Depressed Mood and Other Psychiatric Manifestations of Cushing's Syndrome: Relationship to Hormone Levels

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Thirty-five consecutive patients with Cushing's syndrome were studied prospectively prior to treatment. A consistent constellation of psychiatric disturbances was found, including impairments in affect (depressed mood and crying), cognitive functions (decreased concentration and memory), and vegetative functions (decreased libido and insomnia). A statistically significant relationship was found between the overall psychiatric disability rating and cortisol and ACTH level. The relationship of depressed mood and hormone levels was examined. Low ACTH levels were significantly associated with milder rather than pronounced depressed mood. The implications of the similarities in psychiatric manifestations between Cushing's syndrome and the primary affective disorders are discussed.

INTRODUCTION

The relationship of endocrine and metabolic factors to mental symptomatology has long been of interest to behavioral scientists and clinicians. Psychiatric disturbances of psychotic dimensions associated with the exogenous administration of steroid hormones have been particularly well recognized (1, 2). Hypercortisolism also occurs spontaneously; individual case reports as well as reviews confirm that emotional disturbances are frequent features of its clinical presentation (3). However, prospective studies describing the specific neuropsychiatric abnormalities in patients with Cushing's syndrome, their frequency, and their relationship to the abnormal hormone levels present in this disease are lacking.

Patients with spontaneous Cushing's syndrome provide a unique opportunity to study the relationship between cortisol and adrenocorticotrophin (ACTH) and psychiatric symptomatology. Since the disease may originate in several ways, patients present with differing profiles of cortisol and ACTH. In the majority of cases, there is excessive secretion of ACTH, usually by the pituitary gland, occasionally by a paraendocrine tumor, which causes excessive cortisol secretion by the adrenal glands. In other cases, an adrenal tumor secretes excessive cortisol, which then suppresses ACTH secretion.

This report describes the relationship of cortisol and ACTH levels with psychiatric symptomatology in 35 consecutive pa-

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tients with spontaneous Cushing's syndrome studied prospectively prior to treatment. Psychiatric features are described, with particular attention to the clinical characteristics of depressed mood, which occurs with high frequency in this disorder. The data to be presented indicate that there is an association between overall psychiatric disability and the level of cortisol and ACTH present in these patients. Furthermore, the data suggest that there may be an association of depressed mood and ACTH levels.

MATERIALS AND METHODS

Subjects

As the beginning phase of a longitudinal study, 35 patients with active Cushing's syndrome were studied prior to initiation of treatment. Twenty-eight were white and seven were black. Seven were male and 28 were female, approximating the expected 1:3 ratio of males to females seen in this syndrome. The mean age was 35, with a range of 19 to 59 years. The diagnosis of Cushing's syndrome was established in these patients by the demonstration of excessive cortisol secretion, as measured by cortisol secretion rates, urinary free cortisol, and plasma cortisol. In addition, cortisol levels lacked the normal circadian rhythm and failed to suppress normally with 2 mg of dexamethasone.

The etiologic type of Cushing's syndrome was determined for each patient on the basis of baseline cortisol and ACTH levels and ACTH response to dexamethasone suppression and metyrapone stimulation. Twenty-eight patients had ACTH-dependent Cushing's syndrome, with high cortisol and high ACTH levels. Of these, 22 had pituitary hyperfunction without a detectable pituitary tumor. Four other patients had pituitary macroadenomas. One patient had an ectopic ACTH-producing thymoma. Another patient had ACTH-dependent Cushing's syndrome with unusual hormone patterns that still refuse to yield to classification. Seven patients had ACTH-independent Cushing's syndrome, with high cortisol and low ACTH levels. Of these, five patients had an adrenal adenoma and two patients had an adrenal carcinoma.

Psychiatric Evaluation

Patients were evaluated psychiatrically during their initial diagnostic hospitalization at the time that baseline hormone levels were being obtained. Because of the characteristic physical stigmata of Cushing's syndrome, it was not possible for the evaluator (MNS) to be unaware of the patient's diagnosis. However, at the time of the assessment, the evaluator had no knowledge of the etiologic type of Cushing's syndrome or the hormone levels of the patient.

A semistructured interview technique was designed in order to obtain as comprehensive a phenómenologic description of the psychiatric symptoms as possible. Attention was given to defining the quality and characteristics of these symptoms in addition to simply scoring their absence, presence, and quantitative degree. After a spontaneous recounting of symptoms was elicited, a standardized set of questions was asked. Particular attention was given to affective, vegetative, and cognitive disturbances. Items selected for study were derived from previously reported observations of psychiatric symptoms in Cushing's syndrome, as well as the authors' pilot study of patients with this disease. A semiquantitative rating scale was established in order to allow both for comparisons among patients and for comparison of individual patients with themselves at future stages of treatment. For this newly constructed assessment technique, a disadvantage is that neither reliability nor validity has yet been established. Otherwise useful standard rating scales were not suitable for use with these patients. The Hamilton Psychiatric Rating Scale for depression includes items that are characteristic of the physiologic manifestations of Cushing's syndrome (e.g., muscle weakness, urinary frequency) or the not unrealistic preoccupation with body functioning (4). The Research Diagnostic Criteria are prohibited for use with such patients because of the existence of a specific organic disease causing both physical and mental symptoms (5). Many items from these scales, however, were incorporated into the structured portion of the interview. A mental status examination was also performed.

