Diagnosis and Neuroanatomical Correlates of Depression in Brain-Damaged Patients

Implications for a Neurology of Depression

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• Recognizing depression in brain-damaged patients poses considerable problems. The standard dignostic criteria often are not applicable since the neurological lesion may distort or even obliterate salient features of depression. Patients actually may deny being depressed or dysphoric, not have a depressive affect, or be totally unaware of abnormal vegetative behaviors. Furthermore, brain lesions themselves may produce striking behavioral alterations that can be mistakenly attributed to depression, or striking behavioral changes due to depression may be mistakenly attributed to the brain lesion. Based on five case studies, several clinical guidelines for recognizing and diagnosing depression in brain-damaged patients are offered. These cases also provide a data base to generate initial hypotheses about the neuroanatomical basis of the depressive syndrome. By observing how focal brain lesions modify the signs and symptoms of depression, inferences are made about brain areas crucial for modulating the various features of the depressive syndrome.

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major problem confronting both neurology and psychiatry is to define the neuroanatomical basis of psychiatric disorders. The discovery of antidepressants, anxiolytics, antipsychotics, and neuroendocrine markers strongly argues that specific biological alterations in brain function occur in certain psychiatric disorders but contributes little to understanding their neuroanatomical basis. Changes in the normal patterns of interhemispheric and intrahemispheric processing during motor, sensory, language, and cognitive activities have been observed in both affective and schizophrenic disorders with the use of clinical, neuropsychological, linguistic, and neurophysiological techniques (eg, spectral analysis of EEGs, internal carotid amobarbital sodium [Amytal] injections, unilateral electroconvulsive therapy [ECT], directional preponderance of nystagmus during caloric stimulation, eye movements during mental tasks, electrodermal changes during the orienting response, testing of semantic and syntactical processing of language, focal cerebral blood flow determinations, dichotic listening tests, etc¹⁻¹³). From these data, Flor-Henry and Koles^{1,4} have suggested that depression, dysphoria, anxiety, and sadness relate to functional alterations in the frontotemporal regions of the right hemisphere, while mania, paranoia, euphoria, and anger relate to functional alterations in the left frontotemporal regions. Nevertheless, the precise anatomical correlates for the cognitive and behavioral abnormalities encountered in various psychiatric disorders remains unclear.

Recent neurological investigations by Heilman et al,¹⁴ Tucker et al,¹⁵ and Ross and co-workers¹⁶⁻¹⁸ have suggested a distinct and dominant functional-anatomical organization in the right hemisphere for the modulation of the affective components of language and behavior. These investigations complement many psychological, physiological, and behavioral studies that previously have implicated the right hemisphere in the modulation of emotions,^{4,12,19-24} a notion first hypothesized by Jackson²⁵ nearly a century ago. The disorders of affective language and behavior resulting from focal lesions of the right hemisphere are called "aprosodias."17 The aprosodias can be classified17 in a manner similar to the aphasias,²⁶ which are disorders of *propositional* language (syntax and word choice) that are usually the result of focal lesions in the left hemisphere (Table 1). These findings strongly imply that the signs and symptoms encountered in some of the major affective disorders also might have a neuroanatomical basis.

As with much of our accrued knowledge about the organization of the human brain, both the aphasias and aprosodias were discovered and defined by using the classic neurological method of inferring function through clinicopathological correlations. Similarly, the neuroanatomical basis for psychiatric disorders might be inferred from studying patients who have both a psychiatric disorder and a neurological lesion. If a particular brain lesion reduced or obliterated one or more of the signs and symptoms associated with the psychiatric disorder, then one could infer that the lesioned portion of the brain was critical in modulating that particular sign or symptom. In attempting to carry out this strategy in patients with depression and brain damage, we rapidly discovered that our major impediment was to diagnose reliably the depressive syndrome.

The remarkably consistent descriptions of depression from the time of Hippocrates²⁷ have allowed the development of specific criteria, such as the Research Diagnostic Criteria,28 Washington University criteria,29 and DSM-III,³⁰ for diagnosing depression in patients without brain damage. In brain-damaged patients, however, we found that the neurological lesion may either obliterate or distort criterion signs and symptoms or may prevent collection of adequate historical information because of propositional and affective language disturbances. Furthermore, the depressive disorder can modify the clinical course usually associated with a neurological lesion, and changes in affective behavior resulting from a brain lesion may be misconstrued as being etiologically related to a depressive syndrome. Thus, the usual diagnostic criteria for depression may be inapplicable in these clinical situations.

The problems of disentangling the signs and symptoms of depression from those caused by brain damage are exemplified by the study of Folstein et al.³¹ Although they found an increased incidence of selected depressive fea-

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	Table 1.—The Aphasias and Aprosodias								
	· · · ·				Aprosodias*				
		_	Aphasias		Spontaneous			Comprehension	
-	Fluency	Repetition	Comprehension	Reading Comprehension	Prosody and Gesturing	Prosodic Repetition	Prosodic Comprehension	of Emotional Gesturing	
Motor	Poor	Poor	Good	Good	Poor	Poor	Good	Good	
Sensory	Good	Poor	Poor	Poor	Good	Poor	Poor	Poor	
Global	Poor	Poor	Poor	Poor	Poor	Poor	Poor	Poor	
Conduction	Good	Poor	Good	Good	Good	Poor	Good	Good	
Transcortical motor	Poor	Good	Good	Good	Poor	Good	Good	Good	
Transcortical sensory	Good	Good	Poor	Poor	Good	Good	Poor	Poor	
Mixed transcortical	Poor	Good	Poor	Poor	Poor	Good	Poor	Poor	
Anomic (alexia with agraphia)	Good	Good	Good	Poor	Good	Good	Good	Poor	

*The existence of the conduction and anomic aprosodias has been hypothesized; the others have been described." Motor, sensory, global, and transcortical sensory aprosodias have good anatomical correlation with lesions in the left hemisphere known to cause homologous aphasias.²⁶

tures in patients with right-sided as opposed to left-sided cerebrovascular accidents, they were not certain if their findings were a consequence of lesion location or a specific psychiatric problem. With the recent elucidation of more precise anatomical knowledge about the emotional functions of the right hemisphere,¹⁴⁻¹⁸ disentangling the relationship of depression and brain damage now may be feasible.

