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# The clinical correlates of biological measures of depression.

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THE CLINICAL CORRELATES OF BIOLOGICAL MEASURES OF DEPRESSION

A Master's Thesis Presented

by

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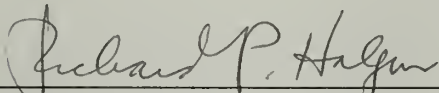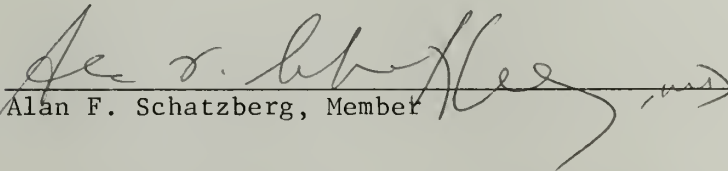
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ABSTRACT

THE CLINICAL CORRELATES OF BIOLOGICAL MEASURES OF DEPRESSION

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Relationships between four biological measures (post-
dexamethasone cortisol, urinary free cortisol (UFC), 3-methoxy-4-
hydroxyphenylglycol (MHPG), platelet monoamine oxidase activity
(MAO)) and clinical symptoms of depression were examined in a
total group of 83 drug free depressed patients (52 female, 31
male), a subgroup of 67 unipolar major depressed patients, and in
female and male patients within these two groups. Patients were
rated using the Hamilton Rating Scale for Depression (HRSD), the
Schedule for Affective Disorders and Schizophrenia (SADS), and
were diagnosed using Research Diagnostic Criteria (RDC) or other
clinical data.  Data were analyzed using Spearman correlations,
multiple regression analyses, discriminant function analyses,
analysis of variance, and Chi Square.

Overall, stronger relationships were observed between the
biological measures and specific clinical symptoms than with
global ratings of either endogeneity or severity of illness.
Several variables were observed to be significantly correlated
with the biological measures in the unipolar group of patients

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but not in the total group, and in some cases stronger associations were observed in the unipolar group as compared to the total group of patients. A greater number of significant correlations were observed between the biological measures and clinical symptoms in the female group of patients than in the male subgroup.

Post-dexamethasone cortisol was most strongly positively related to psychosis, and negatively to somatic anxiety, and guilt. Urinary free cortisol was most strongly negatively associated with overt anger, subjective anger and agitation, and positively with suicidal tendencies. The strongest relationships between MHPG and clinical features were observed in a positive direction between MHPG and agitation and obsessionality. Platelet MAO activity was most strongly negatively associated with somatic anxiety, somatic symptoms and paranoia, and positively with current suicidality. Of the four biochemical measures, only platelet MAO activity was observed to be significantly higher in patients with higher ratings of current suicidality (using the HRSD suicide item) in comparison to patients with lower ratings of current suicidality. Overall these data point to complex relationships between biological measures and clinical correlates.

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CHAPTER I

INTRODUCTION

Major depressive disorder is a complex psychobiological
syndrome with multiple etiologies and presentations. The disorder
involves mood disturbance, various neurovegetative signs, and
often cognitive changes. Physiological theories of major
depressive disorder have examined impairment of brain
neurotransmitters and hormonal systems, as well as circadian
rhythm and REM sleep (Schulberg et al., 1987). Recently, attention
has been paid to clinical laboratory tests which serve as
biological measures of depression. Determining the relationship
between these biological measures and major depression is an
important area of research, one that has been limited by the
seemingly broad label of major depression. Attempts to look at
specific major depressive subtypes have been limited by questions
of the validity of these subtypes (Davidson et al., 1985;
Zimmerman et al., 1985), the heterogeneity of major depressions
(Nelson & Charney, 1981; Schatzberg et al., 1982), and the
continuing question of whether laboratory findings relate more to
syndrome than to specific symptoms or overall severity.
Information gained from research in this area may help to
elucidate the etiology of major depressive disorders, as well as
aid in determination of effective mechanisms for treatment
(Redmond et al., 1986).

Several biological measures of depression have been the focus of study. The dexamethasone suppression test (DST) has been one of the most extensively researched, and has been used to evaluate dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in depressed patients. The measure of urinary free cortisol (UFC) has also been used to evaluate HPA dysfunction and has the advantage of providing an integrated measure of cortisol secretion over time. Another line of investigation has been the measurement of disturbances of noradrenergic neurons in the central nervous system. One such measure is 3-methoxy-4-hydroxyphenylglycol (MHPG), the major metabolite of norepinephrine in the brain. Platelet monoamine oxidase (MAO), the enzyme that deaminates catecholamines and indolamines has also attracted considerable interest as a biological marker of depression.

While much research has been conducted on these biological measures, few have related the findings to the clinical characteristics of major depressive disorder. Of the studies which have examined the relationship of these measures to clinical phenomena, most have focused on an endogenous or melancholic depressive syndrome. This approach may have limitations, however, resulting from a lack of agreement among researchers in the clinical diagnosis of endogeneity or melancholia, despite the aid of operational definitions (Davidson et al., 1985; Zimmerman et al, 1985). Casper et al. (1985) for example, found that "the classic somatic symptoms of depression were present in most

Research Diagnostic Criteria (RDC) subtypes, and were not exclusively associated with the endogenous subtype" (p. 1098).

The uncertainty in clinical diagnosis, and the confounding effect of severity of depression in both the diagnosis of endogenous depression (Kumar et al., 1986), and the biological abnormalities themselves, may in part account for the discrepant findings in studies relating biological measures to clinical diagnosis (Davidson et al., 1985). An alternative to the study of diagnostic subtypes is to examine the relationship between biological variables and specific signs and symptoms of major depressive disorder (Davis et al., 1981). For example, a promising area of research has been the study of the relationship between biological measures of depression and suicide. While this has proved a worthwhile avenue of investigation, Ross (1986) warns against "dealing with symptoms or syndromes as if they were specific diseases" reflecting "specific biological entities" (p. 431).

A review of the major literature concerning relationships between biological measures of depression and endogeneity, severity of illness, and specific endogenous or nonendogenous symptoms will be provided. Suicide will be discussed separately, as it is of greater clinical significance than other nonendogenous symptoms. A review of the previous literature may point to the most useful approach for further study of the relationship between biological measures and clinical features of major depressive disorder.

## Dexamethasone suppression test

The dexamethasone suppression test has received widespread
attention in psychiatry since Carroll et al. (1981) first
presented data on the standardization of this test in melancholic,
other psychiatric, and normal control subjects. The DST is
generally considered a state marker of depression, and following
the paper of Carroll et al. (1981), most researchers have defined
an "abnormal" DST or "non-suppression" as a post-dexamethasone
cortisol level above 5 ug/dL, while a level below 5 μg/dL is
defined as DST "suppression". The extensive interest in the DST
has resulted in considerable debate regarding its usefulness in
clinical practice. In a review article in which Arana et al.
(1985) examined 232 citations involving 4,463 psychiatric cases,
it was concluded that "neither uncritical enthusiasm nor excessive
skepticism about the DST presently is warranted" (Arana et al.,
1985, p. 1200).

Much of the research on the DST has focused on the
relationship between non-suppression of cortisol and the
melancholic or endogenous subtype of depression (Braddock, 1986;
Carroll et al., 1981). Carroll et al. (1981) originally reported
that the use of the DST as a laboratory diagnostic test for
melancholia had a "sensitivity greater than 65%" and a
"specificity and diagnostic confidence close to 95%" (p. 22).
Subsequent reports have provided conflicting evidence. Several
studies have found a significant increase in the nonsuppression

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rate among endogenous patients (Coryell et al., 1982; Feinberg & Carroll, 1984; Zimmerman et al., 1985; Zimmerman et al., 1986; Zhou et al., 1987). Other data suggests that DST non-suppression is not specific to melancholia or endogeneity as a diagnostic state (Berger et al., 1982; Miller & Nelson, 1987; Nasr et al., 1983; Roy et al., 1984; Rubin et al., 1985). As discussed previously, these conflicting results are in part attributable to a lack of diagnostic consistency. Braddock (1986) reports that "the criteria employed by the Newcastle Scale and by Carroll's group seem more successful" at identifying endogenous patients showing a higher rate of nonsuppression, "than the present state criteria of the RDC, DSM-III, and ICD" (p. 367).

One possible explanation for the association of non-suppression on the DST and endogenous depression is that endogeneity is confounded with severity of illness (Kumar et al., 1986), with endogenously depressed patients being more severely depressed than nonendogenous patients (Braddock, 1986). Several studies have reported a positive relationship between severity of illness and DST non-suppression (Baumgartner et al., 1986; Brown et al., 1979), as well as positive correlations between post-dexamethasone cortisol values and severity of illness (Davis et al., 1981; Kumar et al., 1986; Maes et al., 1986; Zhou et al., 1987). Other evidence has suggested a lack of association between either non-suppression on the DST or post-dexamethasone cortisol levels and severity of illness (Berger et al., 1982; Brown & Shuey, 1980; Larsen et al., 1985). Despite the conflicting

findings, Braddock (1986) concludes that "the evidence so far does suggest a relationship between cortisol level and severity" (p. 367).

The study of specific symptoms and their relationship to the DST has been an important area of research. Miller & Nelson (1987) found that individual symptoms were more closely associated with DST results than were subtypes, severity or behavioral factors. Several studies have examined the association between the DST and symptoms which serve as criteria for the RDC subtype of endogenous depression. These criteria as defined by Spitzer et al. (1978) are: distinct quality to depressed mood, lack of reactivity to environmental changes, mood regularly worse in morning, pervasive loss of interest or pleasure, self reproach or guilt, early morning awakening, psychomotor retardation or agitation, weight loss and loss of interest and pleasure (nonpervasive).

Positive relationships between the DST and specific endogenous symptoms of depression have been found. Studies which have examined these relationships are summarized in Table 1 (p. 11), and are discussed in greater detail here. Reus (1982) reported that "independent of diagnosis, non-suppressors are noted to have a greater incidence of classical endogenous signs of dysfunction on admission and a greater incidence of subjective complaints" (p. 317). Among the differences Reus (1982) reported were increased sleep disturbance, anergy, agitation, loss of interest, and self reproach in the non-suppressors as compared to the suppressors. Asnis et al. (1982) described "hypothalamic

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signs" consisting of insomnia, poor appetite, psychomotor retardation and worsening of mood in the morning, and reported that these symptoms were significantly higher in non-suppressors. Rubin et al. (1985) found that post-dexamethasone cortisol values were positively correlated with observed psychomotor retardation, lack of responsiveness during the interview, weight loss, diminished work and activities and insomnia. In addition, non-suppressors had significantly more terminal insomnia (early morning awakening) and diurnal variation than suppressors. Christensen et al. (1986) reported an association between post-dexamethasone cortisol levels and the HDS-6 (a sum of the Hamilton Rating Scale for Depression (HRSD) items depression, guilt, work and interests, retardation, anxiety psychic and somatic general), as well as a positive correlation between retardation (sum of items work and interests and retardation). Several other researchers have noted a positive association between psychomotor disturbance (retardation or agitation) and either non-suppression on the DST or post-dexamethasone cortisol levels (Agren & Wide, 1982; Zimmerman et al., 1986).

Reports also exist of a lack of relationship between the DST and endogenous symptoms (see Table 1, p. 11). Asnis et al. (1982) did not find that suppressors and non-suppressors differed in endogenous features. While Brown and Shuey (1980) noted that suppressors had greater diurnal variation, they also reported that suppressors and non-suppressors did not differ in the endogenous symptoms of agitation, retardation or insomnia. Kaspar & Beckmann

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(1983) also failed to find differences between suppressors and non-suppressors on measures of retardation, agitation, work and interests, and Brown & Qualls (1981) reported no differences between these groups on measures of appetite loss, guilt, insomnia, psychomotor activity, weight loss, diurnal variation, and mood. Finally, Grunhaus et al. (1985) did not find any significant relationship between post-DST plasma cortisol and either early morning awakening or diurnal variation.

Nonendogenous symptoms of depression have also been the focus of study. Major findings from these studies are summarized in Table 1 (p. 11). Several researchers have examined the relationship betwen anxiety and post-dexamethasone cortisol levels. Positive relationships have been reported between non-suppression on the DST and anxiety in some studies (Ceulemans et al., 1985; Christensen et al., 1986; Reus, 1982), but not in others (Asnis et al., 1982). Brown & Shuey (1980) and Brown & Qualls (1981) found significant differences between suppressors and nonsuppressors in the ability to complete self-rating forms, with the non-suppressors being more unable to complete the forms, and exhibiting a greater degree of helplessness. Silberman et al. (1985) found, contrary to expectation, that suppressors showed a larger degree of cognitive impairment than non-suppressors.

There does not appear to be consistent evidence regarding the relationship of the DST to either specific endogenous or nonendogenous symptoms of depression. In the attempt to elucidate the relationship between specific clinical signs and symptoms and

dysfunction of the HPA system as measured by the DST, two studies (Nasr et al., 1983: Zimmerman et al., 1985), have used a different methodological approach, conducting discriminant function analyses on their data.

Zimmerman et al. (1985) attempted to develop a discriminant function that "maximally differentiated between suppressors and non-suppressors" (p. 200) on the DST. They conducted the discriminant function analysis on the 10 RDC criteria for the endogenous subtype, using DST results as the independent variable. They found that only five of the ten endogenous symptoms were significant contributors to the discriminant function separating suppressors and non-supppressors. Four of the five symptoms were scored in the positive direction (mood worse in morning, middle or terminal insomnia, psychomotor disturbance, poor appetite), and only one symptom (pervasive or non-pervasive anhedonia) was weighted negatively.

While Zimmerman et al. (1985) limited their study to endogenous symptoms, Nasr et al. (1983) included all the items on the HRSD in their analysis. In an attempt to "test the hypothesis that the DST accurately identifies distinct subgroups of clinical depression having particular signs and symptoms as measured by the HRSD" (p. 572), Nasr et al. were able to classify patients into suppressors and non-suppressors with an accuracy of 92.5%. "The items that identified the non-suppressors in decreasing power were late insomnia, obsession-compulsion, retardation, psychic anxiety, and loss of insight. The items that accurately identified the

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suppressors were depressed mood, hypochondriasis, weight loss and depersonalization" (p. 572).