Forty-five items (see Tables 1 and 2) were studied by symptom report and/or observation during mental status examination. Each item was scored on a four-point scale (absent, mild, moderate, severe) based on quality, intensity, and frequency. Further,

TABLE 1. Frequency of Psychiatric Symptoms in 35 Patients With Cushing's Syndrome

Symptom	%
Increased fatigue	100
Decreased energy	97
Irritability	86
Impaired memory	83
Depressed mood	74
Decreased libido	69
Middle insomnia	69
Anxiety	66
Impaired concentration	66
Crying	63
Restlessness	60
Late insomnia	57
Social withdrawal	46
Hopelessness	43
Guilt	37
Increased appetite	34
Dreams	31
Early insomnia	29
Decreased appetite	20
Thought blocking	17
Speeding thoughts	14
Elation-hyperactivity	11
Slowing thoughts	11
Perceptual distortions	11
Rapid, loud speech	9
Paranoid thoughts	9
Hyperactivity	9
Depersonalization	3
Persistent anhedonia	3
Derealization	3
Decreased fatigue	3
Increased energy	3

an overall score of psychiatric disability was generated based on two factors: the summation of the raw scores for each of the 45 items in the symptom review and the mental status examination and the clinical global judgment of the seriousness of the psychiatric symptoms and degrees of psychiatric impairment. This overall score ranged from 1 to 4 (mild, moderate, severe, very severe). Individuals rated as having severe psychiatric impairment manifested more marked and disabling affective and vegetative symptoms than those rated as having mild or moderate psychiatric impairment. Those patients rated as having a very severe psychiatric impairment manifested in addition a thought disorder with paranoid ideation and/or confusional states.

Hormone Analysis

Cortisol secretion rate—the amount of cortisol secreted over a 24-hour period—was measured by isotope dilution (6). Total plasma cortisol (which includes both protein-bound and biologically active free cortisol), 24-hour urinary free cortisol, and plasma ACTH were measured by radioimmunoassay (7, 8). Serum dehydroepiandrosterone sulfate (DHEA-S), a mild androgen frequently abnormal in Cushing's syndrome but not anticipated to have major psychiatric effects, was also examined for comparison. DHEA-S was also measured by radioimmunoassay (9). Plasma or serum samples for cortisol, DHEA-S, and ACTH were obtained several times during the day for assessment of circadian rhythm. Where multiple plasma or serum samples were obtained, values were found to vary little during the day, a characteristic of Cushing's syndrome. Since the 8 AM samples were obtained most consistently, these values were used for statistical analysis.

Although efforts were made to obtain the entire battery of baseline hormone levels for each patient, in several instances one particular hormone level is not available because of technical difficulties.

RESULTS

Frequency of Psychiatric Symptoms

Table 1 lists the frequency of psychiatric symptoms reported by the 35 patients. A consistent constellation of symptoms was found at a high frequency (above 50%). These symptoms include impairments in affect (depressed mood, crying), cognitive functions (decreased concentration and memory), and vegetative functions (decreased libido and insomnia).

Description

Irritability-Anger. Increased irritability, a very frequent symptom, was the earliest psychiatric symptom to appear in the majority of cases. It began concomi-

TABLE 2. Frequency of Abnormal Findings in the Mental Status Examination in 35 Patients with Cushing's Syndrome

Abnormal Findings	%
Anxiety	63
Serial 7 subtraction	51
Proverb interpretation	46
Recall of presidents	46
Recall of 3 cities after 15 minutes	31
Sadness	26
Affective lability	17
Perseveration	9
Flight of ideas	6
Thought blocking	6
Paranoid trends	6
Confusion	3
Expansive, euphoric affect	3

tant with the onset of weight gain and prior to the appearance of other physical manifestations of Cushing's syndrome. Patients described themselves as having become overly sensitive, unable to ignore minor irritations, feeling impatient with or pressured by others. Since some patients reported that external noises bothered them excessively, this may be a reflection of a generalized hypersensitivity to stimuli. In addition, an overreactivity and easy development of anger was reported. Patients described feeling that they were often on the verge of an emotional explosion and that the intensity of anger experienced was also increased.

