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dissertation entitled

THE USE OF THE DEXAMETHASONE SUPPRESSION TEST TO IDENTIFY A DISTINCT SUBTYPE OF DEPRESSION

presented by

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has been accepted towards fulfillment of the requirements for

Ph.D. degree in Counseling Psychology

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Date April 19, 1984

THE USE OF THE DEXAMETHASONE SUPPRESSION TEST TO IDENTIFY A DISTINCT SUBTYPE OF DEPRESSION

by

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A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

College of Education

Department of Counseling, Educational Psychology
and Special Education

1984

Charles L. West

ABSTRACT

The major purpose of this study was to explore the relationship between a positive response to the dexamethasone suppression test (DST) and clinical features. Both traditionally endogenous and neurotic symptomatology were included in the investigation. Confirmation of a hypothesized norepinephrine deficit associated with DST nonsuppression was also sought through placing DST nonsuppressors and patients diagnosed endogenously depressed on the noradrenergic medication, desipramine.

A sample of 107 depressed men and women was obtained from a consortium of mental health facilities as well as from self-referral. The Schedule for Affective Disorders and Schizophrenia (SADS) was administered to each subject along with the Differential Diagnostic Depression Scale (DDDS) and the DST. 48 subjects who met Research Diagnostic Criteria (RDC) for major endogenous depressive disorder, definite or probable, and/or demonstrated DST nonsuppression were placed on a 5-week trial with desipramine. Thirty-four patients completed the trial; 14 dropped out because of medication side-effects or because of referral to another facility.

A blood cortisol value of $\geq$4.1 ug/dl was the criterion for DST nonsuppression. Ratings of 46 SADS items and DST

suppression/nonsuppression were used to address the main research questions. T-tests yielded 12 individual SADS items for which DST nonsuppressors had significantly higher ratings: subjective feeling of severity, psychic anxiety, initial insomnia, terminal insomnia, insomnia (severity), appetite loss, weight loss, indecisiveness, dim concentration, psychomotor agitation, lack of reactivity, and functional impairment.

Two discriminant analyses were also performed on the 46 SADS items and DST response. The first analysis, using the entire sample, created a discriminant function which correctly classified 90.65% of the subjects. In order to have the opportunity to immediately cross-validate a derived discriminant function, a second analysis was performed employing half of the sample stratified by diagnosis and DST response; it correctly classified 98.15% of the subjects included. Cross-validation of this second discriminant function on the withheld half of the sample yielded a percentage of correct classification that was significantly better than chance.

Analysis of variance demonstrated that DST nonsuppressors had a significantly larger change score on the Hamilton Depression Rating Scale (HDRS) than suppressors at the end of a 5-week trial of desipramine. However, analysis of covariance , using baseline HDRS scores as the covariate, did not uphold the significance of DST nonsuppression in predicting HDRS change scores. Rather, a

high baseline HDRS score was most predictive of a large change score.

DEDICATION

To My Parents

and Frances

ACKNOWLEDGMENTS

I wish to acknowledge the very large role that others had in the original design and execution of the research project of which my dissertation is but a part. I am most indebted to the staff of the Clinical Center Affective Disorders Clinic who were accepting of my desire to become involved as a research team member.

Gregory Holmes: Aside from his role as principal interviewer and trainer for the endogenous depression project, Greg served as a ready and able consultant for all project concerns. His easy-going personality made work around the clinic much more enjoyable than it might have been. I certainly cannot underestimate the value of the support he offered me during the rough times with the research.

Robert Bielski: Bob was very considerate of my needs throughout my participation in the research project. His having granted me a graduate assistantship not only provided me with financial support but also gave me the opportunity to take on new and previously untried responsibilities. In his role as a committee member, he was a fair critic who offered a clear and insightful perspective on research issues I had to confront.

William Farquhar: Bill was a source of support my entire four years at Michigan State. He taught me as both professor and clinical supervisor and helped me develop professional direction. During the dissertation process, he offered valuable suggestions on how to clearly communicate my ideas on paper.

Christine Shafer: Chris was the main physician in charge of the drug treatment phase of the study. She was always accessible as a consultant and was there as a listening ear when I needed to talk about a patient. I appreciated the respect and warmth she showed me.

Andrew Porter: Dr. Porter handled the design and analysis questions I had about my dissertation with precision and offered solutions that were manageable for my level of understanding of statistics. I greatly valued his input.

Gerald Osborn: Jerry challenged me to develop a research focus that would have some practical application to clinical work.

The dedication of Jay Terbush and Shelley Smithson in their role as interviewers added to the integrity of the project.

Karen Brainard offered some humorous interludes during the all-too-serious project work.

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CHAPTER ONE

THE PROBLEM

Researchers of depressive illness have long sought to identify distinct subgroups among the diverse phenomena labeled depression. Historically, efforts to differentiate depression have involved some form of clinical observation from which a pool of features could be generated. Statistical analysis was then used to identify correlated groups of symptoms, groups of patients with common features, or the frequency of certain symptoms in a given group. Many of these studies were successful in deriving a clinical distinction between endogenous and neurotic depression and the subtypes "neurotic" and "endogenous" were adopted as diagnostic entities in the Diagnostic and Statistical Manual of Mental Disorders, Second Edition (American Psychiatric Association, 1968). However, a limitation of these early studies is that in using factor or cluster analysis, they identified correlated groups of symptoms or groups of patients with common features but did not look to any external criterion, non-clinical in nature, which would aid in the validation of such groups as existing in the actual patient population. Statistical methods alone cannot provide such validation: they only assist the intellect in separating and categorizing phenomena and do so irrespective of the empirical context within which the phenomena appear.

The need for external criteria to validate clinical subgroups has recently given rise to new strategies in depression research using biological markers and anti-depressant drug treatment response (Carroll, 1982). One of the current biological indicators receiving much research attention is hypothalamo-pituitary-adrenal-axis (HPA) dysfunction as indirectly measured by the dexamethasone suppression test (DST). The DST, when positive, serves on the average as a 96% accurate confirmation of the diagnosis of endogenous depression. That is, only 4% of patients who respond positively to the DST and who have been screened with regard to specific psychiatric and medical exclusion criteria (Carroll, 1981) would be expected to be false-positive responders. Unfortunately, it also has been reported to have an approximately 50% false-negative rate among endogenous patients. Carroll (1982) has attributed the large number of false- negative DST's among endogenous depressives to the possibly heterogeneous biological dysfunction behind endogenous depression. It has been presumed by several researchers (e.g., Carroll, 1982, Brown & Shuey, 1980) that patients with identical clinical profiles could respond differently to the DST because their underlying biological abnormalities are different. Such clinical homogeneity coupled with biological heterogeneity thus: one, would confound any attempt to differentiate the clinical features of depressed patients through DST response

and two, would preclude the possibility of eliminating a certain percentage of false-negative DST results.

Need

While biochemical heterogeneity within endogenous depression has received some research validation (e.g., Hollister, 1978), there does exist an equally plausible alternative hypothesis to account for the 50% false-negative rate of the DST among patients diagnosed as endogenously depressed. That rival hypothesis involves the specific set of clinical criteria used for the diagnosis of endogenous depression. If a patient is a normal DST suppressor and does not meet one's criteria for endogenous depression, one is reasonably confident of the clinical implication; a clinical uncertainty, on the other hand, arises when the patient has met the chosen criteria but is a suppressor. Adhering to one's criteria, this latter patient is then defined as a false-negative responder to the DST. But what of the possible insufficency of the clinical criteria one has employed? There may exist other clinical features which, along with those identified in previous research, may be crucial to a profile of endogenous depression as externally validated through the DST. This seems especially likely in view of Klein's (1973) assertion that as a clinical entity, "endogenomorphic" depression need not be exclusive of certain neurotic signs and symptoms, e.g., a clearly

identifiable precipitant. Thus, in order to explore the value of the DST in differentiating subtypes of depression, one needs to expand the range of symptomatology so that it is inclusive not only of the traditional features of endogenous depression, but also of those symptoms usually considered neurotic/reactive.

Purpose

The purpose of the current study is to investigate the value of the dexamethasone suppression test (DST) in
1) isolating a distinct clinical profile of depression and
2) predicting anti-depressant drug treatment response.

Hypotheses

Research Hypothesis:	Positive and negative responders to the dexamethasone suppression test will demonstrate different clinical features.
Exploratory Hypothesis:	Among endogenous depressives, positive responders to the dexamethasone suppression test will have a better clinical response to the noradrenergic drug, desipramine, than will negative responders.

Theory

The assertion that biochemical dysfunction may be implicated in certain types of depressive disorder is not new. The Greek physician Hippocrates believed almost 2500 years ago that the human body contained four "humors" - blood, black bile, yellow bile, and phlegm. He stated that the balance of these (apparently) physiological processes was essential to normal brain functioning and that if one became predominant over the others, physical or mental disease resulted. An overabundance of black bile led, according to Hippocrates, to a deep sadness and hopelessness he termed "melancholia" (Coleman, 1976).

Advances over the last thirty years in our understanding of the biochemistry of depression have led to considerably more complex theorizing about metabolic inbalance in depressive disorders. Biochemical heterogeneity, within "melancholia" (endogenous depression) has been postulated (Shildkraut et al, 1978; Hollister, 1978) from research findings which indicate differential pharmacologic response of patients who demonstrate low or high levels of specific neurotransmitter metabolites, with metabolites of norephinephrine, serotonin, and dopamine being the major ones under current investigation. Hollister (1978) asserts that at least six biochemical types of depression could exist based on either increased or decreased excretion of these metabolites. Brown, Haier, and

Qualls (1980) believe, for example, that the differential response of DST nonsuppressors in their study to noradrenergic medications suggests that cortisol hypersecretion is associated with a decrease in levels of norepinephrine.

While cortisol hypersecretion may be tied to norepinephrine deficiency and may thus be suggestive of one biological subtype of depression, researchers are not in agreement regarding efforts to identify consistent clinical characteristics of this subtype. Carroll (1982) has investigated the sensitivity (true-positive rate, or proportion of endogenous patients in whom an abnormal response occurs) and specificity (true-negative rate, or proportion of nonendogenous patients in whom a normal response occurs) of the DST in the context of the Research Diagnostic Criteria (Spitzer and Endicot, 1978) category of endogenous depression and the Diagnostic and Statistical Manual for Mental Disorders III (American Psychiatric Association, 1980) diagnosis of major depression with melancholia. He has asserted that no consistent clinical profile emerges in association with DST nonsuppression that would assist the researcher in increasing the DST's average 50% sensitivity rate. He states further that because the DST is a dynamic challenge test and not an unobtrusive measure of current neuroendocrine function, one may always expect a certain percentage of endogenously depressed patients not to have an abnormal response to that specific challenge even

though they could have some other form of neuroendocrine inbalance which would qualify them as "endogenously" depressed. However, attempts to clinically define a depressive subtype specifically linked to DST nonsuppression may have thus far been obscured precisely because such research has been limited to the clinical context of RDC and DSM III diagnoses. No research has to date investigated clinical symptomatology outside of the parameters of these diagnostic categories which might be reliably associated with DST nonsuppression.

Summary and Overview

This chapter described both the purpose and need for this study: to explore the depressive subtyping capability of the dexamethasone suppression test (DST) without regard for the restrictions of symptom range imposed by current diagnostic classification systems. Additionally, current theory was presented about biological heterogeneity in depression, along with discussion of the limitations of the DST as a marker of a specific depressive subtype.

Chapter II is a review of the literature that addresses the nature of depressive subtypes as defined by clinical, neuroendocrinological, and drug treatment response criteria. Chapter III contains a description of the study sample, instruments, design, procedures, and analysis plan. In Chapter IV, the data analysis is presented. Chapter V

contains a summary of the study, conclusions, a review and of recent findings in the literature, a discussion of results and recommendations for future research.

CHAPTER TWO

REVIEW OF THE LITERATURE

At the beginning of the twentieth century, Freud suggested that depressive disorders were a heterogeneous group, noting that some may be physiologic in origin while others more distinctly psychogenic: "Even in descriptive psychiatry the definition of melancholia is uncertain; it takes on various clinical forms (some of them suggesting somatic rather than psychogenic affections) that do not seem definitely to warrant reduction to a unity" (Freud, 1917, p.124).

Since Freud's observations, many researchers (e.g., Lewis, 1938; Eysenck, 1970; and Kendell, 1976) have attempted to differentiate the collective phenomena of depressive illness into psychogenic and somatic subtypes, more recently referred to as the "neurotic" versus "endogenous" distinction. There have been four basic approaches to the separation of these subtypes: one, the use of clinical features alone; two, clinical features and a biochemical criterion; three, clinical features and treatment response; and four, a biochemical criterion and treatment response. In the review to follow, these approaches to the subtyping of depression will be examined, with heaviest emphasis placed on the literature dealing with clinical features and a biochemical criterion.

Clinical Features of Depressive Subtypes

Up until the last decade, most studies designed to investigate the neurotic/endogenous distinction relied on data gathered through clinical observation. Typical of such studies is one by Kiloh and Garside (1963). They conducted a factor analytic study with 53 endogenous and 61 neurotic depressives diagnosed with "reasonable confidence" through a psychiatric interview. Product moment correlations were calculated between 35 clinical features and a summation factor analysis was carried out. Two factors were derived, one a general depression factor, the second a bipolar factor whose loadings were very similar to the correlation coefficients between diagnosis and each feature. The bipolar factor thus provided a clear differentiation between neurotic and endogenous depression. The following were clinical features which correlated significantly ($P < .05$) with diagnosis, listed here in order of magnitude of correlation and according to diagnosis suggested by presence of feature. Endogenous depression: early awakening, depression worse in morning, distinct quality of depression, retardation (used inclusively to describe the subjective experience of slowness of thought and action and objective psychomotor slowing), duration one year or less, age 40 or over, depth of depression (undefined), failure of concentration, weight loss of 7 pounds or more, and previous attacks. Neurotic depression: reactivity of depression,

presence of precipitants, self-pity, variability of illness, hysterical features, inadequacy, initial insomnia, depression, worse in evening, sudden onset, irritability, hypochondriasis, and obsessionality. It should be noted that the authors do not report to what degree the absence of any particular feature under one diagnostic category is suggestive of the other diagnosis, nor do they provide a composite correlation of all endogenous or neurotic features with diagnosis.

The concept of endogenous depression was reviewed by Rosenthal and Klerman (1966) and found to consist historically of three elements: a particular clinical pattern of symptoms and signs, a relative absence of environmental precipitation and environmental influence on the course of illness, and a relatively well-adjusted premorbid personality. In another study, Rosenthal and Gudeman (1967) conducted their own clinical investigation of depressive symptom patterns and specifically tested the concept of an endogenous pattern of depression. The patient sample consisted of 100 acutely depressed women between the ages of 25 and 65, about half of whom were inpatients. Patients evidencing signs of schizophrenia, organic brain disease, sociopathy, or alcoholism were excluded. Thirty two symptom areas, historical background and personality traits were assessed. The resulting endogenous symptom cluster included lack of reactivity to the environment, feelings of worthlessness, retardation, difficulty in concentrating,

sadness, guilt, visceral symptoms, agitation, middle-of-the-night insomnia, loss of interest, and a subjective quality of depression as different from normal experience. Patients with this group of symptoms tended not to show environmental precipitants (- 0.23 correlation) to their depression but did have certain premorbid characteristics, including obsessional and depressive personality traits, lack of emotional reactivity, and a history of previous depressive and manic episodes. While this study replicates the results of several previous factor analytic studies (Rosenthal and Klerman 1966; Kiloh and Garside 1963; and Hamilton and White 1959) and is representative of them, Rosenthal and Gudeman caution that factor analysis describes patterns of symptoms but says nothing about groups of patients, i.e., the symptom pattern is an intellectual construct which may or may not exist in any actual group of patients. Additionally, the authors comment that the term "endogenous" has been misused in the United States, often applied to the presence or absence of a precipitant regardless of the symptom pattern. They maintain that the endogenous pattern does not have the total absence of an environmental precipitant as its most important criterion and that "endogenous" should more correctly refer to the tendency of the illness to run its course once it has fully developed, with a lack of reactivity to the environment. They thus suggest that the descriptor "autonomous" might be preferred over "endogenous".

Klein (1973), too, has noted that the term "endogenous" has had different meanings for different investigators. He therefore advocates that a more inclusive term, "endogenomorphic", be used to label patients who exhibit the traditional symptom pattern of endogenous depression, whether or not precipitants are present. He does not thereby suggest that the precipitant factor be simply glossed over, but rather hypothesizes that the precipitant or reactive component is conceptually independent of the endogenous profile in depressive illness. That is, as Klein remarks, "... the endogenomorphic depressions are conceptually divided into endogenous depressions and precipitated endogenomorphic depressions" (p. 449), the former without a clear precipitant and the latter with a precipitant while still characterized by traditional endogenous features.

Akiskal (1983) asserts that closer scrutiny needs to be given to the long-term profile of depressive disorders. Major depressive disorders like endogenous depression most often occur within the context of chronic, low-grade dysthymia and neurotic features. Among his proposed chronic depressives subtypes, Akiskal postulates that episodes of primary major depression can either have a late onset pattern of major depression with residual chronicity, or an early, insidious onset (usually before age 25) of lower-grade depression leading to episodes of major depression followed by a fluctuating course of low-grade depression and major depressive episodes. While commenting

that endogenous depression can ".... serve as a breeding ground for neurotic personality developments", Akiskal appears to relegate neurotic/reactive components of endogenous depression to the status of concurrent features distinct from the core profile of affective illness. However, given the complexity of the nosological framework of depression which Akiskal has himself constructed, with all of its admixture of affective and non-affective components, and given the lack of long-term empirical evidence to verify his hypotheses, he may be premature in discounting the usefulness of "neurotic" symptomatology in deriving subtypes of affective illness.

Nelson and Charney (1981) provide an extensive review of the major literature on endogenous depression. They cover four major types of studies: multivariate analysis, symptom frequency, instrumental measures, and treatment response. Of particular significance to the examination of a clinical profile of endogenous depression are the multivariate analysis studies, which include the statistical methods of factor analysis, cluster analysis, and discriminant function analysis. In their discussion of 20 factor analytic studies which they reviewed, the authors comment that while these studies vary in item definition, rating methods, and sample size and thus do not have comparable symptom loadings, the consistent association of a symptom with the endogenous factor under these varied conditions in fact increases the generalizability of the finding. Symptoms with strong factor

loadings (>.50) in the majority of the studies reviewed were psychomotor retardation, lack of reactivity and severity of depressed mood; symptoms with strong factor loadings in 50% of the studies and moderate loadings (.49 to .30) in the other half were loss of interest, declusional thinking, distinct quality of mood, guilt, agitation, and morning worsening. Low factor loadings (< .30) were found for a group of symptoms which have traditionally been used as criteria for the diagnosis of major depressive illness- suicidal thinking or attempts, weight loss, difficulty falling asleep, and midnight awakening. Loss of appetite and loss of energy, presumed by the Research Diagnostic Criteria (Spitzer, Endicott and Robbins, 1978) and the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (American Psychiatric Association, 1980) to be criteria of major depressive illness, have not received much attention in factor analytic studies (only 2 studies used these criteria).

Nelson and Charney (1981) found 9 cluster analytic studies of major depressive illness, 8 of which identified an endogenous cluster. The ninth study, to be noted, involved a highly select sample of chronic depressives of advanced age- variables not usually associated with endogenous depression. As with the factor analytic studies, severe depressed mood, retardation and lack of reactivity had strong association with the endogenous depressive group in the cluster analytic studies. Three symptoms of moderate

loading in the factor analytic studies- guilt, agitation, and delusional thinking- received similar support in the cluster studies, as did, although to a lesser extent, the symptoms of loss of interest, early morning awakening, morning worsening, difficulty concentrating and mid-night awakening; distinct quality (which received a moderate loading in the factor studies) and weight loss (which had a low loading) received support in only two studies. Review of discriminant function analysis and symptom frequency studies did not yield consistent findings. The four discriminant function studies examined all dealt with a psychotic/neurotic distinction rather than a non-psychotic endogenous/neurotic differentiation. The only consistent finding in these studies was that the symptom of psychomotor change (retarded or agitated) had a heavy loading for distinquishing psychotic from neurotic depressives. The data presented by Nelson and Charney on four symptom frequency studies revealed no consistent symptom frequencies across all four studies. In summary, the authors conclude from the multivariate and symptom frequency studies that psychomotor change is the symptom having the single strongest association with endogenous depression. Strong association across several type of studies were also found for severity of depressed mood, lack of reactivity, depressive delusions, self-reproach and loss of interest. Distinct quality of mood, diurnal morning worsening, and difficulty concentrating received moderate support, although it is

noted that further research is needed before these symptoms can be deemed as appropriate for inclusion in an endogenous profile as the other symptoms mentioned above.

Nelson and Charney (1981) report three major findings in their review of objective instrumental measures of depressive symptomatology: one, sleep awakening does not appear useful as a criterion for distinquishing endogenous from neurotic depression; two, telemetric recording of depressed patients' motor activity indicates a psychomotor change (either retarded or agitated), although clear differences between endogenous and reactive patients have not yet been found; and three, decreased ability to concentrate, as measured by psychological testing, has not been supportive of presumed differences among subtypes of depression.

Endicott and Spitzer (1977) conducted a two-year follow-up study of 33 patients rated endogenous major depressive disorder and 21 patients diagnosed non-endogenous major depressive disorder using the Research Diagnostic Criteria (RDC). The Research Diagnostic Criteria, developed by Spitzer, Endicott and Robbins (1978), delineate sets of specific inclusion and exclusion criteria for functional psychiatric disorders of various types, with greatest attention paid to the subtyping of affective disorders like depression (see Appendix F for a comparison of RDC Major Depressive Disorder, Endogenous Subtype and DSM III Major Depressive Disorder with Melancholia). The authors tested

the hypothesis that endogenous depressives have less residual symptomatology after a major episode than those nonendogenous. Although not statistically significant, the data trends indicated this hypothesis to be false. 81% of nonendogenous vs. 72% of endogenous patients showed Global Assessment Scale (GAS) ratings above 60, indicative of minimal symptomatology or impairment in functioning. 39% of endogenous vs. 24% of nonendogenous patients were still too impaired to work at the time of follow-up. Endicott and Spitzer acknowledge the tentative nature of their findings given the small sample they used but comment that the clinical lore suggesting that the presence of endogenous features is a good prognostic sign should be more thoroughly examined.