The following case reports illustrate the vexing problems of recognizing depression in brain-damaged patients, and clinical guidelines for diagnosing the depressive syndrome in these patients are offered. In those cases where a well-defined anatomical lesion could be documented by computed tomography (CT), inferences about the neuroanatomical basis of the depressive syndrome are made.

PATIENTS AND METHODS

The patients to be described primarily were referred to us because of behavioral problems. None had been given a diagnosis of depression prior to referral, suggesting that depression may be largely unrecognized in the brain-damaged population. All patients underwent a dexamethasone suppression test (DST), since this test has been shown to be a valuable neuroendocrine marker for endogenous depression.³²⁻³⁶

The DST was performed by giving dexamethasone (1 mg orally) at midnight and measuring serum cortisol levels at 8 AM, 4 PM, and 11 PM the following day. Nonsuppression was defined by one or more cortisol levels in excess of 5 μ g/mL after dexamethasone. Sixty percent to 80% of psychiatric inpatients with depression are reported to have nonsuppression that reverts to normal suppression with effective antidepressant treatment.³⁶

All patients underwent CT scanning, which constitutes the anatomical data base for our inferences about the neurological basis of depression (Fig 1 through 4, Table 2).

To date, our clinicopathological correlations suggest that the signs and symptoms of depression may be divided into four major categories. (1) The verbal-cognitive set consists of the actual words and syntactical arrangements used by the patient to convey to the examiner, through propositional language, the depth and severity of his dysphoria, his "understanding" of the causes for his mood, and his notions about himself and his future. (2) The affect category refers to the facial expressions, body postures, and emotional components of speech from which the clinician infers the depth, nature, and severity of the patient's dysphoria (mood). (3) The category of vegetative behavior includes the changes in appetite, sexual drive, sleep, and motivational level that accompany most depressions. These also help the clinician infer the depth and severity of a patient's dysphoria. (4) Mood refers to the actual inner feelings of dysphoria that a patient experiences, which the clinician can only infer from the patient's verbal-cognitive set, affect, and vegetative behavior.

Although there is a general consensus that "unipolar depression" comprises a heterogeneous group, controversy remains as to which subclassification system is most valid.37 Klein38 and others have suggested that unipolar depression can be categorized into at least the following two distinct groups: endogenous (endogenomorphic) depression, with derangements in the pleasure-reward system, and nonendogenous depression, with an underlying pessimistic personality disorder. Recent studies using biological markers, such as the DST and the sleep EEG, have supported this endogenous-nonendogenous dichotomy in unipolar patients.^{36,36} Endogenous depressions are characterized by a distinctly unreactive mood with pervasive anhedonia, marked vegetative signs, abnormal biological markers, and a good response to antidepressants. Nonendogenous depressions are characterized by fewer and less severe vegetative signs, fewer if any abnormalities in biological markers, a variable response to antidepressants, and, possibly, a better response to selected psychosocial interventions.⁴⁰⁻⁴² Typically, patients with endogenous depression provide verbal-cognitive constructs that are insufficient to account for the depth and severity of their dysphoria, whereas the verbal-cognitive constructs provided by patients with nonendogenous depressions appear better matched to their dysphoria in both timing and intensity.38.43

REPORT OF CASES

CASE 1.-Left Hemisphere's Contribution to Verbal-Cognitive Set.-An 81-year-old woman was referred for neurological evaluation six weeks after having a cerebrovascular accident that involved the left superiortemporal and inferior parietal lobes with a resulting Wernicke's aphasia. Following the cerebrovascular accident and a brief hospitalization, she began to have severe behavioral changes that subsequently led to her dismissal from two nursing homes.

Extreme irritability, negativism, and explosive outbursts were noted. She was unwilling to assist in routine personal hygiene, refused food, displayed no interest in social interaction, and was observed to continuously stare out the window. She either ignored or displayed marked annoyance to the presence of music, people, and television and often refused to speak to anyone. Because of her intolerable behavior, she was given haloperidol. According to her daughter, however, the medicine only "quieted her down" but still left her "seething underneath."

This clinical course is very atypical for patients with chronic Wernicke's aphasia. Such patients are usually excessively verbal, cooperative, and easygoing. They maintain personal hygiene, seek social interaction, and eat with normal gusto.

Extensive interviews with the patient's daughter revealed a history that previously had been overlooked that strongly suggested that the patient had an endogenous depression. Until the death of her husband four years prior to the stroke, the patient had been energetic and outgoing, with a wide range of interests. She then moved from New York to Dallas and was noted to have a marked and progressive reduction in social interactions with a loss



of general interest. She became notorious for refusing to participate in family activities and tended to talk negatively about herself, her life, and her future. Anorexia, with a 13.5-kg (30lb) weight loss, was evident prior to the stroke. Midnocturnal and early-morning insomnias, memory problems, and poor concentration also were reported. There was no previous history of depression, mania, or other psychopathological syndromes.

On neurological examination, the patient had fluent but severely paraphasic speech with very poor comprehension and repetition. She was inattentive and often stared off into space while being interviewed. She was totally unable to report her internal affective state, the presence of vegetative symptoms, or her preferences for food, television, and other environmental activities. Mild psychomotor retardation was evident, and she was generally irritable and uncooperative.