Verbal dyscontrol was frequent; patients noted that they were overly argumentative and unable to "hold their tongue." They also felt like expressing their irritation and frustration motorically, such as by smashing objects. Although most could restrain themselves, a few patients reported actual motor outbursts. Patients were frightened by their irritability and potential for verbal or physical dyscontrol. They described being on guard for a flare-up of anger and fleeing from a confrontation to avoid a feared loss of control.

Mood Disturbances: Depressed Mood. Depressed mood was reported by three-quarters of the patients. Many described that they would wake up depressed and remain depressed throughout the day or the next day as well. Alternatively, the onset of depressed mood and/or crying might occur during the day. Patients stressed that the onset of depression was sudden, at times with a rapid shift at some point during the day.

Some patients described hypersensitivity and oversentimentality as determinants leading to crying spells. For some patients, crying was experienced as their only available behavioral response to anger, frustration, and feelings of inability to respond effectively. Patients also described the spontaneous onset of depressed mood or crying in the absence of any preceding upsetting thought or event. There was a range in the intensity of depressed mood. Some patients described short spells of sadness; others experienced feelings of hopelessness and giving up. Six patients had had suicidal thoughts. Two of these patients had made suicide attempts since the onset of the Cushing's syndrome.

Social withdrawal, when present, was related to feelings of discomfort in large groups. Patients experienced shame because of their physical appearance and did not wish to be seen in public. Moreover, the unstructured setting of a large group elicited a decreased sense of focus, alertness, and clarity that led to a generalized sense of uneasiness. Most patients

reported an increased desire to have contact with significant family members. However, as noted previously, sporadic withdrawal might occur because of the patient's need to remove him/herself from a situation of overstimulation that elicited the fear of impending emotional dyscontrol. Guilt, when present, was not excessive, self-accusatory, or irrational. It was related primarily to remorse about the frequent and uncontrollable angry outbursts and inability to function as well as previously at work and in the family. Hopelessness, when present, was attributed to the existence of a chronic illness with increasing physical and emotional disability that so far had proved undiagnosable and untreatable.

The time course of the mood disturbances was noteworthy. Patients reported that their mood disturbances were intermittent rather than sustained. Although there were intervals when they felt unpleasure, these patients did not describe persistent anhedonia. They did not experience the unrelenting, unremitting inability to experience pleasure that is characteristic of patients with endogenous major depressive illness. There were intervals when they retained the capacity for pleasure and found enjoyment in hobbies, activities, and interpersonal relationships. At times, some patients found it difficult to initiate such activities; once others mobilized them, they would enjoy them.

The duration of each depressive episode was usually 1 to 2 days and rarely longer than 3 days at a time. A frequent weekly total of dysphoria was reported as being 3 days per week. There was no regular cyclicity, however, so that patients could not predict when a depressive day would occur.

Mood Disturbances: Elation-Hyperactivity. A minority of patients had experienced episodes of elation-hyperactivity early in the course of the disease. As the disease progressed and new physical signs of Cushing's syndrome began to appear, this type of episode became rare or disappeared entirely. The quality of these episodes of elation was described most frequently as a "high." Patients were more ambitious than usual and might attempt to do more than their ability and training made reasonable. Increased motor activity was present, with restlessness and rapidly performed activities. Three patients reported finding, to their embarrassment, that their speech was both loud and rapid. In one of the most severely disturbed patients, who had an ectopic ACTH-secreting thymoma, a typical full-blown manic syndrome with increased pressure of speech, rhyming of words, and paranoid ideation was present.

Cognitive Disturbances. Difficulty with concentration was frequently noted. Patients complained of mind-wandering when reading, watching television, and during the course of conversations. They reported a decreased ability to focus their minds, inattention, distractibility, and shortened attention span.

Difficulty with reasoning ability, comprehension, and processing of new information was reported. There were disturbances in the rate of thinking: some patients reported episodes of rapid and scattered thinking; others complained of slow and ponderous thinking. Blocking occurred, so that patients would experience their thoughts suddenly gone and their minds becoming blank while thinking or speaking.

Patients complained of not being able to think of or articulate the proper word, using incorrect words while speaking, ordering words incorrectly in a spoken phrase, and misspelling simple words.

Impairment of memory was one of the most frequent symptoms. Patients reported problems with registration of new information, which could be related in part to impaired concentration. They commonly repeated themselves in ongoing conversations. They easily forgot items such as appointments made, names of people, and location of objects. Difficulty occurred with recall of important dates in their personal or medical histories.

Disorientation and Confusion. Two patients mentioned having difficulty recalling the day of the week. Three of the four most severely disturbed patients experienced at least one confusional episode of severe degree.

Basic Biological "Vegetative" Drives. Data on three areas of basic biological "vegetative" drives were reported:

1) *Appetite and Eating Behavior:* Fifty-two percent of the patients had an alteration in their appetite: in 34%, appetite had increased, in 20%, it had decreased.

