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Concurrent Use of REM Latency, Dexamethasone Suppression, Clonidine, and Apomorphine Tests as Biological Markers of Endogenous Depression: A Pilot Study

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Abstract. In a sample of 12 major depressive inpatients, endogenous subtype (8 primary and 4 secondary) defined by Research Diagnostic Criteria, we compared the sensitivity of four potential biological markers: latency of rapid eye movement (REM) sleep (recorded during at least 4 consecutive nights), dexamethasone suppression, and the clonidine and apomorphine tests. Shortened REM latency (less than 50 minutes during at least 1 night) identified 67% of depressives (87% of primary and 25% of secondary); nonsuppression after dexamethasone identified 50% of depressives (62% of primary and 25% of secondary); blunted growth hormone (GH) response after clonidine identified 75% of depressives (100% of primary and 25% of secondary); and blunted GH response after apomorphine identified 42% of depressives (62% of primary and 0% of secondary). Ninety-two percent of patients were correctly identified by at least one biological marker (100% of primary and 75% of secondary depressives). Of 67% of patients positive on at least two biological markers, all were primary depressives (100%). These four biological markers do not necessarily identify the same population, suggesting that their concurrent use may yield the highest level of diagnostic sensitivity.

Key Words. Endogenous depression, rapid eye movement (REM) latency, dexamethasone suppression test, clonidine test, apomorphine test, biological markers.

For the last 10 years, two potential biological markers of endogenous depression have aroused increasing interest: the latency of rapid eye movement (REM) sleep and the dexamethasone suppression test (DST). REM latency (RL) seems specifically shortened in primary endogenous depressives (for review, see Kupfer, 1976; Kupfer et al., 1983) and about 50% of endogenous depressives exhibit an abnormal "escape" after dexamethasone intake (for review, see Carroll, 1982). More recently, the growth hormone (GH) response after clonidine (an adrenergic agonist) and after apomorphine (a dopaminergic agonist) has been found to be blunted in endogenous depressives (Matussek et al., 1980; Ansseau et al., 1982).

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It is probable that these potential biological markers, the mechanisms of which seem quite different, do not identify the same population of depressive patients, as suggested in recent studies with concurrent use of RL and DST (Berger et al., 1982; Blumer et al., 1982; Feinberg, 1982; Rush et al, 1982).

The purpose of this study was threefold: (1) to compare the sensitivity of RL in the diagnosis of endogenous depression with that of three neuroendocrine markers: dexamethasone suppression, clonidine, and apomorphine tests; (2) to determine if these biological markers identify the same patients; and (3) to estimate the sensitivity of their concurrent use.

Methods

Subjects. The sample was composed of 12 inpatients newly admitted to the Psychopharmacology Unit of the University Hospital of Liège, Belgium. Patients met Research Diagnostic Criteria (RDC) for major depressive disorder, endogenous subtype (Spitzer et al., 1978) and *DSM-III* for major depressive episode with melancholia (American Psychiatric Association, 1980). They also had a score of at least 6 on the Newcastle endogenicity scale (Carney et al., 1965) and at least 21 on the entire Hamilton Depression Scale (Hamilton, 1960) at the end of a 14-day drug washout period. All evaluations were performed by two independent research psychiatrists who used semistructured interviews and were unaware of laboratory results.

The sample included 9 males and 3 females, aged 28 to 61 years (mean = 48.7 ± 11.6). Patients were classified as primary (n = 8; aged 39 to 61; mean = 54.2 ± 7.7) or secondary (n = 4; aged 28 to 53; mean = 37.7 ± 10.7), according to RDC. Individual sex, age, and diagnosis are displayed in Table 1. Two patients were bipolar I, and a third was delusional.

Patients were free of medical illness, as evidenced by history, physical examination, electrocardiogram, electroencephalogram, chest x-ray, and routine laboratory tests. They had also been free of any medication for at least 2 weeks at the time of the study. Subjects spent 6 consecutive nights in the sleep laboratory, following which they underwent clonidine, apomorphine, and dexamethasone suppression tests (in that order), with at least 3 days between each procedure. Neuroendocrine tests were performed randomly during the menstrual cycle in premenopausal female patients (#10 and #12).

