

Mechanisms of Mania after Brain Injury

12 Case Reports and Review of the Literature

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Twelve patients who developed mania after a brain lesion are reported. Ages ranged from 20 to 83 years. Five patients had brain tumors (three frontal meningiomas, one temporal meningioma, and one temporal astrocytoma), four patients had stroke lesions (one frontal, one temporal, and two thalamocapsular), two patients had a traumatic frontal closed head injury, and one patient had a pituitary adenoma resection. Although seven patients had lesions restricted to the right hemisphere, four had bilateral or midline damage and one had a left hemisphere lesion.

Damage to structures functionally connected to the orbitofrontal cortex, mainly in the right hemisphere, seems to be associated with secondary mania. The possible roles of monoaminergic, genetic, and perinatal factors in the pathogenesis of secondary mania are discussed.

The fact that mood disorders may arise after brain lesions has been widely recognized (Babinski, 1922; Gainotti, 1969; Goldstein, 1942). Depression meeting DSM-III (American Psychiatric Association, 1980) criteria for major depression is frequently observed after brain trauma or stroke lesions (Robinson et al., 1984). These depressions are often associated with left frontal damage (Robinson et al., 1984; Robinson and Szetela, 1981), whereas indifference, apathy, and undue cheerfulness are frequently associated with right hemisphere lesions (Denny-Brown et al., 1952; Gainotti, 1969; Robinson et al., 1984). Cross-sectional and longitudinal studies of depression after brain injury have demonstrated that poststroke depression resembles endogenous depression in terms of diagnostic criteria (Robinson et al., 1983), natural history (Robinson and Price, 1982), cognitive impairment (Robinson et al., 1986), clinical manifestations (Lipsey et al., 1986), biological markers (Lipsey et al., 1985), and treatment response (Lipsey et al., 1984).

In contrast to the frequent occurrence of depression after brain injury, clear-cut cases of mania after brain lesions are rare and except for one recent study (Shukla et al., 1987) only sporadic cases have been

reported. We have identified 12 patients who developed mania after vascular, tumoral, or traumatic brain lesions. This relatively large number of cases allowed us to look for unifying aspects of the brain lesions that so rarely lead to mania. Patients were examined by an attending psychiatrist who conducted a standard clinical interview. All patients met DSM-III symptom criteria for organic affective disorder, manic type, and none had a personal history of affective disorder that definitely had occurred before the brain lesion. Although these patients were identified because of the existence of mania rather than brain injury, we examined a consecutive series of patients with mania who had a preexisting brain lesion. There was no other selection bias.

Report of Cases

Patient A was a 66-year-old right-handed man without previous personal history of psychiatric disorder. His familial psychiatric history was as follows: the patient's mother had suffered from an undiagnosed illness leading to prolonged hospitalization, his father had a history of alcohol abuse, and one daughter of the patient had had to be admitted to a psychiatric hospital because of depression.

Seven years before his admission, the patient suffered a myocardial infarction, after which he became emotionally labile. Six years later, he suffered a right hemisphere stroke with left-sided motor and sensory deficits. A CAT scan showed a recent right temporooccipital infarction, calcifications of the basal ganglia, and a mild cerebral atrophy (Figure 1). One year later, he experienced a sudden change in his affect and developed insomnia. He also became increasingly irritable and suspicious; on one occasion he tried to