Matussek, Soldner and Nagel (1981) purport that the validity of a diagnostic syndrome like endogenous depression is questionable if it can only be diagnosed by clinical methods. They attempted to confirm the existence of an endogenous syndrome by using both symptom frequency and cluster analyses on a sample of 198 subjects who had previously been hospitalized for depression. Subjects were selected according to four criteria: 1) they were between the ages of 50 and 65 at the time of the interview; 2) they had no signs of organic brain damage; 3) their depression was not related to alcohol or drug use; and 4) they exhibited no symptoms of schizophrenia. The 198 subjects, 27% male and 73% female, were classified by the RDC into two

categories: endogenous depression (57%) and neurotic depression (29%); 14%(29) remained unclassified because they did not fit the criteria for either group. Using a catalogue of 38 symptoms and characteristics of the course of illness, two or more evaluators rated retrospectively a subject's most recent depressive episode.

Only 4 of 37 symptoms differed significantly between the sexes: males were more openly aggressive, had more of a delayed insomnia, more often had a sudden onset to their depression, and did not have as much weight loss as women. Comparison of the symptom frequency between the endogenous and neurotic depressive groups yielded eight symptoms as significantly more related to endogenous depression. These included morning worsening, non-reactivity, short duration, distinct quality of mood, psychomotor retardation, indecisiveness, sudden onset and delusions. The neurotic depression group had two significantly higher symptoms, sadness and neuroticism (as measured by the Maudsley Personality Inventory).

The cluster analysis determined eight symptoms as being characteristic of the endogenous depressive syndrome: distinct quality of the depressive mood, loss of reactivity, withdrawal from social contact, inhibition, disturbance of the circadian rhythm, physiological disturbances (appetite loss, weight loss or sleep disturbances), typical characteristics of the course (sudden onset, relatively short duration, remission in the interval), and absence of a

precipitant. Matussek, Soldner and Nagel note that while absence of a precipitant is not a necessary criterion for the diagnosis of endogenous depression, when no precipitant is in fact indicated, that absence is significant (P .001). They conclude that retrospective use of a statistical procedure like cluster analysis can detect an endogenous depressive syndrome, although that syndrome does not appear to be defined by the presence or absence of single items, nor by a syndrome with distinct boundaries. The authors suggest that the construct of an endogenous "component" with varying levels of strength might be applicable to all depressive illness.

Feinberg and Carroll (1982) have derived a discriminant index to classify depressed patients as endogenous or non-endogenous. One hundred sixty-five patients were initially separated into endogenous and non-endogenous groups using Carroll's (1980) diagnostic criteria drawn from the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1977), clinical interviews, the 17-item Hamilton Depression Rating Scale (Hamilton, 1960) and response to treatment. The Schedule for Affective Disorders and Schizophrenia (SADS) is a clinical interview instrument from which RDC, DSM III, or Hamilton ratings can be derived. Only those patients with a Hamilton score of 10 or more were selected for the discriminant function analysis group to validate the clinical diagnostic classifications (used during the initial assessment phase of

the study). To insure that severity of illness did not account for the differences between groups found in the discriminant function, the authors regressed total score of the Hamilton, a severity index, on each clinical variable and used the residuals after regression as the clinical variables in a new discriminant analysis. They acknowledged that this method of adjustment was not correct since some clinical variables are items in the Hamilton, but stated that the error introduced was toward reducing the contribution of the clinical features in the discriminant function and that, therefore, their method was acceptable. The item weights and cutting scores from the discriminant functions were then converted from adjusted data (coefficients) to integers (multiplying raw data by 10 and rounding to the nearest whole number). The index derived for distinquishing unipolar endogenous from non-endogenous has eight items, each followed by its respective weight and scoring range: decreased appetite (9,0-2), guilt (6,0-4), agitation (4,0-4), (affective) delusions (3,0-8), work and interests (3,0-4), retardation (2,0-4), loss of pleasure (2,0-2) and precipitants present (-6,0-1). Cross-validation of the discriminant function index was conducted with a separate group of 52 patients, each meeting the same diagnostic criteria used with the orginal analysis group. All clinicians involved with the second group were blind to the discriminant function which had been derived. Correct classification through the discriminant index (DI) of the

analysis group and the cross-validation group was high: 82% and 81%, respectively. The DST was not used in this study as a discriminant but only to verify that the DI group had frequencies of non-suppresion (sensitivity) similar to that of groups with clinical diagnostic classification.

Psychoneuroendocrinological Evidence for Depressive Subtypes

Efforts to specify a consistent profile of endogenous depression through clinical features alone have been hampered by the lack of an Archimedean point that all researchers could agree upon. The currently most promising source for such an external criterion is the field of psychoneuroendocrinology. Ettigi and Brown (1977) have reviewed the recent literature on the neuroendocrine abnormalities involved in affective disorders. Research relevant to depressive disorders has revealed many potential candidates for biological dysfunction which could contribute to affective and behavioral symptomatology. Cortisol hypersecretion linked to hypothalamo-pituitary-adrenal axis (HPA) dysfunction is one of the areas which has received the most attention. Previously thought to be the result of such factors as stress, anxiety, or depressive decompensation, cortisol hypersecretion has in more recent studies been found to occur in apathetic patients or even in patients while asleep, and thus is indicative of a more fundamental dysfunction. Most investigation of HPA abnormalities

reflected in cortisol hypersecretion has involved the dexamethasone suppresion test (DST). Dexamethasone is a synthetic corticosteroid which when adminstered to a normal subject leads to the suppression of pituitary adrenocorticotropic hormone (ACTH). Depressed subjects, however, fail to show normal suppression following the administration of dexamethasone and have significantly higher post dexamethasone cortisol blood plasma levels than normals.

Another group of corticosteroids which have been researched in connection with depression are the 17-hydroxycorticosteroids (17-OHCS). Early studies showed high levels of 17-OHCS in the urinary excretion of depressives. However, the studies reviewed by Ettigi and Brown (1977) indicate that 17-OHCS levels are: one, not consistently correlated with severity of depression; and two, do not correlate highly with level of cortisol secretion. Similarly, 3 methoxy-4-hydroxyphenylglycol (MHPG), the principle metabolite of brain norephenephrine, has thus far proved to be an inconsistent correlate with depressive disorders. A more recent study by Hollister et al (1980) not included in the Ettigi and Brown review highlights the problems with MHPG levels and depression. In their study of nortriptyline response in patients with low or normal-high excretion levels of MHPG, they were unable to find a significant relationship between improvement during nortriptyline treatment and initial MHPG levels.

Additionally, the researchers note that the collection of urine for MHPG testing requires the most careful supervision in an inpatient setting and that the excretion level of MHPG varies considerably within patients.

A variety of other measures of neuroendocrine disturbance have been investigated- e.g., growth hormone, thyroid-stimulating hormone, prolactin and luteinizing hormone- but will not be examined here because of the relatively few carefully controlled studies conducted in these areas.

Finally, Ettigi and Brown (1977) comment that recent research evidence taken together has served to increase the complexity of a biochemical model of affective disorders. The often cited catecholamine hypothesis of depression proposes that a relative deficiency of, or imbalance between, catecholamines and indoleamines (notably norepinephrine and serotonin) is linked to depression. Ettigi and Brown assert that this hypothesis is a gross oversimplification and that the "... simultaneous effects of other biogenic amines, hormones, and ionic changes will ultimately be included in any comprehensive formulation of the biochemistry of affective disorders" (p. 498). Nevertheless, the authors do not discount the practical value of attempting a reclassification of depression based on the metabolic activity of specific biogenic amines, (e.g., ACTH as measured by the dexamethasone suppression test and MHPG as determined by urinary excretion levels),

although the clinical utility of this latter procedure is still open to question.

In a recent study using 122 depressed patients classified by RDC criteria, Schatzberg et al (1983) found no differences in mean urinary MHPG levels between unipolar depressed patients and control subjects. Patients with unipolar depression did appear, however, to have a wide range of MHPG levels, from low to intermediate to very high. The authors suggest that differences in patient sampling in previous studies may have accounted for the variation in MHPG levels found from study to study. They further hypothesize that different levels of MHPG may correspond to at least three subtypes of unipolar depression and that " ... specific clinical characteristics may be associated with these biological differences" (p. 473).

Carroll, Feinberg, Greden et al (1981) administered the dexamethasone suppression test to 438 subjects in an attempt to standardize the test for the diagnosis of major depressive disorder with melancholia (see Appendix E for a comparison of Criteria for RDC "endogenous" and DSM III "melancholia"). Using DSM III criteria derived from the Schedule for Affective Disorders and Schizophrenia, 215 patients (both outpatients and inpatients) were diagnosed major depressive disorder with melancholia, 100 with nonendogenous depression, 53 with other psychiatric disorders (e.g., schizophrenia, personality disorders) and 70 as normal. Severity of depression was clinician rated

with the Hamilton Depression Rating Scale (HDRS) and self-rated through the Carroll Rating Scale for Depression (CRSD).

Using marginal and interval probability analyses, the authors compared the diagnostic performance associated with plasma cortisol criterion values of 3, 4, 5, and 6 ug/dl for the 368 patients with psychiatric diagnoses. 8 a.m., 4 p.m., and 11 p.m. postdexamethasone blood samples were taken with inpatients, while only a 4 p.m. sample was drawn for the outpatient series. Reviewing the DST results, the researchers propose that a plasma cortisal value of 5 ug/dl be used for the diagnosis of melancholia. This criterion gave an overall test sensitivity (true-positive rate) of 43% and a specificity (true-negative rate) of 96%. The diagnostic confidence (proportion of abnormal test results that are true-positive) for melancholia with a greater than 5 ug/dl blood cortisol criterion was 94%.

Carroll et al comment that, because of some variability across patients in the cycling of cortsol secretion, the inpatient serial blood tests at 8 a.m., 4 p.m., and 11 p.m., can always be expected to generate a greater DST sensitivity to cortisol hypersecretion and that the 4 p.m. blood sampling alone used with outpatients is a practical compromise. A rather dramatic difference in sensitivity apparently occurs if one administers a 1-mg as opposed to a 2-mg dosage of dexamethasone: there is a 72% and 188% gain

in sensitivity for inpatients and outpatients, respectively, when using the 1-mg dose.

The researchers found that approximately 50% of the patients with melancholia had plasma cortisol concentrations equivalent to those of patients with other psychiatric diagnoses and of normals. They thus remark that while a positive DST result can be used with high confidence to support a diagnosis of melancholia, a negative DST result should not be considered a criterion to rule out melancholia. No differences were found between DST suppressors and non-suppressors in HDRS scores, in CRSD ratings, in age (mean age 48), in sex, or in recent history of psychotropic drug intake. Carroll et al theorize that the only 50% hit-rate of the DST for patients diagnosed as melancholic/endogenous (DSMIII/RDC) may be indicative of a certain neuroendocrine heterogeneity within melancholia that needs to be more fully explored.

Carroll (1982) has recently reviewed eight studies which attempted to differentiate endogenous depression (variously defined) from non-endogenous depression or from other psychiatric diagnoses labeled "miscellaneous" (by Carroll). An additional two studies were examined which compared 1) primary unipolar depression with secondary depression and 2) primary unipolar depression with miscellaneous comparison patients. The 10 studies with a total of 573 subjects yielded an average DST sensitivity of 45% and an average specificity of 96%. The author notes that

variations in clinical diagnostic criteria could have affected the results with DST sensitivity and advocates a greater uniformity in the use of criteria for the diagnosis of melancholia or endogenous depression.

Further reviewing his and others' research with the DST, Carroll remarks that the predictive use of an abnormal DST result for good response to anti-depressant medication is still unclear. The preferential effectiveness of certain anti-depressants in patients with abnormal DST results is also still being explored. However, there is already an indication that the DST can serve as valuable confirmation of a positive clinical outcome. In a study of electroconvulsive therapy (ECT) with melancholia patients, Albala, Greden, Tarika and Carroll (1981) report that a pre-ECT abnormal DST response will convert to normal, post-ECT, before clinical improvement is noticed. Similarly, an initially abnormal DST response that has not converted to normal after pharmacotherapy may indicate that the patient is at a serious risk of early relapse.

In their review of an intensive single case study, Rothschild and Schatzberg (1982) caution that while the DST was useful in determing the biological response to ECT and tricylcic antidepressant treatment, normalization of a DST does not necessarily mean that a patient is on the road to full recovery. Their study patient, in fact, relapsed twice, one time reverting to a nonsuppression pattern within two weeks after showing suppression, the other after four weeks.

In view of their experience, the authors suggest that serial DSTs should be conducted for several weeks after initial re-conversion to DST suppression.

Carroll's reporting of the sensitivity and specificity of the DST has not been without recent disconfirmatory evidence. Coryell, Goffney, and Buchardt (1982) conducted a study of 65 inpatients and their response to the DST, the patients falling within one of 3 categories: 17 (26.2%) had major depression without melancholia, 34 (52.3%) had major depression with melancholia, and 14 (21.5%) had depression with psychotic features. A second rater gave 50 (76.9%) patients the diagnosis primary depression and 15 (23.1%) secondary depression (primary depression following the DSM III definition of no other type of psychiatric illness evident prior to the depressive disorder). Of the 50 patients with primary depression, 26 (52.0%) had melancholia and 13 (26%) had psychotic features; the secondary group contained 8 (53.3%) patients with melancholia and 1 (6.7%) with psychotic features. Subjects were given a 1-mg dose of dexamethasone at 11 p.m. and had their blood drawn the following day at 8 a.m. and/or 4 p.m.; most patients reportedly had plasma taken at both times. Any patient with a post DST level greater than 5 ug/dl at either time period was considered a nonsuppressor.

Although not statistically significant, the rate of nonsuppression was actually higher among patients without melancholia than it was for patients with melancholia. 6 of

17 (37.3%) patients without melancholia were nonsuppressors, while 9 of 34 (26.5%) patients with melancholia were nonsuppressors, as were 7 of 14 (50.0%) patients with psychotic features. A striking contrast was noted in frequency of abnormal DST results among the patients when rated according to the primary-secondary distinction. 22 (44.0%) of the patients with primary depression were nonsuppressors but none of those with secondary depression were nonsuppressors. The difference, computed in a chi-square statistic, was significant ($p < .005$). In their discussion of their findings, Coryell et al comment that Carroll's (1982) review article cited studies that used a global conceptualization of melancholia rather than one characterized by specific, operationalized criteria like those in the DSM III. While not accusing Carroll and his group of such inprecision, the authors conclude that the vagueness of many prior studies limits the application of their own results to these studies.

While the Coryell et al study may present findings genuinely discrepant with those of Carroll, recent research conducted by Amsterdam, Winokur, Caroff and Conn (1982) may offer challenging results of less credibility because of its serious methodological flaws. In their study, 46 women and 18 men fulfilling RDC and Feighner and associates criteria for primary affective disorder were given the DST. 41 patients were diagnosed as primary unipolar depression and 23 as bipolar illness. All depressed patients had a Hamilton

Depression Rating Scale score of 16 or above on the 17-item scale. The authors emphazise that subjects were drug free for at least 7 days prior to the DST; patients taking neuroleptics had been stopped for 2 weeks. Standard medical conditions and illness complications which may potentially offset the DST result were carefully screened out. The DST itself involved a 1-mg dose of dexamethasone taken orally at 10 p.m., with blood sampling the following day at 8 a.m. and 4 p.m. Cortisol was measured by means of a single anti-body technique with a radioimmunoassay, using post-DST cortisol levels greater than 5.0 ug/dl as the criterion for nonsuppression.

Results indicated that patients and controls did not differ significantly in mean serum cortisol levels at either 8 a.m. or 4 p.m. postdexamethasone. No significant intergroup differences were found in the distribution of suppressors and nonsuppressors ($X^2 = .6$, $p > .20$), e.g., in the areas of age, sex, length of illness or (for depressed patients) severity of illness. Nonsuppressors included 10 (24.4%) of 41 unipolar depressed patients, 5 (29.4%) of 17 bipolar depressed patients and 1 (16.7%) of 6 bipolar patients in a hypomanic phase. The overall rate of 31 nonsuppresion at 4 p.m. among depressed patients was 25.9%, compared with 15.1% of the "healthy" volunteers. Since Amsterdam et al did not subgroup the primary unipolar depressives as endogenous/nonendogenous, it is impossible to say how their relatively low DST sensitivity for depressed

patients would compare with the average sensitivity of 45% reported by Carroll (1981) for the DST with melancholia. The authors, however, do make the mistake of comparing their rate of sensitivity when using a 1-mg dose of dexamethasone with the findings of studies using a 2-mg dose, apparently attempting to justify the low frequency of nonsuppression among their sample. As previously mentioned, Carroll (1981) has found that the dose of dexamethasone has a strong effect on the sensitivity of the DST. For the specific DSM III diagnosis of major depressive disorder with melancholia, he reports that among inpatients the sensitivity of the DST was 67% with 1 mg and 39% with 2 mg, significantly different by X^2 analysis at the $p < .005$ level. Carroll observed, by constrast, that the specificity of the DST was not affected by the dose of dexamethasone. This latter finding again seriously calls into question the sampling or the experimental methodology employed by Amsterdam et al. They had a 15.1% nonsuppression rate among their control group of normals, far in excess of the average 4% of normal persons noted by Carroll as having false-positive DST results.

Peselow, Goldring, et al (1983) recently conducted a DST study with depressed outpatients, the results of which do not confirm the findings of Amsterdam et al. Eighty-eight outpatients with primary affective disorder (unipolar or bipolar), meeting RDC criteria for major depressive episode and having Hamilton Depression Rating Scale scores of 16 or greater participated in the study. Patients were further

divided into definite endogenous (53 patients) and non-endogenous (35 patients) groups following the RDC, along with a control group of 49 normals (35 men, 14 women). Observors (presumably in the subject's family) were assigned to verify that the subject took 1 mg of dexamethasone at 11 p.m., with blood drawn the following day at 4 p.m. to determine cortisol levels. The authors comment that it was impractical and unwise for 41 of the study patients to discontinue their medications and be drug free a minimum of 5 days before testing. Those taking medications were taking lithium or antidepressants or a combination of the two. The cortisol levels of all subjects were measured against three criterion values- 3 ug/dl, 4 ug/dl and 5 ug/dl- to further explore the question of the appropriate plasma cortisol criterion for a positive DST with outpatients. Results indicated that at all cortisol criterion values there was a greater frequency of non-suppression among patients with primary affective disorder (X^2 ranged from $p < .02$ to $p < .001$) and that patients in the endogenous subgroup had significantly higher mean cortisol levels than controls ($p < .02$). No significant difference in DST sensitivity rates was found between those subjects on medication or off, although this potentially biasing factor was not examined with respect to a patient's subgroup membership (endogenous/nonendogenous). In addition, unlike the findings of Amsterdam et al (1982), the current study's data indicate that only 4% of normals were nonsuppressors at the 5 ug/dl

or above criterion (consistent with Carroll). However, the authors mention only in passing the very significant finding that no differences were found in mean cortisol levels between the endogenous and nonendogenous subgroups or between the nonendogenous subgroups and controls.

Brown and Shuey (1980) conducted a study to assess the depression subtyping capability of the dexamethasone depression test. Forty-eight hospitalized patients meeting RDC criteria for major depressive disorder were selected. In addition to the DST, subjects were administered the Hamilton Rating Scale for Depression (HRS), the Zung Self-Rating Depression Scale (SRS) and the Profile of Mood States (POMS). Ratings of tension-anxiety and depression-withdrawal were made for blood draws at 8 a.m., 4 p.m., and 11:30 p.m. following a midnight ingestion of 2 mg of dexamethasone and baseline blood sampling of the previous night. Results of study showed that 9 patients (50%) with primary depression (following RDC criteria) were dexamethasone nonsuppressors while only 6% of those with secondary depression were nonsuppressors; 5 patients or (35%) of the nonsuppressors but only 2 (or 5%) of the suppressors met RDC criteria for endogenous depression. (Percentage figures are drawn from a group total of 18 primary depressives, and 29 secondary depressives). An analysis of the clinical characteristics of suppressors and nonsuppressors revealed that, as drawn from HRS scores, diurnal variation was greater in the suppressors and nonsuppressors showed greater helplessness. In addition,

five (45%) of the nonsuppressors were unable to complete the self rating forms while only two (5%) of the suppressors were unable to complete these forms. Suppressors and nonsuppressors did not differ significantly in any other clinical characteristics, e.g., anxiety, agitation, retardation, insomnia, frequency of physical illness, nor in anxiety-tension or depression-withdrawal ratings made at the three of each blood sampling.

In the Brown and Shuey study, both suppressors and non-suppressors were treated with a variety of medication, most receiving tricyclic antidepressants. Nine (82%) of the nonsuppressors were rated as having a good response to treatment (marked improvement, or return to premorbid functioning) while only 14 (39%) of the suppressors had a good response to treatment. Poor and good responders did not differ systematically in treatment regimen, nor did response treatment correlate with length of hospitalization. The authors note that the results of treatment are open to question because the present research was not designed as a response study and consequently did not control for extraneous influences on drug treatment response. Separation of clinical differences between DST positives (nonsuppressors) and DST negatives (suppressors) was confounded by the variable primary/secondary; this latter variable needs to be held constent if one wishes to explore the effect of the variable, DST response. In addition, given the small sample of nonsuppressors (9 primary, 2 secondary),

any observations about no differences between suppressors and non-suppressors are inconclusive.

In a study by Schatzberg et al (1983), 88 patients (77 inpatient, 11 outpatient) meeting any of five possible DSM III diagnoses- major depressive disorder, bipolar depressive disorder, dysthymic disorder, situational disorder with depressed mood and borderline personality organization- were examined for differential cortisol levels following adminstration of the DST. A control group of 31 "medically and psychiatrically healthy" subjects free of medications interactive with the DST was included in the study design. With a criterion for nonsuppression of 5 ug/dl or more, it was found that only 1 of 31 controls (3%) failed to suppress, compared with 41 of the 88 identified patients (47%). Among patients diagnosed with major depressive disorders, the frequency of nonsuppression was somewhat higher in mood-congruent psychotics (10 of 14 or 71.4%) as opposed to nonpsychotics (18 of 31, or 58.1%). 7 of 9 psychotic major depressives had post-dexamethasone cortisol levels of 15 ug/dl or more, suggestive of a distinct depressive subgroup. Additional DST level clusterings at 2 ug/dl and 10 ug/dl indicated two other possible biological subgroups. The authors comment, however, that further research is needed to determine if these subgroups can be discriminated on the basis of other biological measures, clinical features (including severity of illness), and response to treatment.