Although the number of subjects in the Nasr et al. (1983) study was considerably smaller (N=40) than that of the Zimmerman et al. (1985) study (N=257), and could have affected the validity of the results, the Nasr et al. study, does suggest the importance of including nonendogenous as well as endogenous variables in future analyses. The recent study by Miller & Nelson (1987) also supports this conclusion. They reported that DST nonsuppression was associated with certain "vegetative" signs of depression (initial insomnia, agitation, loss of sexual interest and weight loss), but not with the "psychological" symptoms (loss of interest, anhedonia and guilt).

Table 1

<u>STUDIES OF THE RELATIONSHIP BETWEEN POST-DEXAMETHASONE CORTISOL
AND ENDOGENOUS AND NONENDOGENOUS SYMPTOMS</u>

| <u>Study</u> | <u>Findings</u> | <u>N</u> |
|---|---|---|
| Reus (1982) | Non-suppressors on DST had increased sleep disturbance, anergy, agitation, loss of interest, self reproach, and anxiety as compared to suppressors | N = 118 |
| Asnis et al. (1982) | Non-suppressors on DST had increased insomnia, poor appetite, and psychomotor retardation | N = 30 10 Males 20 Females |
| Rubin et al. (1985) | Post-dexamethasone cortisol positively correlated with psychomotor retardation, lack of responsiveness during interview, weight loss, and diminished work and activities; non-suppressors had increased early morning awakening and diurnal variation | N = 64 31 Males 33 Females |
| Christensen et al. (1986) | Significant association between post-dexamethasone cortisol and HSD-6[a] score, retardation, and psychic anxiety | N = 35 12 Males 23 Females |
| Agren & Wide (1982) | Non-suppression on DST associated positively with summed score of agitation and retardation | N = 51 |
| Zimmerman et al. (1986) | DST results positively related to psychomotor disturbance | N = 257 |
| Asnis et al. (1982) | Non-suppressors and suppressors on DST did not differ in severity of endogenous features | N = 40 11 Males 29 Females |

[a] HDS-6 = A sum of Hamilton Rating Scale for Depression items
depression, guilt, work and activities, retardation,
anxiety psychic, and somatic general

Table 1 (continued)

STUDIES OF THE RELATIONSHIP BETWEEN POST-DEXAMETHASONE CORTISOL
AND ENDOGENOUS AND NONENDOGENOUS SYMPTOMS

| Study | Findings | N |
|---|---|---|
| Brown & Shuey (1980) | Suppressors on DST had greater diurnal variation; no difference between suppressors and non-suppressors on ratings of agitation, retardation or insomnia; non-suppressors were more unable to complete rating forms and had greater degree of helplessness | N = 49<br>39 Males<br>10 Females |
| Kaspar & Beckman (1983) | No difference between suppressors and non-suppressors on measures of retardation, agitation, and work and interests | N = 67<br>15 Males<br>52 Females |
| Brown & Qualls (1981) | No difference between suppressors and non-suppressors on measures of appetite loss, guilt, insomnia, psychomotor activity, weight loss, diurnal variation and mood; non-suppressors more unable to complete rating forms and had greater degree of helplessness | N = 39<br>8 Males<br>31 Females |
| Grunhaus et al. (1985) | No significant relationship between post-dexamethasone cortisol and either early morning awakening or diurnal variation | N = 49 |
| Ceulemans et al. (1985) | Higher levels of anxiety in DST non-suppressors than in controls | N = 40<br>23 Male<br>17 Female<br>20 controls |
| Silberman et al. (1985) | Suppressors showed larger degree of cognitive impairment than non-suppressors | N = 27<br>8 Males<br>19 Females |
| Zimmerman et al. (1986) | Psychomotor retardation and depressed mood significantly greater in non-suppressors | N = 187<br>55 Males<br>132 Females |

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## Dexamethasone suppression test and suicide

One of the most extensively researched areas in the examination of the relationship between clinical characteristics of depression and altered biochemistry, has been the study of suicide and suicidal behavior. Several studies have examined the association between suicidal behavior and HPA dysregulation as measured by the DST. These studies have included suicide completers, suicide attempters, and suicide contemplators. While these groups may appear to be distinct, they may in fact represent a continuum of suicidality. Stallone et al. (1980) for example, found that "attempters and contemplators were a good deal more similar to one another than either one was to the nonsuicidals" (p. 386).

Several studies have found a relationship between suicide and non-suppression on the DST. Coryell & Schlesser (1981) in one of the few studies to examine biological abnormalities in suicide completers, found a higher incidence of suicide completion in patients with abnormal DST's. Due to the length of time however between the DST and the actual suicide completion, these results must be regarded as equivocal. Others have examined past suicide attempts, and have found a greater rate of non-suppression in suicide attempters vs. non-attempters (Banki et al., 1984; Targum et al., 1983), and in "violent and nonviolent " attempters vs. nonsuicidal patients (Banki et al., 1984). Reus (1982), in the one study to find a positive association between the DST and

suicidality assessed at the time of biochemical measurement, reported that DST non-suppression was associated with "increased thoughts of suicide", thus suggesting the relationship between HPA dysfunction and suicide "contemplators".

Other researchers have failed to confirm the positive association between DST non-suppression and either past or present suicidality. Secunda et al. (1986) found no significant differences between suicide attempters and non-attemptors in post-dexamethasone cortisol levels. They did find significantly lower pre-dexamethasone levels in the suicide attempters however. Brown et al. (1986) studied three groups of patients: patients who had recently attempted suicide (within 28 days before the DST), past attempters, and non-attempters, and found that plasma cortisol levels did not differ significantly between the three groups. They also found that there were no significant differences in mean cortisol levels between "patients rated as having active suicidal intent" (on HRSD suicide item) and "patients with passive or no suicidal ideation" (p. 319). Zimmerman et al. (1986) reported that there were no significant differences between suppressors and non-suppressors on the DST in either frequency of past suicidal thoughts or serious past suicide attempts. They did find that past nonserious suicide attempts were significantly more frequent in the suppressors.

The positive relationship between HPA dysfunction and suicidality has not been well documented. Further research may help to clarify whether the tendency of depressed patients to

attempt suicide may be exacerbated by an underlying

neurobiological disorder reflected by HPA dysregulation, and

whether depressed suicidal patients with abnormal DST's may

represent a high-risk group for recurrence of suicidal behavior.


## Urinary Free Cortisol


Urinary free cortisol (UFC), an integrated measure of

cortisol over time, has also been used to evaluate HPA dysfunction

and may have the potential to yield more information than can be

obtained from occasional blood samples. The study of UFC however,

has received much less research attention than the DST. Studies

examining UFC in patients with major depressive disorder

have generally found elevated levels of UFC as compared to

"normal" controls or patients with other psychiatric disorders

(Carroll et al., 1976; Rosenbaum et al., 1983).

Few studies have been conducted which examine the

relationship between UFC and endogeneity, severity, specific

endogenous symptoms, or nonendogenous symptoms. Those studies

which have examined the relationship between UFC and specific

endogenous or nonendogenous symptoms are summarized in Table 2 (p.

17). Berger et al., (1982) did not find a significant difference

between endogenous and nonendogenous patients in UFC levels.

Kathol (1985) studied recovered depressed patients and controls,

and found a positive correlation between Beck Depressive symptoms

and UFC in the group of recovered patients, but not in the controls. Agren & Oreland (1982) reported a significant positive relationship between early morning awakening and UFC, and Berger et al. (1982) found a positive association between UFC and weight loss.

The study of the relationship between suicide and UFC has also received little attention. Agren & Wide (1982) reported that UFC was highly significantly correlated with less past suicide proneness. In addition they found that 20% of the variance of UFC was explained by the Schedule for Affective Disorders and Schizophrenia (SADS) items of "seriousness plus medical lethality of worst ever suicide attempt", "anger worst week", and "overt anger last week". UFC was also found to correlate negatively with anger scores. This study points to the important relationship between suicide and expression or experience of anger.

Table 2

STUDIES OF THE RELATIONSHIP BETWEEN UFC AND ENDOGENOUS AND
NONENDOGENOUS SYMPTOMS

| Study | Findings | N |
|---|---|---|
| Kathol et al. (1985) | Positive correlation between UFC and Beck Depression Inventory score in recovered depressed patients | N = 7 |
| Agren & Oreland (1982) | Positive correlation between UFC and early morning awakening | N = 51 22 Males 29 Females |
| Berger et al. (1982) | Positive association between UFC and weight loss | N = 45 22 Males 23 Females |

## 3-methoxy-4-hydroxyphenylglycol (MHPG)


MHPG, the major metabolite of norepinephrine from the brain, has been measured in plasma, urine, and cerebrospinal fluid (CSF). Although a substantial portion of plasma and urinary MHPG may be of peripheral origin (Halbreich et al., 1987), with the exact fraction of urinary or plasma MHPG derived from the brain uncertain (Schatzberg et al., 1982), it is generally agreed that both urinary and plasma MHPG "have their place in psychiatric research" (Filser et al., 1986, p. 96).

MHPG has been studied in relation to the monoamine hypothesis of depression which has suggested that depression is caused by insufficient activity of monoaminergic neurons. Studies examining MHPG in major depressive disorder have found differences in urinary MHPG in various subtypes of depressive disorders (Schildkraut et al., 1978; Schatzberg et al., 1982), as well as higher CSF MHPG levels in depressed subjects as compared to controls (Koslow et al., 1983).

One study has reported on MHPG and its relationship to endogeneity. Nelson and Charney (1981) comment that "decreased MHPG may be specific to endogenous depression". More has been written about MHPG in relation to severity of illness. The majority of reports have failed to find a significant relationship between severity and MHPG as measured in urine (Davis et al.,1981), plasma (Roy et al., 1986) and CSF (Redmond et al.,

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1986). Recently however, Schatzberg et al. (1989) found a significant main effect for severity on MHPG, with the more severely depressed patients having higher MHPG values.

Several studies have suggested a positive relationship between MHPG and endogenous symptoms. A summary of these studies is presented in Table 3 (p. 21). Agren (1980) found a significant positive correlation between CSF MHPG and both "distinct quality of mood" and "lack of energy". Redmond et al. (1986) reported that sleep disturbance was significantly correlated with CSF MHPG in depressed patients, and found that depressed patients with "higher" retardation scores had significantly higher CSF MHPG concentrations than patients with "low" or "middle" retardation scores.

Nonendogenous symptoms of depression have also been studied in their relationship to measures of MHPG (see Table 3, p. 21). Positive associations between MHPG and anxiety have been reported (Roy et al., 1986; Redmond et al., 1986). In addition, depressed patients with increased somatization have been found to have higher levels of CSF MHPG ( Redmond et al., 1986). In contrast to these findings, a study of afternoon continuous plasma levels of MHPG (Halbreich et al., 1987) found almost no association between plasma MHPG and clinical symptoms.

Overall, the research examining MHPG in relation to endogeneity, severity, and specific endogenous and nonendogenous symptoms, does not appear to provide a consistent picture. Using a somewhat different methodological approach to examine the clinical

correlates of MHPG, Agren (1980), using symptom scores on the
SADS, performed a series of multiple regression analyses. His
results revealed that "high- and low-MHPG syndromes could be
isolated" (p. 211). In his sample of unipolar patients, Agren
identified a "high-MHPG syndrome characterized by Lack of Energy,
Overt Anger, Self Pity and Somatic Preoccupation", and a "low-MHPG
syndrome" characterized by "Discouragement, Demandingness,
Subjective Anger, Suicidal Tendencies, Indecisiveness, and
Obsessions-Compulsions" (p. 218). Again, the use of a more complex
method of data analysis suggests the importance of examining both
endogenous and nonendogenous symptoms simultaneously.

Table 3

STUDIES OF THE RELATIONSHIP BETWEEN MHPG AND ENDOGENOUS AND
NONENDOGENOUS SYMPTOMS

| Study | Findings | N |
|-------|----------|---|
| Agren (1980) | Significant positive correlation between CSF MHPG and distinct quality of mood and lack of energy | N = 33<br>12 Males<br>21 Females |
| Redmond et al. (1986) | CSF MHPG significantly and positively correlated with sleep disturbance; patients with higher retardation scores had significantly higher CSF MHPG levels than patients with "low" or "middle" retardation scores; positive correlation between MHPG and anxiety; patients with increased somatization were found to have higher levels of CSF MHPG | N = 99 |
| Roy et al. (1986) | Positive correlation bewteen plasma MHPG and anxiety symptoms | N = 51<br>11 Males<br>40 Females |
| Halbreich et al. (1987) | Almost no association between plasma MHPG and clinical symptoms | N = 42<br>15 Males<br>27 Females |

## MHPG and suicide

Most of the work exploring the relationship between suicide and the metabolites of monoamine neurotransmitters has focused on associations between low levels of the serotonin metabolite, 5-hydroxindoleacetic acid (5-HIAA) in CSF, and suicidal behavior (Agren, 1980; Asberg & Traskman, 1981). As a result, less attention has been paid to MHPG, the metabolite of norepinephrine, and its association to suicide.

Several studies have found a negative relationship between MHPG and past suicidality. Secunda et al. (1986) reported that suicide attempters had significantly lower urinary and plasma MHPG levels than patients who had never attempted suicide. Agren (1980) also found a negative correlation between CSF MHPG and suicidal tendencies occurring during the worst week of the current episode. Mann et al. (1986) observed an increase in $\beta$-adrenergic binding in frontal cortices of violent suicide victims as compared with matched controls, and stated that "this suggests that there may also be a concomitant reduction in presynaptic noradrenergic activity associated with suicide" (p. 954).

In contrast to the findings of a negative association between MHPG and suicide, Traskman et al. (1981) found no significant difference in MHPG levels between either of two types of suicide attempters studied (violent vs. nonviolent), and a control group. A positive relationship between CSF MHPG and suicide was found by Brown et al. (1982) in a sample of patients with various

personality disorders. Brown et al. (1982) found that in particular, patients with histories of aggressive and suicidal behavior had higher levels of CSF MHPG. This contradictory finding may in part be explained by the population of patients studied. A study by Agren (1980) in which it was found that MHPG correlated significantly with the SADS item "Suicidal Tendencies ", also points to the relationship between suicidality and anger or aggressiveness. Agren (1980) found that "subjective anger was positively, and overt anger negatively associated with thoughts of suicide"(p. 225). Agren suggests that noradrenergic neurons apparently play a role both in the "conveying" of the emotion of anger, and in "executing the death wish" (p. 235).