2) *Libido:* A decrease in libido was also frequent. Several patients remarked that this symptom appeared very early in the course of their disease.

3) *Sleep and Dreams:* Difficulty with sleep, particularly middle night insomnia and late insomnia (early morning awakening), was found in more than 50% of the patients. Difficulty with early insomnia (not falling asleep at bedtime) was not as frequent. One-third of the patients reported an alteration in the frequency or quality of their dreams. Some noted an absence of dreams; others reported a marked increase in their frequency and intensity. Their dreams had become bizarre, often frightening, and very vivid. These patients also reported that they had lost the ability to wake themselves out of a nightmare.

Perceptual Disorders. Perceptual distortions were rare. Three nondelirious patients did report instances when door frames or pictures on the wall appeared to be slanted, yet when measured or observed by others this was not the case. One patient reported an episode of a visual illusion during which a metal shower bar seemed to be bending out of shape as she was watching it.

Mental Status Examination

The frequency of abnormal findings in the mental status examination is shown in Table 2. Notable are the difficulties with serial 7 subtractions, interpretation of proverbs, and recall of presidents seen in close to 50% of the patients. Difficulty with recall of 3 cities after 15 minutes was seen in more than 30% of the patients.

Overall Psychiatric Disability

The overall psychiatric disability scores of the 35 patients were as follows: Thirty-four percent were rated as having a mild psychiatric disability, 26% moderate, 29% severe, and 11% very severe psychiatric disability.

There was variability in the clinical presentation of the four patients rated as having a very severe psychiatric disability. One of the two patients with pituitary ACTH-dependent Cushing's syndrome was depressed with paranoid ideation.

The other was troubled predominantly by episodic confusional states. One patient with an ectopic ACTH-secreting thymoma was manic with paranoid ideation. One patient with still unclassified ACTH-dependent syndrome was depressed and confused with paranoid ideation.

Association of Hormone Levels with Overall Psychiatric Disability

The association of cortisol and ACTH levels with overall psychiatric disability rating is shown in Figure 1.

An analysis of variance revealed a statistically significant relationship between the overall psychiatric disability score and the degree of cortisol elevation as measured by the cortisol secretion rate ($p = 0.00$), urinary free cortisol ($p = 0.00$), and plasma cortisol at 8 AM ($p = 0.02$). For each of these three measures of cortisol, the most severely disturbed group of patients (those manifesting a thought disorder with paranoid ideation and/or confusional states) had the highest hormone levels and were clearly differentiated from the rest of the sample.

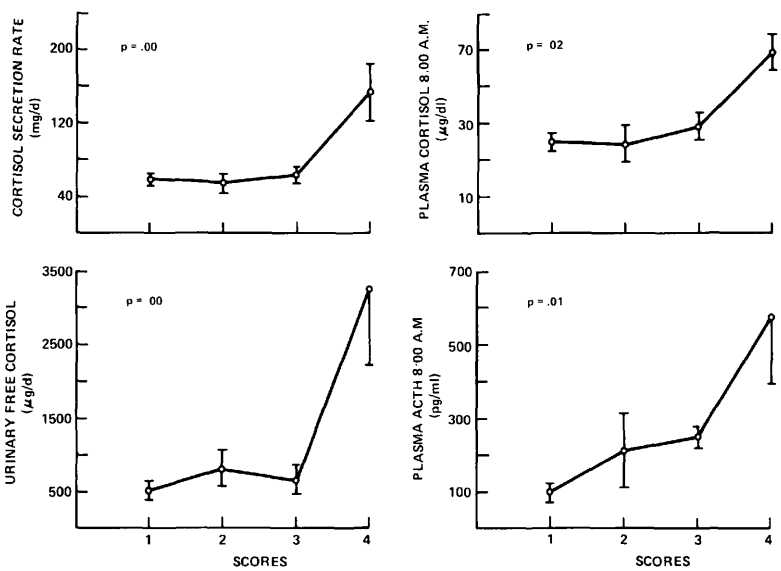

Fig. 1 Relationship between severity of overall psychiatric disability and hormone levels in Cushing's syndrome. (mean ± SEM) Of all 35 patients, 34% had an overall disability rating of 1 (mild), 26% of 2 (moderate), 29% of 3 (severe), and 11% of 4 (very severe).

There was also a statistically significant relationship found between the overall psychiatric disability rating and ACTH ($p = 0.01$). In contrast, such a relationship was not found between the overall disability rating and serum DHEA ($p = 0.66$).

Association of Hormone Levels with Depressed Mood

The association of cortisol and ACTH levels with the specific symptom, depressed mood, is of particular interest. Analysis of these data will be presented in several forms.