Sleep Recordings. Polygraphic sleep recordings were performed for six consecutive nights with a paper speed of 10 mm/second and included 6 bipolar EEG leads (F_3C_3, C_3P_3, P_3O_1, F_4C_4, C_4P_4, P_4O_2), horizontal and vertical electro-oculograms, and chin electromyogram. Recordings were visually scored independently by two trained observers according to the criteria of Rechtschaffen and Kales (1968). Sleep onset was defined by the first epoch (30 seconds) of Stage II and RL by the time between sleep onset and first REM period (3 minutes). Intermediate wakefulness (between sleep onset and first REM period) was not excluded.

For the first five patients, the first 2 nights (considered as habituation nights) were not recorded; however, for all subsequent patients, all nights were recorded and analyzed.

DST. The DST was performed according to the simplified procedure described by Carroll et al (1981): oral intake of dexamethasone, 1 mg (administered by a nurse), at 11 p.m. and blood collection (10 cc) at 4 p.m. on the following day. Cortisol was measured by radioimmunoassay (Sulon et al., 1978).

Clonidine and Apomorphine Tests. Both tests were performed according to the same procedure: at 7 a.m. after an overnight fast, an indwelling catheter was inserted in a forearm vein. Blood samples of 10 cc were collected every 20 minutes for 40 minutes before and 120 minutes after injection at 8 a.m. of either of the following: clonidine, 0.15 mg, diluted in saline to

Table 1. Sample of endogenous depressives and individual results: REM latencies during 6 consecutive nights, cortisol after DST and GH peak level after clonidine and apomorphine tests

#	Sex	Age	P/S	U/B	PS	REM latency (minutes)						Cortisol after DST (μg/dl)	GH after CLO (ng/ml)	GH after APO (ng/ml)
						1	2	3	4	5	6			
1	M	54	P	Bi		—	—	0	2.5	0	0	2	3.5	2.1
2	M	60	P	U	+	—	—	447	27	175	265.5	12.3	2.3	3.6
3	F	61	P	U		—	—	111.5	9.5	0	7.5	8.9	1.6	2.7
4	M	39	P	U		91	80	152.5	—[1]	163	116	< 2	1.7	2.2
5	M	61	P	Bi		39.5	34	2.5	16.5	84.5	52.5	5.6	1.8	2.4
6	M	55	P	U		87	82	38	53.5	29.5	55	< 2	1.6	35.1
7	M	57	P	U		32	182	55.5	15.5	25	127.5	8.4	0.7	9.7
8	M	47	P	U		179.5	194	339.5	72	17	135	21.6	3.9	10.4
9	M	53	S	U		—	—	87	52	55	55.5	< 2	13.2	27
10	F	36	S	U		—	—	262.5	88.5	58.5	68.5	< 2	1.8	18.5
11	M	28	S	U		51	60	63	91.5	82	57.5	26.3	10.5	44.1
12	F	34	S	U		29	33.5	40.5	35.5	34	32.5	< 2	12.8	14.5

P/S = primary/secondary; U/B = unipolar/bipolar; PS = psychotic; GH = growth hormone; DST = dexamethasone suppression test; CLO = clonidine; APO = apomorphine.

1. No REM period during this night.

obtain 20 cc, intravenously in 10 minutes; or apomorphine, 0.5 mg, diluted in saline to obtain 0.5 cc, subcutaneously.

GH was measured by radioimmunoassay (Franchimont, 1968). Test results were included if basal GH level (T_0) was below 5 ng/ml, and were analyzed from GH peak values following injection.

Cutoff Values. A cutoff RL of 50 minutes or less was chosen. This value, proposed by Kupfer (1976), gave a sensitivity of 95% and a specificity of 100% for endogenous depression when applied to a sample of endogenous depressives, neurotic depressives, and controls (Kupfer et al., 1983). It is also the cutoff value used by Berger et al. (1982, 1983) to diagnose endogenous depression in studies in which no healthy volunteer experienced any night with shorter RL.