## Platelet monoamine oxidase activity

Platelet MAO is one of the most extensively researched enzymes in relation to personality traits and psychiatric disorders (Agren & Oreland, 1982). It has been of particular interest to researchers in biological psychiatry as it is the enzyme that deaminates catecholamines and indolamines. It has been suggested that MAO activity may "provide some indication of the turnover of monoamines which, as neurotransmitters, may be involved in the development of depression" (Georgotas et al., 1986, p. 247).

While strong relationships have been found to exist between platelet MAO activity and personality traits, studies investigating platelet MAO activity in affective disorders have been less definitive. Several studies have found platelet MAO activity to be lower in bipolar depressives (Mann, 1979; Murphy & Weiss, 1972) and higher in unipolar depressives (Reveley et al., 1981), particularly females (Bridge et al., 1985; White et al., 1983; Mann, 1979).

The relationship between the endogenous or melancholic subtype and platelet MAO activity has been discussed by several researchers. Some have found a positive relationship between platelet MAO activity and endogenous depression. Mann (1979) discusses the possibility that "altered MAO activity may be a feature of endogenous rather than reactive depression" (p. 735), and Samson et al. (1985) report finding significantly higher MAO in "nonschizotypal unipolar endogenous depressed patients than in nonschizotypal bipolar endogenous depressed patients, or nonschizotypal unipolar other patients" (p. 547). In contrast, White et al. (1983) found higher platelet MAO in nonendogenously depressed females than in female controls. Davidson et al. (1980) reported no significant differences in platelet MAO activity between endogenous and nonendogenous patients, after adjusting for the effects of age and sex.

The lack of consistency in the studies examining the relationship between the diagnosis of endogeneity and platelet MAO activity may again be related to a lack of diagnostic agreement.

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Georgotas et al. (1986), for example, in a study of patients ≥ 55 years of age, found no significant difference in platelet MAO activity between endogenous and nonendogenous patients (using RDC criteria) after the effects of age and sex had been controlled for. However, using the DSM-III criteria for major depression with melancholia, they found that melancholic patients had significantly higher platelet MAO activity than those without melancholia, after the effects of age and sex were taken into account.

The possibility of the confounding effects of severity of illness on the relationship of platelet MAO activity to endogeneity has been discussed by several researchers. Some have reported a significant positive correlation between total score on the HRSD and platelet MAO activity (Gudeman et al., 1982;, Mann, 1979; Samson et al., 1985). Samson et al. state that "the presence of a definite endogenous depressive syndrome was associated with greater overall symptom severity in both unipolar and bipolar depressed patients" (p. 547). They suggest that "unipolar endogenous depression of high severity is characterized by high platelet MAO activity" (p. 553) as well as nonsuppression on the DST.

Several studies have reported on the association between platelet MAO activity and specific symptoms of endogenous depression. A summary of these studies is presented in Table 4 (p. 28), and discussed in greater detail here. A negative correlation between platelet MAO activity and guilt has been reported in

total groups of patients (Perris et al., 1980; Schalling et al., 1980), and in females only (Perris et al., 1984) A positive correlation between platelet MAO activity and guilt has also been reported (Schalling et al., 1980). Agren & Oreland (1982) found that unipolar patients with higher levels of platelet MAO activity woke up earlier than they had before becoming depressed. Schatzberg et al. (1985) found platelet MAO activity to be positively associated with early morning awakening, as well as with difficulty falling asleep, and "middle insomnia". The endogenous symptoms of anhedonia and mood autonomy were reported to be positively correlated with platelet MAO activity (Georgotas et al., 1986), as were the symptoms of depressed mood, weight loss, agitation, and decreased energy and activity (Gudeman et al., 1982). With the possible exception of guilt, it appears that most reports find a positive relationship between some of the endogenous symptoms of depression and platelet MAO activity.

Many of the studies reporting on nonendogenous symptoms of depression and their relationship to platelet MAO activity (see Table 4, p. 28) have focused on anxiety. Davidson et al. (1980) found platelet MAO activity to correlate positively with anxiety, and Georgotas et al. (1986) reported that platelet MAO activity was significantly related to somatic anxiety, but not to psychic anxiety. Khan et al. (1986) were "unable to demonstrate that MAO-B activity differentiated among anxious, depressed, or control subjects" (p. 848), and found a "poor correlation between MAO-B and severity of anxiety symptoms" (p. 848).

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To further explore the relationship between clinical symptoms and platelet MAO activity, Gudeman et al. (1982) performed a multiple regression analysis using 21 items from the Clinical Inventory for the Diagnosis and Classification of the Affective Disorders (CIDCAD). They report that "this analysis identified six clinical items" (p. 631) (abdominal heaviness, decrease in social activity, agitation, decrease in emotional receptivity, weeping (with a negative coefficient), and the presence of a major stress precipitant) "each of which accounted for a significant portion of the variance of MAO activity" (p. 631). This statistical approach may yield results which may prove to be of clinical relevance. Gudeman et al. (1982) report that most of the symptoms they found to be associated with higher platelet MAO activity (both endogenous and nonendogenous symptoms) "would be included in one or more of the clinical features" (p. 632) reported by other researchers to be responsive to treatment with MAO inhibitors.

Table 4

<u>STUDIES OF THE RELATIONSHIP BETWEEN PLATELET MAO ACTIVITY AND
ENDOGENOUS AND NONENDOGENOUS SYMPTOMS</u>

| <u>Study</u> | <u>Findings</u> | <u>N</u> |
|---|---|---|
| Perris et al. (1980) | Weak negative correlation between platelet MAO activity and guilt | N = 30 <br> 14 Males <br> 16 Females |
| Perris et al. (1984) | Negative correlation between platelet MAO activity and guilt in females | N = 143 <br> 60 Males <br> 83 Females |
| Agren & Oreland (1982) | Unipolar patients with higher levels of MAO activity woke up earlier than they had before becoming depressed | N = 51 <br> 22 Males <br> 29 Females |
| Schatzberg et al. (1985) | Platelet MAO activity positively correlated with early, middle, and late insomnia | N = 50 <br> 23 Males <br> 27 Females |
| Georgotas et al. (1986) | Positive association between MAO and anhedonia, mood autonomy; MAO significantly related to somatic anxiety but not to psychic anxiety | N = 67 <br> 24 Males <br> 43 Females |
| Gudeman et al. (1982) | Positive correlation between MAO and depressed mood, weight loss, agitation, decreased energy and activity | N = 32 <br> 18 Males <br> 14 Females |
| Davidson et al. (1980) | Platelet MAO activity significantly higher in depression secondary to chronic anxiety | N = 88 <br> 17 Males <br> 71 Females |
| Kahn et al. (1986) | No difference in levels of MAO-B activity between anxious, depressed or control subjects; poor correlation between MAO- B and severity of anxiety symptoms | N = 163 <br> 94 Males <br> 69 Females |

## Platelet MAO activity and suicide

Several studies have considered the relationship between platelet MAO activity and past suicidality, and conflicting evidence has been found. Low platelet MAO activity has been reported in depressed patients who have made particularly serious suicide attempts (Gottfries et al., 1980). Buchsbaum et al. (1977) found that males with low MAO and AER (averaged evoked response) augmenting, showed a significantly increased incidence of suicide attempts in comparison with either non-augmenting low MAO or high MAO patients. In contrast, Oreland et al. (1981) did not find any difference in the level of platelet MAO activity between suicidal and non-suicidal patients. In a study of brain MAO activity, Grote et al. (1974) "found no significant difference for MAO activity in 28 brain areas when 19 controls were compared with 14 depressives suicides or with 11 alcoholic studies" (Reveley et al., 1981, p. 259).

The relationship between platelet MAO activity and suicide may be complicated by the fact that unipolar and bipolar depressed patients have been found to have significantly different levels of platelet MAO activity, as well as different rates of suicide attempts. Bipolar depressed patients have been reported to be more likely to attempt suicide than unipolars (Secunda et al., 1986), and to have lower platelet MAO activity (Mann, 1979; Murphy & Weiss, 1972). Impulsivity and monotony avoidance have also been found to be related to lower levels of platelet MAO activity in

both depressed patients and normal controls (Schalling et al.,
1980; Perris et al., 1980; Perris et al., 1983;  Perris et al.,
1984), and perhaps are also associated with bipolar depression.


### Biological measures and their inter-relationship


The majority of studies have focused on the measurement of
one biological measure of depression in a population of patients.
Several studies have examined two or more biological measures, and
have attempted to understand the inter-relationship between
catecholamine systems, HPA activity, and platelet MAO activity.
Studies of severely depressed patients have reported significantly
positive correlations between cortisol and MHPG as measured in 24-
hour urine collection or plasma ( Stokes et al., 1981; Jimerson et
al., 1983; Rosenbaum et al., 1983; Zhou et al., 1987).

Other studies have examined the relationship of platelet MAO
and HPA activities. Positive correlations have been observed
between platelet MAO and 24-hour urinary free cortisol in unipolar
depressed patients (Agren & Oreland, 1982). In addition, it has
been observed that depressed patients with high platelet MAO
activity are more likely to be DST non-suppressors than are
patients with low platelet MAO activity (Georgotas et al., 1986;
Hartong et al., 1985), Schatzberg et al., 1983b; Schatzberg et
al., 1985). Reports also exist of positive correlations between

platelet MAO activity and post-dexamethasone cortisol levels

(Meltzer et al., 1988; Schatzberg et al., 1987).

Several of the studies examining the relationship between HPA

and platelet MAO activity have found that specific clinical

symptoms have been associated with both biochemical measures

studied. Schatzberg et al. (1985) found that both post-

dexamethasone cortisol levels and platelet MAO activity were

correlated with total HRSD score (a measure of severity), and

early, middle and late insomnia. Agren & Oreland (1982) reported a

significant positive correlation between both urinary free

cortisol, platelet MAO activity, and early morning awakening.

Finally, Georgotas et al. (1986) hypothesized that one reason that

higher MAO activity has been found in DST non-suppressors may be

that anxiety and agitation which have been found to be associated

with higher platelet MAO activity, may also "account for some

cases of DST non-suppression" (p. 255).

Studies reporting on the clinical correlates of biological

measures of depression often present discrepant findings, and

point to a complex relationship between HPA activity,

catecholamine systems, platelet MAO activity, and specific signs

and symptoms. Many of the studies are complicated by the use of

diagnostic categories, particularly the endogenous, non-endogenous

distinction. Due to the lack of a valid operational definition of

endogenous depression (Zimmerman et al., 1985), this diagnostic

subtype does not consistently identify a homogeneous group of

patients, and has also been found to be confounded with severity of illness ( Kumar et al., 1986).

Studies which organize data from biological measures of depression around "symptoms and their severity rather than diagnostic groups" (Davis et al., 1981, p. 1560) may prove to be of more potential use clinically. Even more promising are studies which have used either a multiple correlational approach or discriminate function in the analysis of their data. These approaches have allowed researchers to disregard diagnostic labeling while simultaneously examining both endogenous and nonendogenous symptoms. Further research is needed in the attempt to elucidate the relationship between biological measures of depression and their clinical correlates. Future studies must take into consideration the effects of sex and age on biological measures, as well as distinguish between unipolar and bipolar depressed patients. In addition, further studies are needed to measure several biological factors in the same group of people, and to examine the inter-relationship between these biological measures, as well as their association with clinical characteristics.

## Purpose of study

The present study was conducted in order to more fully explore the relationship between four biological measures (post-dexamethasone cortisol, urinary free cortisol, urinary MHPG, platelet MAO activity) and clinical symptoms of depression.

The majority of previous studies in which relationships between biochemistry and clinical symptoms have been examined, have focused on major depressive disorder without consideration of subtypes. Most of these studies have also investigated relationships between clinical features and biological measures in combined groups of females and males. Despite reports of associations between biochemical measures and age and severity, few studies have controlled for these effects.

In this study, associations between biochemistry and clinical symptoms were studied not only in the total group of patients, but in a subgroup of patients diagnosed with unipolar major depression as well. Further analyses were performed on female and male patients separately. It was anticipated that different relationships would be observed between biological measures and clinical symptoms in the total group of patients as compared to the unipolar patients, and in the female subgroups as compared to the male subgroups. In the present study the effects of age and severity were controlled for in order to determine whether relationships between the biological measures and clinical

symptoms would remain after these effects were statistically removed.

Previous research has primarily examined the relationship between biological measures and endogeneity, severity, endogenous symptoms, and/or nonendogenous symptoms. In the present study these relationships were also examined in order to determine whether the biological measures would relate more strongly to overall endogeneity and severity, or more to specific symptoms of depression. Both endogenous and nonendogenous symptoms were studied in an attempt to determine whether endogenous or nonendogenous symptoms would be more frequently and strongly related to the biological measures. Based on findings from previous reports, in the present study it was anticipated that non-suppressors and suppressors on the DST would be able to be distinguished from one another on the basis of clinical symptoms, and that a "high" and "low" MHPG syndrome could be identified.

In the present study the relationship between biological measures and suicidality was a primary focus. Much of the previous literature which has examined this relationship has focused on past suicidality, most often in either suicide victims or suicide attempters. In the present study both past suicidality (occurring during the worst week of the current episode), and current suicidality (occurring during the same week as the biological measurement) were studied in order to more fully explore the relationship between suicidality and biological measures, as well as to determine whether assessment of past or present suicidality

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affected these relationships. This study was also designed to examine whether patients with higher ratings of suicidality would differ biochemically from patients with lower ratings of suicidality.

The present study is one of the few to examine relationships between clinical symptoms and more than one biological measure. It was designed to assess different aspects of biological functioning (HPA activity, noradrenergic activity, platelet MAO activity) simultaneously in the same group of patients, and to explore whether the presence of specific clinical symptoms was related to more than one biological measure.

This study was designed as an exploratory study with the intention both of confirming or disconfirming previous reports, as well as suggesting areas for further exploration of the relationship between biological measures and clinical correlates.