A repeated CT scan (Fig 1) revealed only one lesion, as previously described, and a dementia workup produced negative

results. Since the history provided by the daughter strongly suggested that a depressive syndrome had been present *prior* to the stroke, a diagnosis of endogenous depression was made (Table 2). Sleep-onset, midnocturnal, and early-morning insomnias and marked anorexia were confirmed by hourly nursing observations, and a DST revealed nonsuppression with a 4 PM serum cortisol level of 11.6 μ g/dL after dexamethasone.

Gradually increasing dosages of amytriptyline hydrochloride at bedtime (up to 50 mg/day) were administered over two weeks, and her sleep pattern, food ingestion, general mood, social interaction, and interest in personal hygiene were monitored carefully. Within three weeks, her sleep pattern normalized and she began to eat with enthusiasm, gaining 2.25 kg (5 lb). She became far less irritable and negative and showed significant improvements in general interest, social interaction, and attention. The neurological examination now indicated a classic Wernicke's aphasia. The patient became talkative, smiled frequently, and secmed inter-



Fig 4.—Computed tomographic scan of patient 4. Infarction (arrowheads) involves most of right frontal and parietal lobes, with extension into posterosuperior temporal lobe. There is also infarction of left anteromedial frontal lobe.

with patient's age.



	Tabl	e 2Clinicopatholo	gical Summa	ry of Cas	es 1 Throug	ih 4	
Lesion Distribution,* Neurological Case Deficits, and Type of Depression			Depressive Verbal- Cognitive Set	Vegetative Depres-Behavioral sive Abnormal- Affect† ities		Dysphoric Mood‡	Dexamethasone Suppression Test
1	L	Wernicke's aphasia; endogenous depression	No	Yes	Severe	Dysphoria inferred from affect and vegetative behavior	Nonsuppressive
2	R	Motor aprosodia; L hemiplegia with sensory loss; nonendogenous depression	Yes	No	Mild	Dysphoria inferred from verbal- cognitive set	Normally suppressive
3	R	Motor aprosodia; L hemiplegia with sensory loss; endogenous depression	Yes	No	Severe	Dysphoria inferred from verbal- cognitive set and vegetative behavior	Nonsuppressive
4	R	Mixed transcortical aprosodia; L hemiplegia with sensory loss; endogenous depression	No	No	Severe	Dysphoria inferred from vegetative behavior	Nonsuppressive

*Lesion distribution is based on the patients' computed tomographic scans. The lesions are projected on lateral brain templates using the atlas of Matsui and Hirano.⁶²

†Affect refers to nonpropositional language and motor behavior from which an internal feeling state may be inferred.

\$Mood refers to the actual internal feeling state experienced by the patient that is usually inferred by the examiner from the patient's verbal-cognitive set, affect, and vegetative behavior.

ested in attempting to converse and communicate even though her aphasia made coherent discourse impossible.

After two weeks with amitriptyline treatment, a repeated DST showed normal suppression. Because her behavior had improved so markedly, the patient's family, who previously had insisted that she go to a nursing home, decided to care for her in their own home! At follow-up four months later, a continued excellent therapeutic response to amitriptyline was noted.

Clinicopathological Correlations.-This case illustrates the difficulty of diagnosing depression in a patient with severe comprehension deficits from aphasia. Since taking a history was impossible, we had to depend on direct observations of the patient's behavior and secondary sources of historical information. Although haloperidol partially controlled her behavior, a more appropriate and specific treatment led to substantially greater therapeutic effects. The DST corroborated our psychiatric diagnosis.

As a consequence of the Wernicke's aphasia, patient 1 lost her verbal-cognitive capacities and was unable to communicate her depression to the examiner and family through propositional language. Nevertheless, she continued to display affective behaviors (negativism, irritability, social withdrawal, and psychomotor retardation) and vegetative behaviors (insomnia, anorexia, and weight loss) consistent with endogenous depression. These severe behavioral abnormalities are virtually never seen in the recovery phase of uncomplicated Wernicke's aphasia. Therefore, we can infer that the patient's internal feeling state (mood) was one of dysphoria even though there could be no validation of this inference through propositional language.

In contrast to patients with Wernicke's aphasia, patients who have Broca's aphasia from lesions involving the left inferior frontoparietal region are characterized by nonfluent speech and poor repetition with relatively preserved auditory comprehension.²⁶ Clinical experience suggests that when persons with Broca's aphasia are depressed, they usually will have a mood-congruent verbal-cognitive set even though they have great difficulty expressing it through propositional language. The examiner can elicit this verbal-cognitive set by either questioning the patient using a yes-no or multiple-choice interview format" or by using standard rating scales,⁴⁵ such as the Hamilton Rating Scale for Depression.⁴⁶ so long as reading and/or auditory comprehension are relatively intact. These observations coupled with those from patient 1 suggest that the verbal expression of a depressive verbal-cognitive set requires both Broca's and Wernicke's areas, whereas the internal formulation of a depressive verbal-cognitive set depends on Wernicke's area.

CASE 2.-Right Hemisphere's Contribution to Depressive Affect.-A 34-year-old man was admitted to the hospital following the rapid onset of left hemiplegia. He had no previous history of neurological, psychiatric, or medical problems other than hypertension, for which he intermittently took methyldopa. Initial examination revealed a dense left hemiplegia with hemisensory loss and a left hemianopsia with head and eyes deviated to the right. He was lethargic and dysarthric but not aphasic. The presumptive diagnosis was a cerebrovascular accident in the distribution of the right middle cerebral artery. A CT scan revealed a right inferior frontoparietal stroke (Fig 2, Table 2).