In the first group of analyses, each hormone is considered separately. As shown in Table 3, 2 × 2 tables were constructed. Depressed mood scores were collapsed into two categories: milder (0, 1) and pronounced (2, 3). Cortisol secretion rate, urinary free cortisol, and ACTH levels were also collapsed into two categories. Although the data suggest that higher cortisol levels are more likely to be associated with milder rather than pronounced depressed mood, this relationship did not reach statistical significance.

TABLE 3. The Relationship of Depressed Mood to Cortisol and ACTH Levels

		Depressed Mood Score		
		0, 1	2, 3	p
Cortisol Secretion Rates	moderate	9	3	= 0.70
	high	13	8	
Urinary Free Cortisol	moderate	7	7	= 0.14
	high	14	4	
Plasma ACTH	low, normal	10	0	= 0.01
	moderate, high	10	10	

The association of ACTH and depressed mood did reach statistical significance (Fisher exact probability = 0.01). Of 10 patients with low or normal ACTH levels, all reported milder rather than pronounced depressed mood. No patient with a pronounced depressed mood had a low or normal ACTH level. It should be noted that patients with moderate to high ACTH levels were not necessarily severely depressed and were equally likely to show milder or pronounced depressed mood.

The data in their original noncategorized form were also analzyed using an analysis of variance. With this method of analysis, the association between depressed mood and ACTH, the three measures of cortisol and DHEA, each examined separately, did not reach statistical significance.

In the next group of analyses, the data were examined in order to study the relationship of depressed mood and the levels of cortisol and ACTH considered together. The results of these analyses suggest that depressed mood may be associated with the balance between ACTH and cortisol.

Figure 2 depicts the relationship between depressed mood scores and the levels of urinary free cortisol and plasma ACTH. (Urinary free cortisol is used because it is directly correlated with the level of biologically active free cortisol in plasma.) In the upper half of the figure, this relationship is shown for the entire sample of 35 patients; in the lower half, for the patients with pituitary ACTH-dependent Cushing's syndrome without a detectable pituitary tumor. Depressed mood scores on a 4-point scale (none, mild, moderate, severe) are shown on the horizontal axis. For each mood score, the mean urinary free cortisol level is shown in crosshatched bars on the left and the

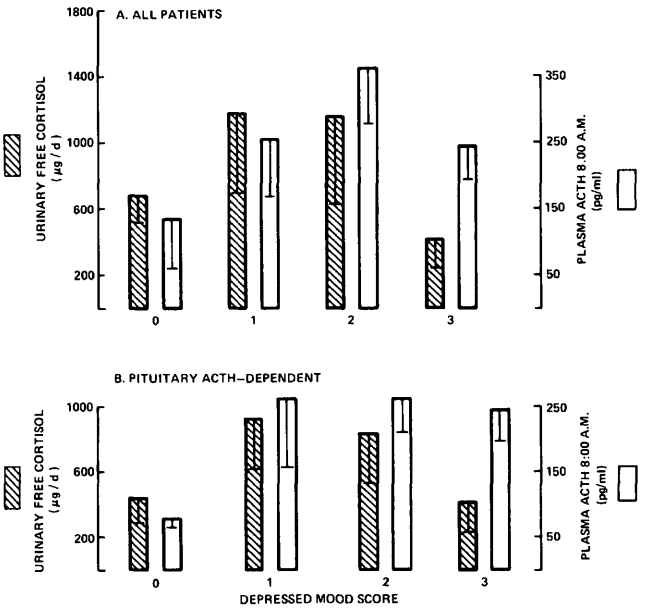

Fig. 2. Relationship between depressed mood scores and mean (± SEM) levels of cortisol and ACTH in Cushing's syndrome. Of all patients (upper half of figure), 26% had a depressed mood score of 0 (none), 42% of 1 (mild), 23% of 2 (moderate), and 9% of 3 (severe).

mean ACTH level is shown in open bars on the right. It can be seen that at each of the four depressed mood scores, there are differences in the relative proportion of cortisol to ACTH: as the depressed mood score increases, the relative proportion of cortisol to ACTH decreases.

The "corelationship" of ACTH and cortisol with depressed mood was explored further. The ratio of free cortisol to ACTH was generated for each patient, and an analysis of variance was performed. The results of this analysis are depicted in Figure 3. The top panel of the figure shows this relationship for the total sample; the middle panel only for patients with pituitary ACTH-dependent Cushing's syndrome without a demonstrable pituitary tumor. Although statistical significance is not reached, a tendency is suggested: as the degree of depression increases, the ratio of cortisol to ACTH decreases. For the patients with adrenal adenomas, shown in the bottom panel, this relationship is readily apparent and reaches statistical significance.