Drug Treatment Response and the Subtyping of Depression

A further source of biochemical differentiation for depressive subtypes is the area of drug treatment response. In an extensive review of the literature on tricylcic antidepressant response, Bielski and Friedel (1976) note that while the pharmacologic evidence weighs in favor of depression being divided into endogenous and neurotic subtypes, support also exists for Klein's (1973) endogenomorphic group, inclusive of some neurotic features, as being tricylcic responsive. The authors comment that clinical "lore" has often claimed that amitryptyline, which blocks serotonin uptake, is most effective with agitated and severely depressed patients; imipramine, metabolized as desipramine and blocking noradrenaline uptake, on the other hand, is presumed more effective with clients exhibiting psychomotor retardation. They found, however, that the clinical features associated with positive response to amitryptyline and imipramine greatly overlapped: insidious onset, weight loss, middle/late insomnia and psychomotor retardation with imipramine response; anorexia, middle/late insomnia, psychomotor retardation and psychomotor agitation with amitryptyline response. Because they found that the studies they reviewed lacked uniform diagnostic criteria, had numerous methodologic flaws, and presented contradictory evidence, Bielski and Friedel caution that their summary of these studies be viewed as suggestive but inconclusive.

Nelson and Charney (1981) provide evidence in their review of treatment response studies which suggests that there may be at least two endogenous or "autonomous" depressive states: a retarded anhedonic group and an agitated delusional type. Retarded depression is most responsive to tricyclics but may worsen with administration of an antipsychotic medication (e.g., thioridozine, perphenazine). Agitated delusional depression appears to require both an antidepressant and an antipsychotic to produce beneficial results; agitated depressives respond poorly to antidepressants alone.

Prusoff et al (1980) conducted a study to test the usefulness of the RDC subtypes in the prediction of differential response to amitryptyline and short-term interpersonal psychotherapy (IPT) in a 16-week controlled, clinical trial using 81 ambulatory depressed patients. The study design involved an evaluation of the efficacy of IPT and amitryptyline each alone, in combination , and compared with a nonscheduled treatment control group. Both patients with a situational depression and those with an endogenous depression responded to combined treatment. Patients with an endogenous depression did not respond to IPT alone, whereas those with a situational depression responded to IPT or tricyclic medication in isolation. A methodological problem arises, however, with the authors having dichotomized their patient sample as endogenous or reactive. Studies by Rosenthal and Gudeman (1967), Klein (1975), and Kendell and

Gourlay (1970) do not support the notion that psychosocial stress provides a sufficient criterion for separating "reactive" from endogenous depression. Interestingly, Prusoff et al themselves note that in their study depressive illness could be classified as both situational and endogenous.

Stewart, Quitkin et al (1983) have recently tested the value of the RDC and severity of illness (Hamilton Depression Rating Scale- HRDS) in predicting differential response to desipramine and placebo among mildly to moderately depressed outpatients. 103 subjects between the ages of 18 and 64 years, with HDRS scores between 4 and 18, and meeting RDC criteria for major, minor or intermittent depressive disorder were selected for the study. Exclusion criteria, while covering the standard areas, also included previously adequate treatment with any tricyclic antidepressant for two weeks during the current depressive episode. Three assessment instruments were administered at baseline and after a 10-day period of placebo wash-out: the Hamilton (HDRS), the Clinical Global Impression Scale (CGI) and the self-rated Symptom Checklist (SCL-90). A CGI global improvement rating of 1 or 2 ("very much improved" or "much improved") was the criterion for defining a patient as a responder.

Those patients showing nonresponsiveness at the end of placebo therapy were randomly assigned to double-blind treatment with desipramine or placebo. Sixteen patients were

placebo responders and another 23 dropped out, six before randomization and 17 after; there were no significant differences in droupout frequency between groups. Desipramine dosage levels started at 50 ug daily and built to a maximum of 300 ug daily by study day 25 and were continued another 17 days (for a total of six weeks monitored treatment). CGI ratings were made weekly and on the final study day the HDRS and SCL-10 were also completed.

Results showed that patients improved significantly more frequently with desipramine than with placebo, (X^2=4.65, p .05). Again, treatment response was defined as a 1 or 2 rating on the CGI. The more subjective ratings of the CGI were corroborated by responders showing significantly lower SCL-90 scores and HDRS scores than nonresponders. When examining Research Diagnostic Criteria (RDC) categories for differential response to placebo and desipramine, it was found that patients with major depressive disorder demonstrated a significant difference ($p < .005$), while those with intermittent depressive disorder did not; patients with minor depressive disorder were too few to run statistical computations. No subtype under major depressive disorder (MDD) showed significant differences between desipramine and placebo responsiveness, including the endogenous subtype.

When focusing on HDRS scores, however, Stewart, Quitkin et al found that severity of illness was significantly related to desipramine response in patients belonging to any

MDD subtype. Their data reveal that a HDRS score of 14 or above (after a placebo wash-out period) coupled with a diagnosis of MDD (irrespective of subtype) is a better predictor of desipramine response than diagnostic classification by itself. Specific desipramine effect (drug response minus placebo response rate) was 79% for MDD plus HDRS of 14 or above, while only 44% for MDD alone. The authors hypothesize that the higher specific drug treatment effect created when including severity of illness as a classification variable may reflect a relatively homogenous population whose underlying biochemical dysfunction may also be homogenous.

Brown, Haier and Qualls (1980) examined the value of the DST in predicting differential tricyclic response. Nineteen patients who met RDC criteria for primary major depressive disorder underwent the dexamethasone suppression test and then were randomly assigned to one of two drug treatment groups: desipramine/impramine or amitryptyline/clomipramine. The authors hypothesized that because some evidence exists to associate cortisol hypersecretion with noradrenaline deficiency, one would expect DST nonsuppressors to show a more favarable response to impramine/desipramine (noradrenergic medications) and not to amitryptyline/clomipramine (serotonergic medications); suppresors, by contrast, would show an opposite pattern of drug responsiveness. Before treatment and after one and two weeks of treatment, patients completed the Beck Depression

Inventory and were rated on a modified version of the Hamilton Depression Rating Scale. The authors state that DST nonsuppressors treated with desipramine and imipramine (4 patients) showed "considerable improvement" as assessed on a global rating scale (developed by the researchers), while nonsuppressors (4 patients) showed no improvement ($p=.029$, Mann-Whitney U.); suppressors (5 patients), on the other hand, improved with amitryptyline and clomipramine while non-suppressors (6 patients) did not ($p < .026$). However, results of this study are questionable not only because of the small number of patients used but also because of two basic methodological flaws. One, global treatment response was rated on a continuous scale from -2 (considerable decline) to a +2 (considerable improvement). Yet all suppressors were given rounded whole number ratings (from -2 to +2) while 5 of 11 nonsuppressors were given decimal values (e.g., .6, .7, 1.4). One would suspect that raters were either trained differently on the use of the scale or had different rating styles with actual cases. Two, drug treatment response was gauged at the end of two weeks when three weeks is the more accepted (minimum) duration for antidepressant drug treatment. Finally, Brown et al themselves note in passing that changes in the Beck and Hamilton ratings from baseline to week one and from baseline to week two were not significantly different between treatment groups.

Nelson, Orr, Stevenson, and Shane (1982) conducted a study to explore the usefulness of hypothalamic-pituitary-adrenal axis variables in predicting antidepressant response. The subjects of the study were 28 inpatients (24 women, 4 men) meeting RDC criteria for major depressive disorder, endogenous subtype. Within two days after hospital admission, a detailed psychiatric history was taken and a battery of four rating scales were administered: the 21-item Hamilton Depression Rating Scale, the Roskin Three Area Assessment, the Brief Psychiatric Rating Scale, and a seven-point global severity of illness scale. Ratings were repeated four weeks later on an outpatient basis. The HPA activity evaluation conducted when patients were in a drug-free state involved three components: one, a 24-urine specimen was taken for measurement of urinary free cortisol excretion (UFC); two, blood samples were at 8 a.m. and 11:30 p.m. pre-dexamethasone; and three, a 2 mg dose of oral dexamethasone was administered after the 11:30 blood sample, with post-dexamethasone blood samples drawn the following day at 8 a.m., 4 p.m. and 11:30 p.m. Cortisol level of urinary and serum samples were assayed in duplicate using a double-antibody iodine 125 radioimmunoassay. Postdexamethasone nonsuppression was defined as a cortisol value of more than 5 ug/dl in any of the three samples taken post-DST. After psychiatric and endocrinologic evaluation, all patients were randomly assigned to one of two antidepressant treatments: 13 received imipramine and 15

amitriptyline. All patients received 150 mg daily of the chosen drug for four weeks; no drug serum level was obtained at the end of that period.

Nelson et al computed their results statistically using the following procedures: between group comparisons by the two-tailed Mann-Whitney U test; within groups correlations by the two-tailed Spearman rank-order method. While they report that 57% of patients had at least one abnormally high cortisol value, either baseline or after dexamethasone administration, only five patients (18%) were post-dexamethasone nonsuppressors. Carroll (1981) has stated that baseline (pre-dexamethasone) cortisol values are highly variable and are therefore unreliable for differentiating patients from one another, unlike post-DST values which do have a very high specificity (96%). There were almost no significant pretreatment differences between normal and abnormal groups on psychiatric ratings. Elevated (abnormal) UFC excretion values did have significantly more diurnal variation of mood ($Z=2.09$, $p < .05$) and less insight ($Z=2.14$, $p < .05$) as measured on the subscales of the Hamilton, and durinal variation was also significantly greater ($z=2.57$, $p < .05$) in patients with elevated baseline serum cortisol levels (either at 8 a.m. or 11:30 p.m.).

Treatment response was evaluated through comparison of scores on the four rating scales for depression before and after treatment. The only significant finding which emerged was that improvement on the Brief Psychiatric Rating Scale

Summary and Conclusions

Many clinical studies attempting to distinguish subtypes of depression have been sucessful in statistically separating an endogenous depression subtype from neurotic or reactive depression subtypes. However, not all of the symptoms commonly associated with an endogenous profile (i.e., in the RDC or DSM III) have received equal research validation in the literature. Symptoms receiving consistent support include psychomotor change, severity of depressed mood, lack of reactivity, depressive delusions, self-reproach, and loss of interest.

Research into neuroendocrinological correlates with depression has yielded some promising results. A positive response to the dexamethasone suppression test, for example, appears to offer highly specific confirmation of the diagnosis of endogenous depression. But while the DST's true-positive rate is high (96%), its false-negative rate among patients diagnosed endogenously depressed is also relatively high (an average 50%). Carroll (1982) and others have asserted that patients with clinically homogenous profiles may respond differently to the DST because of the biological heterogeneity underlying endogenous depression. One may thus always expect a certain number of patients clinically diagnosed as endogenous depressive to show a "false-negative" DST result. A fundamental question that

arises, however, is whether the DST positive and negative endogenous depressives are, in fact, clinically homogeneous. The assertion of no clinical differences between these two groups has been made within the context of: 1) the limited range of symptomatology covered by RDC and DSM III diagnostic categories and 2) research projects with very small numbers of subjects. No study to date has re-investigated the possible clinical differences between DST positive and negative groups outside of the breadth of symptoms considered "core" endogenous, i.e., differences inclusive of those symptoms that were considered neurotic depressive in previous statistical derivations of an endogenous depressive profile. Finally, while some evidence exists to suggest that depressive subtypes respond differentially to antidepressants, it is still unclear whether any component of HPA activity or any profile of clinical features can serve as a reliable predictor of drug treatment response.

CHAPTER THREE

METHODOLOGY OF THE STUDY

In Chapter Three, a description is provided of the clinical research instruments and the biological test employed in this study. A presentation follows of the research sample, procedures, and data analysis.

Instruments

Spitzer and Endicott (1978) and other participants in the National Institute of Mental Health Clinical Research Branch Collaborative Program on the Psychobiology of Depression have developed the Schedule for Affective Disorders and Schizophrenia (SADS), a clinical interview instrument which they believe reduces information variance (between research groups) in both descriptive and diagnostic evaluation of a subject. The SADS, while designed for companion use with the Research Diagnostic Criteria (RDC) for formulating clinical diagnoses, is also comprehensive enough in its coverage of symptomatology to be used to derive Diagnostic and Statistical Manual III for Mental Disorders diagnoses (Nelson, Charney, and Quinlan, 1981). The current study only includes Part I of the SADS, which describes the features of the current episode of illness from two perspectives: when the symptoms were the most severe during the current episode and, for many items, the severity of the symptoms for the week

prior to the interview (which may or may not also be the time of greatest severity).

Ratings of 46 items of the SADS (see Figure I) were chosen for analysis with a subject's response to the dexamethasone suppression test (DST). These items comprised all of the scalar items rated during the SADS interviews. Items included those from the entire SADS section "Dysphoric Mood and Related Symptoms" as well as two items regarding general level of functioning. Analysis of all items with a time differential was based on ratings of the patient's clinical state during the week prior to the interview. This restriction was made because of the state-dependent quality of the DST: it can only serve as a marker of biological dysfunction underlying depression when the patient is in the midst of a depressive episode. The relationship between DST response and clinical variables would thus be most meaningful when ratings of the most recent clinical state are employed. Post-DST plasma cortisol levels were assayed using a Gammacoat (^{125}I) radioimmunoassay kit (Clinical Assays). This assay procedure is a more specific one than that used by Carroll and associates (1981). The St. Lawrence Hospital Department of Pathology (1982) has recently conducted research which indicates that a cortisol level of 4.1 ug/dl using the Gammacoat (^{125}I) is equivalent to 5.0 ug/dl as derived from competitive protein binding (employed by Carroll). Therefore, in the current study a serum

Figure 3-1

Symptoms and Characteristics
of Depressive Illness Chosen from the
Schedule for Affective Disorders and Schizophrenia
(see Appendix C)

Symptoms and Characteristics	Scale
Classification of Current Condition	1-5
Period of Greatest Severity	1-5
Subjective Feelings of Depression	1-7
Distinct Quality of Mood	1-4
Association with Specific Concerns	1-4
Worrying	1-6
Self-Reproach	1-6
Negative Evaluation of Self	1-6
Discouragement about Future	1-6
Suicidal Tendencies	1-7
Panic Attacks	1-3
Somatic Anxiety	1-6
Psychic Anxiety	1-6
Phobia	1-6
Obsession or Compulsions	1-6
Insomnia (severity)	1-6
Middle Insomnia	0-1
Initial Insomnia	0-1
Terminal Insomnia	0-1
Sleeps More Than Usual	1-6

Subjective Feeling of Lack of Energy	1-6
Appetite	1-6
Weight Loss	1-6
Increase in Appetite	1-6
Weight Gain	1-6
Somatic Preoccupation	1-6
Indecisiveness	1-6
Difficulty Concentrating	1-6
Loss of Interest	1-6
Social Withdrawl	1-6
Depersonalization	1-6
Subjective Feeling of Anger	1-6
Overt Irritability	1-6
Agitation	1-6
Psychomotor Retardation	1-6
Reactivity	1-6
Mood Worse in Morning	1-4
Mood Worse in Evening	1-4
Alcohol Abuse	1-6
Libido	0-2
Drug Abuse	1-6
Antisocial Behavior	1-6
Suspiciousness	1-7
Non-Delusional Ideas of Reference	1-3
Memory Disturbance	1-6
Functional Impairment	1-6

cortisol level greater than 4.1 ug/dl was adopted as the criterion for cortisol nonsuppression.

For those subjects diagnosed major depressive disorder, endogenous subtype following Research Diagnostic Criteria (RDC), response to a five-week trial of desipramine was compared with response to the DST at initial evaluation. Drug treatment response will be defined as the change score between the Hamilton Depression Rating Scale score extracted from the SADS at initial evaluation and the Hamilton score at the end of the five-week desipramine trial (using a regular 18-item Hamilton). Endicott, Cohen et al (1981) have reported that no loss occurs when using the extracted Hamilton from the SADS instead of the real Hamilton and that, in fact, the extracted Hamilton is slightly more reliable because of the use of a six-point rating of severity for each item of the SADS. The authors provide a conversion table which indicates how SADS item ratings are to be collapsed to calculate a comparable Hamilton rating.

SADS Variable	SADS	Hamilton	HDRS Variable
Psychomotor	0-2	0	Retardation
Retardation	3	1	
	4	2	
	5	3	
	6	4	

The extracted Hamilton total score is then obtained by summing the calculted scores and adding a constant of +2.

Subjects

The current study is essentially a post hoc examination of data gathered through a research project entitled "Self Reported Symptomatology in Major Depressive Illness" led by Gregory Holmes. The author served as one of the clinical interviewers with this project whose primary objective was to validate the Differential Diagnostic Depression Scale (DDDS), a self-report measure designed to distinquish endogenous from non-endogenous forms of depression.

Subjects were recruited for the study through two main sources: 1) referral from area inpatient psychiatric units, psychiatric outpatient clinics or private mental health professionals; 2) self-referral in response to direct public solicitation in the local paper for study participants.

Initial recruitment of subjects continued until 50 individuals with endogenous depression and 50 individuals with non-endogenous depression were obtained; an additional seven subjects were seen and added to the original pool of one hundred in order to allow for an increase in the number of DST positives in the study (n=27). These diagnoses were determined by the research team using a combination of criteria described in the next section (Holmes, 1982).

Subjects were between the ages of 18 and 65 and were free of medical illnesses that might invalidate the results of the laboratory test described in the procedures section. Subjects were excluded if their depression was secondary to

other psychiatric illness. These exclusion criteria are listed in Figure 3-2. Depressed subjects qualified for inclusion in this study if, during the initial screening or intake they presented with subjective complaints of depression, dysphoria, or experience a loss of interest or pleasure in their usual activities. Patients did not qualify as subjects if depression was suspected by the clinician but denied by the patient (Holmes, 1982).

Procedure

Initial screening of the subjects for this study occurred at either time of admission to a psychiatric unit or at time of intake at a psychiatric outpatient clinic. Several clinical facilities in the Lansing area were selected as primary patient sources based on their willingness to collaborate in the study. Initial screening of patients from these sites was conducted by the unit or clinic staff as part of the routine procedure used for evaluation at the time of admission or intake (Holmes, 1982).

During the admission or intake procedure, or as soon as it was deemed clinically appropriate by unit or clinic staff, those patients who did qualify for inclusion were informed by the staff as to the nature of the study and asked if they would be willing to participate. At that time, they were told that their decision to participate did not influence their eligibility for treatment. If they were

Figure 3-2

Psychiatric and Medical Exclusion Criteria

Psychiatric

1. Schizophrenia
2. Bipolar Depression
3. Organic Brain Syndrome
4. Alcoholism
5. Anorexia Nervosa

Medical*

1. Pregnancy, high dose estrogen therapy other than oral contraceptives.
2. Cushing's disease or syndrome
3. Severe weight loss where body weight 80% of ideal weight
4. Hepatic enzyme induction (phenytoin sodium, barbiturates, meprobamate)
5. Uncontrolled diabetes mellitus (hypoglycemia, acidosis)
6. Major physical illness; trauma; fever; dehydration; nausea
7. Temporal lobe epilepsy; use of reserpine or narcotics
8. Addison's disease
9. Corticosteroid therapy
10. Hypopituitarism
11. High dose benzodiazepines (25mg/day of diazepam)
12. Other endocrine disease
13. Spironolactone therapy

* Adapted from B. J. Carroll, M. Feinberg, J. F. Greden, et al, 1981

willing to participate, consent forms were obtained for each subject (Appendices A and B) (Holmes, 1982).

The clinic or unit staff contacted a designated member of the research team when a qualified subject indicted their willingness to participate in the study. With inpatients, arrangements were made as soon as possible for a convenient time for research interviewers to meet with the patient at the unit. Patients initially screened during an intake at an outpatient facility were referred directly to the Psychiatry Clinics of the Michigan State University Clinical Center for evaluation as a study patient. Self-referrals screened by phone contact with Gregory Holmes were also seen for evaluation at the Psychiatry Clinics (Holmes, 1982).

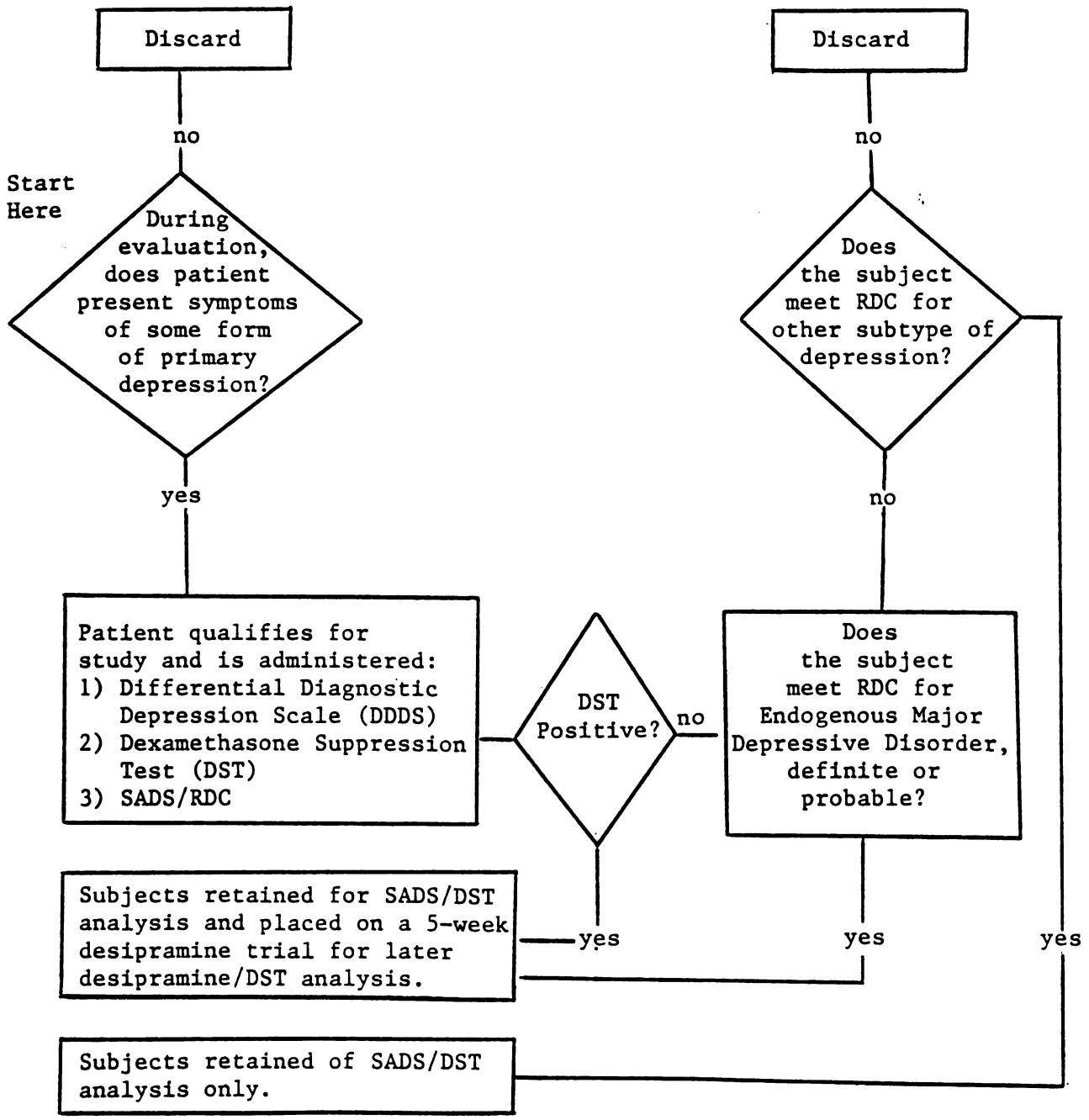
Figure 3-3 presents a flowchart of a study participant's progression through each phase of the study. Participants were asked to complete three procedures as soon as possible after the intake/admission. These procedures were as follows:

1. Each depressed subject (who passed initial screening) was asked to complete the Differential Diagnostic Depression Scale (DDDS).
2. Each subject was interviewed by a member of the research team following the semi-structured format of the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978). A research diagnosis was then derived from the SADS using the Research Diagnostic Criteria (RDC)

Figure 3-3

Subject Progression Through

Study Phases*



* Adapted from Holmes (1982)

formulated by Spitzer and Endicott (1978).