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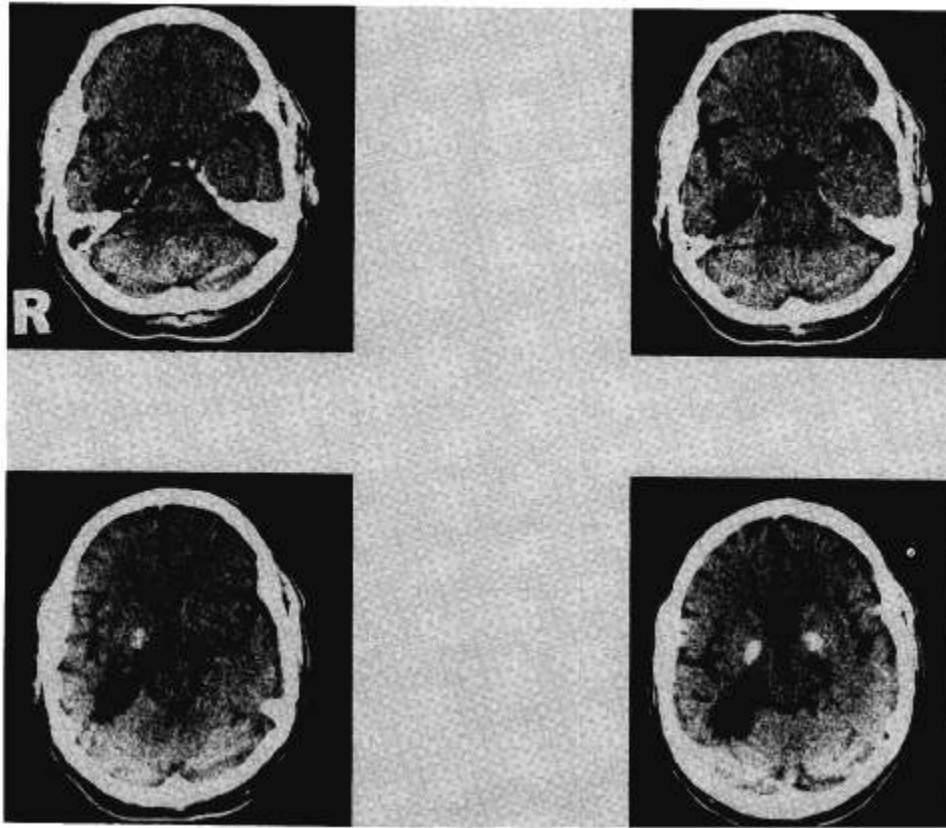


FIG. 1. Enhanced CAT scan showing an ischemic infarction involving the inferomedial temporal lobe (hippocampus and parahippocampal gyri) as well as the occipitotemporal and lingual gyri. There is also a bilateral calcification of the basal ganglia.

strike his daughter because he thought she had taken some of his money. He began to talk more frequently and extensively on the telephone, joked inappropriately, and began to give money away. In addition, a marked change in his sexual behavior took place. He was discovered to have made inappropriate sexual advances toward his 13-year-old granddaughter and later joked about it. After this episode, he was admitted to the hospital.

On admission, his speech was loud and his affect inappropriate, but he was alert. On physical examination, he had a left brachiorural hemiparesis, a left hemisensory deficit, and a left homonymous hemianopia. On the Mini-Mental State Exam (MMSE) (Folstein et al., 1975), he scored 28 out of 30. The patient joked all the time. He stated that he felt "the best he had ever felt," was a "very intelligent person," and would "win the lottery." He confessed to increased interest in sex as well as increased energy. He flirted with the nurses and was hypertalkative but had difficulty sleeping. A repeat CAT scan did not show any changes compared with the previous one. Endocrine and electrolyte studies were normal. The patient was put on neuroleptics, after which the manic symptoms subsided.

Patient B was a 27-year-old right-handed man with-

out previous personal history of psychiatric disorder. The patient's familial history was positive for depression in his mother and alcoholism in his father.

Six years before his index admission, he suffered the acute onset of a right-sided hemiparesis and aphasia. A CAT scan showed a small infarct in the left frontal lobe secondary to an embolic source from the heart (the patient had a mitral valve prolapse). He had been maintained on aspirin since then with no recurrence of stroke symptoms. After a few weeks, the hemiparesis as well as the aphasia resolved. One month after the stroke, however, the patient suffered a severe depression and had a suicide attempt, as well as delusions and paranoid ideation. He was started on chlorpromazine. One month later, his mood changed and he experienced his first manic swing, which lasted for 3 weeks. Lithium was added to his treatment, after which the patient had six hospitalizations for mania and depression, always associated with his serum lithium level falling below the therapeutic range. One week before his admission to our hospital, the patient had discontinued lithium because he was "feeling good." Since that time, his mood continued to gradually elevate. On admission, the patient rated his mood "20 out of 10." He was elated and had slept very little during the previous week. He demonstrated pressured

speech, racing thoughts, and hyperactivity. On physical examination, no neurological deficits were observed. He scored 29 out of 30 on the MMSE. Shortly before this last manic episode, the patient reported that he was engaged, it was the first anniversary of his father's death, and he had just moved to Baltimore from another city. Lithium therapy was reinstated and the patient experienced a rapid recovery. At 5 months follow-up, he remained euthymic with serum lithium levels within the therapeutic range.