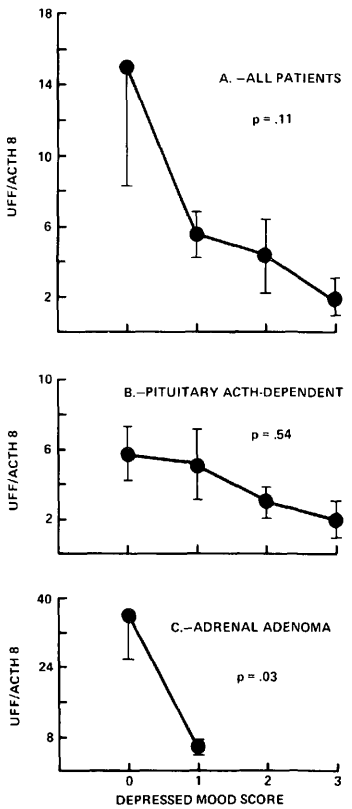

Fig. 3. Relationship between depressed mood score and the ratios of urinary free cortisol to ACTH (UFF/ACTH 8) (mean ± SEM).

Relationship of Depressed Mood and Etiologic Type of Cushing's Syndrome

As noted previously, it is of interest to compare the association of depressed mood and etiologic type of Cushing's syndrome since these types have differing profiles of ACTH and cortisol and different pathways of origin of the illness. Table 4 shows the 2 times 2 table constructed to compare depressed mood scores in patients with pituitary ACTH-dependent Cushing's syndrome without a demonstrable pituitary tumor (high cortisol, high ACTH levels) and in patients with adrenal adenomas (high cortisol, low ACTH levels). Although statistical significance is not reached, all the patients with adrenal adenomas reported milder rather than marked depressed mood. Using Student's t-test, the mean cortisol levels of these two etiologic subgroups were not significantly different; the mean ACTH levels were significantly different ($p < 0.05$).

TABLE 4. Comparison of Depressed Mood in Subtypes of Cushing's Syndrome

	Depressed Mood Score		
	0,1	2,3	*p*
Pituitary ACTH-dependent	15	7	0.28
Adrenal adenoma	5	0	

DISCUSSION

A constellation of symptoms including irritability, mood disturbance, impaired memory, poor concentration, decreased libido, and insomnia occurred with high frequency in Cushing's syndrome. Additional psychiatric symptomatology of greater severity, such as paranoid and confusional states, were much less frequent and were associated with particu-

larly high cortisol and ACTH levels. The four patients in the present study with the most severe overall psychiatric disability had a mean cortisol secretion rate of 157 mg per day, which is the equivalent of approximately 40 mg of prednisone per day. This parallels the observation that during steroid therapy the probability of developing an acute psychotic reaction is highest when daily doses greater than 40 mg of prednisone or its equivalent are administered (1, 2).

Although an age-matched control group of hospitalized patients with nonendocrine illness was not studied, the constellation of psychiatric symptoms that develop in Cushing's syndrome and the quality of the symptoms argue for a pathogenesis over and above a nonspecific response to severe physical illness. Irritability and decreased libido occur early, often before patients are aware that they have any physical problem other than a steady increase in weight. Depressed mood is experienced not simply as the demoralization common to patients with medical illness, but also as episodic sadness and crying often occurring in the absence of depressing thought content. The characteristic disorders of memory and concentration occur in patients who have no disorientation or overt clouding of consciousness. Of the 35 patients in the study, the electroencephalographs (EEGs) of only two were characteristic of delirium. (Both had been classified as having very severe psychiatric disability prior to knowledge of EEG findings.)

A consistent pattern of premorbid functioning or personality type was not found as a possible predisposing factor. Although some patients had stormy premorbid psychosocial functioning, others had stable family lives and work histories. No single personality trait such as obsessive-compulsive or hysteric predominated among these patients.

The relationship of depressed mood to cortisol and ACTH levels is of particular interest. When the data were examined in categorized form with each hormone considered separately, higher cortisol levels were more likely to be associated with milder rather than pronounced depressed mood, although statistical significance was not reached. In contrast, lower ACTH levels were significantly associated with milder rather than pronounced depressed mood. Further, the work reported here suggests that the relative proportion of cortisol to ACTH, rather than the level of either hormone by itself, may be related to the severity of depressed mood. Although higher ACTH levels in themselves were not uniformly associated with more severe depressed mood, there was a tendency for the degree of depressed mood to increase as the ratio of cortisol to ACTH decreased. Even though the relationship was not statistically significant, this pattern showed some specificity. That is, when items related to depressed mood, such as crying, guilt, and hopelessness, were examined, this pattern of increasing severity with decreasing cortisol/ACTH ratios was also noted. In contrast, greater difficulties with concentration tended to occur with increasing cortisol/ACTH ratios.