Nonsuppression after DST was defined as a cortisol level higher than 5 μg/dl, based on the data published by Carroll (1982) showing that application of this criterion to a single 4 p.m. blood sample yielded a sensitivity of 57% and a specificity of 96% in endogenous depressive inpatients. The cutoff GH peak following clonidine or apomorphine challenge was defined as 5 ng/ml. In studies of Lal et al. (1975) and Matussek et al. (1980), 25 of 45 (55%) clonidine tests performed in normal volunteers and 8 of 12 tests (67%) performed in neurotic depressives stimulated a GH response higher than 5 ng/ml compared to only 1 of 10 (10%) in endogenous depressives. All seven controls (100%) tested with apomorphine (0.5 mg) presented GH responses higher than 5 mg/ml (Rotrosen et al., 1976). Moreover, individual GH peaks following apomorphine, 0.75 mg, published to date were higher than 5 ng/ml in 114 of 121 normal subjects (94%) (review in Ansseau et al., 1982).

Data Analysis. According to Vecchio (1966), the diagnostic sensitivity of each potential biological marker corresponds to the percentage of depressives exhibiting abnormal values, as defined by the cutoff limit.

The correlations between the four biological markers in identifying endogenous depressives were assessed using the Kappa statistic, treating the four markers as four raters and their "interrater" reliability reported as a measure of test similarity.

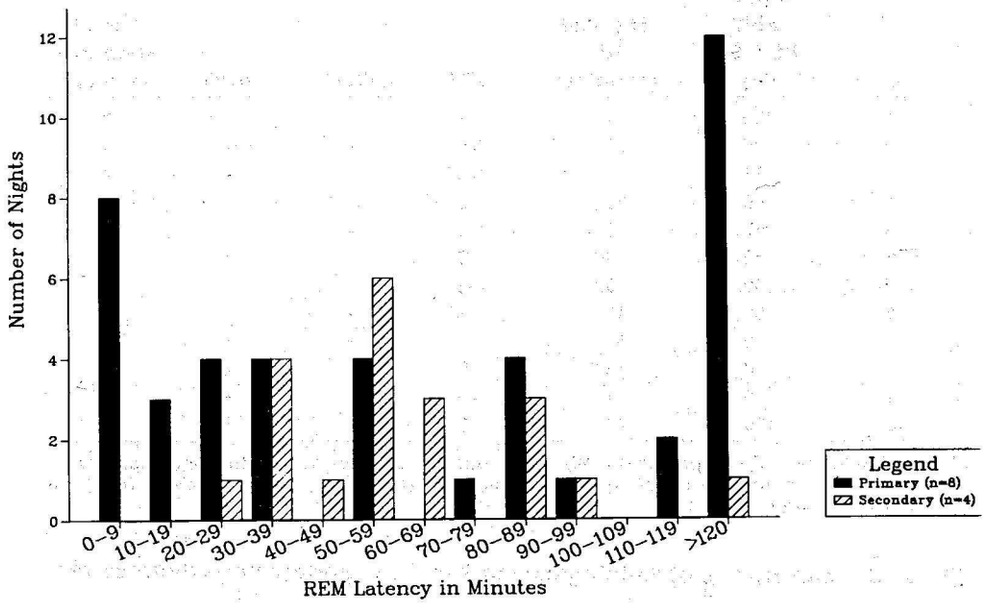
The correlations between sex, age, primary or secondary subtype, shortest RL, and results of neuroendocrine tests were analyzed by a product-moment correlation data matrix. Gender and primary/secondary RDC subtype were coded as 0 or 1 variables.