Patient C was an 83-year-old right-handed woman with no previous personal history of psychiatric disorder. She reported a possible history of an undiagnosed psychiatric disorder in one of her grandparents. She was admitted to the hospital because of left-sided weakness. On examination she showed a left hemiparesis with left hyperreflexia, a left plantar extensor response, and a dense, left hemisensory loss. A CAT scan showed only mild cortical atrophy without focal lesions. Eleven days after the onset of hemiparesis, the patient developed depression with auditory hallucinations and ideas of reference, and she was started on tricyclic antidepressants. She scored 17 out of 30 on the MMSE. Two months after the stroke her mood changed dramatically. The patient was elated, with grandiose delusions, hyperactivity, and diminished sleep. This state lasted for 15 days, after which the patient was transferred to another hospital and lost to follow-up.

Patient D was a 36-year-old right-handed woman without previous history of psychiatric disorder. Familial psychiatric history was positive for depression in her father. Two years before her admission, she suffered an episode of sudden headaches and slurred speech that had been considered secondary to stroke. No lesion was observed on CAT scan, however. Two weeks before her admission, she suffered a new episode of intense headaches with left-sided weakness. A CAT scan showed a right thalamocapsular bleed (Figure 2).

Associated with the resolution of her motor deficits, the patient began to show elation and hyperactivity and had to be admitted to the hospital. On examination, no neurological deficits were observed. The patient was elated and showed pressured speech, flight of ideas, grandiose delusions, suspiciousness, and hypersexuality. She also reported a decreased need for sleep. A repeat CAT scan showed a nonenhancing radiolucency in the right thalamus compatible with a resolving hematoma. An EEG was normal. Endocrine and electrolyte studies were also normal.

Patient E was a 63-year-old right-handed man without previous personal or familial history of psychiatric disorder. Four years before his admission, he developed a progressive blindness in his left eye. A CAT scan showed a $9 \times 7 \times 7$ cm meningioma in the anterior inferior frontal region extending from the crista galli to the suprasellar cistern (Figure 3A). A partial surgical resection of the tumor was performed. Subsequently, he did well until 4 weeks before his admission, at which time his wife noted a change in his behavior. He complained of having "the biggest brain tumor in the world" and also began sleeping less. He began calling people incessantly on the phone to tell them that a national television celebrity had been talking about him on a television show that day and he began to sell his property for trivial sums and otherwise mismanage his finances. During this time he also developed urinary incontinence. On admission he was elated and hyperactive and showed a great interest in sex. Physical examination was essentially unremarkable, except for the blindness of his left eye. He scored 29 out of 30 on the MMSE. Endocrine and electrolyte studies were normal. A repeat CAT scan showed loss of tissue in the right frontal lobe, dilation of both lateral ventricular frontal horns, and a recurrent residual tumor in the lower portion of the frontal fossa (Figure 3B).

Patient F was a 61-year-old right-handed woman

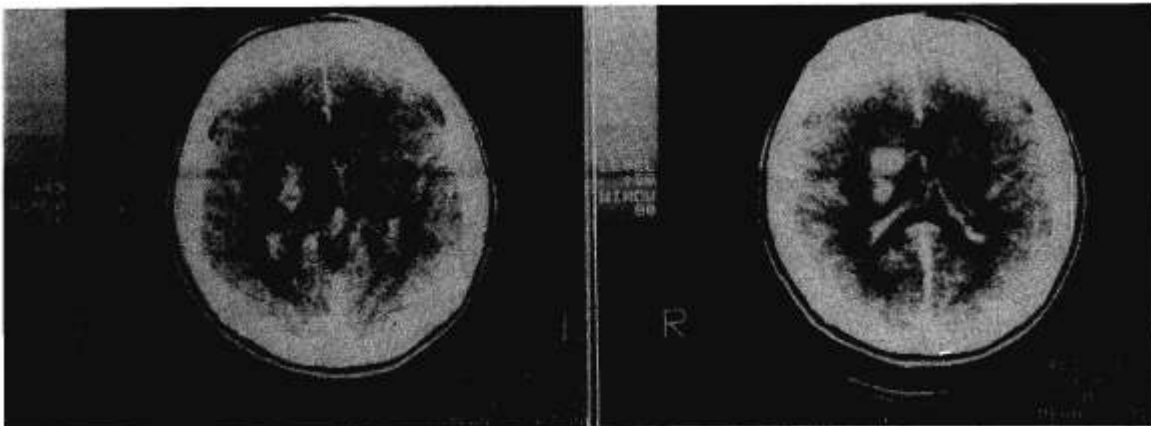


FIG. 2. Enhanced CAT scan showing a right thalamic bleed.