# CHAPTER II

## METHODS

This study included 83 patients with major depressive disorder (52 female and 31 male) who ranged in age from 18 to 65 years (mean ± SD age= 38.5 ± 11.5). All patients were medically and neurologically healthy. Any patient with marked recent weight loss of 20% of body weight was excluded (Carroll et al., 1981). Subjects did not receive psychoactive medication for at least seven days (at least two weeks in the case of two patients who had previously been on MAO inhibitors) before blood was drawn for platelet MAO determination, with the exception of the administration of low doses of a benzodiazepine to six patients for agitation or insomnia. Of these, four received oxazepam, one received lorazepam, and another flurazepam.

Informed consent was gained from all participating patients after a complete explanation of research procedures. Clinical ratings and biochemical measures were obtained during a one week period. During this time period, all patients were rated using the 21-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960). HRSD scores ranged from 11 to 39, with a mean ± S.D. of 24.2 ± 5.4. Forty-three patients were interviewed using the Schedule for Affective Disorders and Schizophrenia (SADS). Patients were diagnosed using Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), or other available clinical data. Of the

83, 67 met criteria for unipolar major depression.  Sixteen met criteria for bipolar disorder. Of those, 5 were bipolar I, eleven were bipolar II. Of the 67 unipolar major depressed patients, 47 and sixteen fulfilled criteria for definite and probable endogenous sub-types respectively. Four were not endogenous.

The presence or absence of psychotic features of depression was rated clinically on a 3 point scale; a rating of 1 indicated the absence of psychotic features, a rating of 2 the probable presence of psychotic features, and a rating of 3 the definite presence of psychotic features. Seventy-six patients received a rating of 1, two patients received a rating of 2, and five patients received a rating of 3.

Suicidality was assessed in two ways. Current suicidality was rated using the HRSD suicide item (item 3), a five point scale ranging from 0 (absence of suicidal ideation) to 4 (serious suicide attempt). Twenty-one patients received a rating of 0, thirty-two a rating of 1, twenty a rating of 2, and nine a rating of 3. No patients received a rating of four, and one patient had missing data.

Past suicidality was rated using the SADS item suicidal tendencies (item 246), which assesses suicidality occurring during the worst week of the current episode or during the worst week of the past year. This item ranges from 1 (absence of suicidal ideation) to 7 (serious suicide attempt). Eight patients received a rating of 1, four patients a rating of 2, ten patients a rating of 3, sixteen patients a rating of 4, and one patient each,

ratings of 5, 6, and 7. In this study, all clinical ratings were performed by raters who were blind to the biochemical data.

Each patient had blood samples drawn using a simple needle stick. Blood samples were drawn between 8 a.m. and 9:30 a.m. for determination of platelet MAO activity. When two platelet MAO activity levels for a patient were available, mean values were used in the data analysis. Blood was drawn for the determination of cortisol at 4 p.m. on days 1 and 2 of the study. A 1 mg. dose of dexamethasone was given at 11 p.m. on day 1 of the study. All patients had at least one MAO level drawn on a day other than that following the administration of the dexamethasone. Sixty-seven patients collected 24 hr. urine specimens for MHPG and UFC determination over a two or three day period. Patients were given detailed instructions concerning the collection of 24-hour urine specimens; the completeness of the collection was ascertained by careful interviews, with specific documentation and recording of possible urine losses, and by measurements of 24-hour urine volume and creatinine excretion. Mean values of urinary measurements were used for data analysis.

Differential centrifugation was used to isolate the platelets, and platelet MAO activity was determined by measuring deamination of 12 C-tryptamine bisuccinate by methods described by Orsulak et al. (1978) and by Gudeman et al. (1982); activity is expressed as nanomoles tryptamine deaminated per hour per mg. protein. On several occasions, levels of MAO activity isolated in platelets that were obtained by this differential centrifugation method were compared with those levels from platelets obtained by

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the Corash procedures (Corash et al., 1977) and similar values were observed for platelet MAO activity (Mooney et al., 1981).

Plasma cortisol levels were determined with radioimmunoassay (RIA) methods, as described by Schatzberg et al. (1983a). Non-suppression was defined as a 4 p.m. post-dexamethasone cortisol level> 5 $\mu$g./dl. (Carroll et al., 1981; Schatzberg et al., 1983a).

Total 24-hour urine collections were obtained with acetic acid as preservative and aliquots were stored at $-20°$ C until analysed. Urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) was determined by electron capture gas chromatography using a modification of the method of Dekirmenjian and Maas (1970). Under routine operations, the interassay coefficient of variation was 6.2%. Urinary free cortisol was determined by radioimmuno assay using a commercially available (Amersham cortisol $I^{125}$ radioimmunoassay system) antibody specific for cortisol and $I^{125}$ labled antigen following the method described in the NEDH Laboratory of Pathology Chemistry Procedure Manual. Biochemical determinations were performed by laboratory personnel blind to the clinical diagnosis.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS-X). Separate multiple regression analyses were performed using each of the biochemical measures as the dependent variable, and age and severity as the independent variables in the analyses involving post-dexamethsone cortisol and platelet MAO activity, and age, severity, creatinine and total volume of urine as independent variables in the analyses involving urinary free cortisol and MHPG. Standardized residuals from these

regressions were then correlated with the items from the HRSD and selected items from the SADS using Spearman correlations. Here these are referred to as partial correlations. Zero-order Spearman correlations were also calculated between the biological measures and clinical symptoms. Only the correlations between the biological measures and age, severity and endogeneity are presented here.

Correlations were calculated for the following groups: the total group of patients, the group of unipolar major patients, and the group of bipolar patients. Correlations were also computed for females and males separately within these diagnostic groups. Data from the bipolar patients are not reported on here, as the small sample size in the bipolar group, particularly in the female and male subsets make questionable the interpretation of the results.

Correlations attaining p values of < .05 were considered significant, however, due to the large number of correlations computed in this study, the Bonferroni correction was applied. Data were interpreted both with and without this correction (see Discussion, p. 68).

Multiple regression analyses were performed after the computation of the correlation matrices, using each of the biochemical measues as the dependent variable, and using variables that had been observed to be significantly correlated with the specific biochemical measure, as well as age, sex and severity, as independent variables. Data were also analyzed using analysis of variance (ANOVA), covarying for age, sex and severity, discriminant function analyses, and Chi Square.

CHAPTER III


RESULTS


## Post-dexamethasone cortisol and clinical symptoms


Table 5 lists all significant correlations between post-dexamethasone cortisol and clinical symptoms in the total group of patients and in the female and male subgroups. In the total group of patients (see Table 5, p. 43) guilt was the only endogenous symptom to correlate significantly (negatively) with post-dexamethasone cortisol after controlling for the effects of age and severity. The nonendogenous symptom somatic anxiety was also significantly and negatively correlated with post-dexamethasone cortisol. The presence of psychotic symptoms, and the age of onset of the illness, were also observed to be positively associated with post-dexamethasone cortisol, but age ($r = -.17$, $p = NS$) and severity of illness ($r = .20$, $p = .08$) were not significantly related with post-dexamethasone cortisol in the total group of patients. The relationship between post-dexamethasone cortisol and endogeneity was stronger than that observed with age and severity ($r = .21$, $p = .06$), but was also not significant.

In the female subgroup a similar pattern of relationships between post-dexamethasone cortisol and clinical symptoms emerged. In females, even stronger relationships were observed between post-

dexamethasone cortisol and guilt, somatic anxiety, psychosis, and age of onset of the illness. In addition, a significant positive correlation with endogeneity was observed in females. In the male patients completely different associations were observed, with the only significant correlations occurring between post-dexamethasone cortisol and the endogenous symptom psychomotor retardation (positive correlation), and between post-dexamethasone cortisol and the nonendogenous symptom subjective anger (negative correlation).

TABLE 5

## PARTIAL CORRELATIONS[a] BETWEEN POST-DEXAMETHASONE CORTISOL AND CLINICAL SYMPTOMS IN THE TOTAL GROUP OF PATIENTS

### Post-dexamethasone Cortisol: All patients (N=83)

|  | r | p |
|---|---|---|
| Guilt (H)[b] | -.26 | .02 |
| Somatic anxiety (H) | -.34 | .002 |
| Psychosis | .26 | .02 |
| Age of onset of illness (S)[c] | .44 | .01 (N=33) |

### Post-dexamethasone cortisol

|  | Females (N=52) | | Males (N=31) | |
|---|---|---|---|---|
|  | r | p | r | p |
| Guilt (H) | -.39 | .005 | -.03 | NS |
| Somatic anxiety (H) | -.38 | .005 | -.33 | .07 |
| Psychosis | .34 | .01 | .03 | NS |
| Age of onset (S) | .56 | .004 (N=24) | .20 | NS (N=9) |
| Endogeneity | .28 | .05 | .08 | NS |
| Psychomotor ret[d] (S) | -.14 | NS (N=24) | .54 | .05 (N=14) |
| Subjective anger (S) | .02 | NS (N=25) | -.68 | .005 (N=15) |

[a] Spearman correlations (two-tailed) were computed after the effects of age and severity on post-dexamethasone cortisol had been controlled for.

[b] (H)= Item from Hamilton Depression Rating Scale

[c] (S)= Item from Schedule for Affective Disorders and Schizophrenia

[d] ret= retardation

After Bonferroni correction, p values < .002 are significant.

In the unipolar major group (See Table 6, p.45), none of the endogenous symptoms correlated with post-dexamethasone cortisol, after the effects of age and severity had been removed. As observed in the total group of patients, post-dexamethasone was again significantly and negatively correlated with somatic anxiety, and positively correlated with the age of onset of illness. Additionally, in the unipolar major patients the length of the current illness was observed to be negatively associated with post-dexamethasone cortisol.

In both unipolar females and males, the nonendogenous symptom somatic anxiety was negatively and significantly associated with post-dexamethasone cortisol. Aside from this common finding, different patterns of relationships between post-dexamethasone cortisol and symptoms emerged in females and males. In female unipolar patients the only endogenous symptom to correlate significantly (negatively) with post-dexamethasone cortisol was guilt. Significant positive correlations were also observed in female unipolars between post-dexamethasone cortisol and the nonendogenous symptom obsessionality, as well as with age of onset of the illness. In male unipolars, three different negative significant correlations were observed between post-dexamethasone cortisol and the following nonendogenous items: gastrointestinal symptoms, somatic symptoms, and subjective anger.

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TABLE 6

PARTIAL CORRELATIONS[a] BETWEEN POST-DEXAMETHASONE CORTISOL AND CLINICAL SYMPTOMS IN UNIPOLAR MAJOR PATIENTS

Post dexamethasone cortisol: All Unipolar patients (N=67)

| | r | p |
|---|---|---|
| Somatic anxiety (H)[b] | -.38 | .001 |
| Age of onset (S)[c] | .39 | .05 (N=26) |
| Length of illness (S) | -.38 | .04 (N=29) |

| | Post-dexamethasone cortisol | | | |
|---|---|---|---|---|
| | Females (N=42) | | Males (N=25) | |
| | r | p | r | p |
| Somatic anxiety (H)[b] | -.38 | .01 | -.44 | .03 |
| Age of onset (S)[c] | .49 | .04 (N=19) | .14 | NS (N=7) |
| Length of illness (S) | -.36 | NS (N=20) | -.54 | NS (N=9) |
| Guilt (H) | -.33 | .03 | .006 | NS |
| Obsessionality (H) | .49 | .03 (N=19) | .24 | NS (N=12) |
| Gastrointestinal symptoms | .12 | NS | -.39 | .05 |
| Somatic Symptoms | .04 | NS (N=41) | -.41 | .04 |
| Subective anger (S) | .11 | NS (N=21) | -.58 | .04 (N=13) |

[a] Spearman correlations (two-tailed) were computed after the effects of age and severity on post-dexamethasone cortisol had been controlled for.

[b] (H) = Item from Hamilton Rating Scale for Depression

[c] (S) = Item from Schedule for Affective Disorders and Schizophrenia

After Bonferroni correction, p values < .003 are significant.

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To more fully examine the relationship between clinical symptoms and post-dexamethasone cortisol, a multiple regression analysis was performed on the total group of patients using forced entry of variables. In this analysis, variables which were observed to be significantly correlated with post-dexamethasone cortisol, as well as age, sex and severity, were used as the independent variables, and post-dexamethasone cortisol was set as the dependent variable. This analysis identified three items (p < .03) which accounted for a significant portion of the variance (multiple R = .62, R square = .38, p = .001). These items were psychosis and endogeneity which entered in a positive direction, and guilt which entered in a negative direction.

In order to examine the clinical difference between suppressors (N=59) and non-suppressors (N=24) of post-dexamethasone cortisol on the items of the HRSD, a discriminant function analysis was performed. Only one symptom, paranoia, was a significant contributor (p = .04) to the discriminant function separating suppressors and non-suppressors. Patients were able to be classified into suppressors and non-suppressors with only 51.8 % accuracy.

## Post-dexamethasone cortisol and suicide

Analysis of variance, covarying for the effects of age, sex, and severity was used to compare the mean levels of post-dexamethasone cortisol in those patients with a rating of 2 or

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above on the HRSD suicide item (mean ± SD post-dexamethasone
cortisol = 3.68 ± 4.12), and those patients with a HRSD suicide
rating of less than 2 (mean ± post-dexamethasone cortisol = 4.11 ±
4.65). No significant effects for either group (F = 1.16, p = NS)
or covariates were observed.

In those patients with HRSD suicide ratings of 2 or above,
seven were non-suppressors, and 2 were suppressors. In patients
with HRSD suicide scores of less than 2, seventeen were non-
suppressors and 36 were suppressors (Chi square = .25, df = 1, p =
NS).


## Urinary free cortisol (UFC) and clinical symptoms


Table 7 lists all significant correlations between UFC and
clinical symptoms in the total group of patients and in the female
and male subgroups. In the total group of patients in whom urinary
free cortisol was measured (N=38) (see Table 7, p. 49), two
endogenous symptoms, agitation and guilt, and two nonendogenous
symptoms, subjective anger and overt anger were observed to be
negatively and significantly correlated with urinary free cortisol
after the effects of age, severity, creatinine and total volume of
urine had been controlled for. Correlations of only trend
significance were observed between UFC and age (r = .31, p = .06),
and UFC and severity (r = .28, p = .09). No significant
relationship was observed between UFC and endogeneity (r = .11, p
= NS).

In the subgroup of females, significant negative partial correlations were again observed between urinary free cortisol and the endogenous symptom agitation (as measured on both the HRSD and SADS), but not with guilt. In contrast to findings in the total group, in females the nonendogenous symptoms paranoia (negative correlation), and increased sleep (positive correlation, were also observed to be significantly associated with urinary free cortisol.