The lethargy, hemianopsia, dysarthria, and head and eye deviation cleared over seven days. A flat monotonic voice, devoid of emotion, and the absence of spontaneous gesturing were noted. He comprehended the emotional components of language and gesture but could not repeat sentences with affective variation. These deficits in emotional behavior are consistent with the newly described syndrome of *motor aprosodia* that is a consequence of *right* frontal opercular brain damage.¹⁷

About 17 days later, he began to show intermittent and uncontrollable crying that was an "all-or-none" phenomenon. The patient complained that he had no control over these emotional outbursts and that they did not necessarily correlate with his mood or the content of his conversation. (These findings in braindamaged patients are known as *pathological laughing and crying.*⁴⁷) Nevertheless, in his totally flat and aprosodic voice he stated that he felt "hopeless," "depressed," and "helpless," but he denied having suicidal thoughts. Over the next two weeks, however, he reported suicidal ideation and feelings of being severely depressed, with mild midnocturnal insomnia and a decrease in general interest. No appetite or weight disturbances were noted.

On mental status evaluation, this cooperative and fully oriented man was given to intermittent crying for which he often had no explanation. He ascribed his sad mood to his physical impairment and the occupational consequences of his stroke. He was hopeless and blamed himself for the stroke, since he had complied poorly with his antihypertensive treatment. Attention and concentration were intact. The patient had no dysarthria, aphasia, or generalized intellectual impairment. However, his speech was aprosodic and unaccompanied by gesturing. This aprosodic-agestural state, a consequence of the neurological lesion, gave the patient a flattened affect, making it impossible to assess accurately the depth and strength of his internal mood through nonverbal behavior. *He did not have a depressive affect*.

Because of his suicidal ideation, imipramine hydrochloride (150 mg/day) was begun. A complete remission of all depressive symptoms occurred within 14 days, although his flattened affect and motor aprosodia remained unchanged. A DST prior to treatment revealed normal suppression.

Clinicopathological Correlations.-This patient probably had a "reactive" (nonendogenous) depression as he became aware of the consequences of his neurological disability. Although his symptoms remitted in association with imipramine treatment, he also confronted and resolved some of the issues and concerns generated by the stroke.

Specific neurological lesions in the right hemisphere appear to result in aprosodic-agestural speech with retained comprehension of the affective components of language,^{16,17} as was encountered in this patient. Because these patients have a flattened affect, the physician is unable to utilize affective behaviors as clues by which to infer the patient's internal mood state. Consequently, clinicians may *disbelieve* the patient's propositional statements about their mood, since such statements will be delivered in an unconvincing, flat, monotone devoid of affective qualities. To avoid overlooking depression in these patients, strict attention must be paid to their propositional language statements about inner mood. The agestural-aprosodic state that follows right frontal brain lesions, however, is a distinct neurological entity that should not be confused with or misinterpreted as a depressive affect.¹⁷

Although patient 2's verbal-cognitive constructions were related in time and intensity to his reports of dysphoria, he did not show a typical depressive affect, even though his depression was severe enough for him to contemplate suicide. Thus, this case suggests that the right inferior frontoparietal lobes are crucial for organizing and modulating the affective behaviors that typically accompany depression. Apparently, however, they are not critical for the development of either the verbal-cognitive set or the dysphoric mood.

CASE 3.-Right Hemisphere's Contribution to Depressive Affect.-A 70-vear-old man was hospitalized following a syncopal episode. Two years previously, he had sustained an embolic stroke secondary to atrial fibrillation that caused a left hemiparesis and hemisensory loss that resolved over time. On admission, he had a grade 2/6 apical pansystolic murmur, atrial fibrillation, and mild weakness of the left upper extremity. One week later, he had a second right hemispheric stroke that caused a severe left hemiplegia with sensory loss. He was noted to have acute delirium with hallucinations. After 11/2 weeks, however, he was only mildly inattentive and could do six numbers forward on testing immediate recall. Recent and remote memory were intact. There was no aphasia, but his speech was aprosodic and agestural, which produced a flattened affect. Prosodic repetition was very poor, but comprehension of the emotional components of speech and gesture was good and he was given the diagnosis of motor aprosodia.17

The patient had little insight into his deficits and denied depression. During examination, however, he had multiple and uncontrollable laughing and crying spells that had an all-or-none quality. He denied feeling sad or happy during these episodes, which is consistent with the syndrome of pathological laughing and crying. A CT scan confirmed an "old" right superior parietal stroke and a new right inferior frontal stroke (Fig 3, Table 2).

Over the next few weeks, marked insomnia, severe anorexia, lack of interest in activities, and the gradual admission of dysphoria ("I feel blue") were noted. Although he denied suicidal thoughts, he showed guilt and self-blame. He was preoccupied with the whereabouts of his wife, whom he believed was unfaithful and had run off with another man. He also spoke of a severe injury to the right eye that he incurred during World War II and began to recount harrowing war experiences.

An independent history then was obtained from his wife, who had been visiting him daily in the hospital. None of his WW II ruminations or his alleged eye injury was substantiated. Five years prior to his stroke, the patient had retired from his usual occupation because of difficulties with concentration and memory. He lost virtually all interest in previous hobbies and activities and began watching television all day. He cried frequently and talked intermittently about feeling worthless. Following WW II, he apparently had had a severe episode of depression that would have met Research Diagnostic Criteria²⁸ for a major depressive disorder. His wife recalled that during that episode he also was preoccupied with an alleged severe injury to the right eye and harrowing war experiences. This history coupled with the current symptoms of dysphoria, anorexia, and insomnia led us to the diagnosis of endogenous depression, psychotic type.