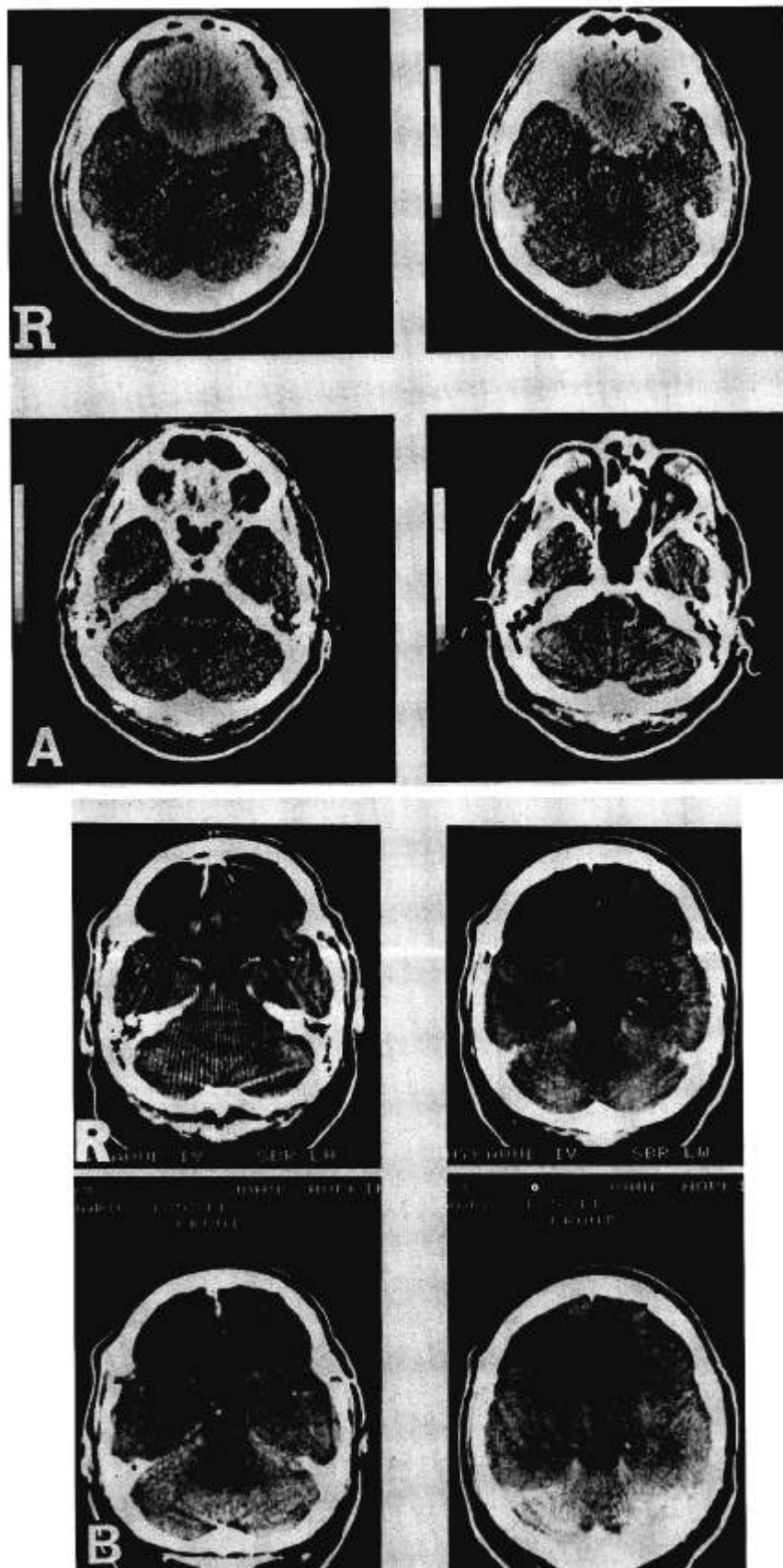


FIG. 3. A, enhanced CAT scan showing a huge meningioma in the anterior inferior frontal region extending from the crista galli to the suprasellar cistern. B, CAT scan showing loss of tissue in the right frontal lobe and dilation of both lateral ventricular frontal horns.

with no previous personal history of psychiatric disorder. Familial history was positive for an unknown but prolonged psychiatric disorder in the patient's mother that developed after a car accident.