In the male subgroup of patients, a different pattern was observed. As in the total group, subjective anger was negatively correlated with UFC, however in males the endogenous symptom retardation was also observed to be significantly and positively correlated.

TABLE 7

PARTIAL CORRELATIONS[a] BETWEEN URINARY FREE CORTISOL (UFC) AND
CLINICAL SYMPTOMS IN THE TOTAL GROUP OF PATIENTS

TOTAL GROUP

UFC: All Patients (N=38)

| | r | p |
|---|---|---|
| Agitation (H)[b] | -.50 | .002 |
| Guilt (S)[c] | -.41 | .05 (N=24) |
| Subjective anger (S) | -.60 | .002 (N=24) |
| Overt anger (S) | -.53 | .009 (N=23) |

| | UFC: Females (N=23) | | Males (N=15) | |
|---|---|---|---|---|
| | r | p | r | p |
| Agitation (H) | -.60 | .002 | -.38 | NS |
| Guilt (S) | -.34 | NS (N=14) | -.27 | NS (N=10) |
| Subjective anger (S) | -.41 | NS (N=13) | -.84 | .001 (N=11) |
| Overt anger (S) | -.44 | NS (N=12) | -.45 | NS (N=11) |
| Agitation (S) | -.58 | .05 (N=12) | .31 | NS (N=10) |
| Paranoia (S) | -.65 | .03 (N=11) | -.55 | NS (N=10) |
| Retardation (H) | -.06 | NS | .62 | .02 |
| Increased sleep (S) | .69 | .009 (N=13) | .26 | NS (N=9) |

[a] Spearman correlations (two-tailed) were computed after the
effects of age, severity, creatinine and total volume on UFC had
been controlled for.

[b] (H)= Item from Hamilton Rating Scale for Depression

[c] (S)= Item from Schedule for Affective Disorders and
Schizophrenia

After Bonferroni correction, p values < .003 are significant.

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In the unipolar major group of patients (see Table 8, p. 51), urinary free cortisol again correlated negatively with agitation, as well as with another endogenous symptom, psychomotor retardation (positive correlation). In the unipolar group, the nonendogenous symptoms of subjective and overt anger again correlated negatively with urinary free cortisol, and a positive correlation with the nonendogenous symptom obsessionality was observed as well.

In female unipolar patients, fewer significant correlations were observed, with only the correlation between urinary free cortisol and the endogenous symptom agitation attaining significance. In the male unipolar subgroup, no significant correlations with endogenous symptoms were seen, and the relationships between urinary free cortisol and nonendogenous symptoms paralleled those of the total unipolar group; significant partial correlations were observed between urinary free cortisol and subjective and overt anger, and a positive significant partial correlation between urinary free cortisol and obsessionality was observed as well.

TABLE 8

PARTIAL CORRELATIONS[a] BETWEEN URINARY FREE CORTISOL AND CLINICAL
SYMPTOMS IN UNIPOLAR MAJOR PATIENTS

|  | UFC: All Unipolar Patients (N=32) | |
|---|---|---|
|  | $r$ | $p$ |
| Agitation (H)[b] | -.47 | .007 |
| Obsessionality (S)[c] | .54 | .02 (N=18) |
| Subjective anger (S) | -.65 | .003 (N=19) |
| Overt Anger (S) | -.69 | .002 (N=18) |
| Psychomotor retardation (S) | .51 | .04 (N=17) |

|  | UFC: Females (N=19) | | Males (N=13) | |
|---|---|---|---|---|
|  | $r$ | $p$ | $r$ | $p$ |
| Agitation (H) | -.61 | .006 (N=19) | -.26 | NS (N=13) |
| Obsessionality (S) | .11 | NS (N=10) | .95 | .00 (N=8) |
| Subjective anger (S) | -.28 | NS (N=10) | -.77 | .02 (N=9) |
| Overt anger (S) | -.61 | .08 (N=9) | -.73 | .03 (N=9) |
| Psychomotor retardation (S) | .42 | NS (N=9) | .40 | NS (N=8) |

[a] Spearman correlations (two-tailed) were computed after the
effects of age, severity, creatinine and total volume on UFC had
been controlled for.

[b] (H) = Item from Hamilton Rating Scale for Depression

[c] (S) = Item from Schedule for Affective Disorders and
Schizophrenia

After Bonferroni correction, p values < .003 are significant.

A multiple regresssion analysis using forced entry of variables was performed in the total group of patients in order to further explore the relationship bewteen urinary free cortisol and clinical symptoms. In this analysis the dependent variable was urinary free cortisol, and the independent variables were those that had been observed to be significantly correlated with urinary free cortisol, as well as age, sex, severity, and suicidal tendencies. Suicidal tendencies was entered as an independent variable based on previous findings suggesting that past suicidality may play a part in explaining the total variance of UFC. Overt anger, and subjective anger were significant negative contributors, and suicidal tendencies, and severity were significant positive contributors to the variance of urinary free cortisol ($p < .05$) (multiple R= .63, R square = .40, $p = .0006$).

## Urinary free cortisol and suicide

An analysis of variance covarying for the effects of age, sex and severity was used to compare the mean levels of urinary free cortisol in those patients in the total group with a HRSD rating of 2 or above (mean ± SD urinary free cortisol = 105.65 ± 44.49), and those patients with a HRSD suicide rating of less than 2 (mean ± SD urinary free cortisol = 97.48 ± 31.94). Significant effects for age (F= 4.43, $p = .04$), sex (F= 7.96, $p = .008$), and severity (F = 4.31, $p = .05$) were observed, however, the main effect for group was non-significant (F= .05), P = NS).

## MHPG (3-methoxy-4-hydroxyphenylglycol) and clinical symptoms

In the total group of patients (see Table 9, p. 54) for whom
values for MHPG, creatinine and total urinary volume were
available (N=64), only the nonendogenous symptom depressed mood
correlated significantly and negatively with MHPG after the
effects of age, severity, creatinine and total volume on MHPG had
been controlled for. Neither age (r= .13, p = NS), severity (r =
.11, p = NS) nor endogeneity (r = -.02, p = NS) were significantly
correlated with MHPG in the total group. In the female and male
subgroups, again only nonendogenous symptoms were observed to
correlate significantly with MHPG, with paranoia correlating
positively with MHPG in females, and somatic symptoms correlating
positively in males.

TABLE 9

<u>PARTIAL CORRELATIONS</u>[a] <u>BETWEEN 3-METHOXY-4-HYDROXYPHENYLGLYCOL</u>
<u>(MHPG) AND CLINICAL SYMPTOMS IN THE TOTAL GROUP OF PATIENTS</u>

TOTAL GROUP

<u>MHPG: All Patients (N=64)</u>

|  | <u>r</u> | <u>p</u> |
|---|---|---|
| Depressed Mood (H)[b] | -.26 | .04 |

|  | <u>MHPG: Females (N=42)</u> | | <u>Males (N=22)</u> | |
|---|---|---|---|---|
|  | <u>r</u> | <u>p</u> | <u>r</u> | <u>p</u> |
| Depressed mood (H) | -.22 | NS | -.33 | NS |
| Paranoia (H) | .31 | .05 | -.31 | NS |
| Somatic symptoms (H) | -.05 | NS (N=41) | .46 | .03 |

[a] Spearman correlations (two-tailed) were computed after the
effects of age, severity, creatinine and total volume on MHPG had
been controlled for.

[b] (H) = Item from Hamilton Rating Scale for Depression

After Bonferroni correction, p values < .007 are significant.

In the unipolar major group (see Table 10, p. 56) the only endogenous symptom to correlate significantly (positively) with MHPG was agitation, and the only nonendogenous symptom to correlate was obsessionality. In the female subgroup, correlations with agitation and obsessionality were nonsignificant, however in females MHPG correlated significantly with three other nonendogenous symptoms: depressed mood (negative correlation), paranoia, and number of suicide attempts (positive correlations). In the male unipolar patients only the correlation between the endogenous symptom agitation and MHPG attained statistical significance.

In a multiple regression analysis performed on the total group of patients, in which MHPG was dependent and variables which had attained significance in the correlation analyses, as well as age, sex, and severity were the independent varables, sex, agitation and obsessionality were found to contribute significantly in a positive direction ($p < .05$) to the variance of MHPG (multiple $R = .57$, R square $= .32$, $p = .0005$). These findings did not appear to be due to an interaction effect of sex with agitation and obsessionality, as sex was not significantly correlated with either agitation ($r = .01$, $p = NS$) or obsessionality ($r = .06$, $p = NS$).

TABLE 10

PARTIAL CORRELATIONS[a] BETWEEN MHPG AND CLINICAL SYMPTOMS IN UNIPOLAR MAJOR PATIENTS

MHPG: All Unipolar Patients (N=67)

|  | r | p |
|---|---|---|
| Obsessionality (H)[b] | .28 | .05 (N=53) |
| Agitation (S)[c] | .44 | .01 (N=30) |

| | MHPG: Females (N=42) | | Males (N=25) | |
|---|---|---|---|---|
| | r | p | r | p |
| Obsessionality (H) | .21 | NS (N=35) | .34 | NS (N=18) |
| Agitation (S) | .28 | NS (N=20) | .77 | .009 (N=10) |
| Depressed mood (H) | -.33 | .05 (N=36) | -.10 | NS (N=18) |
| Number suicide attempts | .49 | .04 (N=18) | .00 | NS (N=7) |
| Paranoia (S) | .53 | .04 (N=15) | -.40 | NS (N=9) |

[a] Spearman correlations (two-tailed) were computed after the effects of age, severity, creatinine and total volume on MHPG had been controlled for.

[b] (H) = Item from Hamilton Rating Scale for Depression

[c] (S) = Item from Schedule for Affective Disorders and Schizophrenia

After Bonferroni correction, p values < .004 are significant.

## MHPG and suicide

A discriminant function analysis using variables which had been observed to be significantly correlated with MHPG in zero-order correlations, was performed in the total group in order to determine whether patients with "high" levels of MHPG (using a median split) could be separated from those with "low" MHPG on the basis of clinical symptoms. Only one symptom, suicidal tendencies (as rated on the SADS) was a significant contributor (p = .005) to the discriminant function separating patients with "high" MHPG from those with "low" MHPG. Patients were able to be classified into" high" and "low" MHPG groups with 64.1 % accuracy.

An analysis of variance covarying for the effects of age, sex, and severity was used to compare mean levels of MHPG in the subgroup of patients with a score of 3 and above on the SADS item suicidal tendencies (N= 27) (mean ± SD MHPG = 2585.11 ± 1089.74) to those with a score of less than 3 on the SADS item suicidal tendencies (N = 12) (mean ± SD MHPG = 2087.33 ± 632.12). A significant effect for sex (F= 24.35, p = .000) was observed, however a main effect for group did not attain significance (F = .24, P = NS).

In the total group of patients, a similar analysis of variance, covarying for age, sex and severity was performed. Patients with a HRSD suicide rating of 2 and above (mean ± SD MHPG + 2282 ± 718.64) were compared to those with a HRSD suicide rating of less than 2 (mean ± SD MHPG = 2496.28 ± 1001.79). Again, a

significant effect for sex (F = 32.22, p = .000) was observed, as well as a significant effect for severity (F = 7.89, p = .007). A significant main effect on MHPG was not observed (F= 1.15, p = NS).

## Platelet monoamine oxidase (MAO) activity and clinical symptoms

In the total group of patients (See Table 11, p. 60), platelet MAO activity was not significantly correlated with any endogenous symptoms after the effects of age and severity on platelet MAO activity had been controlled for. Platelet MAO activity was also not observed to correlate significantly with either age (r = .009, p = NS), or severity (r = .08, p = NS), and although correlated more strongly with endogeneity (r = .21, p = .06), this correlation did not attain statistical significance. Significant partial correlations were observed between platelet MAO activity and the nonendogenous symptoms of suicide (positive correlation), somatic anxiety, somatic symptoms, and genital symptoms (negative correlations).

In the female subgroup a similar pattern was seen, with platelet MAO activity again correlating with the nonendogenous symptoms suicide, somatic anxiety, somatic symptoms, and in addition correlating with obsessionality (positively). In females the correlation between platelet MAO activity and genital symptoms did not attain significance. Although no significant association between platelet MAO activity and specific endogenous symptoms

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were observed, overall endogeneity was significantly and
positively correlated with MAO in females. In males, somatic
anxiety was again observed to be negatively correlated with
platelet MAO activity, and a negative correlation with paranoia
was observed as well.

TABLE 11

PARTIAL CORRELATIONS[a] BETWEEN PLATELET MONOAMINE OXIDASE ACTIVITY AND CLINICAL SYMPTOMS IN THE TOTAL GROUP OF PATIENTS

TOTAL GROUP

Platelet MAO : All patients (N=83)

|  | r | p |
|---|---|---|
| Suicide (H)[b] | .26 | .02 |
| Somatic anxiety (H) | -.32 | .003 |
| Somatic symtoms (H) | -.27 | .02 |
| Genital symptoms (H) | -.22 | .05 |

| Platelet MAO: | Females (N=52) | | Males (N=31) | |
|---|---|---|---|---|
|  | r | p | r | p |
| Suicide (H) | .32 | .02 (N=51) | .02 | NS |
| Somatic anxiety (H) | -.27 | .05 | -.55 | .001 |
| Somatic symptoms (H) | -.30 | .03 | -.21 | NS |
| Genital symptoms (H) | -.27 | .06 | -.12 | NS |
| Endogeneity | .30 | .03 | .04 | NS |
| Obsessionality (H) | .45 | .001 (N=51) | -.21 | NS |
| Paranoia (S) | .09 | NS (N=18) | -.70 | .01 (N=12) |

[a] Spearman correlations (two-tailed) were computed after the effects of age and severity on platelet MAO activity had been controlled for.

[b] (H) = Item from Hamilton Rating Scale for Depression

[c] (S)= Item from Schedule for Affective Disorders and Schizophrenia

After Bonferroni correction, p values < .003 are significant.

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In the unipolar major group (see Table 12, p. 63) platelet MAO activity correlated significantly with overall endogeneity, however no relationship with specific endogenous symptoms was observed. As in the total group, platelet MAO activity correlated significantly with the nonendogenous symptoms of suicide (positive correlation), somatic anxiety, and somatic symptoms (negative correlations). In addition, a negative correlation with paranoia was observed.