3. Each depressed subject was given the dexamethasone suppression test (DST), a laboratory test for plasma cortisol level. If the subject was on an inpatient unit, 1 mg. of dexamethasone was administered at 11 p.m. by unit staff. A blood sample was drawn by hospital staff the following day at 4 p.m. If the subject was seen at the Psychiatry Clinics, they were given the 1 mg for self-administration at 11 p.m. and instructed to report to the laboratory of St. Lawrence Hospital for the blood sampling the following day at 4 p.m.

All information obtained through the above three procedures was considered confidential and held in a secure location by the research team leader. Because procedures #2 and #3 have significant implications for clinical diagnosis and treatment of depression, this information was released by the study site if so authorized by the individual subject (Holmes, 1982).

For those subjects whose RDC diagnosis was major depressive disorder, endogenous subtype (probable or definite), or whose DST response was positive ($\geq$4.1 ug/dl), a five- week trial response to desipramine was added as a fourth study procedure. Approximately 50 , subjects qualified for this phase of the study and were treated at their initial site, either inpatient or outpatient. Treatment consisted of an initial dosage of 50 mg at bedtime

with progressive increase to 150 mg withn 2 weeks according to subject tolerance. The 150 mg dosage level was maintained during the third week. Subjects who responded positively at the end of the three week period continued at 150 mg for an additional two weeks. Those patients who did not respond at the end of three weeks had their dosage increased to 200-250 mg each night, depending upon response and side effects. Care was taken that any medications which affect desipramine plasma levels were discontinued during the five-week drug treatment trial. At the end of week five, plasma was drawn for desipramine levels (Bielski, Schafer and Holmes, 1982).

Both inpatients and outpatients were evaluated at weeks one, three, and five following the institution of medication. Subjects were seen more often when clinically indicated. Evaluation consisted of the Hamilton Depression Rating Scale (see Appendix E) being completed by a trained rater; the Zung Depression Rating Scale was also completed by the patient him/herself at week zero when the medication trial was begun. Positive response to medication was defined as a Hamilton score of 7 or less, or 50% or less of the week zero derived Hamilton score. Subjects who met this criterion for drug treatment response within the first week were to be excluded from the data analysis as placebo responders. This rationale was adopted in view of the consistent finding in the literature that the usual response time for tricyclic drug treatment is approximately 3 weeks (Bielski and Friedel, 1975; Bielski, Schafer and Holmes,

1982). No subject in the current study, however, was found to be a placebo responder.

Design

The design for the study follows a correlational model. First, the degree of association was measured between individual clinical variables and a dichotomized biochemical variable. Second, the dichotomized biochemical variable was used to define group membership of study subjects. An attempt was then made to identify the relative weightings of clinical variables associated with membership in group one as distinguished from group two. Lastly, for a subset of study subjects the relationship between the dichotomized biochemical variable and a change in a composite clinical variable was examined after introduction of a pharmocologic variable.

Research and Exploratory Hypotheses

A. Research Hypotheses:

1. DST suppressors and nonsuppressors will demonstrate differences on individual clinical items drawn from the Schedule for Affective Disorders and Schizophrenia.
2. A linear combination of clinical items taken from the Schedule for Affective Disorders and Schizophrenia

will separate DST suppressors from nonsuppressors.

B. Exploratory Hypotheses:

1. Probable and definite endogenous DST nonsuppressors placed on a desipramine trial will demonstrate greater improvement on the Hamilton Depression Rating Scale than DST suppressors.

Analysis

A separate analysis plan was conducted for each hypothesis. For the research hypothesis, analysis was performed on the 46 items drawn from the Schedule for Affective Disorders and Schizophrenia (SADS) in relation to values on the dexamethasone suppression test (DST). Three separate statistical analyses were conducted to examine the relationship between SADS items and the DST. First, Student's t-tests were performed on each SADS item with regard to dichotomized DST values. Because the homogeneity of variance assumption was found to be in violation between DST response groups, Mann-Whitney U tests were also conducted. An item by item analysis was thus conducted to expand the range of symptoms examined beyond those included in RDC and DSM III diagnostic categories. DST values were dichotomized because: 1) $\geq$ 4.1 ug/dl is the established criterion for a positive response to the DST; and 2) the distribution of DST values (see Figure 3-4) is such that anything other than a dichotomy would result in insufficient

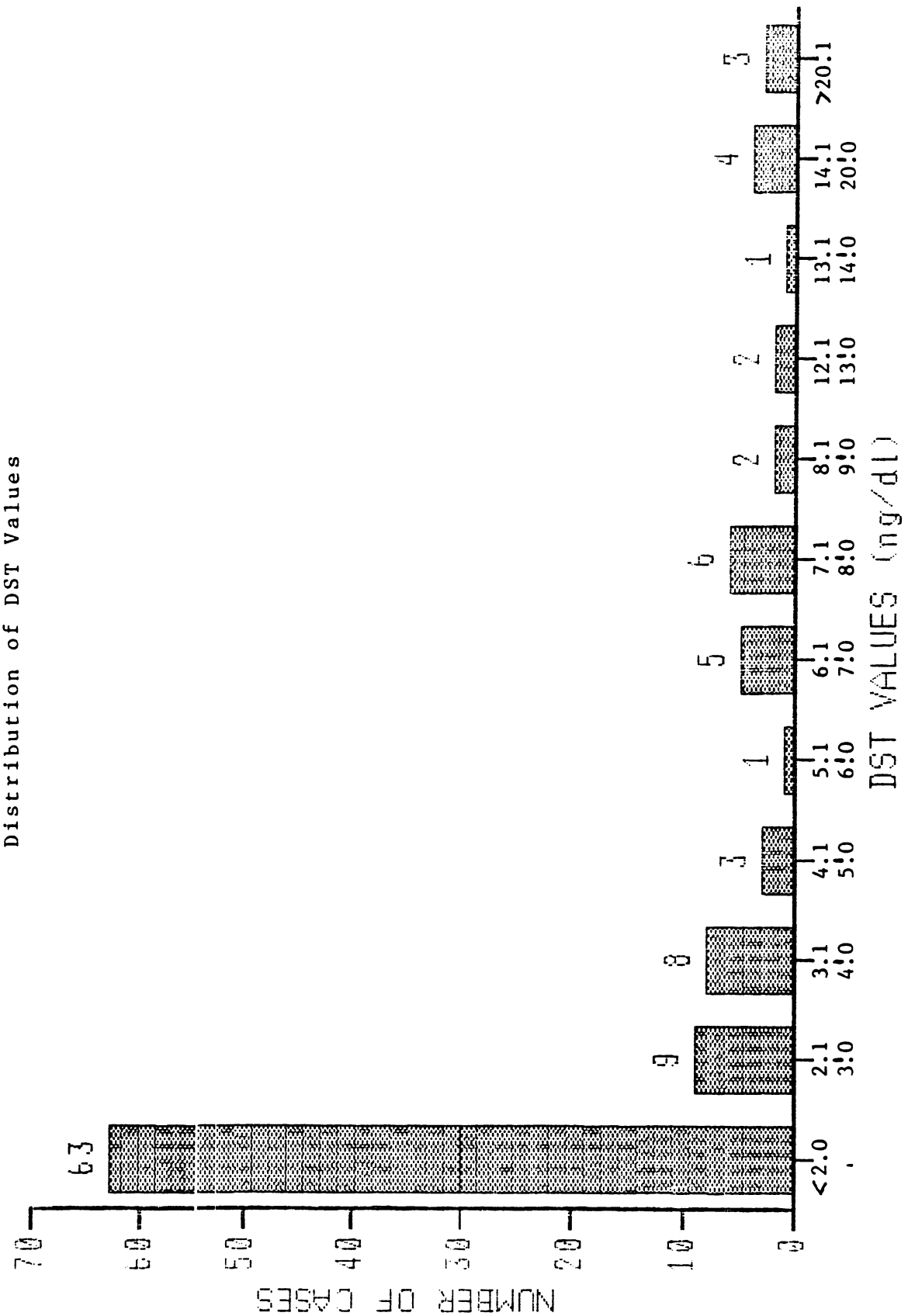
numbers of subjects in any smaller established interval, e.g., 4.1-10 ug/dl, 10-15 ug/dl, 15-20 ug/dl, and 20 ug/dl. The continuous DST values (2-26 ug/dl) were represented as follows:

DST Values	Analysis Value
< 4.1 ug/dl	0
≥ 4.1 ug/dl	1

Second, a discriminant analysis was conducted on the 46 SADS items using DST response as the designation of group membership. This statistical method will be employed to determine which linear combination of clinical item best separated DST suppressors from nonsuppressors. Third, a discriminant analysis was conducted on the 46 SADS items using only one half of the study sample drawn randomly from the total sample stratified by DST response (suppression/nonsuppression) and RDC diagnosis (definite endogenous, probable endogenous, and nonendogenous). This stratification procedure was used to insure that the subsample created had the same distribution characteristics as the total sample. The remaining half of the entire sample was then withheld as a cross-validation group for the discriminant function derived from the first half of the sample.

Figure 3-4

Distribution of DST Values



The analysis for the exploratory hypothesis was conducted on Hamilton Depression Rating Scale (HDRS) total scores derived from SADS ratings at the time of the interview and on HDRS total scores at week five of the desipramine trial.

It should be noted that only two of the cells in a 2 X 2 matrix addressing RDC diagnosis and DST response were considered in this analysis.

Figure 3-5

RDC Diagnosis

		END*	NEND#
DST	+	24	3
	-	35	45

* endogenous

\# nonendogenous

The analysis examined the distribution of Hamilton change scores (response to treatment) for cells 1 and 3, comprising a total of 34 subjects. Cell 2 was excluded

because it contained only 3 subjects, two of whom had questionable diagnoses. One subject met the criteria for endogenous symptomatology but not the criterion of mininum duration (2 weeks); the other may have had endocrinological complications which could have produced a false-positive DST. Cell 4 was excluded from the analysis because nonendogenous, negative DST subjects were not given a desipramine trial in this study. Not including cells 2 and 4 of the above matrix compromised the quality of the analysis because it was then impossible to evaluate the differential contribution of diagnosis and DST response toward the prediction of treatment response. The current design allowed only for the analysis of DST response as a predictor of treatment response exclusively within the subtype of endogenous depression. Analysis of variance was performed to estimate the value of the DST in predicting response to desipramine as measured by the change in HDRS scores between week zero and week five. Analysis of covariance was then conducted to determine the predictive value of the DST in conjunction with HDRS baseline (week zero) scores, i.e., HDRS scores at week zero were used as a covariate to be regressed on HDRS mean change scores for DST suppressors and nonsuppressors.

Summary

The Schedule for Affective Disorders and Schizophrenia (SADS), a semi-structured interview format, was employed as the primary clinical research instrument with this study. Data from the SADS were used in conjunction with response to the dexamethasone suppression test (DST) to explore the clinical features of a possible subtype associated with DST nonsuppression. A sample of 107 depressed men and women was obtained through outside referral from an inpatient unit, outpatient clinics, and private practitioners, as well as through self-referral in response to a publicized description of the study. The SADS was administered to each subject along with the Differential Diagnostic Depression Scale (DDDS) and the DST. Forty-eight subjects who met either Research Diagnostic Criteria (RDC) for major endogenous depressive disorder, definite or probable, or who demonstrated a positive response to the DST were placed on a five-week trial of the noradrenergic drug, desipramine. Thirty-four patients completed the trial; fourteen dropped out of the study either because of medication side-effects or because of referral to another facility.

An analysis plan was presented for both research and exploratory hypotheses. Two parametric statistical procedures were then used to examine the association between clinical features and DST response: one, student's t-tests with individual SADS items and DST response; two,

discriminant analysis to isolate a linear combination of SADS items which might best separate DST suppressors from nonsuppressors. A non-parametric statistic, the Mann-Whitney U test, was used as a validity check for the t-tests. To test the exploratory hypothesis of a correlation between DST nonsuppression and response to a desipramine trial, analysis of variance was performed. In addition, analysis of covariance was conducted to explore the value of the DST toward predicting desipramine response when adjusting for HDRS baseline scores.

CHAPTER FOUR

RESULTS OF THE DATA ANALYSIS

In Chapter Four, the results of the statistical analyses performed for both research and exploratory hypotheses are presented. The first section is devoted to the presentation of the results of the Student's t-tests, Mann-Whitney U Tests, and discriminant analyses conducted on the clinical features of the two groups identified as positive or negative responders to the dexamethasone suppression test. The second section presents results of analysis of variance and analysis of covariance procedures conducted on Hamilton scores to determine the value of the DST in predicting response to the noradrenergic drug, desipramine.

T-Tests:

The original analysis plan included the use of multiple t-tests to investigate the relationship between individual SADS items and DST response. The results appear in Table 4.1. DST nonsuppressors had significantly higher ratings ($p=.05$ or less) than suppressors on thirteen items: subjective feeling about the severity of depression ($p=.002$), psychic anxiety (.029), initial insomnia ($p=.001$),

Table 4.1: T-Test Results for SADS Items Using Entire Sample
(Two-Tailed Probability)

Symptom	(DST+) Group 1 M	SD	(DST-) Group 2 M	SD	DF	T-Value	Significance
Classification	2.57	1.45	2.18	1.44	45.21	1.21	.232
Time Period	1.62	.91	1.66	.96	43.19	- .20	.845
Severity	3.81	1.29	4.66	1.10	51.75	-3.31	.002
Distinct Quality	2.60	1.10	2.92	1.14	43.76	-1.29	.203
Specific Concerns	2.50	.92	2.48	.93	44.52	.09	.929
Worrying	3.51	1.26	3.51	.93	60.33	- .03	.979
Self-Reproach	3.25	1.34	3.33	1.27	47.16	- .29	.773
Negative Evaluation	3.52	1.25	3.25	1.31	39.56	.94	.354
Discouragement	3.31	1.10	3.40	1.04	47.18	- .40	.690
Suicidal Tendencies	2.35	1.24	2.62	1.52	38.38	- .86	.394
Panic Attacks	1.60	.82	1.85	.94	39.95	-1.23	.225
Somatic Anxiety	2.80	1.28	3.22	1.21	47.02	-1.53	.132
Psychic Anxiety	3.03	1.07	3.59	1.11	43.28	-2.25	.029
Phobia	1.48	1.23	1.29	1.03	53.07	.79	.432
Obsessions/Compul.	2.12	1.48	1.81	1.27	51.89	1.05	.299
Initial Insomnial	.38	.49	.74	.44	48.80	-3.47	.001
Middle Insomnia	.45	.50	.66	.48	46.50	-2.00	.051
Terminal Insomnia	.23	.42	.55	.50	39.31	-2.93	.006
Insomnia (severity)	2.85	1.47	3.77	1.12	58.73	-3.42	.001
Sleeps More	2.13	1.51	1.74	1.28	52.20	1.32	.192
Lack of Energy	3.27	1.25	3.70	.99	56.11	-1.81	.076
Appetite Loss	1.28	.14	1.60	.30	37.91	-3.41	.002
Weight Loss	1.51	.90	3.25	1.81	30.45	-4.82	.00001

Table 4.1: T-Test Results for SADS Items Using Entire Sample
(Two-Tailed Probability)

Symptom	(DST +) Group 1 M	SD	(DST -) Group 2 M	SD	DF	T-Value	Significance
Appetite Gain	1.61	1.20	1.18	.78	69.25	2.17	.033
Weight Gain	1.90	1.52	1.07	.26	91.70	4.64	.0001
Somatic Preoccup.	1.96	1.20	1.96	1.19	45.28	- .00	.999
Indecisiveness	2.75	1.21	3.33	1.10	48.73	-2.30	.025
Dim Concentration	3.15	1.37	3.77	1.18	51.19	-2.28	.027
Loss of Interest	3.07	1.53	3.66	1.44	47.19	-1.81	.076
Social Withdrawl	2.90	1.39	3.07	1.41	44.30	.56	.581
Depersonalization	1.37	.80	1.80	1.39	31.98	-1.81	.079
Subjective Anger	3.01	1.24	3.37	1.07	51.30	-1.43	.159
Overt Irritability	2.51	1.24	2.77	1.28	43.69	- .94	.354
Agitation	1.96	1.09	2.55	1.21	43.98	-2.39	.021
Psy/motor Retardation	1.90	.90	2.25	1.19	36.66	-1.43	.162
Libido	.85	.76	1.14	.77	44.58	-1.74	.088
Reactivity	3.10	1.27	3.81	1.00	54.67	-2.91	.005
AM Worsening	1.88	1.19	2.00	1.33	40.98	- .39	.699
PM Worsening	1.88	1.19	1.96	1.37	40.04	- .26	.800
Alcohol Abuse	.22	.74	1.25	.65	50.48	- .23	.822
Drug Abuse	1.11	.55	1.37	.79	34.89	-1.57	.126
Antisocial Behavior	1.15	.63	1.25	.71	41.03	- .71	.484
Suspiciousness	1.71	1.09	1.92	1.03	47.06	.91	.366
Ideas of Reference	.97	.27	1.07	.38	35.35	-1.24	.225
Memory Disturbance	1.37	.70	1.44	.50	61.92	- .56	.581
Functional Impair.	1.87	.96	2.55	.93	45.92	-3.25	.002

terminal insomnia (p=.006), insomnia- severity (p=.001), appetite loss (p=.002), weight loss (p=.00001), indecisiveness (p=.025), dim concentration (p=.027), agitation (p=.021), reactivity (p=.005), and functional impairment (p=.002). Two items had a significant association with DST suppression: appetite gain (p=.033) and weight gain (p=.00001). It was, however, discovered that with all but two of these items, the homogenity of variance assumption did not hold. It was thus decided that a non-parametric statistic, the Mann-Whitney U test, would be employed to check the validity of the Student's t-tests.

Mann-Whitney U Tests:

The Mann-Whitney test is considered the non-parametric analog of the two independent sample t-test (Pfaffenberger and Patterson, 1977) and, as such, is a test that is sensitive to both the central tendency and distibution of scores. It is designed to determine whether two random samples have been drawn from the same or different populations. The results (see Table 4.2) of the Mann-Whitney U tests conducted on the 46 SADS items and DST response closely mirror the findings of the Student's t-tests. This outcome suggests that there are significant differences between DST suppressors and nonsuppressors on a univariate level and that the results of the t-tests are not an artifact resulting from violation of the homogeneity of variance assumption.

Table 4.2: Results of Mann-Whitney U Tests
(Corrected for Ties)

Symptom	U	Z	Significance
Severity	680.1	-2.96	.0331
Psychic Anxiety	748.0	-2.47	.0133
Initial Insomnia	698.5	-3.16	.0016
Middle Insomnia	846.0	-1.93	.0526
Terminal Insomnia	736.5	-3.05	.0023
Insomnia (severity)	683.5	-2.91	.0035
Appetite Loss	644.0	-3.33	.0008
Weight Loss	438.5	-5.00	.00001
Indecisiveness	771.0	-2.28	.0223
Dim Concentration	810.0	-1.99	.0460
Agitation	757.5	-2.45	.0142
Lack of Reactivity	718.0	-2.77	.0056
Functional Impairment	683.0	-2.99	.0028
Increased Appetite	683.0	2.00	.0448
Weight Gain	786.0	2.60	.0091

Discriminant Analyses:

It will be recalled that the homogeneity of variance assumption was not upheld for individual SADS items and the groups DST +, DST-. The assumption of equal covariance matrices was consequently also in violation. Because discriminant analysis is relatively robust with respect to this violation and because no nonparametric equivalent exists for discriminant analysis, discriminant analyses were still performed on the 46 SADS items to determine which linear combination of clinical items, with respective weightings, would best separarte DST nonsuppressors from suppressors. Two discriminant analyses following the RAO stepwise procedure were run on the Michigan State University computer using the Statistical Package for the Social Sciences (SPSS). Both used DST suppression or nonsuppression as the specification of group membership. The first discriminant function constructed involved the use of all 27 nonsuppressors in the study, with none held back for cross-validation purposes. The standardized canonical discriminant function coefficients and classification results for this analysis are presented in Tables 4.3 and 4.4. The rationale for conducting a discriminant analysis based on all subjects, without the immediate possiblity of cross-validating the function constructed, was that the nonsuppression group contained only 27 subjects and may,

Table 4.3: Standarized Discriminant Function Coefficients for Discriminant Analysis Using Entire Sample

Variable	Coefficient
Weight Loss	.64154
Psychic Anxiety	.59174
Indecisiveness	.48633
Lack of Reactivity	.42449
Depersonalization	.40760
Functional Impairment	.35372
Non-Delusional Ideas of Reference	.33453
Classification	.31166
Severity of Depression	.28551
Terminal Insomnia	.27944
Depression/Concerns	-.18640
Drug Abuse	-.26658
Concern with Bodily Functioning	-.20960
Discouragement	-.23920
Suicidal Tendency	-.24956
Diurnal Mood Variation AM	-.25659
Psychomotor Retardation	-.31386
Weight Gain	-.36279
Phobia	-.41175
Negative Evaluation of Self	-.51090
Obsessions/Compulsions	-.53056

Table 4.4: Discriminant Function Classification Results for Discriminant Analysis Using Entire Sample

Actual Group	Number of Cases	Predicted Group Membership	
		1	2
Group 1 (DST-)	80	74	6
Percentage		92.5	7.5
Group 2 (DST+)	27	4	23
Percentage		14.8	85.2

because of its small size, already be inadequate for estimating the within-group variance of nonsuppressors. The stepwise procedure eliminated 25 of the original 46 items as having too small a unique contribution to be included in a discriminant function to separarte DST suppressors from nonsuppressors. Clinical items whose canonical discriminant function coefficients were closest to the group centroid associated with DST nonsuppression (2.07667) were weight loss, psychic anxiety, indecisiveness, and lack of reactivity. Those items closest to the group centroid of DST suppressors (-.70088) were obsessions/compulsions, negative evaluation of self, phobia, and weight gain. Seven of the ten items with weighting toward the DST nonsuppression group - weight loss, psychic anxiety, indecisiveness, lack of reactivity, functional impairment, severity of illness, and terminal insomnia - are consistent with the results of the univariate analyses (Student's t-tests and Mann-Whitney U tests). The percentage of grouped cases correctly classified for this sample was 90.65 (X^2=85.498, p=.00001).