Patients with adrenal adenomas, because of their suppressed ACTH production, have a high cortisol/ACTH ratio. In our study, less severe depressive symptoms were seen in such patients as compared with those with pituitary-ACTH disorders. Unfortunately, since adrenal adenomas occur infrequently, the number of patients with adenomas in our series is small and this observation did not reach statistical significance. The

finding is supported, however, by two previous reports. In a review of 78 cases of Cushing's syndrome reported in the literature, Carroll (10) found that although ⅔ of patients with pituitary-ACTH disturbances had "a problem with depression," only ¼ of patients with predominantly adrenal tumor disease had depression. This difference was highly statistically significant. Second, in a recent clinical study, Cohen (11) found that 3 of 8 patients with adrenal tumors were free of psychiatric disorder, whereas only 1 of 21 patients with bilateral adrenal hyperplasia (pituitary ACTH-dependent disease) were free of psychiatric disorder, a difference that was also statistically significant. The high ratio of cortisol to ACTH in patients with adrenal adenomas reflects the different pathway of origin of Cushing's syndrome, which may be the critical factor for the presence and degree of depressed mood and other psychiatric symptoms. For example, although there is insufficient data to support the hypothesis, it has been suggested that some cases of pituitary ACTH-dependent Cushing's syndrome result from a primary disorder in the limbic system leading to an overproduction of corticotrophin releasing factor (CRF) and thence to increased secretion of ACTH and cortisol (12).

In Addison's disease, a low cortisol/ACTH ratio is a consistent metabolic feature: primary failure of the adrenal cortex leads to subnormal levels of cortisol, and hypersecretion of ACTH occurs due to the lack of feedback inhibition by cortisol. Clinically, depression has been reported as a frequent finding in Addison's disease (13). Thus, in this disease, depressed mood is associated with a low cortisol/ACTH ratio.

These observations support the speculation by Sachar (14) and others that excess ACTH itself exerts primarily a depressing effect on mood, whereas excess corticosteroids may tend to produce mostly elation. However, it seems likely that the phenomenon is more complex than a simple arithmetic effect based on the relative proportion of the two hormones. We have observed a small number of patients with normal cortisol levels and highly elevated ACTH levels who are not severely depressed despite a low cortisol/ACTH ratio. (These patients, who did not have active Cushing's syndrome and thus did not meet the criteria for inclusion in this study, had developed ACTH-secreting pituitary macroadenomas postadrenalectomy.) It may be that normal levels of cortisol stabilize important psychoneurophysiologic systems and protect against the effects of elevated ACTH levels. Conversely, abnormally elevated or deficient levels of cortisol, as in active Cushing's syndrome or Addison's disease, respectively, may destabilize these important systems, making the nervous system more vulnerable to the effects of elevated ACTH. A similar mechanism has been proposed by Prange (15) with regard to the role of neurotransmitters in affective disorders. He has suggested a "permissive hypothesis" in which a central indoleaminergic deficit may permit the development of affective disorder but is insufficient in itself so that an associated decrease in catecholamine activity is required for the onset of depression.

Patients with Cushing's syndrome meet criteria for organic brain syndromes and indeed are so classified in DSM-III as examples of Organic Affective Syndrome. Their affective lability, irritability, impaired concentration, and distractibility are characteristic of organic etiology. Abnormalities during mental status testing

are present despite most patients' efforts to perform well. However, these patients demonstrate some unique features. Although they complain of feeling "foggy," which may represent some clouding of consciousness, they are not disoriented. Although a small minority report visual illusions, most have neither visual nor auditory hallucinations. Most retain some capacity for abstract thinking and many, though not all, continue to retain employment because their cognitive impairment is not at the level of severe deterioration.

At the same time, patients with Cushing's syndrome demonstrate many of the clinical features of a primary depressive disorder, particularly the vegetative ones such as disturbances of sleep, libido, and appetite. Indeed, the majority of patients with Cushing's syndrome could meet the DSM-III diagnostic criteria for a Major Depressive Disorder (except for the exclusion of an Organic Mental Disorder). Although similar in many respects to the major depressive disorders, the depression seen in Cushing's syndrome has certain unique characteristics. Irritability is a prominent and consistent feature. Depressed affect is intermittent, with episodes of 1–3 days duration, recurring very frequently at irregular intervals. Because of this, patients do not experience the relentless depressed mood and unremitting persistent anhedonia so characteristic of most patients with primary endogenous depression. Psychomotor retardation, although present in many patients, is usually not so pronounced as to be clinically obvious and is usually apparent only in retrospect after improvement with treatment. The majority of these patients are not withdrawn, apathetic, monosyllabic, unspontaneous, or hopeless. Significant cognitive impairment including disorder of memory is a consistent and prominent clinical feature of patients with Cushing's syndrome.

It is of interest that a syndrome so clearly organic in etiology has many features associated with primary depressive disorder. This may suggest the presence of similarities in the pathophysiology of Cushing's syndrome and depressive disorders.