In the female and male subgroups (see Table 13, p. 64), no endogenous symptoms were significantly associated with platelet MAO activity. In females only, overall endogeneity was observed to be significantly correlated with platelet MAO activity. The pattern of relationships between nonendogenous symptoms and platelet MAO activity was completely different in female and male patients. In the female subgroup, platelet MAO correlated significantly with suicide, psychic anxiety, obsessionality (positive correlations), somatic symptoms and genital symptoms (negative correlations). In males, none of theses symptoms were significantly related to platelet MAO activity. Instead, significant negative correlations were observed between platelet MAO activity and somatic anxiety, paranoia and depressed mood.

A multiple regression analysis was performed on the total group of patients to further examine the relationship between platelet MAO activity and clinical symptoms. In this analysis, platelet MAO activity was the dependent variable, and the independent variables (those which had attained statistical

significance in the correlational analyses as well as age, sex and severity), were forced into the equation. Five variables accounted for a significant portion of the variance (p < .05) (multiple R = .66, R square = .43, p = .0000). Sex, somatic anxiety and somatic symptoms entered negatively, and severity and current suicidality (HRSD), entered positively.

TABLE 12

PARTIAL CORRELATIONS[a] BETWEEN PLATELET MONOAMINE OXIDASE ACTIVITY
AND CLINICAL SYMPTOMS IN UNIPOLAR MAJOR PATIENTS

Platelet MAO:  All Unipolar Patients (N=67)

| | $r$ | $p$ |
|---|---|---|
| Endogeneity | .26 | .03 |
| Suicide (H)[b] | .36 | .003 (N=66) |
| Somatic anxiety (H) | -.27 | .03 |
| Somatic symptoms (H) | -.30 | .02 (N=66) |
| Paranoia (S)[c] | -.40 | .05 (N=25) |

[a] Spearman correlations (two-tailed) were computed after the
effects of age and severity on platelet MAO activity had been
controlled for.

[b] (H) = Item from Hamilton Rating Scale for Depression

[c] (S) = Item from Schedule for Affective Disorders and
Schizophrenia

After Bonferroni correction, p values < .002 are significant.

TABLE 13

<u>PARTIAL CORRELATIONS[a] BETWEEN PLATELET MONOAMINE OXIDASE ACTIVITY</u>
<u>(MAO) AND CLINICAL SYMPTOMS IN UNIPOLAR MAJOR FEMALES AND MALES</u>

UNIPOLAR MAJOR GROUP

<u>Platelet MAO</u>

|  | <u>Females (N=42)</u> | | <u>Males (N=25)</u> | |
|---|---|---|---|---|
|  | <u>r</u> | <u>p</u> | <u>r</u> | <u>p</u> |
| Endogeneity | .31 | .05 | .15 | NS |
| Suicide (H)[b] | .35 | .03 (N=41) | .24 | NS |
| Somatic anxiety (H) | -.24 | NS | -.53 | .007 |
| Somatic symptoms (H) | -.33 | .04 (N=41) | -.18 | NS |
| Paranoia (S) | -.11 | NS (N=15) | -.85 | .002 (N=10) |
| Psychic anxiety (H) | .38 | .01 | -.36 | .08 |
| Genital symptoms (H) | -.33 | .04 (N=39) | -.02 | NS (N=23) |
| Obsessionality (H) | .49 | .001 (N=41) | -.16 | NS |
| Depressed mood (H) | .14 | NS | -.45 | .02 |

[a] Spearman correlations (two-tailed) were computed after the effects of age and severity on platelet MAO activity were controlled for.

[b] (H) = item from Hamilton Rating Scale for Depression

[c] (S) = Item from Schedule for Affective Disorders and Schizophrenia

After Bonferroni correction, p values < .002 are significant.

## Platelet MAO and suicide

Analysis of variance, covarying for the effects of age, sex
and severity was used to compare the mean levels of platelet MAO
activity in those patients in the total group with a HRSD rating
of 2 or above (mean ± SD MAO = 8.27 ± 2.77 nanomoles of tryptamine
deaminated per hour per mg of protein), and those patients with a
HRSD suicide rating of less than 2 (mean ± SD MAO = 6.67 ± 2.43
units). Significant main effects on platelet MAO activity were
observed for group (F = 5.52, p = .02), and for sex (F = 8.32, p =
.005).

Analysis of variance, covarying for the effects of age, sex,
and severity was also used to examine levels of platelet MAO
activity in the subgroup of patients for whom ratings on the SADS
item suicidal tendencies were available (N= 41). Higher levels of
platelet MAO activity were observed in those patients with ratings
of 3 or above on the item suicidal tendencies (mean ± SD MAO =
6.91 ± 2.16), as compared to patients with ratings of less than 3
on the suicidal tendencies item (mean ± SD MAO = 6.53 ± 2.02). No
significant effects for either covariates or group (F = .46, p =
NS) were observed however.

## Inter-relationship of post-dexamethasone cortisol, platelet MAO activity and clinical symptoms

In the total group of patients, post-dexamethasone cortisol was significantly correlated with platelet MAO activity ($r = .28$, $p = .01$) (Spearman correlation, two-tailed). These two biochemical measures correlated similarly with a number of specific clinical symptoms.

In the total group of patients, significant negative correlations were observed between somatic anxiety and both post-dexamethasone cortisol and platelet MAO activity. In addition, both post-dexamethsone cortisol and platelet MAO activity were correlated similarly with overall endogeneity ($r= .21$, $p = .06$). In the subgroup of females, somatic anxiety was once more correlated with both biochemical measures. In addition, endogeneity was observed to be positively and significantly correlated with both post-dexamethasone cortisol and platelet MAO activity in females. In the male subgroup, there were no common significant correlations between both biochemical measures and specific clinical symptoms.

In the total group of unipolar patients, somatic anxiety was again observed to be negatively correlated with both post-dexamethasone cortisol and platelet MAO activity. A similar finding was observed in the male unipolar subgroup, however in the female unipolar patients, the only symptom signicantly related to both biochemicals was obsessionality.

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<u>Inter-relationship of MHPG, UFC and clinical symptoms</u>

In the total group of patients, MHPG was significantly correlated with UFC ($r = .47$, $p = .003$) ($N = 38$) (Spearman correlation, two-tailed). Despite the association of these two biochemicals, few clinical symptoms were observed to be significantly correlated with both. In both the total group of patients and in the subgroup of males, there were no similar significant correlations. In the subgroup of female patients, paranoia was significantly correlated with both biochemicals, however a positive correlation was observed between MHPG and paranoia, while UFC was negatively correlated with paranoia.

In the total group of unipolar patients, obsessionality was positively correlated with both MHPG and UFC. Agitation was significantly correlated with both biochemicals, however once again, a significant positive relationship between MHPG and agitation was observed, while UFC was negatively correlated with agitatiton. In neither the female or male subgroups were clinical symptoms observed to be significantly correlated with both MHPG and UFC.

CHAPTER IV


DISCUSSION


Data in this study point to complex relationships between
post-dexamethasone cortisol, urinary free cortisol, MHPG, platelet
MAO activity and clinical correlates. Several general patterns did
emerge, however. Overall, stronger relationships were observed
between the biological measures and specific clinical symptoms
than with either endogeneity or severity of illness. A greater
number of significant correlations were observed between the
biological measures and nonendogenous symptoms of depression, than
with endogenous symptoms. In general, different patterns of
correlations were observed in the total group of patients as
compared to the unipolar patients, and in the female subgroup as
compared to the male subgroup. Sex differences observed in this
study must be interpreted with caution however, as the sample was
predominately female, and the relatively small sample size in the
male subgroup may have contributed to the fewer significant
correlations observed in males.


Relationships between post-dexamethasone cortisol and endogeneity,
psychosis, and severity


In this study, endogeneity was found to be significantly
(positively) correlated with post-dexamethasone cortisol in female

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patients only. Although endogeneity was one of three significant contributors to the total variance of post-dexamethasone cortisol, the correlation between endogeneity and post-dexamethasone cortisol in the total group did not attain statistical significance. Overall these data suggest a significant yet weak relationship between post-dexamethasone cortisol and endogeneity.

While many studies have reported higher rates of DST non-suppression in endogenously depressed patients (Coryell et al., 1982; Feinberg & Carroll, 1984; Zimmerman et al., 1985; Zimmerman et al., 1986; Zhou et al., 1987), few studies have examined correlations between endogeneity and post-dexamethasone cortisol. One of the few studies to do so (Kumar et al., 1986), reported a moderate yet significant correlation between endogeneity and post-dexamethasone cortisol ($r = .27$, $p = .02$), a finding consistent with that of the present study.

In this study, post-dexamethasone cortisol was found to be more strongly related to endogeneity in female patients. While previous studies have reported no sex effect on DST results (Asnis et al., 1982; Brown & Shuey, 1980; Carroll et al., 1981; Maes et al., 1986), none of these have examined the relationship between endogeneity and post-dexamethasone cortisol levels separately in females and males.

Data in this study point to a significant relationship between post-dexamethasone cortisol and psychosis. Psychosis was found to be positively correlated with post-dexamethasone cortisol in both the total group of patients and in the subgroup of

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females. In addition, psychosis was observed to be one of three significant variables to contribute significantly to the total variance of post-dexamethasone cortisol. These findings are consistent with other reports of high levels of post-dexamethasone cortisol in psychotic patients (Rothschild et al., 1987).

In the current study, the relationship between post-dexamethasone cortisol and severity of illness attained only trend significance. This finding is consistent with other reports of a lack of association between post-dexamethasone cortisol and severity (Berger et al., 1982; Brown & Shuey, 1980; Larsen et al., 1985), but is in contrast with an even greater number of reports finding severity to be positively associated with post-dexamethasone cortisol (Davis et al., 1981; Kumar et al., 1986; Maes et al., 1986; Zhou et al., 1987).

Overall, post-dexamethasone was observed to be weakly but significantly related to endogeneity, strongly related to psychosis, and only very slightly related to severity. Based on the results of the regression analysis, it was anticipated that endogeneity, psychosis and guilt would be more strongly related to post-dexamethasone cortisol than other clinical signs and symptoms, however this did not prove to be the case.

## Post-dexamethasone cortisol and endogenous symptoms

Many studies have reported an association between post-dexamethasone cortisol and specific endogenous symptoms of

depression (Asnis et al., 1982; Christensen et al., 1986; Reus, 1982; Rubin et al., 1985). In the present study however, very few significant relationships between post-dexamethasone cortisol and endogenous symptoms were observed. This finding is consistent with our observation of a weak relationship between overall endogeneity and post-dexamethasone cortisol.

In this study, guilt was the only endogenous symptom to be correlated (negatively) with post-dexamethasone cortisol in the total group of patients; this relationship was observed to be even stronger in female patients. These findings are in contrast to previous studies reporting a positive relationship between guilt and post-dexamethasone cortisol (Christensen et al., 1986; Reus, 1982; Schatzberg et al., 1987).

Psychomotor retardation, another endogenous symptom of depression, was also found to be significantly (positively) associated with post-dexamethasone cortisol in the present study, however this relationship attained statistical significance in only the subgroup of males. This finding is consistent with other reports of a significant positive relationship between post-dexamethasone cortisol and retardation (Agren & Wide, 1982; Schatzberg et al., 1987; Zimmerman et al., 1986), however in these studies, post-dexamethasone cortisol and retardation were observed to be significantly related in combined groups of females and males, rather than in males only.

Given the relatively small number of endogenous symptoms observed to be significantly correlated with post-dexamethasone

cortisol, the findings from this study can be viewed as consistent with reports of an overall lack of relationship between post-dexamethasone cortisol and specific endogenous symptoms (Asnis et al., 1982; Brown & Qualls, 1981; Grunhaus et al., 1985: Kaspar & Beckman, 1983).

## Post-dexamethasone cortisol and nonendogenous symptoms

In this study, although stronger and more numerous correlations were observed between post-dexamethasone cortisol and nonendogenous symptoms of depression, these correlations were generally in a negative direction. The observation of very few significant positive correlations between post-dexamethasone cortisol and nonendogenous symptoms is similar to the finding of few positive relationships between post-dexamethasone cortisol and endogenous symptoms, and suggests that lower rather than higher levels of post-dexamethasone cortisol may be associated with the presence of specific clinical symptoms of depression.

Of the nonendogenous symptoms to correlate significantly with post-dexamethasone cortisol, somatic anxiety was the most strongly correlated, with significant negative relationships appearing in all of the patient groups, with the exception of the total male subgroup. This finding is in contrast to previous reports which have found a positive association between anxiety and post-dexamethasone cortisol (Ceulemans et al., 1985;

Christensen et al., 1986; Reus, 1982). These studies however, have not reported specifically on somatic anxiety, nor have they examined post-dexamethasone cortisol/anxiety relationships in specific subgroups.

Two other symptoms related to somatic disturbance, somatic symptoms, and gastrointestinal symptoms, were found to be negatively correlated with post-dexamethasone cortisol in the group of male unipolar patients. These findings are in contrast to a previous report of Christensen et al. (1986), in which ratings on the HRSD items somatic symptoms and gastrointesinal symptoms were combined into one score and found to be positively correlated with post-dexamethasone cortisol. Differences between the Christensen et al. study and the present one may be due both to gender differences, as well as to the unipolar diagnosis, since in the current study, positive yet insignificant relationships between both somatic symptoms and gastrointestinal symptoms were observed in the unipolar female group, while no significant relationship was observed bewteen these symptoms and post-dexamethasone cortisol in the total group of patients.

In this study, the nonendogenous symptoms obsessionality and subjective anger were also found to be significantly related to post-dexamethasone cortisol. These correlations were significant in only the unipolar female and male subgroups respectively, and may reflect chance findings, as few reports of relationships between these symptoms and post-dexamethasone cortisol exist in the literature. Schatzberg et al. (1987) did report finding a

significant correlation between post-dexamethasone cortisol and obsessionality, however, this association was in a negative direction while in the current study a positive correlation was observed.

Two other features of depressive disorder, the age of onset of the illness, and the length of the illness were found to be significantly related to post-dexamethasone cortisol in this study. The positive association between the age of onset of illness and post-dexamethasone cortisol, observed in the total group of patients and the unipolar patients, with stronger relationships in females, has not previously been reported. It is an intriguing finding however, as it suggests that age of onset may play a role in the biological expression of the disorder.