The second analysis used half of the subjects from the total sample stratified by diagnosis. Standardized canonical discriminant function coefficients and classification results for the stratified sample analysis are presented in Tables 4.5 and 4.6. A discriminant function composed of 21 items resulted from the stepwise procedure, which was then cross-validated on the withheld half

Table 4.5: Standardized Discriminant Function Coefficients for Discriminant Analysis Using Split/Stratified Sample

Variable	Coefficient
Psychic Anxiety	1.51449
Diurnal Mood Variation AM	1.39740
Psychomotor Agitation	1.33162
Middle Insomnia	1.22449
Sleeps More	1.20609
Functional Impairment	.90527
Antisocial Behavior	.81160
Weight Loss	.79548
Appetite Loss	.76403
Diurnal Mood Variation PM	.43896
Non-delusional Ideas of Reference	- .31502
Panic Attacks	- .47272
Phobia	- .53064
Terminal Insomnia	- .55904
Discouragement	- .60586
Alcohol Abuse	- .64859
Negative Evaluation of Self	- .71696
Dim Concentration	- .71962
Self-Reproach	- .73842
Indecisivenes	- .80436
Worrying	-1.44933

Table 4-6: Discriminant Function Classification Results for Discriminant Analysis Using Split/Stratified Sample

	Initial Analysis Group			Cross-Validation Group		
	Number of Cases	Predicted Group Membership		Number of Cases	Predicted Group Membership	
		1	2		1	2
Group 1 (DST+)	14	14	0	13	9	4
Percentage		100.0	0		64.2	35.8
Group 2 (DST-)	40	1	39	40	13	27
Percentage		2.5	97.5		32.5	67.5

of the stratified sample. The group centroids for the nonsuppression and suppression groups were 3.56213 and -1.24675, respectively. Clinical items most closely associated with the nonsuppression group were psychic anxiety, psychomotor agitation, diurnal mood worsening, and middle insomnia; worrying, indecisiveness, self-reproach, and dim concentration, on the other hand, were related to suppression. The percentage of cases correctly classified for the initial analysis group was 98.15 (X^2=71.583, p= .00001). For the cross-validation group, correct classification was 67.93%. Classification accuracy with this latter group was still significantly better than chance ($p<.005$).

It shall be noted that the item composition is quite different for the discriminant function generated for the entire sample compared with that for the split/stratification sample. Only weight loss and psychic anxiety maintained an association with the DST nonsuppression group across discriminant functions. Diurnal mood variation AM moved from identification with the suppression group in the entire sample discriminant function to identification with the nonsuppression group in the split/stratification sample. Indecisiveness and nondelusional ideas of reference were weighted toward the nonsuppression group in the entire sample discriminant function but emerged as associated with suppression in the split/stratification sample. The differences in item

composition between the two discriminant functions were largely an artifact of the larger within-group variance of the DST nonsuppression group (N=14) used in the split/stratification discriminant analysis. That is, given the greater likelihood that DST nonsuppressors in the smaller split/stratification sample would differ as much from each other as they would from members in the suppression group, it is highly improbable that the same clinical items would be weighted toward the nonsuppression group as were found in the discriminant function of the entire sample. Thus the most significant finding of the discriminant analysis based on the split/stratification sample remains the fact that the function derived, of whatever item composition, could still separate a cross-validation sample of DST suppressors and nonsuppressors better than would be expected by chance.

It will be recalled that the DST is a state-dependent biological measure and is usually only sensitive when an individual is in the midst of a depessive episode. A chi-square analysis was therefore conducted to examine the possible relationship between time of greatest severity in the present depressive episode and DST response (see Table 4.7). Time of greatest severity was measured through the patient's subjective rating (SADS item "time period") of whether his/her illness was most severe during the two weeks up until the study evaluation or prior to that time. No significant association was found (X^2=.47247, p=.4919).

Table 4.7: Interaction of Time of Greatest Severity with DST Response

		DST Response	
		DST-	DST+
Time	Past Week	16	14
	Prior to Past Week	19	10

A second additional analysis was conducted on the subhypothesis that DST nonsuppressors experience more severe symptomatology than suppressors, i.e., these former would score higher on a severity of depression measure like the Hamilton Depression Rating Scale (HDRS). A Student's t-test was performed on HDRS baseline scores and DST response. Results revealed that DST nonsuppressors in this study's sample did have an overall more severe illness than suppressors (see Table 4-8).

Table 4.8: T-Test Results for Severity of Illness Based on HDRS Scores

DST- Group 1		DST+ Group 2		DF	T-Value	Significance
M	SD	M	SD			
16.42	7.06	22.26	7.52	105	-3.65	.001

The exploratory hypothesis of the study involving the relationship between DST response and response to a desipramine trial (as measured by a change in Hamilton scores) was examined for the 34 subjects who completed the trial using analysis of variance (ANOVA) and analysis of covariance (ANCOVA) procedures. A one-way ANOVA was performed on DST response (+,-) and each of three sets of Hamilton (HDRS) scores:

1) Pretest HDRS scores.
2) Posttest HDRS scores.
3) HDRS change scores.

The results of these analyses are presented in Tables 4.9, 4.10, and 4.11.

Table 4.9: ANOVA Results for DST and Dependent Measures

	MS	F	Significance
Pretest	36.813	1.261	.270
Postest	81.715	2.108	.156
Change	228.222	4.132	.050

Table 4.10: ANCOVA of DST with Posttest Using Pretest as Covariate

	MS	F	Significance
Pretest	22.82	.591	.418
DST	103.313	2.678	.112
Explained (variance)	63.067	1.634	.211

Table 4.11: ANCOVA of DST with Change Scores Using Pretest as Covariate

	MS	F	Significance
Pretest	696.084	18.040	.001
DST	103.313	2.678	.112
Explained (variance)	799.398	10.359	.001

Only the HDRS change scores had a significant univariate relationship (p=.050) with DST response, i.e., the magnitude of change in HDRS scores between week zero and week five was greater on the average for DST nonsuppressors than suppressors. An analysis of covariance conducted on pre- and posttest HDRS scores did not yield a significant result. A second ANCOVA performed using pretest scores as the covariate with change scores as the dependent variable did result in significant findings. However, DST response no longer constituted a significant factor in a linear equation designed to predict a favorable response to desipramine. Rather, the pretest scores' strong negative correlation with HDRS change scores (P=-.5906) served as the most significant component (p=.001) of the predictive equation. A correlation matrix including DST response and the three dependent measures pretest, posttest, and change score appears in Table 4.12.

Table 4.12: Correlation Matrix for DST Response and Dependent Measures

	Posttest	Change	Pretest	DST
Posttest	1.0000	.7224	.1314	-.2486
	p=.00	p=.001	p=.229	p=.078
Change	.7224	1.000	-.5906	-.3382
	p=.001	p=.00	p=.001	p=.025
Pretest	.1314	-.5906	1.000	.1947
	p=.229	p=.001	p=.00	p=.135
DST	-.2486	-.3382	.1947	1.000
	p=.078	p=.025	p=.135	p=.00

Two hypotheses subordinate to the major exploratory hypothesis were also investigated. First, the question was posed that if DST nonsuppressors demonstrate a greater magnitude of response to a desipramine trial, there might also be a proportionately larger number of desipramine responders among nonsuppressors than among suppressors. Patients were categorized responders if their Hamilton change score was 7 or less, or 50% or less of their baseline (week zero) Hamilton score. A chi-square test of significance was then performed on the dichotomized variables responder/nonresponder and DST suppression/nonsuppression. Results (see Table 4.13) do not show a significantly higher frequency of desipramine response within the DST nonsuppression group as compared with the suppression group (X^2=1.10436, p=.2933).

Finally, it has been argued recently in the literature (Smith, Glass, and Miller, 1982) that psychotherapy conducted concurrently with drug treatment does not produce an interactive effect superior to either intervention in isolation. The hypothesis that DST nonsuppressors receiving psychotherapy and desipramine at the same time would have a higher frequency of response to desipramine (i.e., as reflected in HDRS scores) was tested by chi-square analysis. The results (see Table 4.14) do not indicate a positive interactive effect (X^2=1.5909, p=.2817) between psychotherapy and desipramine for the 7 patients in this study who received both forms of treatment .

Table 4.13: Interaction of Desipramine Responsiveness with DST Response (N=34)

		Responder	
		No	Yes
DST	-	9	11
	+	3	11

X^2=1.104, p=.293

Table 4.14: Interaction of Psychotherapy with DST Response (N=34)

		Responder	
		No	Yes
Psycho-therapy	No	8	9
	Yes	4	3

X^2=1.590, p=.281

Summary

The major hypothesis in this study involved the relationship between response to the dexamethasone suppression test and clinical features. This hypothesis was examined from two perspectives. One, the association between individual clinical items and DST response was explored through the calculation of Student's t-tests. DST nonsuppressors had significantly higher ratings ($p<.05$) on twelve SADS items. These items were severity, psychic anxiety, initial insomnia, terminal insomnia, insomnia (severity), appetite loss, weight loss, indecisiveness, dim concentration, agitation, lack of reactivity, and functional impairment. DST suppressors had significantly higher ratings for the items weight gain and appetite gain. While it was ascertained that the homogeneity of variance assumption underlying the valid use of the t-test was in violation, execution of Mann-Whitney U tests, the nonparametric analog to the t-test, yielded the same clinical items as significantly related to DST nonsuppression and at close to the same levels of significance.

Two, the relationship between DST response and a linear combination of clinical variables was examined through two separate discriminant analyses. The first discriminant analysis involved the use of the entire sample, with no subjects withheld for cross-validation. A discriminant function was derived which correctly classified 90.85% of

the cases (X^2 =85.498,p=.00001). Discriminant function canonical coefficients with the highest loadings toward DST nonsuppression were weight loss, psychic anxiety, indecisiveness and lack of reactivity; those toward DST suppression were obsessions/compulsions, negative evaluation of self, phobia, and weight gain. A second discriminant analysis was conducted on one half of the entire sample stratified by diagnosis, with the other half held back for cross-validation of the function derived from the first half. The discriminant function calculated for the split/stratified sample correctly classified 98.15% of the cases employed (X^2=71.583,p=.00001). Discriminant function canonical coefficients with the highest loadings toward the DST nonsuppression group in this split sample were psychic anxiety, diurnal mood worsening AM, psychomotor agitation, and middle insomnia; those toward the suppression group were worrying, indecisiveness, self-reproach, and dim concentration. Cross-validation of this function on the withheld half of the stratified sample yielded 67.93 percent correct classification. Although a 30.22 percent drop in classification accuracy occurred between initial derivation of this discriminant function and its cross-validation, the cross-validation percentage of correct classification was still significantly better than chance ($p < .005$).

Two additional subhypotheses were explored. The first involved the possible association between time of greatest severity in a subject's current depressive episode and

response to the DST. A chi-square test performed did not establish a significant association (X^2=.47247,p=.4919). The second examined the hypothesis that DST nonsuppressors would score significantly higher than suppressors on a measure of severity of illness. A student's t-test conducted on derived HDRS scores at week zero did demonstrate that DST nonsuppressors experienced more severe symptomatology than suppressors (p=.019).

The exploratory hypothesis focused on the relationship between DST response and response to a five-week desipramine trial as measured by a change in HDRS scores. Univariate analyses were first conducted on DST response and HDRS pretest, posttest, and (post minus pre) change scores. Only change scores emerged as having a significant association (p=.050) with DST nonsuppression. Secondly, analysis of covariance (ANCOVA) was performed using DST response as the independent variable, HDRS pretest scores as the covariate and HDRS posttest scores as the dependent variable; a second ANCOVA was executed using HDRS change scores as the dependent variable. DST response did not have a significant loading in a linear equation to predict HDRS posttest scores when using pretest scores as the covariate. Rather, a large pretest score emerged as being significantly predictive of a large change score.

CHAPTER FIVE

SUMMARY AND CONCLUSIONS

Summary

This investigation was an attempt to explore the relationship between response to the dexamethasone suppression test (DST) and clinical and pharmacologic variables. The need for this study arose from the observation that no previous research had examined this relationship outside of the restricted symptom coverage of already established diagnostic categories, i.e., those defined by the Research Diagnostic Criteria or by the Diagnostic and Statistical Manual of Mental Disorders III. It was suggested that an abnormal response to the DST may serve as a discriminating variable for defining a distinct biological subtype of depression

Until the last decade, the literature on depression relied almost exclusively on statistical analysis of clinical features to derive depressive subtypes. The endogenous/neurotic distinction among depressives was thus created. With the introduction of biological measures of depressive states like MHPG levels and the DST, researchers attempted to establish the depressive subtype membership of patients through the existence of specific forms of biological dysfunction. While Carroll (1982) has commented that the DST, as an indirect marker of HPA disorder, has an

unreliable association with specific clinical features, neither he nor any other researcher has reported the systematic investigation of the DST as a discriminant for a clinical depressive subtype. The little research which has focused on the subtyping capability of the DST has been marred by methodological flaws or small sample sizes. The literature reporting on the use of the DST to predict anti-depressant medication response is also inconclusive. Although several researchers (e.g., Brown, Haier, and Qualls, 1980) have hypothesized a differential response of DST nonsuppressors to noradrenergic tricyclics, these studies have involved small samples and thus can offer only tentative conclusions.

The current study aimed to overcome the shortcomings of earlier research by: one, gathering initial clinical data through the Schedule for Affective Disorders and Schizophrenia (SADS), a standardized, semi-structured interview format which can be used reliably by other researchers; two, by further testing the hypothesis that DST nonsuppressors respond more favorably to noradrenergic medications (e.g., desipramine) than do suppressors; and three, by using a large enough sample of subjects to make statistical analysis meaningful.

A sample of 107 depressed patients (77 women, 30 men) was obtained from a consortium of mental health facilities in the Lansing area as well as from self-referral in response to a newspaper article about the study. For those

patients who passed the initial screening, the SADS was administered, along with the Differential Diagnostic Depression Scale (DDDS) and the DST. Forty-eight subjects who met either Research Diagnostic Criteria (RDC) for major endogenous depressive disorder, definite or probable, or who were DST nonsuppressors, were begun on a trial of the noradrenergic medication, desipramine. Thirty-four patients completed the five-week trial.

Ratings of forty-six SADS items and response to the DST were used to address the first study question: Is there a relationship between individual clinical variables and response to the DST? Both Student's t-tests and Mann-Whitney U tests revealed that DST nonsuppressors had significantly higher ratings on twelve items. These were: subjective feeling of severity, psychic anxiety, initial insomnia, middle insomnia, terminal insomnia, insomnia (severity), appetite loss, weight loss, indecisiveness, dim concentration, psychomotor agitation, lack of reactivity, and functional impairment. DST suppressors had higher ratings on two SADS items: increased appetite and weight gain.

The same forty-six SADS items were employed with DST response to examine the second question: Can a linear combination of clinical variables be generated which would separate the group of DST nonsuppressors from the group of suppressors? Two discriminant analyses were conducted to respond to this question. First, an analysis was executed

using the entire study sample (n=107). A discriminant function was derived which correctly classified 90.65% of the subjects. Those clinical items most strongly associated with the DST nonsuppression group were: weight loss, psychic anxiety, indecisiveness, and lack of reactivity; those associated with suppression were obsessions/compulsions, negative evaluation of self, and phobia. Secondly, a discriminant analysis was performed using one half of the entire sample stratified by diagnosis. The discriminant function derived correctly classified 98.15% of the subjects included. Items with the highest loadings toward the DST nonsuppression group in this sample were psychic anxiety, diurnal mood worsening AM, psychomotor agitation, and middle insomnia; those toward the suppression group were worrying, indecisiveness, self-reproach, and dim concentration. Although a 30.22% drop in classification accuracy occurred with the cross-validation group in comparison with the initial derivation group, the percentage of correct classification with the cross-validation group was still significantly better than chance.

Two questions ancillary to the major research hypotheses were posed. One, in view of the DST's state-dependent quality, do more DST nonsuppressors report their depression being most severe at the time of their study evaluation (and DST administration) than at some earlier time during the current episode? A chi-square analysis revealed that they do not. Two, do DST

nonsuppressors experience more severe symptomatology than suppressors? A t-test conducted on DST response and total derived Hamilton scores at week zero of the study did demonstrate that DST nonsuppressors have a more severe depressive illness.

Derived total Hamilton scores at week zero and direct Hamilton ratings at week five of a desipramine trial served as data for the major exploratory hypothesis: Does a patient who fails to suppress normally on the DST respond more favorably to a noradrenergic medication like desipramine than does a DST suppressor? Results of univariate analyses indicated a relationship between DST nonsuppression and a significantly larger Hamilton change score (week five minus week zero scores) than with suppression. However, an analysis of covariance using Hamilton pretest scores as the covariate did not uphold the significance of the DST as a variable predicting desipramine response. Rather, a large Hamilton pretest score emerged as the most significant factor toward prediction of a large change score. Finally, two secondary questions were addressed. One, is there a higher frequency of response to desipramine among DST nonsuppressors than suppressors? Hamilton change scores were dichotomized as responder/nonresponder following an established criterion of response. Chi-square analysis did not demonstrate a significantly greater proportion of responders falling within the nonsuppression group. Two, do patients who are in psychotherapy concurrently with drug

treatment more often show clinical responsiveness than do patients who are only on medication? Results of a chi-square analysis did not suggest such an interactive effect.

Conclusions

Conclusions Drawn From a Review of the Literature:

1) Previous studies have demonstrated that the dexamethasone suppression test has an average specificity of 96% and sensitivity of between 40 and 70% when using a 1-mg dose of dexamethasone.
2) The few studies which have attempted to clinically separate DST suppressors and nonsuppressors either used a limited range of symptoms on which to base such a differential or were methodologically flawed.
3) There have been discrepant findings regarding support of the hypothesis that DST nonsuppression is associated with deficiency of the neurotransmitter, norepinephrine. Noradrenergic medications like desipramine have not been consistently shown to be more effective with DST nonsuppressors than suppressors.

Conclusions From the Current Study:

1) The current study had the following nonsuppression rates across Research Diagnostic Criteria categories: definite

endogenous- 57.1% (16/28); probable endogenous- 25.8% (8/31); and nonendogenous- 6.3% (3/48); the specificity for endogenous depression was thus 93.7%. These rates are comparable to those reported in the literature.

2) DST nonsuppressors had significantly higher ratings on the individual clinical items subjective feeling of severity, psychic anxiety, initial insomnia, terminal insomnia, insomnia (severity), appetite loss, weight loss, indecisiveness, dim concentration, psychomotor agitation, lack of reactivity, and functional impairment were associated with DST nonsuppression. DST suppressors had higher ratings on the items increased appetite and weight gain.

3) A discriminant analysis performed on SADS items and membership in the DST suppression or nonsuppression groups generated a function which correctly classified 90.65% of the cases in the total sample.

4) A second discriminant function derived after analysis of one half of the sample stratified by diagnosis correctly classified 98.15% of those cases. The second half of the stratified sample held back for cross-validation dropped to 67.93 percent correct classification. Cross-validation classification accuracy was, however, still better than chance.

5) A patient's report of greatest severity of illness occurring at the time of evaluation was not related to a

higher frequency of DST nonsuppression.

6) DST nonsuppressors did demonstrate more severe depressive symtomatology than suppressors at the time of evaluation.

7) DST nonsuppressors had a better response to desipramine than suppressors as reflected in change scores on a clinical measure.

8) When DST response and baseline scores on a clinical measure were considered together in predicting desipramine response (defined in terms of the same measure), DST response was no longer a significant predictive factor. Rather, a patient's having a large baseline score on the clinical measure was most predictive of a large change score (pre minus post).

9) There was no significant difference in the proportion of DST suppressors and nonsuppressors who responded to desipramine.

10) Psychotherapy did not make a significant interactive contribution to a patient's response to desipramine (for the small number of patients who were receiving both forms of treatment in this study, N=7).

A Review of Recent Findings in the Literature

Hirschfeld, Koslow, and Kupfer (1983) published a summary of a recent conference on the DST paneled by leading researchers in neuroendocrinology, psychopathology, and

general clinical psychiatry (e.g., B. Carroll, W. Brown, D. Klein, and R. Spitzer). It was the consensus among members of the conference that while the DST should continue to be used as a research instrument, until nonsuppression rates are determined for the normal population and for specific diagnostic groups (e.g., schizophrenia and schizo-affective disorder), the DST should not be used as a routine screening device or in differential diagnosis. Content of the conference relevant to the current study included the observations that: the clinical differences between DST suppressors and nonsuppressors should be further investigated using new strategies, i.e., ones that do not rely on the DSMIII or RDC categories; the relationship between severity of illness and DST nonsuppression has received inconsistent support; and there is preliminary evidence to indicate that nonsuppressors respond more favorably to noradrenergic tricyclic antidepressants.

The current study yielded specificity and sensitivity rates for the DST and endogenous depression comparable to those previously cited by Carroll (1982) and others. Recent findings in the literature, however, can no longer lead one to conclude that a concensus exists regarding the DST's specificity to endogenous depression. Several researchers (Coppen et al, 1983; Castro et al, 1983) have provided evidence that not only certain groups of non-depressive patients (e.g., schizophrenics and alcoholics) show

dexamethasone nonsuppression but that a significant proportion of nonendogenous depressives do as well.

While significant rates of DST nonsuppression among non-depressive psychiatric disorders may be borne out with further investigation, reports of the DST's lack of specificity to endogenous depression within the more focused area of the affective disorders are, upon close examination, not as credible. Coppen and associates (1983) found a 49% rate of nonsupression in patients diagnosed as nonendogenous major depressive disorder, as well as a 40% rate of nonsuppression among their sample of neurotic depressives. These figures, taken out of context of how the diagnositc categoreis nonendogenous and neurotic were defined by these researchers, are largely misleading. Although the International Classification of Diseases (ICD) was used to assign patients to the category "major depressive disorder", the subcategories endogenous and nonendogenous were speficied by a patient's score on the Newcastle index. It is erroneous to assume that patients found to be nonendogenous in this fashion would be similarly rated under any of the more frequently used diagnostic systems, i.e., many Newcastle nonendogenous patients could conceivable fall into at least the probable major depressive category in the RDC (Kasper and Beckman, 1983). Additionally, it is unclear whether Carroll's (1981) exclusion criteria (medical, pharmacologic, and clinical) were followed by Coppen and his colleagues in their assignment of patients to the ICD

category eurotic depressive disorder who would later be given the)ST.