A DST revealed nonsuppression, with a serum cortisol level of 13.6 μ g/dL at 4 PM after dexamethasone. Subsequent clinical deterioration from two episodes of ventricular tachycardia with cardiac arrest and a third stroke precluded the initiation of antidepressant treatment.

Clinicopathological Correlations.—This case illustrates the critical role of an independent history in substantiating and clarifying clinical observations. The difficulty in correctly gauging the depth of a patient's dysphoria in the presence of a motor aprosodia is again apparent. Nevertheless, patient 3 was able to describe his mood through propositional language and displayed vegetative signs of depression. Although initially his inattention and delusional state were attributed to his brain lesions, it became obvious, with further history, that he had an endogenous depression, psychotic type. The abnormal DST further substantiated our clinical impression.

As with patient 2, when this patient spoke about his dysphoria and delusions (verbal-cognitive set), he did not evidence moodcongruent affective behaviors that are typically associated with endogenous depression. The brain lesion associated with this patient's loss of affective behavior is best correlated with this second stroke involving the right inferior frontal region. Thus, this area in the right hemisphere appears to be crucial for modulating the depressive affect, but it is not necessary for the formulation or expression of the depressive verbal-cognitive set, the dysphoric mood, or the vegetative signs associated with endogenous depression. The previous negative inferences also hold true for the right midsuperior parietal area, which was destroyed by the first stroke.

CASE 4.-Right Hemisphere's Contribution to Depressive Affect and Verbal-Cognitive Set.-A 35-year-old woman was in good health until the acute onset of a subarachnoid hemorrhage. A left internal carotid berry aneurysm was clipped successfully, but she sustained a postoperative left hemiplegia and hemisensory loss due to an ischemic infarction in the right hemisphere. Six months later, she was admitted to the hospital for rehabilitation. She was noted by the rehabilitation personnel to be very difficult to work with since she was negative, irritable, and either unwilling or unable to cooperate in her physical therapy.

On examination, she was alert, awake, and attentive. Recent and remote memory and proverb interpretations were intact. She was aware of her neurological deficits but had no true emotional reaction to them. She was not aphasic but had aprosodic-agestural speech that gave her a flattened affect. Prosodic repetition was relatively preserved, but comprehension of the emotional components of speech and gesturing was poor. (This constellation of findings is consistent with the syndrome of mixed transcortical aprosodia, which, in this patient, probably evolved from a global aprosodia.17) She had a severe left hemiplegia, global left hemisensory loss, and urinary incontinence. A CT scan showed a large right supra-Sylvian infarction with extension into the superiorposterotemporal lobe and a small left anterofrontal infarction (Fig 4, Table 2). She specifically and consistently denied every sign and symptom of depression, including dysphoria, anorexia, anhedonia, easy fatigability, impaired thinking, suicidal ideation, and guilt both during hospitalization and in clinic follow-up.

Three months after her initial evaluation, the patient's mother accompanied her to clinic, and a radically different history was obtained. Her mother had noted over the previous six months that the patient had marked anorexia ("eats like a bird"), severe insomnia, and excessive irritability with verbal and physical assaults of her children, behaviors quite unlike her former self. She often required several people to assist her in and out of bed, a degree of dependency that was far out of proportion to her neurological deficits. She avoided social interactions and preferred to remain in her room by herself. In addition, a consistent history of pathological affect regulation characterized by uncontrollable laughing or crying at the slightest stimulus was obtained.

Review of her hospital record substantiated a 27-kg (60-lb) weight loss, and a diagnosis of endogenous depression was made. A DST revealed nonsuppression, with a serum cortisol level of 12.6 μ g/dL at 4 PM after dexamethasone.

Treatment with desipramine hydrochloride (125 mg at bedtime) led to marked resolution of her irritability, dependency, anorexia, and insomnia. She became socially interactive and motivated to assist in her rehabilitation. Her energy level was increased, and she gained 9 kg (20 lb). Her pathological laughing and crying completely abated. A repeated DST revealed normal suppression.

Clinicopathological Correlations.-The absolute necessity of obtaining a history from nonpatient sources in neurologically impaired patients is underscored once again. This is especially important when the patient evidences "denial of illness,"⁴⁸ a well-documented consequence of right-sided brain lesions. This patient denied every sign and symptom of depression, even when confronted with her mother's observations concerning her sleep, appetite, weight change, and irritability. To further complicate matters, the patient had a mixed transcortical aprosodia that caused her to have difficulty in both expressing and comprehending the affective components of language. The value of the DST as an adjunct to diagnosis also is demonstrated.

In addition to denying all the signs and symptoms of depression, the patient spoke indifferently about her neurological deficits, a finding that persisted even after successful treatment of her depression. The only occasion when she spoke with notable concern was during a discussion about her brother, who two years prior to her stroke had been arrested and sent to prison for armed robbery. The patient had been very close to him and was devastated by his trial and incarceration. She spoke of being "sad," "brokenhearted," "torn apart," and "disappointed," even though her voice patterns and behavior were without affect. Yet, whenever she spoke about her devastating neurological deficits she never displayed a similar affectively charged verbal-cognitive set.

This patient provides us with the greatest insight into the anatomical basis of depression. Since she denied every sign and symptom of depression, including vegetative features, her verbalcognitive set ("I'm not depressed ... I feel good") actually was totally irrelevant to her inferred internal mood state and depressive disorder. In contrast, when she talked about her brother's incarceration, her expressed verbal-cognitive construction of this event was affectively appropriate, demonstrating that her verbalcognitive capacities were intact. This striking dissociation can be explained by the fact that when she initially experienced the pain and loss of her brother, her brain was intact. Therefore, any affective information processed in the right hemisphere could be transferred across the corpus callosum to the propositional language areas in the left hemisphere, which could then construct and ultimately learn an appropriate affectively charged verbal-cognitive set. On the other hand, when we questioned her about her internal feelings concerning her neurological deficits or her mood state, we actually were interviewing an isolated left hemisphere that could not access the emotional information stored and processed in her damaged right hemisphere. Thus, her left hemisphere gave us irrelevant, misleading, and affectless propositional responses. This is similar to some of the experiences that Gazzaniga and Le Doux** report when dealing with patients with "split brain.'