Several months before admission, the patient suffered a progressive left hemiparesis with a left homonymous hemianopia and a left hemihypesthesia. A CAT scan showed a right temporoparietal meningioma along the tentorium and the lateral sinus; subtotal removal of the tumor was performed. Immediately after surgery the patient experienced a marked behavioral change. She was elated and hyperactive, showed pressure of speech, showed decreased need for sleep, and refused psychiatric treatment. Three years later she was admitted again because of intense headaches. A repeat CAT scan revealed the recurrence of meningioma (Figure 4). Some weeks later, the patient suffered several episodes of transient ischemia with weakness on her left side. An angiogram revealed a severe stenosis of the right carotid artery, and an endarterectomy was performed. Six months later, a new CAT scan showed no changes compared with the previous one. At the time of this evaluation, the patient was again manic, but she refused psychiatric treatment.

Patient G was a 48-year-old right-handed woman without previous personal history of psychiatric disorder. Family history was positive for one of the patient's brothers, who had been admitted to a psychiatric hospital because of aggressive behavior. During the 2 years before her admission, the patient alternated between periods of elation and depression. She became a street person, sometimes lying on the streets and at other times staying in missions. During the last year before her admission, she displayed marked hypersexuality, loud, abusive, and pressured speech, irritable mood, and threatening behavior toward her family. On admission, the patient showed no vision in the left eye and was unable to converge her eyes. A fundoscopic examination demonstrated left papilledema. During the examination her speech was tangential and often contained inappropriate sexual remarks. She appeared elated, stated that she felt unusually well, and was very excited and full of energy. Her MMSE score was 26 out of 30. Endocrine and electrolyte studies were normal. A CAT scan showed a subfrontal and midline meningioma involving both frontal lobes (Figure 5). The tumor could be only partially removed. One month after surgery, the patient showed mild hypomania.

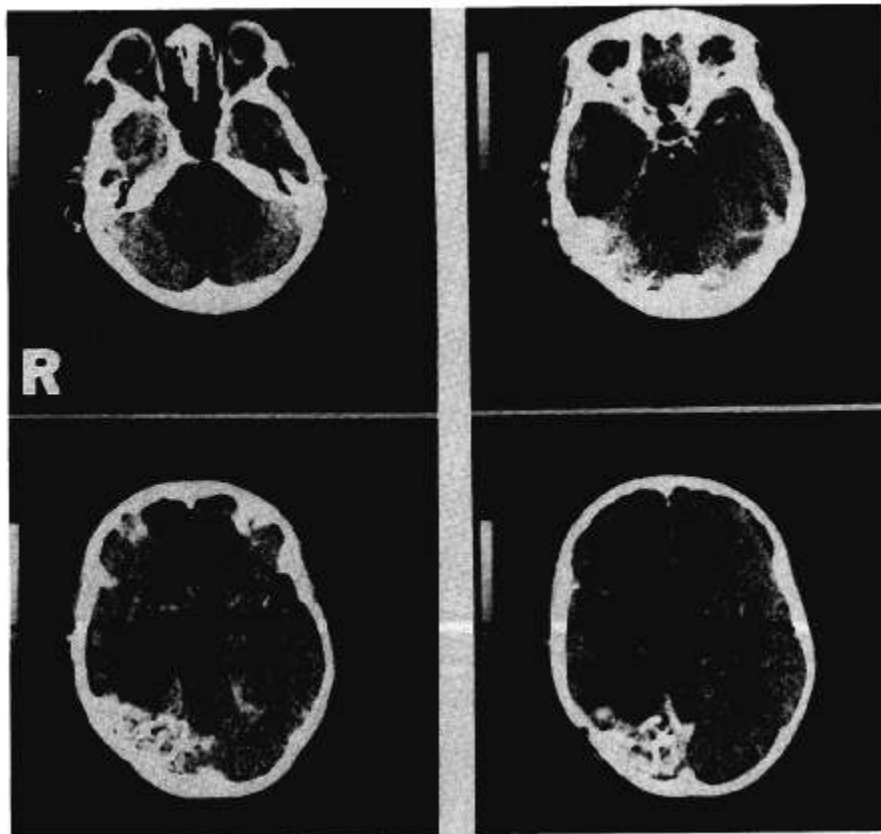


FIG. 4. Enhanced CAT scan showing a postsurgical lucency involving the temporal (hippocampal and parahippocampal gyri) and occipital (lingual gyrus and striate cortex) lobes. The increased density near the lambdoidal suture, sharply enhanced after iodine injection, may represent recurrent meningioma.