Kasp : and Beckman (1983) investigated DST nonsuppre sion within the context of three different diagnosti systems: the ICD, the RDC, and the Newcastle index. Si ty-seven depressed men and women were evaluated upon hosp tal admission and were given the DST. One mg of dexametha one was administered at 11 p.m. followed by a single bl od draw at 8 a.m. the next day. A blood level above 4 u /dl was used as the criterion for nonsuppression. Results ndicated 55% of ICD endogenous depressives, unipolar subtype, 51% of RDC definite major depressive disorder, and 53% of Newcastle endogenous were DST nonsuppre sors. While ICD neurotic and RDC minor depressive disorder emonstrated rates of nonsuppression of only 6% and 9%, respe tively, the Newcastle neurotic category had 23% of its memb rs to show nonsuppression. Differences in the severity of symptomatology and in individual clinical features ere examined by means of the Hamilton Depression Rating S ale. DST nonsuppressors, regardless of diagnosis, were mor severely depressed, had more loss of interest, gastroint stinal symptoms, somatic symptoms, and lack of insight an suppressors. Kasper and Beckman comment that a direct a sociation between DST nonsuppression and severity of illne s suggests a state variable in operation rather than a di stinct depressive subtype. They further hypothesize that the elationship between DST nonsuppression and somatic

complaints supports the interpretation of an "unspecific" stress response pattern in nonsuppressors related to pituitary-adrenal cortical system activation. Lastly, the authors point to the rate of nonsuppression among neurotic depressives diagnosed by the Newcastle index as a clear indication of how specificity rates for the DST vary because of discrepant criteria for diagnostic classification. Although Kasper and Beckman appear to have been careful in most respects with their research design, their having instituted an 8 a.m. blood draw for the DST constitutes a serious methodological abberation. Carroll et al (1981), in an article on the standardization of the DST, reported that only 24% of their total number of abnormal test results were detectable based on blood samples taken at 8 a.m. Blood is usually drawn at 8 a.m., 4 p.m., and 11 p.m. when a patient is hospitalized, and at 4 p.m. when only a single blood draw is possible. One may therefore hypothesize that while Kasper and Beckman's reported rates of DST nonsuppression (51% for RDC major depressive disorder) were not unusual, a certain percentage of those patients who suppressed abnormally at 8 a.m. may not have at 4 p.m. and vice versa. Thus the focus by these authors on eliminating threats to the DST's specificity imposed by diagnostic inconsistency may have led them to overlook a crucial factor in the accurate identification of DST nonsuppression.

The evidence for the value of the DST in predicting a patient's response to tricyclic anti-depressants is still

contradictory. Two recent studies highlight the opposing claims. Ettigi and his colleagues (1983) conducted a study to investigate the separate and combined significance of the DST and an amphetamine challenge test toward prediction of a positive response to a desipramine trial. They report that in their sample of eleven DST nonsuppressors who met criteria for DSMIII major depressive illness, ten (91%) had a positive response to desipramine, while only three of seven suppressors (43%) responded favorably. Positive responders were defined as patients who, after a 4-week desipramine trial, were "able to function and make plans for discharge". A question, however, arises with this study regarding how "able to function" was measured, i.e., no specific target symptoms were mentioned for determining response to desipramine. Extein, Kirstein, Pottark, and Gold (1983) retrospectively examined the differential effectiveness of the DST and a thyrotropin-releasing hormone test in predicting response to tricyclics and/or electroconvulsive therapy. Nineteen patients who met criteria for RDC major depressive disorder were DST nonsuppressors. Eight of the ten DST nonsuppressors and six of the nine suppressors responded to tricyclics, resulting in no significant difference in frequency of response between the two groups. However, this study has two basic flaws: one, both noradrenergic (desipramine/imipramine) and serotonergic (nortriptyline/amitriptyline) tricyclics were administered, thus confounding the possible differential

effects of each type; two, scores on the self-administered Zung Depression Rating Scale were used as one of the primary determinants for a patient's favorable response to treatment, when the Zung has long been thought to have questionable validity (Carroll, 1982).

Kline and Beeber (1983) conducted a study to investigate the relationship between DST nonsuppression and weight loss. The records of twenty-seven hospitalized depressed patients were retrospectively reviewed. Thirteen of fourteen DST nonsuppressors identified among this sample were found to have weight loss of between 0.9 to 5.4 kg; none had weight loss exceding 10% of normal body weight. The authors hypothesize that since weight loss is one of the criteria for the DSMIII diagnosis major depressive disorder with melancholia, weight loss may be the key variable for the specificity of the DST to melancholia with any particular sample of depressed patients. Two other studies appear to support Kline and Beeber's hypothesis. Berger et al (1983) reported that with their sample of nine nonsuppressors diagnosed endogenous or neurotic depressive, seven had an average weight loss of 0.91 ± 0.76 kg during the week prior to the administration of the DST. The implication of this finding is that melancholic patients who do not have weight loss of marked or anorectic proportions, and thus are not diagnosed melancholic through a positive rating on the clinical feature weight loss, could still demonstrate DST nonsuppression from even mild downward

fluctuations in normal body weight. Berger et al also examined the relationship between DST nonsuppression and weight loss in normals. Nine (37.5%) of 24 subjects placed on a diet of 1,000 to 1,3000 kcal per day for two weeks demonstrated DST nonsuppression after suppressing normally during two baseline DST's. Edelstein et al (1983) placed eighteen healthy, depression free, obese subjects on a protein-sparing diet who suppressed normally on a basesline DST. After eight to twelve weeks of fasting, five (27.5%) of the group of eighteen showed DST nonsuppression. These five subjects weighed less initially and lost a significantly greater percentage of their ideal body weight than the suppressors (average loss of 13.5 kg, 17.6% of total body weight). While Edelstein et al acknowledge that the design of their study did not permit the separation of weight loss from administered diet as the cause of abnormal HPA activity, they caution that the DST should not be relied upon for confirmation of the diagnosis of endogenous depression with patients who have weight loss in the range of 9-22.5 kg (the range of weight loss among their subjects).

Discussion

The following discussion has been divided into seven subsections which address a variety of issues raised by the findings of the study.

The Timing of DST Sensitivity for a Depressed Patient

It is necessary, before interpreting the results of the current study, to review the characteristics of the key variable examined, response to the dexamethasone supppression test (DST). With the exclusion of nondepressive disorders in this study, the DST was a state biological marker whose sensitivity to endogenous depression was dependent on a patient being tested in the midst of a major depressive episode. The state-dependency of the DST was examined by stating the hypothesis that those RDC probable or definite endogenous subjects tested at the time of greatest severity of their depression (i.e., severity as reported at the time of the SADS interview) would have a significantly higher frequency of nonsuppression than would subjects who reported their depression being at its worst at least two weeks prior to their evaluation with the study. The data did not confirm this hypothesis. Nonsuppressors were just as likely to report the greatest severity of their current depressive episode occurring over two weeks prior to the study evaluation as they were to report feeling the worst at the time of the evaluation. This finding suggests that the state-sensitvity of the DST varies across endogenously depressed patients because of individually variable lengths to the period of HPA dysfunction detectable by the DST and current assay procedures. Such variability in DST sensitivity periods could confound attempts to

clinically separate DST suppressors and nonsuppressors if one includes in the analysis group only subjects who are diagnosed endogenous depressive (probable or definite). The risk is then run that a certain percentage of the suppressors among this group may have not suppressed normally at another time during their current episode and may not present a significantly different clinical profile than those subjects who were negative responders to the DST within a few days of the interview. There is no research evidence yet available on the average time lapse between normalization of HPA functioning and clinical improvement. It is therefore conceivable that a depressed patient who had HPA dysfunction detectable by the DST could revert to normal cortisol suppression well before clinical change would be noted.

It should now be clear that while creating a subset of the entire sample in this study (i.e., only RDC probable and definite endogenous) would have brought the ratio of DST suppressors to nonsuppressors down from 3:1 to about 1.4:1 and would thus have created a more even balance in group size for statistical analysis, it would, at the same time, have been difficult to assess whether an endogenous depressive who demonstrated DST suppression at the time of the evaluation would not have at some previous or later point in his/her episode. Having included, on the other hand, both endogenous and nonendogenous patients in the analysis pool provided the opportunity for the DST

suppression group to be more firmly weighted with individuals who most probably would not fail to suppress normally on the DST at any point during their depressive episode. That is, given the rigorous exclusion criteria of the present study, it was reasonable to assume that the nonsuppression rate of nonendogenous patients in the sample reflected the low rate of nonsuppression for RDC nonendogenous reported elsewhere (Carroll, 1982; Schatzberg et al, 1983).

DST Nonsuppression and the Traditional Concept of Endogenous Depression

Specific clinical differences between the entire sample of DST suppressors and nonsuppressors did emerge. Many of the clinical features found to be significantly related to DST nonsuppression have their analogs in the profile of "endogenous depression" isolated by previous research using largely statistical analysis of clinical features without the inclusion of psychobiological correlates. In Table 5-1, adapted from Nelson and Charney's (1981) analysis of a large body of previous research on endogenous depression, a summary is presented of the relative importance of specific symptomatology in a profile of endogenous depression. Five of the twelve symptoms which emerged as significant in the univariate analyses of the current study - lack of reactivity, severity of depressed mood, terminal insomnia,

Table 5.1: Association of Symptoms with Endogenous Depression

Symptom	Type of Study				
	Factor	Cluster	Discriminant Function	Symptom Frequency	Treatment Response
Retardation	St[#]	St	St	M[@]	St
Agitation	Sl[*]	M	St	Sl	M
Reactivity	St	St		M	
Severity	St	St		M	
Self-reproach	M	St	Sl	M	M
Loss of interest	M	M		M	M
Distinct quality	M	Sl		M	
Lower Concentration	Sl	Sl		M	
AM mood worsening	Sl	M		Sl	
Weight loss	SL	SL		Sl	
Initial insomnia	N[¢]				
Middle insomnia	Sl	Sl		Sl	
Terminal insomnia	Sl	M	Sl	Sl	Sl
Depressive delusions	M	M	M	M	M
Suicidal thoughts/ attempts	Sl			N	

[#]Strong, [@]Moderate, [*]Slight, [¢]None

psychomotor agitation, and dim concentration - are consistent with the weightings of symptoms reviewed by Nelson and Charney. However, the symptom weight loss, while having the strongest association with DST nonsuppression in the current study as indicated by both the univariate analyses and by the discriminant analysis using the entire sample, has been given only a "slight" association with endogenous depression by previous researchers. In addition, functional impairment, indecisiveness, appetite loss, initial insomnia, and insomnia (severity), all significant in the findings of the current study, apparently have not been included as possibly associated symptoms in prior studies. The symptoms psychic anxiety and initial insomnia emerging as significant in the current findings are the most discrepant with previous research of endogenous depression. Both of these symptoms have traditionally been regarded as indicative of neurotic depression (Kiloh and Garside, 1963; Rosenthal and Gudeman, 1967).

Stress and DST Nonsuppression

The association of relatively high levels of psychic anxiety with DST nonsuppression also appears to grant stress some role in the psychobiological dysfunction behind endogenous depression. However, the boundaries between such terms as "stress", "anxiety", and "arousal" remains unclear (Sweeney and Maas, 1979), leaving it possible to confer on

stress significance both as an insidious factor underlying a symptomatological pattern and as symptom (anxiety) consciously experienced. The symptom status of anxiety in the context of endogenous depression is supported by Akiskal's (1983) observation that it is not uncommon for patients with affective illness to develop neurotic personality traits. Thus DST nonsuppressors may become anxious in response to the core affective illness rather than depressed as a consequence of chronic anxiety (stress).

Weight Loss and DST Nonsuppression

Recent reports in the literature have presented data which indicates an association between DST nonsuppression and weight loss in normals as well as depressives. DST nonsuppression in normals following the loss of less than 20% of normal body weight requires further research to determine the causative factors involved. The significance of weight loss for depressives with DST nonsuppression is also not clear. Research thus far has investigated the relationship between the individual variables weight loss and DST response across diagnostic categories and not within the context of other individual symptoms. The results of the current study offer support for a strong association between failure to suppress normally on the DST and weight loss but also point to other clinical features having a concurrently significant association with DST nonsuppression.

Severity of Illness and DST Nonsuppression

An association between DST nonsuppression and global severity of illness has received inconsistent support, with most studies reporting no significant relationship (Carroll, 1982; Brown and Shuey, 1980; Mendlewicz et al, 1982). Kasper and Beckman (1983) interpreted their finding of DST nonsuppression associated with severity of illness as indicating that DST nonsuppression is a state variable tied to an "unspecific" stress response pattern. Such an interpretation was based largely on "somatic complaints" having been the only cluster of symptoms significantly related to DST nonsuppression in their sample. However, as outlined above, the results of the current study are not supportive of the view that DST nonsuppression is either due to any single somatic symptom (e.g., weight loss) or nonspecific in its implications.

While global severity of depression alone does not account for the differential response to dexamethasone among patients in the current study, it should be pointed out that most symptom differences found between DST suppressors and nonsuppressors from SADS ratings were not based on the presence or absense of a symptom but on the level of severity of that symptom. The assessment of severity with DST nonsuppressors thus moves from being important globally to having significance in specifically defined areas of symptomatology.

Toward a Revised Concept of Endogenous Depression

This study provides support for the DST as a functional index (Carroll, 1981) which may serve to further specify the clinical classification of endogenous depression. Symptoms for which DST nonsuppressors reported higher severity levels included many of the symptoms identified in prior research as "endogenous". However, the current findings place in the forefront certain "vegetative" features: weight loss, appetite loss, lack of reactivity, and insomnia. It is hypothesized that cortisol hypersecretion reflected in DST nonsuppression may be associated with these specific vegetative signs.

It is not clear from the results of the discriminant analyses in this study what specific weighting would be given the clinical features in a redefined classification of endogenous depression based on DST nonsuppression. While it is promising that a discriminant function derived from the small split/stratification sample still classified a cross-validation sample (of equal size) significantly better than chance, there is no expectation that a similar linear combination of clinical features separating DST suppressors from nonsuppressors would be generated with an independent sample; the variation possible in composition and loading of this linear combination has already been demonstrated in the differences between the split/stratification and entire sample discriminant functions computed in this study. The

point to be made here is that it is possible to statistically separate DST suppressors from nonsuppressors within the context of a multiple-variable profile. Discriminant analysis will, however, have to be performed on a much larger sample of DST nonsuppressors before a reliable function will be isolated. A discriminant function index could then be formulated following the technique outlined by Feinberg and Carroll (1982) so that the clinician in the field could readily identify a patient who would most likely fail to suppress normally on the DST.

Prognostic Value of DST Nonsuppression

If one already concedes the future construction of a reliable discriminant function index for predicting DST nonsuppression, what prognostic significance would a "positive" index finding have? Is identifying a potential nonsuppressor anything more than satisfaction of nosological curiosity? Certainly, the findings of the current study indicate that DST response has less prognostic value than a clinical index of severity of illness. While there were no significant differences in baseline severity of illness for those DST suppressors and nonsuppressors who began a desipramine trial (34 of the total 107 patients in the sample), a large change score on the clinical measure used was significantly associated with a high (severe) baseline score, regardless of DST response. Thus the magnitude of a

patient's clinical response to desipramine had more to do with how severely ill he/she was initially than with DST nonsuppression. This association is neither difficult to understand nor particularly meaningful: the more severely ill patient has a larger interval for clinical improvement over a five-week period than does a less severely ill patient. A much more meaningful statistical finding would have been that a higher proportion of DST nonsuppressors than suppressors responded favorably to desipramine. In that case the nosological significance of DST nonsuppression would have translated into prognostic significance. To summarize, based on the findings of the current study, the prognostic value of DST response has yet to be determined. The hypothesized association between DST nonsuppression and a norepinephrine deficit differentially responsive to a noradrenergic tricyclic currently lacks support and must be further investigated.

DST Sensitivity and Diagnostic Classification Systems

Finally, relating the results of the current study to the diagnostic categories major endogenous depressive disorder of the RDC and major depressive disorder with melancholia of the DSMIII, one finds that RDC definite endogenous has a DST sensitivity rate of 55% compared with 29% for DSMIII melancholia. This discrepancy in sensitivity rates can be attributed to the more exclusive diagnostic

criteria with the DSMIII: two symptoms, loss of pleasure in all or almost all activities and lack of reactivity, must be present for DSMIII melancholia, as opposed to the criterion of at least one of the first group of four symptoms- distinct quality of depressed mood, lack of reactivity, AM mood worsening, and pervasive loss of interest- for RDC endogenous (see Appendix F). Carroll's (1982) assertion that the RDC category is overinclusive, while literally true in comparison with the DSMIII, appears to be more of an attribute than a shortcoming when one encounters the heterogeneity of the depressive population, i.e, a more exclusive diagnostic category is of little utility if it has not been first demonstrated to match a real clinical syndrome or disorder.

Suggestions for Future Research

1) One of the crucial issues surrounding the use of the dexamethasone suppression test to isolate a unique depressive subtype is the accurate identification of DST nonsuppressors. As previously discussed, there may be some degree of variability between endogenously depressed patients both in the length of the period of HPA dysfunction detectable by the DST and in the amount of time which elapses between normalization of HPA functioning and significant clinical improvement. Speculation was offered that some DST suppressors who

presented a clinical profile similar to that of nonsuppressors could have, in fact, responded abnormally to the DST at some other juncture in their current depressive episode. It is therefore suggested that a group of patients be followed over the course of at least one entire depressive episode, with the serial administration of the DST, to determine the accuracy of a patient's designation as never having been a DST nonsuppressor. Only then will sufficient safeguards be in place to ensure that future discriminant analysis using DST response is based on a valid and reliable assignment of initial group membership. In addition, an increase in the sample size of DST nonsuppressors would better insure the reliable estimation of within-group variance.

2) While most antidepressants have not been found to alter cortisol activity (Carroll, 1981), these medications do, of course, change a patient's clinical state. This potentially confounding factor in efforts to clinically separate DST suppressors from nonsuppressors proved to be approximately equal across response groups in the current study: 22% (6/27) of nonsuppressors were on a tricyclic antidepressant for one week or longer at the time of evaluation, compared with 20% (16/80) of suppressors. Ideally, subjects should remain at a drug-free, clinical baseline prior to the administration of the DST. Discontinuance of tricyclics one to two weeks before the

DST after a therapeutic regimen had already been instituted could not be expected to return a patient to a true clinical baseline.

3) It is not recommended that future research into clinical differences between DST suppressors and nonsuppressors involve univariate analysis. Univariate analysis was done in the current study because the number of nonsuppressors in the sample was marginal for running multivariate analyses and because there was interest in comparing the findings of individual clinical differences in this study with individual symptoms identified by previous research as being associated with endogenous depression. With a larger sample, procedures like discriminant analysis are the most meaningful for the objective of clinical subtyping: to identify a group of symptoms which covary simultaneously and have different weight with respect to one another.

4) Finally, additional research into the use of the DST as a predictor of response to drug treatment should follow a design that calls for the inclusion of both nonendogenous and endogenous patients. With this more complete design, such questions as the following might be addressed: Do endogenous DST nonsuppressors with a high initial severity rating more frequently respond favorably to drug treatment than nonendogenous DST suppressors with a

similar severity rating? Do endogenous DST nonsuppressors with a low initial severity rating respond favorably less frequently to drug treatment than nonendogenous DST suppressors with high initial severity ratings?

APPENDICES

APPENDIX A

CONSENT FORM A

APPENDIX A

Michigan State University
Consent Form (Form A)

Study: Self Reported Symptomatology in Major Depressive Illness

Investigator: Gregory Alan Holmes, M.A.
Doctoral Candidate, Counseling Psychology
Robert J. Bielski, M.D.
Department of Psychiatry

I, _____, have had the above named study explained to my satisfaction and I freely consent to participate in the study. I have been informed that my decision to participate in this study will in no way alter the treatment I will receive for my depression.

I understand that I have been asked to complete three procedures during this study. These three procedures are as follows:

1. I will be interviewed by members of the research team. The interview will last for approximately 1½ hours, during which time I will be asked questions about my depression.
2. I will be given the Dexamethasone Suppression Test, a blood test for plasma cortisol concentration. I will be given 1 mg of Dexamethasone in a tablet form and be asked to take the tablet at 11:00 p.m. I understand that there is minimal risk in taking this medication. I will then have a small sample of my blood drawn the following day at 4:00 p.m.
3. I will be given the Differential Diagnostic Depression Scale (DDDS), a 163 item questionnaire.

I agree to participate in the procedures described above. I understand that the amount of risk and discomfort involved in this study is very small, being no greater than that usually involved in drawing a small blood sample. I understand that the benefits to me from participating in the study will be a special evaluation of my depression.

I further understand that I may ask questions before signing this consent form, or anytime thereafter, that my participation in this study is voluntary and that I am free to withdraw at any point without penalty.

I further understand that the results from these procedures are confidential and can only be released to others with my written permission.

Signed: _____ _____
(Subject) (Date)

_____ _____
(Witness) (Date)

Copies to: Subject
File

APPENDIX B

CONSENT FORM B

APPENDIX B

CONSENT FORM

Dexamethasone Suppression Test and Desipramine Response in Depressed Patients

Investigators:

Robert J. Bielski, M.D.
Christine L. Shafer, M.D.
Department of Psychiatry
Michigan State University

Gregory Alan Holmes, M.A.
Department of Counseling Psychology
Michigan State University

I _____ agree to participate in this study comparing the treatment response to the antidepressant medication, desipramine, to the results of the dexamethasone suppression test determined prior to entering treatment. I understand that I will be evaluated in the first, third and fifth week after entering treatment in sessions that last approximately one hour. I will be seen by the study physician and also evaluated in interview. I will receive desipramine, a commonly prescribed antidepressant. I understand that the dosage of desipramine may be increased each week, as is standard practice, and that the study physician will follow my progress closely in order to insure safety. At the end of five weeks of treatment, the amount of medication in my blood will be determined. I will undergo venipuncture by trained, licensed personnel and 10cc (about 2 teaspoons) of blood will be drawn.

If I begin treatment as an inpatient, I will be treated in the hospital until discharge. After discharge I agree to participate in the remaining sessions as an outpatient at the MSU Clinical Center. If I am treated as an outpatient, each of the three sessions will take place at the MSU Clinical Center. If I

CONSENT FORM - 2

desire, arrangement for continuing treatment of my depression will be offered to me at the conclusion of my five week participation in this study.