In cases 2 and 3, the right hemisphere lesion *spared* the posterosuperior temporal-posteroinferior parietal lobes (the homologue of Wernicke's area in the right hemisphere),¹⁷ and both patients displayed a mood-congruent verbal-cognitive set when depressed. However, in case 4 the neurological damage involved the right posterosuperior temporal-posteroinferior parietal lobes, suggesting that this area is crucial for modulating and communicating the affective set via the corpus callosum to Wernicke's area in the left hemisphere for the formulation of a mood-congruent verbal-cognitive set (case 1), and to the right inferior frontal region for expression of the depressive affect (cases 2 and 3).

We cannot be sure that this patient was truly dysphoric, since her left hemisphere denied being dysphoric, but was her right hemisphere dysphoric? Without ways to verbally question her right hemisphere, we only can infer dysphoria based on her striking clinical and biological evidence for an endogenous depression. The same question and inferential process also applies to patient 1, whose Wernicke's apahsia, which was secondary to a left hemisphere lesion, also prevented us from directly ascertaining if she was dysphoric.

A final clinicopathological correlation in this patient concerns the anatomical origin of endogenous depression. If her depression, with its inferred dysphoria, originated in her relatively intact left hemisphere, then one would have expected the patient to have provided a mood-congruent verbal-cognitive set. Since this was not the case, we suspect that her depression was initiated by structures in the right hemisphere that were not involved by the stroke. Exactly which right hemisphere structures, however, cannot be ascertained in this patient using clinicopathological correlations. A likely candidate, based on ablation and stimulation studies in humans and animals, might be the amygdala,³⁰⁻³² with its powerful limbic and hypothalamic connections and known involvement in the modulation of inner emotional states.

CASE 5.-Closed Head Trauma and Depression.-A 38-year-old woman was referred for neuropsychiatric evaluation two years after a motor vehicle accident that had rendered her unconscious and semicomatose for approximately 2½ weeks, with gradual recovery. The EEG evidence of slowing over the right cerebral hemisphere suggested a destructive process, but a CT scan only demonstrated slightly enlarged ventricles. She was discharged approximately two months later with residual neurological deficits of motor incoordination in her extremities, urinary incontinence, inattention, and a euphoric affect.

One year after her accident, she began to show a progressive decline in her behavior and intellectual abilities. Temper tantrums, marked irritability, extreme uncooperativeness, and refusal to participate in household activities were noted. Thioridazine hydrochloride (10 mg three times a day) was begun, but it only blunted some of her more extreme outbursts.

We first examined this patient two years after the accident. Further history disclosed that she had pathological laughing and crying spells for the past year. Both the family and the patient concurred that she had no trouble sleeping or eating and had, in fact, gained 13.5 kg (30 lb). The family's report of irritable behavior, however, was denied by the patient. She did admit that for approximately one year she had experienced continuous sadness and helplessness without suicidal ideation.

On admission, she was awake, alert, and cooperative, with intact attention, immediate recall, and recent and remote memories. Proverb interpretation was very concrete. Her affect was extremely labile, swinging from uncontrollable laughing to crying that was unrelated to the context of the discussion. In between the spells of pathological affect regulation, she spoke in a flat monotone without prosodic inflection or gesturing, which created a flattened affect. Insight into her illness was good even though she had little insight into the impact of her behavior on her family. She was not aphasic, but her speech was aprosodic, with poor ability to repeat with emotional variation. Comprehension of the verbal and gestural components of emotional language was relatively good, which is consistent with the syndrome of motor aprosodia.17 Copying figures, handwriting, calculations, and rightleft orientation were intact. The cranial nerves were normal. Motor examination revealed mild flexion weakness at her left hip, with some spasticity in her left lower extremity that was greater than in her right lower extremity. The reflexes were slightly increased on the left side, with a left upgoing toe. Her sensory examination was intact, but her gait was wide based and slightly spastic.

A repeated CT scan showed mild enlargement of the ventricles, with definite atrophy of the prefrontal regions bilaterally. A DST showed normal suppression.

A regimen of nortriptyline hydrochloride treatment (50 mg at bedtime) was begun; after 2½ weeks, the dose was increased gradually to 100 mg at bedtime. She was seen in follow-up one month later and had sustained a remarkable improvement in her behavior, with total resolution of her dysphoria. She no longer demonstrated pathological laughing or crying, irritability, or insomnia. She was once again helping around the house and taking on responsibilities. Her neurological deficits remained unchanged.

Clinicopathological Correlations.—This case again demonstrates the value of interviewing family members to help clarify the clinical history and was included to illustrate that the strategies for diagnosing depression in patients with closed head trauma are the same as for patients with strokes (cases 1 through 4). Detailed clinicopathological correlations, however, could not be made because the CT scan did not define the extent of her brain lesions, which is often the case in patients with closed head trauma.

COMMENT

Diagnosing Depression in Brain-Damaged Patients

While a transient sense of discouragement, hopelessness, sadness, or demoralization may follow any neurological injury, some patients actually may have a true biological depression.^{31,33,34} The depression may develop *following* the neurologic insult (cases 2, 4, and 5) or *preexist* the insult (cases 1 and 3). The diagnosis and appropriate pharmacological treatment of the depression, however, is critical since untreated depression may impair recovery from the neurological damage (cases 1, 2, 4, and 5) or may interfere with rehabilitation (cases 2 and 4).³³ Furthermore, neuroleptics may be administered inappropriately in attempts to reduce behavioral problems that arise from the combination of brain damage and depression (cases 1 and 5), thus leaving the depression untreated.