Results

RL. Individual values of RL during the 62 nights of recording are displayed in Table 1 and their distribution is represented in Fig. 1. RL was shorter than 50 minutes during 24 nights (39%) and shorter than 20 minutes (sleep onset REM period, or SOREMP) during 11 nights (18%). Eight depressives (67%) presented an RL shorter than 50 minutes during at least 1 night: seven primary (87%) and one secondary (25%). The number of nights with an RL shorter than 50 minutes was 1 for two primary depressives (17% of the whole sample, 25% of primary), 2 for one primary depressive (8% of the whole sample, 12% of primary), 3 for two primary depressives (17% of the whole sample, 25% of primary), 4 for two primary depressives (17% of the whole sample, 25% of primary), and 6 for one secondary depressive (8% of the whole sample, 25% of secondary). If one used RL data only from the last 4 recording nights (analyzed for each patient), the same proportion of depressives was identified by the cutoff of 50 minutes as was identified using all recording nights.

SOREMPs were present in five patients (42%): all were primary depressives (62%). Two patients exhibited a SOREMP during 1 night and one of them, respectively, during 2, 3, or 4 nights.

Fig. 1. Distribution of REM latencies in 12 endogenous depressives studied for 62 nights



DST. Individual cortisol levels after DST are displayed in Table 1. Six patients (50%) were nonsuppressors: five primary depressives (62%) and one secondary depressive (25%). These results correspond to a sensitivity of 50% for the diagnosis of endogenous depression and 62.5% (specificity of 75%) for the diagnosis of primary depression.

Clonidine Test. All tests were interpretable. Individual GH peak levels after clonidine are displayed in Table 1. Nine patients (75%) exhibited a blunted response: eight primary (100%) and one secondary (25%) depressives.

Apomorphine Test. All tests were interpretable. Individual GH peak levels after apomorphine are displayed in Table 1. Five patients (42%) presented a blunted response; all were primary (62%) depressives.

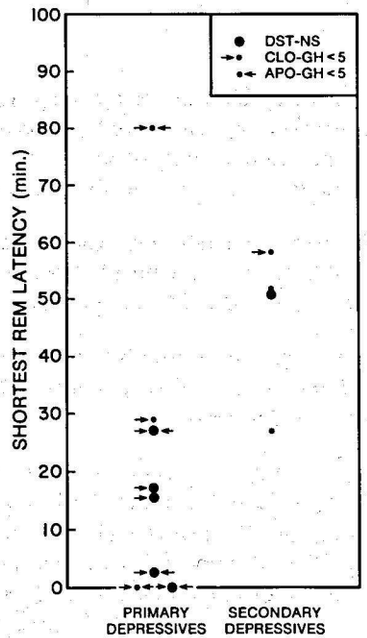
Concurrent Results. The summary of concurrent abnormalities in these four biological markers is displayed in Table 2 and Fig. 2. Eleven patients (92%) presented at least one pathological result: all the primary (100%) and three secondary (75%) depressives. Eight patients (67%) exhibited at least two abnormalities and this group comprised the whole sample of primary depressives (100%). Six patients (50%) showed a disturbance of at least three biological markers (75% of the primary depressives and none of the secondary depressives) and three patients (25%) of all four parameters (37% of the primary depressives and none of the secondary depressives).

Table 2. Summary of results of 4 biological markers for 12 endogenous depressives including 8 primary (#1-8) and 4 secondary (#9-12)

#	Nights with RL < 50 (%)	Shortest RL (minutes)	DST	CLO	APO	No. of abnormal markers
1	100	0	S	-	-	3
2	25	27	NS	-	-	4
3	75	0	NS	-	-	4
4	0	80	S	-	-	2
5	67	2.5	NS	-	-	4
6	33	9.5	S	-	+	2
7	50	15.5	NS	-	+	3
8	33	17	NS	-	+	3
9	0	52	S	+	+	0
10	0	58.5	S	-	+	1
11	0	51	NS	+	+	1
12	100	29	S	+	+	1

RL = REM latency; S = suppression; NS = nonsuppression after dexamethasone suppression test (DST); + = normal (> 5 ng/ml); and - = blunted GH response after clonidine (CLO) or apomorphine (APO) tests.