I agree to participate in the procedures described above. I understand that taking any additional medications during the study might result in adverse effects. I agree to abstain from medications other than prescription medications approved by the study physician for the duration of the study. I also agree to limit my alcohol intake to either 1 ounce of liquor, 6 ounces of wine, or 12 ounces of beer per day.

I further understand that the amount of risk and discomfort involved in this study is very small, being no greater than that usually involved in drawing of a small blood sample and in the taking of this medication. I understand that symptoms such as dry mouth, drowsiness, blurred vision, and delay in starting urine stream, are common side effects of antidepressants and that I may experience one or more of these symptoms.

I further understand that I should be careful while driving or performing any act requiring dexterity or concentration because of the possible side effect of drowsiness occasionally noted with these medications. I understand that my response to alcoholic beverages may be exaggerated while taking this medication.

I understand that safe use of this medication during pregnancy and lactation has not been established. If female, I am not currently breastfeeding. If female, of childbearing potential, I do not suspect that I am pregnant, I have menstruated within the last month, and, if I am sexually active, I will use contraception while participating in this study. If male, I will use

CONSENT FORM - 3

contraception while participating in this study.

To the best of my knowledge, I am not allergic to the medication in this study or similar substances. I understand that no beneficial effects are guaranteed.

I further understand that the alternatives to treatment with this type of medication is treatment with another medication (MAO inhibitor antidepressant) which has a slightly higher risk of side effects. Another alternative is talking about my problems without medication.

I further understand that I may ask questions before consenting, or anytime thereafter, that my participation in this study is voluntary and that I am free to withdraw at any point without penalty.

I understand that the benefits to me from participating in this study is a special evaluation of my depression. Additionally, my response to desipramine and the desipramine plasma level which will be drawn free of charge may be useful in treatment of subsequent depression, should one occur. Also, if I am an outpatient, I will receive the medication free of charge and a free screening physical examination at the discretion of the study physician.

I understand that all the information gathered in this study will be treated with strict confidence and I will remain anonymous in any publications resulting from this data. Information concerning the treatment of my depression may be specifically released if I so authorize.

I understand that the MSU Clinical Center will gather some information including my name, age, address, and telephone number

for accounting purposes only and that this information will remain confidential. I further understand that beyond this, my identity will also remain confidential. I understand that I will not be paid for my participation. I understand that if I am hospitalized I or my insurance carrier will be billed according to hospital policy. If I am covered by insurance, my insurance carrier will be billed for any outpatient treatment-study visits. If I am not covered by insurance a fee will be negotiated on a sliding scale basis for outpatient visits. Upon request, I will be informed of the results of this study.

If I experience an adverse reaction to the antidepressant medication, I understand that I am to report this to my treating physician if I am an inpatient. If I am an outpatient I should report these adverse effects to my treating physician at the M.S.U. Affective Disorders Clinic, 353-3070, during regular working hours Monday through Friday. Outside of regular working hours, if I am an outpatient, I should contact the Ingham Community Mental Health Center Emergency Service at 374-8000, and they will contact my treating physician for me.

The study and procedures have been explained to my satisfaction.

_____ _____

Date Participant Signature

_____ _____

Date Investigator Signature

xc: participant file

APPENDIX C

SCHEDULE FOR AFFECTIVE DISORDERS AND SCHIZOPRENIA

SCHEDULE FOR AFFECTIVE DISORDERS AND SCHIZOPHRENIA (SADS) SCORESHEET

Card No. 1 (1–2)

Name of Subject Being Interviewed _____ Subject's ID No. _____ (3–10)†

If Relative of Index Subject, Name of Index Subject _____

Study No. _____ (11–12)† Rater's Name _____ Rater's No. _____ (13–14)*

Rater is: Interviewer – 1, Observer – 2 (15)

Age of Subject: _____ (16–17)

Sex of Subject: Male – 1, Female – 2 (18)

Status at Time of Evaluation: Inpatient – 1, Outpatient – 2, Other patient – 3, Nonpatient – 4, Other – 5 _____ (19)

Date of Evaluation: _____ (20–25)†

Group Code: _____ (26–27)

Type of Evaluation: Admission – 1, Follow-up – 2, Other – 3 (28)

Hospital ID No. _____ (29–36)

Form No: 83 (79–80)†

Instructions for use of SADS Scoresheet: Some investigators may prefer to use a scoresheet rather than one protocol per patient. In such cases the rater must refer to the SADS protocol for all definitions and instructions for judging the items, checking or writing in information. The item abbreviations used here are not adequate for completing the form.

page

SADS – PART I

2 CURRENT CONDITION

Classification..... 0 1 2 3 [4 5] → skip to 223 213

3 Duration..... 0 1 2 3 4 5 6 7 8 9 214

Onset..... 0 1 2 3 4 5 6 7 8 9 215

Judgment/stress..... NA 0 1 2 3 4 5 6 216

Associated with.....

Pregnancy..... YES 217

Menopause..... YES 218

Medication..... YES 219

Physically ill..... YES 220

Death..... YES 221

4 Stressful event... 0 1 2 3 4 222

TREATMENT

Outpatient..... 0 1 2 3 223

Psychiatric Hosp.... [0] 1 2 → skip to 225 224

No. of Hospitaliz.... 1 2 3 4 5 6 7 8+ 225

† Keypunch: Duplicate on all cards.

*If it is a reliability study, duplicate Rater No. in 77–78 on all cards.

page

Treatment received

ECT..... 2

Lithium..... 2

Antidepressants.. 2

Min Tranquil..... 2

Maj Tranquil..... 2

Other Rx..... 2

Psychoth/couns.. 2

5 Time period 1 2 3 4 5 2

6 DYSPHORIC MOOD AND RELATED SYMPTOMS

Depression..... [0 1 2] 3 4 5 6 7 2

Past week..... 0 1 2 3 4 5 6 7 2

Quality of mood 0 1 2 3 4 2

Depr/concerns..... 0 1 2 3 4 2

7 Worrying..... 0 1 2 3 4 5 6 2

Past week..... 0 1 2 3 4 5 6 2

Self-reproach..... 0 1 2 3 4 5 6 2

Page

Past week ... 0 1 2 3 4 5 6 ... 241

Negative eval ... 0 1 2 3 4 5 6 ... 242

Past week ... 0 1 2 3 4 5 6 ... 243

8 Discouragement ... 0 1 2 3 4 5 6 ... 244

Past week ... 0 1 2 3 4 5 6 ... 245

Suicidal tend ... 0 1 2 3 4 5 6 7 ... 246

Past week ... 0 1 2 3 4 5 6 7 ... 247

No. of gestures ... [NI 0] 1 2 3 4 5 6 7 8 9+ 248

→ skip to 251

Seriousness ... 0 1 2 3 4 5 6 ... 249

9 Medical lethality ... 0 1 2 3 4 5 6 ... 250

Panic attacks ... [0 1 2] 3 ... 251

→ skip to 263

Shortness of brth ... — ... 252

Palpitations ... — ... 253

Chest pain ... — ... 254

Smothering ... — ... 255

Dizziness ... — ... 256

Tingling ... — ... 257

Faintness ... — ... 258

Sweating ... — ... 259

Trembling ... — ... 260

Fear of dying ... — ... 261

No. of consec.wks ... 1 2 3 4 5 6 7 8 9+ ... 262

10 Somatic anxiety ... 0 1 2 3 4 5 6 ... 263

Past week ... 0 1 2 3 4 5 6 ... 264

Psychic anxiety ... 0 1 2 3 4 5 6 ... 265

Past week ... 0 1 2 3 4 5 6 ... 266

Phobia ... [0 1 2] 3 4 5 6 ... 267

Past week ... 0 1 2 3 4 5 6 ... 268

11 Type of phobia ... 1 2 3 4 ... 269

Obses/compul ... 0 1 2 3 4 5 6 ... 270

Past week ... 0 1 2 3 4 5 6 ... 271

12 Insomnia ... [0 1 2] 3 4 5 6 ... 272

→ skip to 313

Initial insomnia ... — ... 273

Middle insomnia ... — ... 274

Terminal insomnia ... — ... 275

Past week ... 0 1 2 3 4 5 6 ... 313

Page

Sleeps more ... 0 1 2 3 4 5 6 ... 31

Lack of energy ... 0 1 2 3 4 5 6 ... 3

Past week ... 0 1 2 3 4 5 6 ... 3

13 Poor appetite ... 0 1 2 3 4 5 6 ... 3

Past week ... 0 1 2 3 4 5 6 ... 3

Weight loss ... 0 1 2 3 4 5 6 ... 3

Incr. appetite ... 0 1 2 3 4 5 6 ... 32

Weight gain ... 0 1 2 3 4 5 6 ... 32

14 Conc/bodily func ... 0 1 2 3 4 5 6 ... 32

Past week ... 0 1 2 3 4 5 6 ... 32

Indecisiveness ... 0 1 2 3 4 5 6 ... 32

Dim concentration ... 0 1 2 3 4 5 6 ... 32

15 Loss of interest ... * 0 1 2 3 4 5 6 ... 32

Past week ... 0 1 2 3 4 5 6 ... 32

Social withdrwl ... 0 1 2 3 4 5 6 ... 32

Depersonalization ... 0 1 2 3 4 5 6 ... 32

16 Subjective anger ... 0 1 2 3 4 5 6 ... 33

Past week ... 0 1 2 3 4 5 6 ... 33

Overt irritbity ... 0 1 2 3 4 5 6 ... 33

Past week ... 0 1 2 3 4 5 6 ... 33

Agitation ... [0 1 2] 3 4 5 6 ... 33

→ skip to 341

17 Unable to sit still ... — ... 33

Pacing ... — ... 33

Handwringing ... — ... 33

Pulling, etc ... — ... 33

Outbursts ... — ... 33

Talks on and on ... — ... 34

Past week ... 0 1 2 3 4 5 6 ... 34

Psychomotor ret ... [0 1 2] 3 4 5 6 ... 34

→ skip to 348

Slowed speech ... — ... 34

Inc pauses ... — ... 34

Low speech ... — ... 34

Mute/decr. amt ... — ... 34

Slowed movemt ... — ... 34

Past week ... 0 1 2 3 4 5 6 ... 34

18 Characteristics ... [0 1 2 3 4] ... 34

→ skip to 353

* 0 Normal for age and martial status
1 Mildly decreased drive and satisfactio
2 Definate loss of desire: functional impotence

page

Reactivity ... 0 1 2 3 4 5 6 ... 350

Diurnal mid - am ... 0 1 2 3 4 ... 351

Diurnal mid - pm ... 0 1 2 3 4 ... 352

MANIC SYNDROME

19 Elevated mood ... 0 1 2 3 4 5 6 ... 353

Past week ... 0 1 2 3 4 5 6 ... 354

Less sleep ... 0 1 2 3 4 5 6 ... 355

Past week ... 0 1 2 3 4 5 6 ... 356

More energetic ... 0 1 2 3 4 5 6 ... 357

Past week ... 0 1 2 3 4 5 6 ... 358

20 Incr activity ... 0 1 2 3 4 5 6 ... 359

Past week ... 0 1 2 3 4 5 6 ... 360

Grandiosity ... 0 1 2 3 4 5 6 ... 361

Past week ... 0 1 2 3 4 5 6 ... 362

CHARACTERISTICS OF BEHAVIOR AND IDEATION DURING A PERICD WHICH MIGHT BE "MANIC"

No other evid. ck. here ☐ skip to 415 ... 363*

21 Overt irritability ... 0 1 2 3 4 5 6 ... 364 b=1

Motor hyperactiv ... 0 1 2 3 4 5 6 ... 365 b=1

Accelerat speech ... 0 1 2 3 4 5 6 ... 366 b=1

Accelerated thkg ... 0 1 2 3 ... 367 b=1

22 Intrusive ... ___ ... 368

Public display ... ___ ... 369

Fin indiscretns ... ___ ... 370

Assumes tasks ... ___ ... 371

Antisocial behav ... ___ ... 372

Sexual excesses ... ___ ... 373

Drunkenness ... ___ ... 374

Grossly bizarre ... ___ ... 375

Poor judgment ... 0 1 2 3 4 5 6 ... 413 b=1

Duration ... 0 1 2 3 4 ... 414

23 Alcohol abuse ... 0 1 2 3 4 5 6 ... 415

Drug abuse ... 0 1 2 3 4 5 6 ... 416

24 Antisocial behvr ... 0 1 2 3 4 5 6 ... 417

Distrustfulness ... 0 1 2 3 4 5 6 7 ... 418

Past week ... 0 1 2 3 4 5 6 7 ... 419

Non-del ideas of ref 0 1 2 3 ... 420

*Note: Some items are punched 1 when blank, these are noted by b = 1, when editing, circle 1 for these items.

page

DELUSIONS

25 No evid. ck here ☐ skip to 441 ... 421

Del of reference ... 0 1 2 3 ... 422 b

Being controlled ... 0 1 2 3 ... 424 b

People read mind ... 0 1 2 3 ... 426 b

26 Tht broadcasting ... 0 1 2 3 ... 428 b

Tht insertion ... 0 1 2 3 ... 430 b

Tht withdrawl ... 0 1 2 3 ... 432 b

Persecutory ... 0 1 2 3 ... 434 b=

Jealousy ... 0 1 2 3 ... 436 b=

Guilt or sin ... 0 1 2 3 ... 438 b=

Grandiose ... 0 1 2 3 ... 438 b=

27 Somatic ... 0 1 2 3 ... 438 b=

CHARACTERISTICS OF DELUSIONS REGARDLESS OF TYPE

Severity ... 0 1 2 3 4 5 6 ... 431 b=1 (skip to 441)

Past week ... 0 1 2 3 4 5 6 ... 433 b=1

Sensorium ... 0 1 2 3 ... 435

Other delusions ... 0 1 2 3 ... 436

28 Consis w/mood ... 0 1 2 3 ... 437

Bizarre quality ... 0 1 2 3 4 5 6 ... 438

Multiple delu ... 0 1 2 3 ... 439

29 Fragmentary ... 0 1 2 3 ... 440

HALLUCINATIONS

No evid. ck. here ☐ skip to 458 ... 441*

Auditory ... 0 1 2 3 ... 442 b=1

Running commtry ... 0 1 2 3 ... 443 b=1

2 or more voices ... 0 1 2 3 ... 444 b=1

Non-aff verbal ... 0 1 2 3 ... 445 b=1

30 Visual ... 0 1 2 3 ... 446 b=1

Olfactory ... 0 1 2 3 ... 447 b=1

Tactile ... 0 1 2 3 ... 448 b=1

Grandio/pers. type ... 0 1 2 3 ... 449 b=1

CHARACTERISTICS OF HALLUCINATIONS — ANY TYPE

Severity ... 0 1 2 3 4 5 6 ... 450 b=1 (skip to 458)

Past week ... 0 1 2 3 4 5 6 ... 451 b=1

*Note: Some items are punched 1 when blank, b=1.

SADS

31	Consis w/mood	0 1 2 3	452
	Fragmentary	0 1 2 3	453
	Sensorium	0 1 2 3	454
	At least 1 wk	0 1 2 3	455
	At least 1 mo.	0 1 2 3	456
	Non-affect	0 1 2 3	457
32	Bizarre behvr	0 1 2 3 4 5 6	458
	Catatonic stupor	____	459
	Catatonic rigidity	____	460
	Waxy flexibility	____	461
	Catatonic excitmt	____	462
	Catatonic postur	____	463
	Memory disturb	0 1 2 3 4 5 6	464
33	Funct.imprmt	0 1 2 3 4 5 6	465
	Past week	0 1 2 3 4 5 6	466

ADDITIONAL BEHAVIORAL ITEMS

	Flight of ideas	0 1 2 3 4 5 6	467
34	Inappro affect	0 1 2 3 4 5 6	468
	Blunted affect	0 1 2 3 4 5 6	469
	Distractibility	0 1 2 3 4 5 6	470
	Self-pity	0 1 2 3 4 5 6	471
	Demandingness	0 1 2 3 4 5 6	472
35	Depressed appear	0 1 2 3 4 5 6	473

FORMAL THOUGHT DISORDER

	*Understandability	0 1 2 3 4 5 6	474
36	Loosening - asso	0 1 2 3 4 5 6	475
	*Udrst.past week	0 1 2 3 4 5 6	476
	Illogical thkg	0 1 2 3 4 5 6	513
	Poverty of contnt	0 1 2 3 4 5 6	514
	Neologisms	0 1 2 3	515

SPECIAL ITEMS RELATED TO DIAGNOSIS OR SUB-CLASSIFICATIONS OF SCHIZO-AFFECTIVE DISORDERS

37	Schizo + affect	[0] 1 2 → skip to 525	516
	Delu/hallu	0 1 2	517
	Formal tht dis	0 1 2	518
	Delu/hallu	0 1 2	519
	Preoc. delu/hallu	0 1 2	520

*Formerly this item was called incoherence.
Data can be merged from the different versions.

	Formal tht dis,etc	0 1 2	5
	Mainly Schizo	0 1 2	5
	Mainly affective	0 1 2	5
38	Dur.Schizo feat	0 1 2 3 4 5	5

GLOBAL ASSESSMENT SCALE

	Current worst period ____	525-52
	Wk prior to adm ____	527-52
	Past week ____	529-53
39	Rel/completeness 1 2 3 4 5	53
	Mixed feat - S/A 0 1 2 3 4 5	53
	Dur. S/A Epis	533-53
	Mixed features 0 1 2 3 4 5	53
	Dur. Affect. epis ____	536-53

Family Hx of Dep. Y N

Family Hx of ETOH Y N

SADS - PART II

BACKGROUND

40	Highest grade	0 1 2 3 4 5 6 7	538
	Adol. friendship	0 1 2 3 4 5 6	539
	Marital status	0 1 2 3 4 5	540
41	Work last 5 yrs	0 1 2 3 4 5 6 7 8 9	541
	Outpatient trmt	0 1 2 3 4	542
	Age 1st OP care ____		543-544
42	No. psych. hosp ____		545-546
	Age 1st hosp ____		547-548
	Total time hosp	0 1 2 3 4 5 6 7	549

EPISODES OF MANIC SYNDROME

43	Criterion I	[0] 1 2 3 → skip to 644	550

Criterion II	NO INFO	NO	YES	
Active	X	1	2	551
Talkative	X	1	2	552
Thoughts race	X	1	2	553
Grandiosity	X	1	2	554
Less sleep	X	1	2	555
Distractibility	X	1	2	556

APPENDIX D

RESEARCH DIAGNOSTIC CRITERIA

RESEARCH DIAGNOSTIC CRITERIA (RDC) SUMMARY DATA SHEET

Card No. col. 1 & 2 Date: _____

Name of Subject Being Interviewed _____

Subject's ID Number _____ _____ _____ _____ _____ _____ _____ _____ (3 – 10)+ Sex: _____ Age: _____

If Relative of Index Subject, Name of Index Subject _____

Study No. _____ (11–12)+ Rater's Name _____ Rater's No. _____ (13–14)+ Hospital ID _____ Service: _____

Occasion: Intake–1; Update (Discharge or 2 mos)–2; Update (Specify reason)_____–3. Other _____–4 (15)

Type of Evaluation: SADS–1. SADS–L–2; Unstr. Cl. Int.–3; Case Rec. Only –4; Other (Specify) _____–5 (16)

This scoresheet is designed to summarize judgments made in using the RDC. Many investigators prefer to use one RDC per subject so that they can note which aspects of the specific criteria were met for inclusion and exclusion for given diagnoses. The summary data is then transferred to the Summary Data Sheet for data processing. Other investigators prefer to re-use the RDC protocol and are interested in recording only the summary judgments noted on this scoresheet. If the Summary Data Sheet is the sole record for the subject, the rater should refer to the RDC definition of the ratings being made.

Instructions: Circle the appropriate number for all diagnoses. Refer to the RDC definitions and instructions prior to completing the Summary Data Sheet.

		Diag. Present Episode	Duration Pres. Epis. in Weeks	Age at First Episode	Diag. Previous Episode	Ever Met Criteria
1.	Schizophrenia	1 2 3 (119)	_____ (120-2)	_____ (123-4)	1 2 3 (125)	1 2 3 (126)
	a. Course++ 1 – Acute 2 – Subac. 3 – Subchr. 4 – Chronic (127)					
	b. Phenomenology 1 – Para. 2 – Disorg. 3 – Catat. 4 – Undiff. 5 – Resid. (128)					
2.	Schizo-affective, Manic	1 2* 3* (129)	_____ (130-2)	_____ (133-4)	1 2 3 (135)	1 2 3 (136)
	a. Course++ 1 – Acute 2 – Subac. 3 – Subchr. 4 – Chronic (137)					
	b. Features 1 – Mainly Schiz. 2 – Mainly affect. 3 – Other (138)					
	c. Onset 1 = < 2 days; 2 = < 1 week; 3 = < 1 mo; 4 = < 2 mos; 5 = > 2 mos. (139)					
3.	Schizo-affective, Depressed	1 2* 3* (140)	_____ (141-3)	_____ (144-5)	1 2 3 (146)	1 2 3 (147)
	a. Course++ 1 – Acute 2 – Subac. 3 – Subchr. 4 – Chronic (148)					
	b. Features 1 – Mainly Schiz. 2 – Mainly affect 3 – Other (149)					
	c. Onset 1 = < 2 days; 2 = < 1 week; 3 = < 1 mo; 4 = < 2 mos; 5 = > 2 mos. (150)					
4.	Depressive Synd. Spimp. on Res. Schizo. (Sec. Depression)	1 2 3 (151)	_____ (152-4)	_____ (155-6)	1 2 3 (157)	1 2 3 (158)
	Manic Disorder	1 2† 3† (159)	_____ (160-2)	_____ (163-4)	1 2 3 (165)	1 2 3 (166)

+Keypunch: Duplicate on all cards.

++Course: If the course is best characterized by chronic or subchronic with an exacerbation, note chronic or subchronic here and see item 439-40.

*If the current illness involves cycling of the affective syndrome see items 431-434.

†If cycled during the present episode see items 227-230.