Several bedside clues to the diagnosis of depression in neurologically impaired patients are suggested by these cases (Table 3). Erratic, abnormal, or poor recovery from the neurological insult (cases 1, 3, and 4), a failure to participate appropriately in a rehabilitation program



- 4. Aprosodic voice patterns, lack of emotional gesturing, and euphoric behavior may occur following R hemisphere lesions; these behavioral patterns are *independent* of depression; therefore, do not disregard patient's propositional language statements about dysphoria, guilt, hopelessness, and suicide even if affective behaviors are incongruent with statements; on the other hand, flattened affect should not be misinterpreted as depressive affect
- Abnormal dexamethasone suppression test is valuable biological marker to help establish existence of endogenous depression in some brain-damaged patients
- Trial of antidepressant medication is indicated in all suspected cases; neuroleptics may subdue behavioral problems in brain-damaged patients with depression, leaving depression untreated

(cases 2 and 4), or worsening of a neurological deficit after recovery (case 5) may be the first signs. The clinician then must obtain a careful psychiatric history to determine if the patient is depressed. This history should be obtained from *both* the patient and other family members since neurological insults may prevent accurate history taking, especially when the patient has an aphasia with comprehension deficits (case 1) or denial of illness (case 4). In some cases, vegetative signs may be the only clue to a depression, and these signs should be elicited carefully from the family and, if need be, looked for by nursing personnel (cases 1 and 3).

Aprosodic voice patterns with lack of gesturing frequently are encountered in patients with right hemisphere lesions,^{16,17} causing them to have a flattened affect. In these instances, the patient will be unable to modulate his voice and gestures appropriately. Such patients may report dysphoria in an unconvincing, monotonous, and aprosodic voice (cases 2, 3, and 5), which readily could mislead the clinician into minimizing or discounting verbal reports of dysphoria. Conversely, aprosodic voice patterns and lack of gesturing should not be misinterpreted as indicating the presence of depression. If the patient's right hemisphere lesion is large, causing deficits in comprehension of affective language and denial of illness, then verbal reports concerning mood, depression, affective behavior, or vegetative symptoms may be confabulatory and totally inaccurate (case 4).

A striking finding in this series of patients is that pathological laughing and crying (cases 2, 3, 4, and 5) may constitute a valuable behavioral marker for depression in those brain-damaged patients who have a flattened affect secondary to lesions involving the right inferior frontal lobe. Pathological affect regulation is usually the result of bilateral brain lesions causing pseudobulbar palsy with pseudobulbar affect,²⁶ but none of our patients had pseudobulbar palsy. Although our patient's pathological laughing and crying totally abated with antidepressant treatment (cases 2, 4, and 5), suggesting that depression was the critical factor, both conditions (right-sided brain damage and depression) are necessary since neither alone appears



Fig 5.-Neuroanatomical model of endogenous depression. Numbers and model are explained in Table 4.

Area*	Neurological Syndrome and Function	Postulated Function in Endogenous Depression		
1 (Broca's area)	Motor (Broca's) aphasia; organizes mo- tor output for propositional language	Expression of depressive verbal-cogni- tive set through propositional lan- guage		
2 (Wernicke's area)	Sensory (Wernicke's) aphasia; involved in comprehension of propositional components of language	Internal formulation and ultimate ex- pression of depressive verbal-cogni- tive set through propositional lan- guage		
3	Motor aprosodia; organizes motor out- put for affective components of lan- guage and behavior	Expression of depressive affect through affective components of language and behavior		
4	Sensory aprosodia; involved in compre- hension of affective components of language and behavior	Internal formulation of "depressive-af- fective set" that allows, via corpus callosum, Wernicke's area to formu- late mood-congruent depressive ver- bal-cognitive set and area 3 to ulti- mately express mood-congruent de- pressive affect		
5	Not known	Unknown structure or structures essen- tial for initiating and/or modulating critical features of endogenous de- pression (eg, dysphoria, vegetative behavior, hypothalamic dysfunction)		

*Areas are shown in Fig 5.

sufficient to precipitate pathological affect regulation.

These cases also illustrate the value of the DST as an adjunct in the diagnosis of depression in brain-damaged patients. Three of our five patients demonstrated DST nonsuppression, which was consistent with their diagnosis of endogenous depression (cases 1, 3, and 4). Furthermore, normalization of the DST in cases 1 and 4 occurred in association with clinical remission, similar to the reported experience in patients without brain damage with DST nonsuppressing depressions.³⁶ In brain-damaged patients with normal DSTs but in whom the diagnosis of depression is suspected, antidepressant medication still may be of benefit (cases 2 and 5).

The complicated and often confusing clinical picture of depression in neurologically impaired patients easily can be ascribed to nonspecific agitation, situational adjustment reaction, or the neurological lesion. To avoid these errors and to institute proper treatment, psychiatrists, neurologists, and rehabilitation specialists must become aware of the protean manifestations of depression in brain-damaged patients and apply the correct techniques for making an appropriate diagnosis. Exclusive reliance on standard psychiatric evaluations that depend heavily on criterion signs and symptoms found in depressed patients without brain damage may lead to diagnostic errors.

