling bipolar patients should have had such a high frequency of disagreements (eight of 49 comparisons, or 16%; Table II).

When the DST is performed in psychiatric patients only two or three post-dexamethasone blood samples are drawn in a 24 hr period (Carroll *et al.*, 1981). Since the secretion of corticosteroids is episodic, single blood samples may be taken by chance either at the peak or at the trough of a secretory episode. In principle, therefore, the differential proportionate secretion and the differential rate of clearance of B and F may be used to advantage in this context. Since B is secreted more vigorously than F, a weak pulse of ACTH could raise the plasma B concentration above the criterion value, whereas the plasma F concentration is raised only to the range of borderline abnormal values, especially if the blood sample is drawn early in a secretory episode. In Fig. 1, for example, definitely abnormal plasma B concentrations of 3 – 6 ng/ml would have been found

before the plasma F concentration reached the criterion value of 5 μg/dl on the ascending portion of the secretory episode. The results in Table III support this possibility.

Similarly, blood samples drawn at the end of a secretory episode could yield normal B concentrations but abnormal F concentrations, especially if the respective rates of clearance of the two steroids differed more widely than in the subject shown in Fig. 1. Overall, we observed eight examples of the first type of B-F disagreement and six examples of the second type (Tables II and III). We suggest that these disagreements are due to the physiological mechanisms mentioned above.

Recently, Holsboer *et al.* (1982a; 1982b) also reported on plasma B responses in the DST with depressed patients. They measured several adrenal steroids (F, B, 11-deoxycortisol, 11-deoxycorticosterone and cortisone) and concluded that elevated concentrations of several adrenal steroid products occurs in depressed patients during the DST, sometimes before elevated F values. In particular, they found that high ratios of F : 11-deoxycortisol or B : 11-deoxycorticosterone often are present, and interpreted these elevated ratios to indicate excessive stimulation of the adrenal cortex by ACTH. Thus, measurement of the full spectrum of adrenal corticosteroid secretion in depression may improve the sensitivity of the DST even further than by simply measuring F and B responses.

In summary, plasma B concentrations may be used instead of plasma F concentrations in the DST for melancholia. The specificity and sensitivity appear to be similar for each steroid. The DST results agreed in 93% of 138 comparisons involving normal subjects and several groups of patients. Since the two measures agreed so well overall, we would not propose that plasma B concentrations be measured in all DSTs on psychiatric patients. For practical purposes, plasma B could be measured only in cases where the F-DST result was borderline abnormal (plasma F concentration 3.5 – 5.0 μg/dl). A high plasma B concentration in such cases would be of potential diagnostic value for melancholia. If the plasma F value itself is high, then no further diagnostic information will be obtained from the plasma B value.

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