Fig. 2. Concurrent use of 4 biological markers in 12 endogenous depressives



Eight of the patients were primary depressives, and 4 were secondary depressives. The 4 biological markers were: shortest REM latency (minutes) during 4-6 consecutive nights; nonsuppression (NS) after dexamethasone suppression test (DST), and blunted growth hormone (GH) response (< 5 ng/ml) after clonidine (CLO) and apomorphine (APO) tests.

Comparison of the sensitivity of these four biological markers in this sample of endogenous depressives showed that an abnormal clonidine test identified 75% of patients; shortened RL, 67%; DST nonsuppression, 50%; and an abnormal apomorphine test, 42%. Among primary depressives, these biological markers showed the following rank ordering of sensitivity: abnormal clonidine test (100%), shortened RL (87%), DST nonsuppression (62%), and abnormal apomorphine test (62%). Among secondary depressives, shortened RL, nonsuppression after DST, and abnormal clonidine test showed the same sensitivity (25%); no secondary patient exhibited an abnormal apomorphine test (0%).

Kappa statistics applied to the four biological markers, considered as independent diagnostic "raters" of endogenous depression, gave an overall interrater reliability of Kappa = 0.277 (NS). The Kappa values between each individual pair of markers are presented in Table 3. The only statistically significant reliability is between the clonidine and the apomorphine test (Kappa = 0.385, $p < 0.05$).

The product-moment correlation matrix including gender, age, primary/secondary subtype, shortest RL, cortisol after DST, and GH peak value after clonidine and apomorphine tests (Table 4) showed significant direct correlations between primary/secondary RDC subtype and RL ($p < 0.05$), clonidine test ($p < 0.01$), and apomorphine test ($p < 0.05$); between clonidine and apomorphine tests ($p < 0.05$); and significant inverse correlations between age and primary/secondary subtype ($p < 0.01$), and between age and RL ($p < 0.01$).

Table 3. "Interrater" reliability (Kappa values) between RL, DST, clonidine (CLO), and apomorphine (APO) tests used as biological markers in 12 endogenous depressives

	RL	DST	CLO	APO
RL	—	—	—	—
DST	0.333	—	—	—
CLO	0.400	0.167	—	—
APO	0.211	0.167	0.385[1]	—

1. $p < 0.05$.

Table 4. Product-moment correlation matrix

	Sex	Age	P/S	RL	CORT	CLO	APO
Sex	—	—	—	—	—	—	—
Age	-0.264	—	—	—	—	—	—
P/S	0.408	-0.698[1]	—	—	—	—	—
RL	0.015	-0.685[1]	0.538[2]	—	—	—	—
CORT	-0.263	-0.227	0.013	-0.028	—	—	—
CLO	0.101	-0.494	0.784[1]	0.307	0.115	—	—
APO	-0.104	-0.482	0.606[2]	0.289	0.293	0.512[2]	—

P/S = primary/secondary; RL = shortest REM latency; CORT = cortisol after DST; CLO = GH peak after clonidine; APO = GH peak after apomorphine.

1. $p < 0.01$.
2. $p < 0.05$.