The other significant finding, that of a negative correlation between the length of the illness and post-dexamethasone cortisol in the group of unipolar patients, confirms a finding of Sashidharan et al. (1984), in which it was found that non-suppressors of post-dexamethasone cortisol at the time of study had been ill for shorter periods of time. This finding, in conjunction with that of the current study, suggests that higher levels of post-dexamethasone cortisol may be associated with a more acute form of the illness.

Post-dexamethasone cortisol and discriminant function analyses

In the current study an attempt was made to replicate the findings of Nasr et al. (1983) in which a discriminant function

analysis was conducted using all the items from the HRSD in order to separate suppressors from non-suppressors on the DST on the basis of clinical symptoms. While Nasr et al. (1983) reported being able to discriminate suppressors from non-suppressors with 92.5% accuracy on the basis of 9 clinical symptoms, in the current study only paranoia (a variable not reported to contribute to the discriminant function in the study of Nasr et al.), discriminated between suppressors and non-suppressors, classifying patients with only 51.8 % accuracy.

The finding of the present study also failed to confirm the report of Zimmerman et al. (1985), in which successful discrimination between suppressors and non-suppressors was made on the basis of five endogenous symptoms.

Differences between the present study and those of Nasr et al. (1983) and Zimmerman et al. (1985), may be due to differences in sample size, as the current study used twice as large a sample as the Nasr et al. (1983) study, and was approximately one-third the size of the Zimmerman et al. (1985) study. In addition, the inclusion of patients with psychotic features in the current study may have confounded the results. An interaction effect between paranoia and psychosis, which in this study were observed to be significantly correlated ($r = .27$, $p = .01$), may have contributed to paranoia being the only discriminating variable between suppressors and non-suppressors, particularly since psychosis was previously observed to be positively related to post-dexamethasone cortisol in this study.

## Post-dexamethasone cortisol and suicide

In this study no difference in degree of suicidality was found between supressors and non-suppressors of post-dexamethasone cortisol, or between patients with either "high" or "low" ratings of current suicidality as measured on the HRSD. In addition, post-dexamethasone cortisol was not observed to be correlated with suicide in either the total group or in any of the subgroups of patients.

This finding is consistent with other reports which failed to find a relationship between the DST and suicide (Brown et al., 1986; Secunda et al., 1986; Zimmerman et al., 1986), but is in contrast to those which have reported a positive association (Banki et al., 1884; Coryell & Schlesser, 1981; Reus, 1982). In the current study, although a continuum of suicidality was examined, few patients were severely suicidal at the time of study, a factor which may have affected the results. In general, it appears that in this study, suicidality was unrelated to HPA dysregulation.

## Urinary free cortisol (UFC) and clinical symptoms

Data in this study point to a stronger relationship between UFC and specific clinical symptoms than between UFC and either endogeneity or overall severity. Although severity was one of the four significant contributing variables to the variance of UFC,

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the correlation between UFC and severity did not attain significance.

Of the endogenous symptoms to correlate significantly with UFC, agitation was observed to be the most strongly and most frequently associated. This negative relationship between UFC and agitation was observed in both the total and unipolar groups of patients, however when the sexes were examined separately, significant correlations were observed only in females. The finding of a sex difference in UFC/agitation relationships may be partially an artifact due to the predominance of females in this sample.

Retardation, another measure of psychomotor disturbance, was found to be positively and significantly correlated with UFC in the unipolar group and in the total subgroup of males. This observation of a positive relationship between UFC and retardation, and a negative relationship between UFC and agitation, suggests that retardation and agitation may be opposite manifestations of a common underlying psychomotor disturbance, which is in turn related to UFC.

While no other reports of associations between psychomotor disturbance and UFC exist in the literature, several studies of post-dexamethasone cortisol, another measure of HPA dysfunction, have reported positive associations with either agitation or retardation (Agren & Wide, 1982; Asnis et al., 1982; Zimmerman et al., 1986).

In the current study, the endogenous symptom guilt was also found to be negatively correlated with UFC in the total group of patients. Again, this finding has not been reported in the literature, however, it is consistent with our previous finding of a negative relationship between post-dexamethasone cortisol and guilt.

Of the nonendogenous symptoms to correlate significantly with UFC (subjective anger, overt anger, paranoia, increased sleep, and obsessionality), only the relationships between subjective and overt anger and UFC have been reported in the literature. Further studies are needed to determine whether the significant relationships observed in the present study between UFC and paranoia, increased sleep and obsessionality are simply random findings.

In this study, negative correlations were observed between UFC and both subjective and overt anger as measured on the SADS. These relationships were observed in both the total group of patients and in the unipolar group, but were strongest in males. This finding is consistent with a previous report of Agren & Wide (1982) in which significant negative correlations between anger scores on the SADS and UFC were observed.

Both the present study and the study of Agren & Wide (1982) also point to a relationship between anger, UFC, and suicidality. Agren & Wide (1982) found that seriousness plus medical lethality of worst ever suicide attempt, subjective anger, and overt anger (contributing in a negative direction) explained 20% of the

variance of UFC. In the present study, subjective anger and overt anger were also found to contribute negatively to the variance of UFC, however suicidal tendencies and severity contributed in a positive direction, with all four items explaining 40% of the total variance of UFC.

In contrast to the study of Agren & Wide (1982) in which UFC was associated with less suicide proneness and less anger, in the present study, UFC was associated with less anger, but greater suicidality. Differences between the two studies may partly be accounted for by the differing measures of suicidality. Agren & Wide's finding related to the worst ever suicide attempts, while in the present study, suicidal ideation occurring during the worst week of the current episode was measured by the SADS item suicidal tendencies.

The finding of a negative relationship between UFC and both subjective and overt anger, and a positive association with suicidality, suggests that patients who experience or display less anger may be more likely to have higher UFC levels and may be more suicidal as well. In this study however, we were unble to find significant differences in levels of UFC between patients with either "high" or "low ratings of current suicidality as measured on the HRSD.

## MHPG (3-methoxy-4-hydroxyphenylglycol)

In this study no significant relationship was observed between MHPG and endogeneity. While few studies have reported on the relationship between endogenous status and MHPG, one study (Nelson & Charney, 1981) suggested that decreased MHPG may be specific to endogenous depression. The results of the present study failed to support this hypothesis.

Severity of illness was also found to be unrelated to MHPG in the current study. This finding is consistent with many other reports of a lack of an association between severity and MHPG (Davis et al., 1981; Redmond et al., 1986; Roy et al., 1986).

In this study, the only endogenous symptom to correlate with MHPG was agitation. This correlation attained significance in the unipolar group of patients only, and was considerably stronger in males. Agitation was also observed to be one of three variables to contribute significantly to the total variance of MHPG. A significant relationship between agitation and MHPG has not previously been reported in the literature to our knowledge, however another symptom of psychomotor disturbance, retardation, has been found to be positively associated with MHPG (Redmond et al., 1986). It is possible that overall psychomotor disturbance is related to higher levels of MHPG, and that in unipolar patients, particularly males, this is expressed in the form of agitation, while in other diagnostic groups or in females, it is expressed as retardation.

The significant correlations between MHPG and nonendogenous symptoms (depressed mood, paranoia, somatic symptoms and obsessionality) were relatively weak, and generally differed from the nonendogenous symptoms reported to be significantly related to MHPG in the literature. Only the item somatic symptoms which in the current study was observed to be positively and significantly correlated with MHPG in males, has been discussed in previous reports. Redmond et al. (1986) found that depressed patients with increased somatization had higher levels of CSF MHPG, and Agren (1980) found that "somatic preoccupation" was one of four symptoms to characterize a "high" MHPG group. Further studies are needed in order to determine whether the findings in the current study relating the nonendogenous symptoms of depressed mood, paranoia, and obsessionality to MHPG can be replicated, or are due more to chance findings.

## MHPG and suicide

In this study relationships between MHPG and suicide differed, depending upon whether ratings of past or present suicidality was assessed (SADS vs. HRSD), and the statistical method used. Using ANOVA, higher levels of MHPG were observed in those patients with greater past suicidality (measured on the SADS item suicidal tendencies), as compared to patients with lower levels of past suicidality, however these differences were not

statistically significant. In contrast, the SADS item suicidal tendencies was found to discriminate significantly between a "high" and "low" MHPG group, with the "high" MHPG group associated with greater past suicidality.

Agren (1980) also using discriminant function analysis, found the SADS item suicidal tendencies to be one of six discriminating variables differentiating between patients with high and low MHPG. In his study, however, Agren found MHPG to be negatively associated with suicidal tendencies, while in the present study MHPG was positively yet insignificantly related to MHPG.

In contrast to the finding of a positive association between MHPG and past suicidality using the SADS, a negative non-significant relationship was observed between MHPG and HRSD ratings of suicidality occurring at the time of biochemical measurement. Lower levels of MHPG were observed in patients with higher ratings of current suicidality (measured by the HRSD suicide item), as compared to patients with lower ratings of current suicidality. Again, these differences did not attain statistical significance. The finding of a negative relationship between MHPG and suicidality is consistent with the previously mentioned report of Agren (1980), as well as with a report of Secunda et al. (1986) in which suicide attempters were found to have significantly lower urinary and plasma MHPG levels than patients who had never attempted suicide. In the present study however, only ratings of suicidality occurring at the time of

biochemical measurement were negatively related to MHPG, while in the reports of Agren (1980) and Secunda et al. (1986), ratings of past suicidality were negatively associated with MHPG.

The findings of the current study point to the methodological difficulties involved in studying suicide, and suggest that some of the discrepancies in reports of relationships between suicidality and MHPG may be due to differences in methods of assessment of suicidality.

Relationships between platelet MAO activity and endogeneity and severity

In this study, a significant positive relationship was observed between platelet MAO activity and endogeneity in the total group of unipolar patients. When data from females and males were analyzed separately however, this association was significant in females only, with significant positive relationships observed in both the total and unipolar female subgroups. This data suggests that the association between platelet MAO activity and endogeneity is affected both by gender and diagnosis.

Previous reports have found platelet MAO activity to be higher in women (Bridge et al., 1985; Mann, 1979; White et al., 1983), a finding which may partially account for our observation of a stronger association between endogeneity and platelet MAO

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activity in females. In addition, the finding of a positive association between platelet MAO activity and endogeneity in unipolar patients only, is consistent with a study of Samson et al. (1985) in which higher platelet MAO activity was reported in unipolar endogenously depressed patients compared to bipolar endogenous patients or unipolar nonendogenous patients.

In contrast to several reports (Gudeman et al., 1982; Mann, 1979; Samson et al., 1985), in the current study no significant correlation was observed between platelet MAO activity and severity of the illness. Severity of illness was however, one of five variables to contribute significantly to the total variance of platelet MAO activity, which suggests that perhaps an interaction effect between severity and other clinical symptoms exists. This study included four patients who were only mildly depressed (total HRSD score less than 18), which may have contributed to the lack of significant association between platelet MAO activity and severity.

## Platelet MAO activity and clinical symptoms

In this study, no endogenous symptoms of depression were observed to correlate significantly with platelet MAO activity. This finding is unexpected given the previously observed significant relationship between platelet MAO activity and overall endogeneity. The present finding is in contrast to previous

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reports which have found a negative association between MAO activity and the endogenous symptom guilt (Perris et al., 1980; Perris et al., 1984; Schalling et al., 1980), and positive associations between platelet MAO activity and various forms of sleep disturbance (Agren & Oreland, 1982; Schatzberg et al., 1985).

In this study, several significant relationships between platelet MAO activity and nonendogenous symptoms were observed. Of these, somatic anxiety was the most strongly correlated, with significant correlations observed between platelet MAO activity and somatic anxiety in all the patient groups with the exception of the subgroup of unipolar females. This finding is in direct contrast to studies by Davidson et al. (1980) in which a positive association was observed between platelet MAO activity and anxiety, and Georgotas et al. (1986) in which platelet MAO activity was found to be positively correlated with somatic anxiety. In the study of Georgotas et al., psychic anxiety was found not to relate significantly to platelet MAO activity, while in the present study psychic anxiety was significantly and positively correlated with MAO in unipolar females, and negatively, although insignificantly correlated with platelet MAO activity in unipolar males.

Athough not previously reported in the literature, the present data point to an overall negative association between platelet MAO activity and symptoms which are related to somatic disturbances. In addition to the negative correlation observed

between platelet MAO activity and somatic anxiety, negative correlations were also observed between platelet MAO activity and both somatic and genital symptoms, with somatic symptoms correlating with platelet MAO activity in both the total and unipolar groups as well as in the respective female subgroups, and genital symptoms correlating with platelet MAO activity in the total group. These findings suggest that lower levels of platelet MAO activity may be associated with greater physiological disturbance which manifests itself in somatic symptoms.

The other nonendogenous symptoms observed to be significantly correlated with platelet MAO activity in this study, obsessionality, paranoia, and depressed mood, have also not previously been reported in the literature. In females, higher platelet MAO activity was observed to be associated with more obsessional thinking, while in males and in unipolar patients, lower platelet MAO activity was observed to be related to paranoia. The correlation between depressed mood and platelet MAO activity attained significance in only the subgroup of male unipolar patients. Previous studies have reported relationships between these symptoms and post-dexamethasone cortisol (Schatzberg et al., 1987), however, further research is needed in order to determine whether relationships between obsessionality, paranoia, and depressed mood and platelet MAO activity are more than random findings.

## Platelet MAO activity and suicide

Of the four biochemical measures of depression studied, platelet MAO activty was the most stongly associated with suicidality. Positive correlations were observed between platelet MAO activity and suicide in both the total and unipolar groups. When the sexes were examined separately, this relationship was observed to be strongest in females. In the regression analysis, suicide was observed to be one of five variables to explain the total variance of platelet MAO activity.

Levels of platelet MAO activity were also observed to be significantly higher in patients with higher ratings of current suicidality (assessed at the time of biochemical measurement using the HRSD suicide item) as compared to patients with lower current suicide ratings, even after the effects of age, sex, and severity had been controlled for. This finding suggests that the positive association observed between platelet MAO activity and suicide is not due simply to the higher levels of platelet MAO activity observed in women. Although not significant, higher levels of platelet MAO activity were also observed in patients with higher ratings of past suicidality (based on ratings from the SADS suicidal tendencies item) as compared to patients with lower ratings of past suicidality.