2

	Diag. Present Episode	Duration Pres. Epis. in weeks	Age at First Episode	Diag. Previous Episode	Ever met Criteria
6. Hypomanic Disorder	1 2† 3† (167)	____ (168-70)	____ (171-2)	1 2 3 (173)	1 2 3 (174)
7. Bipolar Depression with Mania (Bipolar 1)					1 2 3 (175)
8. Bipolar Depression with Hypomania (Bipolar 2)					1 2 3 (176)
					59 = (179-80)
9. Major Depressive Disorder	1 2† 3† (219)	____ (220-2)	____ (223-4)	1 2 3 (225)	1 2 3 (226)
Pres. Affect. Epis. 1 – M/D; 2 – D/M; 3 – Changes, now M; 4 – Changes, now D; 5 – Mixed (227)					
Total Duration of Affective Episode (weeks) ____ (228-30)					
a. Primary	1 2 3 (231)			1 2 3 (232)	1 2 3 (233)
b. Secondary*	1 2 3 (234)			1 2 3 (235)	1 2 3 (236)
c. Recurrent (Unipolar)					1 2 3 (237)
d. Psychotic	1 2 3 (238)			1 2 3 (239)	1 2 3 (240)
e. Incapacitating	1 2 3 (241)			1 2 3 (242)	1 2 3 (243)
f. Endogenous	1 2 3 (244)				
g. Agitated	1 2 3 (245)				
h. Retarded	1 2 3 (246)				
i. Situational	1 2 3 (247)				
j. Simple	1 2 3 (248)				
k. Predom. Mood 1 – Dep; 2 – Dep & Euph; 3 – Anx; 4 – Anx & Dep; 5 – Hostile; 6 – Apathetic; 7 – Other (249)					
10. Minor Depressive Disorder	1 2 3 (250)	____ (251-3)	____ (254-5)	1 2 3 (256)	1 2 3 (257)
a. With Anxiety	1 2 3 (258)				
11. Intermittent Depressive Dis.	1 2 3 (259)	____ (260-2)			
12. Panic Disorder	1 2 3 (263)	____ (264-6)	____ (267-8)	1 2 3 (269)	1 2 3 (270)
					59 = (279-80)
13. Generalized Anxiety Disorder	1 2 3 (319)	____ (320-2)	____ (323-4)	1 2 3 (325)	1 2 3 (326)
a. With Depression	1 2 3 (327)				
14. Cyclothymic Personality					1 2 3 (328)
15. Labile Personality					1 2 3 (329)
16. Briquet's Disorder (Somatization Disorder)					1 2 3 (330)
17. Antisocial Personality					1 2 3 (331)

*If Secondary see item 430.

† If cycled during the present episode see items 227-230.

3

	Diag. Present Episode	Duration Pres. Epis. in weeks	Age at First Episode	Diag. Previous Episode	Ever met Criteria
18. Alcoholism	1 2 3 (332)	____ (333-5)	____ (336-7)†	1 2 3 (338)	1 2 3 (339)
19. Drug Use Disorder	1 2 3 (340)	____ (341-3)	____ (344-5)	1 2 3 (346)	1 2 3 (347)
20. Obsessive Compulsive Disorder	1 2 3 (348)	____ (349-51)	____ (352-3)	1 2 3 (354)	1 2 3 (355)
21. Phobic Disorder	1 2 3 (356)	____ (357-9)	____ (360-1)	1 2 3 (362)	1 2 3 (363)
a. Subtypes 1 – Agoraphobia; 2 – Social phobia; 3 – Simple phobia; 4 – Mixed (364)					
22. Unspecified Functional Psychosis††	1 2 3 (365)	____ (366-8)	____ (369-70)	1 2 3 (371)	1 2 3 (372)
					59 = (379-80)
23. Other Psychiatric Disorder†††	1 2 3 (419)	____ (420-2)	____ (423-4)	1 2 3 (425)	1 2 3 (426)
24. Schizotypal Features					1 2 3 (427)
25. Currently Not Mentally Ill	1 2 3 (428)				
26. Never Mentally Ill					1 2 3 (429)

*If Seconcary Major Depressive Disorder, make sure the prior condition as listed on page 18 of the RDC is also noted either above or here.

1 – Preferential homosexuality; 2 – Anorexia Nervosa; 3 – Transsexualism; 4 – OBS (430)

(Specify) _____

†Pres. Schizo-aff. Ep. 1 – M/D, 2 – D/M, 3 – Changes, now M; 4 – Changes, now D; 5 – Mixed (431)

Total Duration of Schizo-aff. Episode .....(weeks)____ (432-34)

++Diagnosis of Schizophrenia or Schizo-affective Disorder is given and course is best described as an exacerbation in a subject with a chronic or subchronic illness. (Skip 435-38)

Total Duration of exacerbation..... (weeks) ____ (439-40)

†† If Unspecified Functional Psychosis, describe here using RDC and DSM-III terms._____

59 = (479-80)

_____

††† If Other Psychiatric Disorder, describe here using RDC and DSM-III terms. _____

_____

Alternative diagnosis for current episode if diagnosis noted above is questioned:_____

Note reason: _____

Narrative Summary Relevant to Psychiatric History:

APPENDIX E

HAMILTON DEPRESSION RATING SCALE

HAMILTON DEPRESSION SCALE - M.S.U. AFFECTIVE DISORDERS CLINIC

DATE

PATIENT _____ MEDICATION - DOSAGE _____

Circle one number per item. Score all items.

1. DEPRESSED MOOD (Sad, blue, gloomy, weepy, pessimistic, helpless, hopeless, worthless)
   - 0 Not depressed
   - 1 Feeling states elicited only on questioning
   - 2 Occasional weeping. Spontaneously reports feeling states
   - 3 Frequent weeping. Obvious behavioral evidence in facies, posture, voice. Speaks mostly about feeling states
   - 4 Exhibits virtually only these feeling states verbally and non-verbally. May have "gone beyond weeping"
2. GUILT FEELINGS AND DELUSIONS
   - 0 Absent
   - 1 Self-reproach, feels he/she has let people down
   - 2 Expresses guilt regarding past errors or misdeeds
   - 3 Present illness is deserved punishment. Ruminations over past errors and sins
   - 4 Severe self-reproach. Guilty delusions, e.g., is making other people ill. Deserves to die. May have accusatory or denouncing auditory or visual hallucinations
3. SUICIDE
   - 0 Absent
   - 1 Feels life is empty, not worth living
   - 2 Recurrent thoughts or wishes about death of self
   - 3 Active suicidal thoughts, threats, gestures
   - 4 Serious suicide attempt
4. INITIAL INSOMNIA (as part of present illness)
   - 0 Absent
   - 1 Mild, infrequent; more than ½ hour occasionally
   - 2 Obvious and severe; more than ½ hour usually
5. MIDDLE INSOMNIA
   - 0 Absent (Rate 1 if hypnotic is being used.)
   - 1 Complains of feeling restless and disturbed during night
   - 2 Wakes during the night; any reading or smoking in bed or getting out of bed except to void
6. DELAYED INSOMNIA
   - 0 Absent
   - 1 Wakes earlier than usual but goes back to sleep
   - 2 Wakes 1 - 3 hours before usual; unable to sleep again
7. WORK AND INTERESTS (Apathy: loss of interest in work, hobbies, social life. Anhedonia: unable to feel pleasure)
   - 0 No disturbance
   - 1 Feels incapable, listless, less efficient. (Rate fatigue, loss of energy under item 13)
   - 2 Has to push self to work or play. No active interests, gets little satisfaction, feels listless, indecisive
   - 3 Clearly decreased efficiency. Spends less time at usual work. In hospital, rate 3 if no spontaneous activity or marked loss of personal tidiness
   - 4 Stopped working because of present illness. Doesn't shave, bathe, etc. Avoids ward activities; works only with urging
8. RETARDATION (Psychomotor slowing of thought, speech, and movement. May vary diurnally)
   - 0 Absent
   - 1 Slightly flattened affect, fixed facial expression
   - 2 Monotonous voice, delayed answering, sits motionless
   - 3 Interview difficult and prolonged. Moves slowly
   - 4 Depressive stupor. Interview impossible
9. AGITATION (may co-exist mildly with retardation)
   - 0 Absent
   - 1 Fidgety. Clenching fists or chair arm, kicking feet
   - 2 Wringing hands, pulling hair, picking at hands or clothes. Restless on the ward, some pacing
   - 3 Can't sit still; much pacing on ward
   - 4 Interview conducted "on the run". Constant pacing. Pulling off clothes, tearing at hair, picking at face
10. PSYCHIC ANXIETY (as part of present illness, NOT part of previous disposition. Includes feeling tense, irritable, apprehensive, fearful, phobic or panic attacks)
    - 0 Absent
    - 1 Minimal distress, admitted only on direct questioning
    - 2 Spontaneously expresses discomfort; worries over trivia
    - 3 Obviously apprehensive in face and speech
    - 4 Severely anxious, panicky, forgetful
11. SOMATIC ANXIETY (physiological concomitants of anxiety such as: fainting, tinnitus, blurred vision, headache, tremor, sweating, flushing, hyperventilation, palpitations, indigestion, belching, diarrhea, urinary frequency)
    - 0 Absent
    - 1 Trivial
    - 2 Mild
    - 3 Moderate
    - 4 Severe
12. APPETITE
    - 0 Normal appetite
    - 1 Eats spontaneously but without relish or pleasure
    - 2 Marked reduction of appetite and food intake. Eats only with urging. Requests or requires laxatives
13. SOMATIC ENERGY
    - 0 Normal
    - 1 Occasional, mild fatigue, easy tiring, aching
    - 2 Obviously low in energy, tired all the time; frequent backaches, headaches, heavy feelings in limbs
14. LIBIDO (Rate only definite change with illness)
    - 0 Normal for age and marital status
    - 1 Mildly decreased drive and satisfaction
    - 2 Definite loss of desire; functional impotence
15. HYPOCHONDRIASIS
    - 0 Absent
    - 1 Mildly preoccupied with bodily functions and physical symptoms
    - 2 Moderately concerned with physical health
    - 3 Morbid convictions of organic disease, e.g., brain tumor, cancer
    - 4 Bizarre delusions (often with guilty associations) e.g., worms eating head, rotting inside, bowels blocked, terrible odor
16. LOSS OF INSIGHT
    - 0 Acknowledges being depressed and ill
    - 1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest
    - 2 Denies being ill at all
17. WEIGHT LOSS (Rate either A or B)
    - A. When rated by history
      - 0 No weight loss
      - 1 Probable weight loss associated with present illness
      - 2 Definite weight loss
    - B. When rated by weekly weight measure
      - 0 Less than 1 lb. during past week
      - 1 Greater than 1 lb. during past week
      - 2 Greater than 2 lb. during past week
18. DIURNAL MOOD VARIATION

    0 1 2 Worse in a.m.

    0 1 2 Worse in p.m.

APPENDIX F

COMPARISON OF RDC AND DSMIII CRITERIA

Comparison of RDC and DSMIII Criteria

Research Diagnostic Criteria*

Endogenous Major Depressive Disorder

A. (1) Distinct quality to depressed mood
   (2) Lack of reactivity to environmental changes
   (3) Mood is regularly worse in the morning
   (4) Pervasive loss of interest or pleasure (some loss in all areas)

B. (1) Feelings of self reproach or excessive or inappropriate guilt
   (2) Early morning awakening or middle insomina
   (3) Psychomotor retardation or agitation
   (4) Poor appetite
   (5) Weight loss
   (6) Loss of interest of pleasure in usual activities (need not be pervasive) or decreased sexual drive

* Taken from Spitzer, R. J., Endicott, J. and Robbins, E. Research Diagnostic Criteria. Archives of General Psychiatry, 35:773-782, 1978.

Diagnostic and Statistical Manual III*

Major Depressive Disorder with Melancholia

A. Loss of pleasure in all or almost all activities

B. Lack of reactivity to usually pleasurable stimuli

C. At least three of the following:
   (a) Distinct quality of depressed mood
   (b) The depression is regularly worse in the morning
   (c) Early morning awakening (at least two hours before usual time of awakening)
   (d) Marked psychomotor retardation or agitation
   (e) Significant anorexia or weight loss
   (f) Excessive or inappropriate guilt

* Taken from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Washington, D. C., APA, 1980

References

Akiskal, H. Dysthymic disorder: psychopathology of proposed chronic depressive subtypes. American Journal of Psychiatry, 140:11-20, 1983.

Albala, A.A., Greden, J. F., Tarika, J., and Carroll, B. J. Changes in serial dexamethasone suppression tests among unipolar depressives receiving electro-convulsive treatment. Biological Psychiatry, 16, 551-60, 1981.

American Psychiatric Association. Diagnostic and Statistical Manual for Mental Disorders, Second Edition, Washington, D. C., APA, 1968.

American Psychiatric Association. Diagnostic and Statistical Manual for Mental Disorders, Third Edition, Washington, D. C., APA, 1980.

Amsterdam, J. D., Winokur, A., Caroff, S. N. and Conn, E. J. The dexamethasone suppression test in outpatients with primary affective disorder and healthy control subjects. American Journal of Psychiatry, 139:3, 287-291, 1982.

Berger, M., Pirke, K., Doerr, P. Krieg, C., and Zerssen, D. Influence of weight loss on the dexamethasone suppression test. Archives of General Psychiatry 40:585-586, 1983.

Bielski, R. J. and Friedel, R. O. Prediction of tricyclic antidepressant response: a critical review. Archives of General Psychiatry, 33:1479-1489, 1976

Bielski, R. J., Shafer, C. L., and Holmes, G. A. Dexamethasone suppression test and desipramine response in depressed patients. Unpublished manuscript, 1982.

Brown, W. A., Johnston, R. and Mayfield, D. The 24-hour dexamethasone suppression test in a clinical setting, relationship to diagnosis, symptoms, and response to treatmnent. American Journal of Psychiatry, 136:543-547,1974.

Brown, W. A., Haier, R. J., and Qualls, C. B. Dexamethasone suppression test identifies subtypes of depression which respond to different antidepressants. The Lancet, 1979, i:928-929.

Brown, W. A. and Shuey, J. Response to dexamethasone and subtype of depression. Archives of General Psychiatry, 37:747-751, 1980.

REFERENCES

Bunney, W. E. and Garland, B. L. Recent advances in the biology of depression. In Stephanis, C.N. (Ed.) Recent Advances in Depression, New York: Pergamon Press, 1983.

Carroll, B. J. Implications of biological research for the diagnosis of depression. In New Advances in the Diagnosis and Treatment of Depression (ed. J. Mendlewiez) Amsterdam: Excerpta Medica, 1977, p. 85-107.

Carrroll, B. J. Neuroendocrine aspects of depression: theoretical and practical significance. In The Psychobiology of Depressive Disorders, Basel: Karger, 1980.

Carroll, B. J. Dexamethasone suppression test and diagnosis of melancholia, reply to G. E. Murphy. Archives of General Psychiatry, 38:1067-1068, 1981.

Carroll, B. J., Feinberg, M., Greden, J. F., Tarika, J., Albala, A. A., Haskett, R. J., James, N. M., Kronfol, Z., Lohr, N., Steiner, M., de Vigne, J. P., and Young, E. A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. Archives of General Psychiatry, 38:15-22, 1981.

Carroll, B. J. The dexamethasone suppression test for melancholia. British Journal of Psychiatry, 140:292-304, 1982.

Castro, P., Lemaire, M., and Toscano-Aguilar, M. Abnormal DST results in patients with chronic schizophrenia. American Journal of Psychiatry, 140:1261, 1983.

Coleman, J. C. Abnormal Psychology and Modern Life, Glenview, Illinois: Scott, Foresman and Company, 1976.

Coppen, A. Abou-Saleh, M., Milln, P., Metcalfe, M., Harwood, J. and Bailey, J. Dexamethasone suppression test in depression and other psychiatric illness. British Journal of Psychiatry, 142:498-504, 1983.

Coryell, W., Goffney, G. and Burkhardt, P. DSM III melancholia and the primary-secondary distinction: A comparison by means of the dexamethasone suppression test. American Journal of Psychiatry, 139:120-122, 1982.

Edelstein, C., Roy-Byrne, P., Fawzy, I. F., and Dornfeld, L. Effects of weight loss on the dexamethasone suppression test. American Journal of Psychiatry, 140:338-341, 1983.

Endicott J. and Spitzer, R. L. Use of Research Diagnostic Criteria and the Schedule for Affective and Schizophrenia to study affective disorders. American Journal of Psychiatry, 136:52-56, 1977.

Endicott J. and Spitzer R. L. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. Archives of General Psychiatry, 35:837-844, 1978.

Endicott, J., Cohen, J., Nee, J., Fleiss, J. and Sarantakos, S. Hamilton Depression Rating Scale: extracted from regular and change versions of the Schedule for Affective Disorders and Schizophrenia. Archives of General Psychiatry, 38:98-103, 1981.

Ettigi, P. G. and Brown, G. M. Psychoneuroendocrinology of affective disorders: an overview. American Journal of Psychiatry, 134:493-501, 1977.

Ettigi, P. G., Hayes, P. E., Narasimhachari, N., Hamer, R. M., Goldberg, S., and Secord, G. J. d-Amphetamine response and dexamethasone suppression test as predictors of treament outcome in unipoloar depression. Biological Psychiatry, 18:499-502, 1983.

Exstein, I., Kirstein, L. S., Pottash, A. L., and Gold, M. S. The dexamethasone suppression and thyrotropin-releasing hormone tests and response to treatment in unipolar depression. International Journal of Psychiatry in Medicine, 12:267-275, 1982-83.

Eysenck, H. J. The classification of depressive illness. British Journal of Psychiatry, 117:241-250, 1970.

Feinberg, M. and Carroll, B. J. Separation of Subtypes of depression using discriminant analysis (I. Separation of unipolar endogenous depression from non-endogenous depression). British Journal of Psychiatry, 140:384-391, 1982.

Freud, S. Mourning and Melancholia (1917) in Collected Papers. London: Hogarth Press Ltd., Vol. 4, 1956.

Gunaga, K. P., Zichus, P. A., and Bowman, H. E. Suppression Test. St. Lawrence Hospital Newsletter, 1982.

Hamilton, M. and White, J. M. Clinical symdrome in depression states. Journal of Mental Science, 105:985-997, 1959.

Hamilton, M. A rating scale for depression. Journal of Neurological Neurosurgery and Psychiatry, 23:56-62, 1960.

Hirschfeld, R. A., Koslow, S. H. and Kupfer, D. J. The clinical utility of the dexamethasone suppression test: summary of a National Institute of Mental Health workshop. Journal of the American Medical Association, 250:2172-2174, 1983.

Hollister, L. The amine hypothesis revisited: a clinician's view. In Depression: Biology, Psychodynamics, and Treatment, New York: Pergamon Press, 1979.

Hollister, L. E., Davis, K. L., and Berger, P. A. Subtypes of depression based on excretion of MHPG and response to nortryptyline. Archives of Genreal Psychiatry, 37:1107-1110, 1980.

Holmes, G. A. Self-reported symptomatology in major depressive illness: a pilot study. Unpublished dissertation, 1982.

Kasper, S. and Beckman, H. Dexamethasone suppression test in a pluridiagnostic approach: its relaionship to psychopathological and clinical variables. Acta Psychiatrica Scandinavica, 68:31-37, 1983.

Kendell, R. E. The classification of depression: a review of contemporary confusion. British Journal of Psychiatry, 129:15-28, 1976.

Kendell, R. E. and Gourlay, J. The clinical distinction between psychotic and neurotic depressions. British Journal of Psychiatry, 117:257-266, 1970.

Kiloh, L. G. and Garside, R. F. The independence of neurotic depression and endogenous depression. British Journal of Psychiatry, 109:415-463., 1963.

Klecka, W. R. Discriminant Analysis. Beverely Hills: Sage Publications, 1980.

Klein, D. F. Endogenomorphic depression. Archives of General Psychiatry, 31:447-454, 1974.

Kline, M. D. and Beeber, A. R. Weight loss and the dexamethasone suppression test. Archives of General Psychiatry, 40:1034-1035, 1983.

Lewis, A. J. States of depression: their clinical and aetiological differentiation. British Medical Journal, 2:875-878, 1938.

Matussek, P., Soldner, M. and Nagel, D. Identification of the endogenous depressive syndrome based on the symptoms and the characteristics of the course. British Journal of Psychiatry, 138:361-372, 1981.

Mendlewicz, J., Charles, G., and Franckson, J. M. The dexamethasone suppression test in affective disorder: relationship to clinical and genetic subgroups. British Journal of Psychiatry, 141:464-470, 1982.

Nelson, J. C. and Charney, D. The symptoms of major depressive illness. American Journal of Psychiatry, 138:1-13, 1981.

Nelson, W. H., Orr, W. W., Stevenson, J. M. and Shane, S. R. Hypothalamic-pituitary-adrenal axis activity and tricyclic response in major depression. Archives of General Psychiatry, 39:1033-1036, 1982.

Peselow, E. D., Goldring, T., Ngaere, S., Fieve, R. R. and Wright, R. The dexamethasone suppression test in depressed outpatients and normal control subjects. American Journal of Psychiatry, 140:245-247, 1983.

Pfaffenberger, R. C. and Patterson, J. H. Statistical Methods for Business and Economics, Homewood: Richard D. Irwin, Inc., 1977.

Prusoff, A. A., Weissman, M. M., Klerman, G. L. and Rounsaville, B. J. Research Diagnostic Criteria subtypes of depression. Archives of General Psychiatry, 37:796-801, 1980.

Rosenthal, S. H. and Klerman, G. L. Content and consistency in the endogenous depressive pattern. British Journal of Psychiatry, 112:471-484, 1966.

Rosenthal, S. H. and Gudeman, J. E. The endogenous depressive pattern: an empirical investigation. Archives of General Psychiatry, 16:241-249, 1967.

Rothschild, A. J. and Schatzberg, A. F. Fluctuating postdexamethasone cortisol levels in a patient with melancholia. American Journal of Psychiatry, 139:129-130, 1982.

Schatzberg, A. F., Orsulak, P. J., Rosenbaum, A. H. Toshihiko, M., Kruger, E. R., Cole, J. O. and Schildkraut, J. J. Toward a biochemical classification of depressive disorders, V: heterogeneity of unipolar depressions. American Journal of Psychiatry, 139:471-475, 1982.

Schatzberg, A. F., Rothschild, A. J., Stahl, J. B., Bond, T. C., Rosenbaum, A. H., Lofgren, S. B., MacLaughlin, R. A., Sullivan, M. A. and Cole, J. O. The dexamethasone suppression test: identification of subtypes of depression. American Journal of Psychiatry, 140:88-91, 1983.

Smith, M. L., Glass, G. V., and Miller, T. I. The Benefits of Psychotherapy. Baltimore: The Johns Hopkins Press, 1982.

Spitzer, R. L., Endicott, J. and Robbins, E. Research Diagnostic Criteria. Archives of General Psychiatry, 35:773-782, 1978.

Stewart, W. J., Quitkin, F. M., Liebowitz, M. R., McGrath, P. J., Harrison, W. M., and Klein, D. F. Efficacy of desipramine with depressed outpatients. Archives of General Psychiatry, 40:202-207, 1983.

Sweeney, D. R. and Maas, J. W. Stress and noradrenergic function in depression. In (Depue, R. A., Ed.) The Psychobiology of Depressive Disorders: Implications for the Effects of Stress. New York: Academic Press, Inc., 1979.