Discussion

RL is shortened (i.e., less than 50 minutes) during at least 1 night in 8 of 12 depressives, a finding consistent with those of Kupfer (1976). In the absence of a standardized procedure, the choice of the cutoff RL may seem somewhat arbitrary. In fact, methodologies proposed for the use of RL as a biological marker of endogenous depression have differed among investigators in many respects, including number of recording nights (1 to 3), choice of cutoff value (30 to 70 minutes), and selection of RL data for assessment of diagnostic performance (night 1; mean of nights 1-2, or 2-3, shortest of 2 consecutive nights; positivity during at least 2 consecutive nights) (Akiskal et al., 1982; Berger et al., 1982; Blumer et al., 1982; Feinberg, 1982; Kupfer et al., 1982, 1983; Reynolds et al., 1983; Rush et al., 1982). These differences may contribute to the divergent reports of diagnostic sensitivity of RL (30% to 95%). In this sample, the increase of the cutoff RL from 50 minutes to 60 minutes permits detection of three more patients (three secondary depressives), with a corresponding increase of overall sensitivity from 67% to 92% and from 25% to 100% for secondary depression. However, our results show a clear intrapatient variability of RL during the 4 or 6 consecutive nights, although technical procedures and environmental conditions were identical. In fact, such intrasubject variability has already been suggested in normals by Spiegel (1981), who classifies RL among the "unstable" individual sleep characteristics. The same variability demonstrated in depressives in our study does not result: (1) from an effect of habituation (first night effect), as it is still evident when only the last 4 nights are considered; (2) from the definition of RL used in this study, as the exclusion of intervening awake time between sleep onset and first REM period does not reduce the intrapatient variability in RL. Most of the sleep studies in depressives are based on 2 (or 3) consecutive nights of recording (without habituation night) and RL is calculated as the average for these 2 (or 3) nights. Our study, with 6 consecutive nights of recording, uses a more longitudinal design, closer to the methodology of Schulz et al. (1979) and Coble et al. (1981). Schulz et al., who studied six endogenous depressives during a total of 90 nights, also found large variabilities in RL and a bimodal distribution with peaks just after sleep onset (SOREMPs) and 60 minutes later; these results were largely confirmed by the more extensive study of Coble et al., who studied 22 depressives, each of them during 26 to 35 nights. Our results provide evidence that in order to use RL as a biological marker of endogenous depression with our methodology (RL of 50 minutes or less on any night), at least 3 nights of consecutive studies should be recorded for the maximal sensitivity.

In our sample, we also found five primary depressives (including the two bipolars) who exhibited a SOREMP during at least 1 recording night. This index, while less sensitive, seems very specific for primary endogenous depression and associated with a particular severity or a poor response to antidepressant treatment (Schulz et al., 1979; Coble et al., 1981). The inverse relationship found between RL and age confirms previous conclusions of an age-related decrease of RL in primary depressives (Ulrich et al., 1980; Gillin et al., 1981; Kupfer et al., 1982).

The sensitivity of the DST for the diagnosis of endogenous depression in this small sample (50%) is in good agreement with the studies of Carroll (1982). However, the use

of an associated 11 p.m. sample could have increased the diagnostic sensitivity; according to Carroll et al. (1981), the single 4 p.m. sample procedure used in this study may fail to detect 18-25% of DST nonsuppressor patients detected by three blood samples. In the present study, shortened RL and nonsuppression after DST do not identify the same depressives (as confirmed by the Kappa statistic and the correlation coefficient): five patients (42%) present both abnormalities (five primary depressives, or 62%), but nine patients (75%) present at least one of them (seven primary, or 87%; two secondary, or 50%). Two studies suggest that shortened RL may be a more sensitive marker of endogenous depression than DST nonsuppression: Rush et al. (1982) found a sensitivity of 56% for RL compared to 20% for DST, whereas Berger et al. (1982) found a sensitivity of 65% and 20%, respectively. Our study may suggest the same trend, even if the sensitivity of shortened RL (67%) is not significantly different from that of DST (50%). Two studies, however, found similar sensitivity for both markers: 45% (Feinberg, 1982) and 40% (Blumer et al., 1982). Results of all these studies are difficult to compare due to their widely differing definitions of cutoff RL: 62 minutes for the mean of 2 recording nights (Rush et al., 1982), 50 minutes during at least 1 of 3 recording nights (Berger et al., 1982), 35 minutes for the mean of 2 recording nights (Feinberg, 1982), and 60 minutes during a single recording night (Blumer et al, 1982). Moreover, the characteristics of depressives included in those studies differ in many respects: inpatients or outpatients, level of severity, and presence of bipolar or psychotic depressives in the sample. Rush et al. (1982) suggest that DST nonsuppressor depressives represent a subgroup among the patients exhibiting shortened RL. Our study may support this hypothesis; all but one of the depressives who exhibited DST nonsuppression are included in the short RL group.