The present study is one of the first to report a positive association between platelet MAO activity and suicide. Other studies have either reported a negative relationship (Gottfries et

al., 1980, Buchsbaum et al., 1981), or no relationship between
MAO activity and suicide (Oreland et al., 1981; Reveley et al.,
1981). Data in this study may differ from previous reports due to
several factors. Unlike other studies, in this study, significant
positive associations between platelet MAO activity and
suicidality were observed when both ratings of current suicidality
and biochemical measurement were obtained during the same one week
period. In addition, the current study focused on depressed
patients only, rather than examining suicide across diagnostic
groups. The methodological approach used in this study may have
contributed to the contrasting findings.


## Inter-relationship of post-dexamethasone cortisol, platelet MAO
## activity and clinical symptoms


In this study post-dexamethasone cortisol was observed to
correlate positively and significantly with platelet MAO activity.
This finding is consistent with previous reports of a positive
association between these two biological meaures (Meltzer et al.,
1988; Schatzberg et al., 1983b; Schatzberg et al., 1985;
Schatzberg et al., 1987). It must be noted however, that in two of
these studies (Schatzberg et al., 1983b and Schatzberg et al.,
1985), a subset of patients (N = 26 and N = 50 respectively) from
the current study were reported on.

Although the biological relationship between these two measures remains unclear, it is possible that both are related to an endogenous subtype of depressive disorder. In this study post-dexamethasone cortisol and platelet MAO activity were observed to be identically although insignificantly correlated with endogeneity ($r = .21$, $p = .06$), as well as being significantly and positively correlated with endogeneity in the subgroup of females.

In this study no significant correlations were observed between either post-dexamethasone cortisol or platelet MAO activity and severity. This finding is in contrast to the study of Schatzberg et al. (1985) which found both measures to be modestly, but significantly, correlated with total HRSD scores in a subset ($N = 50$) of the same patients currently studied.

The one symptom that was observed to be negatively correlated with both post-dexamethasone cortisol and platelet MAO activity in the total group, as well as in several of the subgroups (the total female group, the unipolar group and the group of unipolar males) was somatic anxiety. This finding contrasts with a hypothesis proposed by Georgotas et al. (1986) which suggests that platelet MAO activity is associated with higher anxiety and agitation, symptoms which in turn account for some cases of DST non-suppression. The current findings suggest rather, that a lack of anxiety, at least of a somatic type, may be associated with higher levels of post-dexamethasone cortisol and platelet MAO activity, and that overall, higher levels of both

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biological measures may be related to a depressive syndrome involving more endogeneity and less anxiety.

## Inter-relationship of MHPG, UFC and clinical symptoms

In this study MHPG was observed to correlate positively and significantly with UFC in the total group of patients for whom these measures were available. This finding is consistent with a report of Rosenbaum et al. (1983) and others which found strong significant relationships betwen these two biological measures.

In this study neither MHPG nor UFC were significantly correlated with either severity or endogeneity. In addition, no clear pattern emerged between both of these biological measures and clinical symptoms. Obsessionality was observed to be significantly and positively correlated with both MHPG and UFC in the group of unipolar patients, however the other two symptoms (paranoia and agitation) observed to be significantly correlated with both measures were correlated in opposite directions with each biological measure. Since only a subset of the sample (N= 38) had both MHPG and UFC measurements, it is possible that the overall lack of associations between these two measures and clinical symptoms is due to the small sample size, and that more meaningful relationships would emerge in a larger sample of patients.

Relationships between biological measures and clinical symptoms in
the unipolar group as compared to the total group

In this study separate correlation matrices were calculated
for the total group of patients (a combined group of unipolar and
bipolar patients), and for the unipolar group of patients. Given
the more homogeneous nature of the unipolar group, it was
anticipated that to some extent, different patterns of
relationships between the biological measures and clinical
symptoms would be observed in the unipolar group, while also
anticipating a large degree of overlap between findings in the
two groups due to the majority of the total sample being diagnosed
as unipolar. As anticipated, several variables were observed to be
significantly correlated with the biological measures in the
unipolar group, but not in the total group, and in some cases
stronger associations were observed in the unipolar group as
compared to the total group.

In the correlations between post-dexamethasone cortisol and
clinical symptoms, the variables that were observed to be
significantly correlated in the unipolar group but not in the
total group were length of illness (significant in the total
unipolar group), somatic symptoms, and obsessionality (significant
in the unipolar female subgroup). A stronger relationship between
post-dexamethasone cortisol and somatic anxiety was observed in
the unipolar group.

In the correlations between UFC and clinical symptoms in the unipolar group, relationships emerged between UFC and psychomotor retardation (in the total unipolar group) and obsessionality (in the male subgroup); these relationships were not observed to be significant in the total group. The association between overt anger and UFC was stronger in the unipolar group of patients than in the total group, although in both, the correlations were statistically significant.

Significant relationships between MHPG and obsessionality, agitation, (in the total unipolar group) and number of suicide attempts (in the unipolar female subgroup) were observed in unipolar patients but not in the total group of patients.

In the correlations between platelet MAO activity and clinical symptoms, two variables, endogeneity and paranoia, were significantly related to platelet MAO activity in the total unipolar group, but not in the total group of patients. Psychic anxiety was also observed to be significantly related to platelet MAO activity in unipolar females but not in the total group of females. An even stronger relationship was observed between platelet MAO activity and suicide in the unipolar group as compared to the total group, although again in both, the correlations were significant.

These data point to the usefulness of studying subtypes of depressive disorders. Although not reported in this study, different relationships between biological measures and clinical symptoms were observed in the bipolar group of patients. The data

presented here suggest that symptom patterns may vary in subtypes of depressive disorders and that these symptoms may relate differently to biological measures in subtypes of depressive disorders.

## Relationships between biological measures and clinical symptoms in female and male patients

In this study a greater number of significant correlations were observed between biological measures and clinical symptoms in the female group of patients than in the male subgroup. As stated previously, this finding may be due to the larger sample size of the female subgroup, but may also reflect differences in both biological measures and in symptom patterns in females and males.

Very few symptoms were observed to correlate significantly with the biological measures in both the female and male subgroups. In fact, almost completely opposite patterns of relationships were observed in female and male paients. While these differences will not be discussed in detail here, Tables 5 through 13 demonstrate this pattern clearly.

Of the many symptoms examined in this study, only two were correlated similarly and significantly with biological measures in females and males. Somatic anxiety was correlated significantly with post-dexamethasone cortisol in both unipolar females and males, as well as being correlated significantly with platelet MAO

activity in the total female and male subgroups. Guilt was significantly correlated with post-dexamethasone cortisol in both the unipolar female and male subgroups.

Further studies are needed in order to help determine whether the greater number of symptoms observed to be related to biological measures in females in this study, is due to increased symptomatic complaints in females, different biological mechanisms in females and males, or can simply be attributed to random findings.

## Summary

In this study complex relationships were observed between biological measures and clinical correlates in a total group of 83 patients, a subgroup of 67 unipolar major patients, and in female and male patients in these two groups. Data from all correlations which attained significance levels of $p < .05$ were presented and discussed in an attempt to most fully explore the relationships between four biological measures of depression and clinical signs and symptoms. Due to the large number of correlations calculated in this study however, the risk of a Type II error (a false positive identification of significance due to chance alone) was quite high. After adjusting statistically for this possibility using the Bonferroni correction, fewer, yet significant correlations were still observed between the biological measures and clinical correlates. These statistically more robust

correlations, in conjunction with the regression analyses, provide the most reliable data concerning relationships between biological measures and clinical correlates.

The four key symptoms observed to be related to post-dexamethasone cortisol based on the more stringent criteria were somatic anxiety, guilt, psychosis and endogeneity. Three of these symptoms, guilt, psychosis and endogeneity explained 41 % of the total variance of post-dexamethasone cortisol, while somatic anxiety was observed to be significantly correlated with post-dexamethasone cortisol in the total and unipolar groups even after Bonferroni correction.

UFC was observed to be primarily related to five symptoms (overt anger, subjective anger, suicidal tendencies, agitation, and obsessionality), as well as to sex and severity after more stringent statistical criteria were applied. As reported earlier, overt anger, subjective anger, suicidal tendencies, sex, and severity explained 41 % of the variance of UFC. Correlations between UFC and agitation and UFC and subjective anger remained statistically significant in the total group, after Bonferroni correction, as did correlations between UFC and agitation, subjective anger, and overt anger in the unipolar group. Obsessionality remained significantly correlated with UFC in the male unipolar subgroup after statistical correction.

No significant correlations were observed between MHPG and clinical symptoms after Bonferroni correction. The regression analysis in which sex, agitation, and obsessionality were observed

to explain 32 % of the total variance of MHPG probably provides the best measure of relationships between MHPG and clincal symptoms.

The five key symptoms observed to be related to platelet MAO activity using more stringent statistical criteria were somatic anxiety, suicide, somatic symptoms, obsessionality, and paranoia, as well as sex and severity. Forty-three percent of the variance of platelet MAO activity was explained by somatic anxiety, suicide, somatic symptoms, sex, and severity. Somatic anxiety was also observed to correlate significantly with platelet MAO activity in the total group and total group of males after Bonferroni correction. In the female subgroup and in unipolar males, obsessionality remained significantly correlated with platelet MAO activity after statistical correction, as did paranoia in the subgroup of unipolar males.

These data point to essentially unique relationships between each of the four biochemicals and clinical symptoms. Only three of the symptoms, somatic anxiety, agitation, and obsessionality were observed to correlate with more than one biochemical measure after Bonferroni correction. Further studies are needed to explore whether even these more robustly related symptoms are best explained by chance alone, or can be replicated in the future.

APPENDIX


## Hamilton Rating Scale for Depression


1. Depressed Mood

   0. Absent
   1. These feeling states indicated only on questioning
   2. These feeling states spontaneously reported verbally
   3. Communicates feeling states non-verbally-i.e., through facial expression, posture, voice, and tendency to weep
   4. Patient reports virtually only these feeling states in his spontaneous verbal and non-verbal communication

2. Feelings of Guilt

   0. Absent
   1. Self-reproach, feels he has let people down
   2. Ideas of guilt or rumination over past errors or sinful deeds
   3. Present illness is a punishment, delusions of guilt
   4. Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. Suicide

   0. Absent
   1. Feels life is not worth living
   2. Wishes he were dead or any thoughts of possible death to self
   3. Suicide ideas or gesture
   4. Attempts at suicide (any serious attempt rates 4)

4. Insomnia Early

   0. No difficulty falling asleep
   1. Complains of occasional difficulty falling asleep - i.e. more than ½ hour
   2. Complains of nightly difficulty falling asleep

5. Insomnia Middle

   0. No difficulty
   1. Patient complains of being restless and disturbed during the night
   2. Waking during the night - any getting out of bed rates 2 (except for purposes of voiding)

6. Insomnia Late

    0. No difficulty
    1. Waking in early hours of the morning but goes back to sleep
    2. Unable to fall asleep again if gets out of bed

7. Work and Activities

    0. No difficulty
    1. Thoughts and feelings of incapacity, fatigue or weakness related to activities work or hobbies
    2. Loss of interest in activity: hobbies or work- either directly reported by patient, or indirectly in listlessness, indecision and vacillation (feels has to push self to work or activities)
    3. Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores
    4. Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted

8. Retardation

    0. Normal speech and thought
    1. Slight retardation at interview
    2. Obvious retardation at interview
    3. Interview difficult
    4. Complete stupor

9. Agitation

    0. None
    1. "Playing with" hands, hair etc.
    2. Hand-wringing, nail biting, hair-pulling, biting of lips etc.

10. Anxiety Psychic

    0. No difficulty
    1. Subjective tension and irritability
    2. Worrying about minor matters
    3. Apprehensive attitude apparent in face or speech
    4. Fears, expressed without questioning

## 11. Anxiety Somatic

0. Absent
1. Mild
2. Moderate
3. Severe
4. Incapacitating

{ Physiological concomitants of anxiety, such as: Gastrointestinal- dry mouth, wind, indigestion, diarrhea, cramps, belching

{ cardio-vascular- palpitations, headaches, respiratory- hyperventilation, sighing, urinary frequency, sweating

## 12. Somatic Symptoms Gastro-Intestinal

0. None
1. Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen
2. Difficulty eating without staff urging, requests or requires laxatives or medication for bowels or medication for G. I. symptoms

## 13. Somatic Symptoms General

0. None
1. Heaviness in limbs, back or head. Backaches, headache, muscle aches, loss of energy and fatigability
2. Any clear-cut symptom rates 2

## 14. Genital Symptoms

0. Absent
1. Mild
2. Severe

Symptoms such as: Loss of libido
Menstrual disturbances

## 15. Hypochondriasis

0. Not present
1. Self-absorption (bodily)
2. Preoccupation with health
3. Frequent complaints, requests for help, etc.
4. Hypochondriacal delusions

## 16. Weight Change

A. When rating by history (pre-treatment)
   0. No weight loss
   1. Probable weight loss associated with present illness
   2. Definite (according to patient) weight loss

16. <u>Weight Change</u>

B. On weekly ratings by ward psychiatrist, when actual weight changes are measured
   0. Less than 1 lb. weight loss in one week
   1. One to 2 lb. weight loss in one week
   2. Greater than 2 lb. weight loss in week

17. <u>Insight</u>

   0. Acknowledges being depressed and ill
   1. Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need of rest etc.
   2. Denies being ill at all

18. <u>Diurnal Variation</u>

   0. Absent (no variation in symptoms a.m./p.m.)
   1. Mild (minimal variation in symptoms a.m./p.m.)
   2. Severe (significant variation in symptoms a.m./p.m.)

19. <u>Depersonalization and Derealization</u>

   0. Absent        Such as: Feelings of unreality, nihilistic
   1. Mild                   ideas
   2. Moderate
   3. Severe
   4. Incapacitating

20. <u>Paranoid Symptoms</u>

   0. None
   1. Suspicious
   2. Ideas of reference
   3. Delusions of reference and persecution
   4. Persecutory hallucinations

21. <u>Obsessional and Compulsive Symptoms</u>

   0. Absent
   1. Mild
   2. Severe

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