One line of evidence supporting this view concerns the endocrine abnormalities that have been found in both disorders. In Cushing's syndrome, elevated cortisol levels and resistance to pituitary-adrenal suppression by the synthetic steroid dexamethasone are diagnostic features of the disease. As for depressive disorder, a substantial proportion of depressed patients also show elevated cortisol levels and escape from pituitary-adrenal suppression by dexamethasone (16).

Biogenic amines have been implicated in the hypothalamic regulation of the release of anterior pituitary hormones, including ACTH (17). There is a vast body of literature regarding the relationship of depression and biogenic amines. Although the confirmatory evidence is incomplete, it is possible that at least some depressions are associated with an absolute or relative deficiency of catecholamines, particularly norepinephrine, at important adrenergic receptor sites in the brain (18).

Corticosteroids have significant effects on intracellular electrolytes. Experiments in animals have indicated that glucocorticoids mediate shifts of electrolytes and water at the cellular level and that cortisol can exert effects on brain intracellular sodium (19, 20). Clinical depression has been found to be associated with sodium retention, and an increase in erythrocyte

sodium concentration has been described in association with the successful treatment of depressed patients with lithium carbonate. It has been hypothesized that there may be a subgroup of depressed patients with a genetically determined abnormality affecting movement of electrolytes across the cell membrane (21).

Neuroactive peptides are probably of major importance. One such peptide, β-endorphin, arises from the same pituitary precursor molecule as does ACTH (22). β-endorphin and ACTH are secreted concomitantly in increased amounts in response to an ACTH-releasing stimulus (23). It seems reasonable to expect that when abnormalities in the production of ACTH exist, such as in pituitary ACTH-dependent Cushing's syndrome, abnormal levels of β-endorphin might occur as well. Although plasma levels of β-endorphin in control subjects are low, β-endorphin has been found to be elevated in the plasma of patients with Cushing's disease (24). The role of β-endorphins in psychiatric disease is as yet unclear. Although preliminary studies report changes in psychiatric symptomatology with administration of β-endorphin or the opiate antagonist, naloxone, these early studies are often contradictory and incomplete (25). Since depressed patients have been shown to have increased pain thresholds and pain tolerance when compared with normal subjects, Davis (26) has suggested that a relative excess of endorphins may play a role in both the relative analgesia and psychiatric symptoms seen in patients with depressive disorders.

The clinical similarity between patients with Cushing's syndrome and patients with depressive disorders may have another explanation. It may reflect the limited number of behavioral responses available to diverse physiologic or biochemical disturbances. For example, it is usually impossible to determine the etiology of an acute delirium by any distinguishing features of the clinical presentation. While the search for specificity in the biochemistry of mental disorders proceeds, it is useful to keep in mind that the brain may have a limited number of "final common pathways" and that similar responses to a wide variety of etiologic factors may occur.

This hypothesis would suggest that other neuropsychiatric similarities between Cushing's syndrome and depressive disorder might also exist. One such similarity may be the presence of significant cognitive deficits in both disorders. Cognitive deficits in primary depressive disorders are generally viewed as secondary to disturbances in affect and due to decreased motivation. Individuals with depression are considered to have intact cognitive function provided that they are sufficiently motivated to perform. However, cognitive deficits in depressive disorders may be largely unrecognized since most current research on depression uses instruments that focus on the affective and vegetative characteristics of depression and not on cognitive disorders. The evidence for the existence of significant cognitive deficits in affective disorders has been reviewed recently (27). Further support comes from a study in which patients with affective disorders made significantly more errors on an aphasia screening test measuring language and motor-perceptual dysfunction than did control subjects (28).

SUMMARY

In 35 consecutive patients with Cushing's syndrome studied prior to treatment,

a consistent constellation of psychiatric disturbances was found. Irritability, depressed mood, decreased libido, insomnia, poor concentration, and impaired memory occurred with high frequency in Cushing's syndrome. Psychotic and/or confusional states were much less frequent and were associated with particularly high cortisol and ACTH levels. The constellation of symptoms and their characteristics argue for a pathogenesis over and above a nonspecific response to severe physical illness.

The relationship of depressed mood to cortisol and ACTH levels was examined. Higher cortisol levels were more likely to be associated with milder rather than pronounced depressed mood. In contrast, lower ACTH levels were significantly associated with milder rather than pronounced depressed mood. Furthermore, the data suggest that the relative proportion of cortisol to ACTH may be related to the severity of depressed mood.

The observation that patients with Cushing's syndrome have many features associated with primary depressive disease suggests the presence of similarities in the pathophysiology of both types of disorder. Evidence is reviewed that alterations in biogenic amines, electrolyte shifts, and/or neuroactive peptides may be of significance in both types of disorders. Alternatively, the similar clinical features may reflect the limited number of behavioral responses available to diverse physiologic or biochemical disturbances.

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