This study shows an overlap between patients identified by the clonidine and apomorphine tests, as confirmed by the Kappa statistic ($p < 0.05$) and the correlation coefficient ($p < 0.05$). In fact, all patients who exhibited a blunted response to apomorphine challenge also presented a blunted response to clonidine. But the clonidine test seems to be more sensitive than the apomorphine test (75% vs. 42%), detecting four additional patients. The results of the clonidine test support the concept of decreased sensitivity of central noradrenergic receptors in primary depression (Matussek et al., 1980; Checkley et al., 1981; Ansseau et al., 1982; Charney et al., 1982; Siever et al., 1982; Siever and Uhde, 1984). The results of the apomorphine test also support our earlier conclusion of an associated dopaminergic hyposensitivity in primary depression (Ansseau et al., 1982). However, this assertion is in disagreement with most of the published studies. In fact, the neuroendocrine evaluation of dopaminergic sensitivity in depressives has generally been performed with L-dopa, a less potent and less specific agonist. Relatively few studies have used apomorphine, which is far more potent and specific than L-dopa. The studies that did use apomorphine administered it in a higher dose than in the present study (0.75 mg instead of 0.50 mg), which may explain the negative results (Frazer, 1975; Casper and Davis, 1977; Maany et al., 1979). Finally, in the present study, the samples of patients exhibiting a blunted response to clonidine or apomorphine challenge do not correspond to those showing nonsuppression after DST or shortened RL, as evidenced by the Kappa statistic or the correlation matrix. In this sample, the

primary/secondary classification is supported by three of four markers, with the primary depressives exhibiting a higher rate of abnormality on the RL, clonidine, and apomorphine challenge tests.

These results are theoretically interesting, since these biological markers may relate to differential central receptor sensitivity: the clonidine test to noradrenergic receptors (Matussek et al., 1980), the apomorphine test to dopaminergic receptors (Meltzer et al., 1981), and RL possibly to cholinergic receptors (Sitaram et al., 1980). The neurotransmission anomaly implicated in nonsuppression after the DST is less clear, yet many data also suggest a cholinergic origin (Carroll, 1981). Thus, the results of this study suggest the possibility that receptor abnormalities may vary among individual patients, even if the patients are selected using the same objective diagnostic criteria and present the same clinical features. Possibly, therefore, these biological markers could help to define individual biochemical patterns of depression that could facilitate more specific treatment.

These results also suggest the power of using several biological markers to enhance diagnostic confidence. Indeed, in our sample, the use of four different markers permits one to (1) identify 11 of 12 endogenous depressives (with at least one disturbed marker and (2) separate primary (with at least two abnormalities) from secondary depressives. These preliminary results obviously need to be confirmed in a larger sample.

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Erratum

We have been informed by the authors of this recently published report that their original manuscript contained errors that unfortunately were not detected until after publication. The errors are corrected below:

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Inferential Statistical Methods for Strengthening the Interpretation of Laboratory Test Results

N. Kalter, M. Feinberg, and B.J. Carroll

Table 4. Comparison of Carroll et al., Nuller and Ostroumova, and Schlesser et al., for sensitivity

A.		Carroll et al. DST result			Nuller and Ostroumova DST result			Schlesser et al. DST result		
		+	−	N	+	−	N	+	−	N
Criterion	I	92	123	215	36	16	52	66	80	146
Group	$\overline{I}$	6	147	153	8	77	85	0	151	151
		98	270	368	44	93	137	66	231	297

B.		DST result		
		+	−	N
Carroll et al.	I	92	123	215
Nuller and Ostroumova	I	36	16	52
Schlesser et al.	I	66	80	146
	I	194	219	413

C.		DST result			
		+	−	N	
Carroll et al. plus Nuller and Ostroumova	I	5	203	361	*Corrected values*
Nuller and Ostroumova	I	36	16	52	
		194	219	413	