Neuroanatomical Basis of Depression

Figure 5 and Table 4 provide a model for the functionalanatomical organization of the signs and symptoms encountered in endogenous depression that we have derived from the case reports (Table 2). As with all models, it should not be construed as either proved or final but rather as a working hypothesis with heuristic and predictive power that will be modified as further clinicopathological data accrue. For instance, there is a group of propositional language disorders, known as the transcortical aphasias²⁶ (Table 1), in which the causative lesions usually lie outside the classic peri-Sylvian language areas (eg, Wernicke's and Broca's areas). Patients with transcortical aphasia all have in common the preserved ability to repeat sentences that are spoken to them, which is in distinct contrast to the aphasias associated with peri-Sylvian lesions (Table 1). Although Wernicke's area usually is considered to be responsible for the comprehension of propositional language, the existence of transcortical sensory aphasia strongly suggests that Wernicke's area is only a crucial way station for comprehension and that comprehension is actually a function of the cortex surrounding Wernicke's area.^{26,35}

Similarly, even though our initial study has implicated Wernicke's area as being a crucial structure for the formation of a depressive verbal-cognitive set, it is possible that the areas truly responsible for formulating the depressive verbal-cognitive set will be shown to reside outside Wernicke's area. Nevertheless, we believe our proposed model will prove valuable in unraveling the neuroanatomical basis of depression since it is internally consistent with the known functional-anatomical organization of the propositional²⁶ and affective¹⁷ components of language in the brain.

The model also receives indirect support from Dimond's^{56,57} observations concerning vigilance and consciousness in patients with partial and complete surgical commissurotomies. He hypothesizes that the brain circuits responsible for conciousness in each hemisphere reside "towards the back of the brain" and are unified via the splenium of the corpus callosum. Similarly, based on cases 1 and 4, we hypothesize that Wernicke's area and its homologue in the right hemisphere are responsible for formulating the verbal-cognitive and affective sets in depression, which then interact with each other via the corpus callosum (Fig 5). Recent anatomical data in humans suggests that these particular brain areas are connected through the *splenium*.¹⁵⁸

The model is also consistent with Flor-Henry's^{1,4,39} hypothesis that mania, depression, and schizophrenia relate to functional alterations in the frontotemporal regions of the brain. The interaction of these systems, via the corpus callosum, determines the type of psychiatric disorder encountered. For instance, if a depression (right hemisphere) triggers changes in the left frontotemporal limbic system, then a psychotic melancholia with paranoid delusions may occur.

Three points about our findings and model deserve emphasis. First, depression, even though it is psychiatrically classified as a disorder of affect, is neither a "right"- nor a "left"-hemisphere syndrome; both hemispheres participate in the depressive syndrome, each modulating certain signs and symptoms. This concept is important to understand since we are now on the verge of applying powerful new technologies, such as positron emission tomographic (PET) scanning⁶⁰ and Xenon Xe 133 blood flow scanning,⁶¹ to help elucidate the anatomical-metabolic derangements that accompany depression. Proper interpretation of these types of data will depend on understanding the functionalanatomical organization of the depressive syndrome. To this point, it is interesting that the preliminary studies using the PET 60 and 133 Xe scanning techniques 61 have demonstrated not only asymmetrical but also bilateral metabolic changes in the brains of depressed patients. Perhaps some of the controversies and interpretations surrounding recent electrophysiological and EEG findings showing right-vs-left or left-vs-right asymmetries in depressed patients^{4,12,13} are resolvable if we accept that both hemispheres participate in the depressive syndrome.

Although our initial findings suggest that endogenous depression may be initiated by structures in the right hemisphere, one should not make the assumption that this will hold true for nonendogenous depressions. Since nonendogenous depressions seem to be characterized by verbalcognitive constructions (left hemisphere) that are better

matched in timing and intensity to the patient's dysphoria,^{38,43} perhaps, nonendogenous depressions originate in a left hemisphere structure or structures, which then secondarily effect the areas in the right hemisphere that modulate affective behavior. Such an anatomical basis might account for the better matching of verbal-cognitive constructs to dysphoria in nonendogenous as compared with endogenous depressions. The reason for the poorer matching of verbal-cognitive constructs to dysphoria in endogenous depression can be explained if endogenous depression does, in fact, arise from right hemisphere structures that secondarily affect areas in the left hemisphere that are critical in formulating the verbal-cognitive set. Until further clinicopathological correlations are made, however, the exact anatomical origins of both endogenous and nonendogenous depressions can only be hypothesized.

Last, if the model is correct, then it should predict the existence of certain clinical syndromes not described previously. Although a number of syndromes can be predicted, a crucial patient for validating our basic hypotheses would be one who has both an endogenous depression and a sensory aprosodia secondary to a lesion involving the homologue of Wernicke's area in the right hemisphere (area 4 in Fig 5). Neurologically, the patient would be unable to either repeat or comprehend the affective components of language. The affective components of language and behavior during spontaneous communication, however, would be retained, although mismatching of the affective to propositional components of language might occur. In fact, this patient may even appear euphoric and unconcerned, as has been reported previously in a patient with sensory aprosodia.¹⁷ Because of the pivotal anatomical area destroyed (Fig 5), the usual unfolding of the signs and symptoms comprising endogenous depression should be altered greatly. The patient should not display a depressive verbal-cognitive set (even though his verbal-cognitive capacities are preserved) or affective behaviors consistent with either depression or a flattened affect. The only clinical manifestations of the endogenous depression should be marked changes in vegetative behavior. Treatment with antidepressants, as in case 4, should resolve his vegetative behavioral abnormalities without changing his "inappropriate" verbal-cognitive set or affective behavior.

In summary, this article presents an initial inquiry into the neurology of depression utilizing the technique of clinicopathological correlations. A more thorough understanding of the biology of depressive disorders is likely to ensue by combining our data and hypotheses with future clinical, pharmacological, physiological, and neurochemical investigations. This in turn should establish firmly that depression is primarily a disorder of the brain and not simply a dysfunction of the "mind."²⁷

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