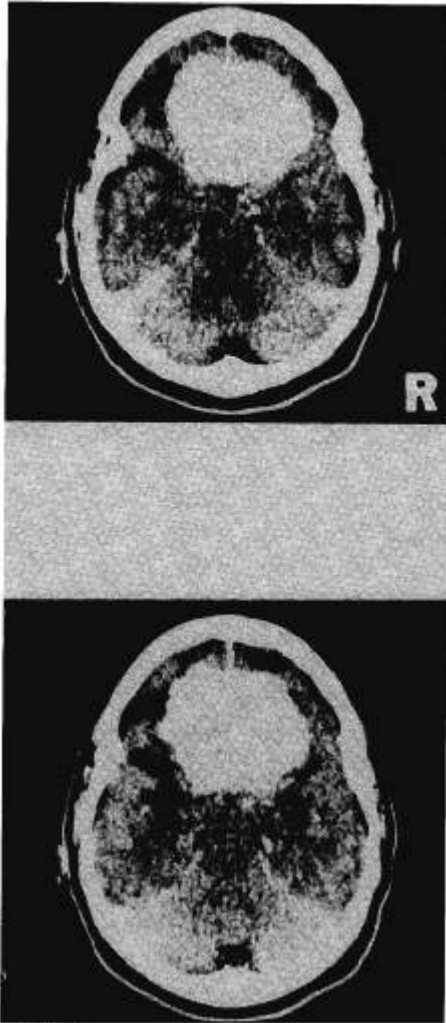


FIG. 5. Enhanced CAT scan showing a meningeoma involving both frontal lobes.

Patient H was a 54-year-old right-handed woman without previous personal or familial history of psychiatric disorder. She was admitted to our hospital because of euphoria and agitation. Before the onset of mental symptoms, the patient was a very talkative but calm woman with a positive attitude. Several years before her admission, her mood changed dramatically. She experienced numerous episodes of mania and spent much of her time in psychiatric institutions; however, she never experienced depression. While she was an inpatient in another hospital, a CAT scan disclosed a small right frontal meningeoma and she was transferred to our hospital for treatment. On physical examination at admission, there were no positive findings. The patient was elated and had an exalted self-attitude. She said that she was a poet and a movie star and that she could also cure the sick with magic words. She had paranoid delusions and auditory hallucinations. She showed severe pressure of speech, flight of ideas, decreased need for sleep, and hypersex-

uality. She scored 28 out of 30 on the MMSE. Endocrine and electrolyte studies were normal. After beginning treatment with lithium, she experienced a rapid resolution of manic symptoms. Surgery was not performed and the patient left the hospital. Some months later, however, she had to be admitted again because of another manic episode after she interrupted her lithium treatment. After resumption of lithium treatment, she again showed a good response and was finally discharged.

Patient I was a 28-year-old ambidextrous man without previous personal or familial history of psychiatric disorder. Three years before admission, he developed psychomotor seizures. An EEG showed slow waves on the right temporal region and CAT scan showed an enhancing tumor in the right temporal lobe. The tumor, a grade II astrocytoma, was completely resected and the psychomotor seizures never recurred. Immediately after surgery his family reported he was a "changed" person. The patient became very aggressive and impulsive, and he was unable to go back to work. One year later, he suffered intense headaches and was admitted to our hospital. A new CAT scan showed the recurrence of the right temporal astrocytoma, causing compression of the right lateral ventricle and moderate shift of midline structures to the left (Figure 6). He was given a course of radiotherapy. During this period, the patient became progressively elated and showed pressure of speech, grandiose delusions, flight of ideas, and hyperactivity.

Patient J was a 74-year-old left-handed man without previous personal or familial history of psychiatric disorder. His right leg had been amputated above the knee during World War II. Ten years before, he had been admitted to a hospital because of polyuria and polydipsia, and a pituitary adenoma was diagnosed. On admission, there was no suprasellar extension, and the tumor was removed through a transphenoidal approach. Since then, the patient experienced severe mood swings, and each year he spent 8 months depressed, 2 months euthymic, and 2 months manic. There was no response to lithium treatment. The patient was admitted to our hospital during one of his manic swings. He was elated and hyperactive, with decreased sleep, flight of ideas, and pressured speech. During previous manic episodes, he also showed hypersexuality, overspending, and second-person auditory hallucinations. There was no previous history of complex partial seizures. On physical examination, he had a mild postural hand tremor. He scored 27 out of 30 on the MMSE. A CAT scan was performed that only showed mild cerebral atrophy.

Patient K was a 24-year-old right-handed man without previous personal or familial history of psychiatric disorder. Nine months before admission, he suffered

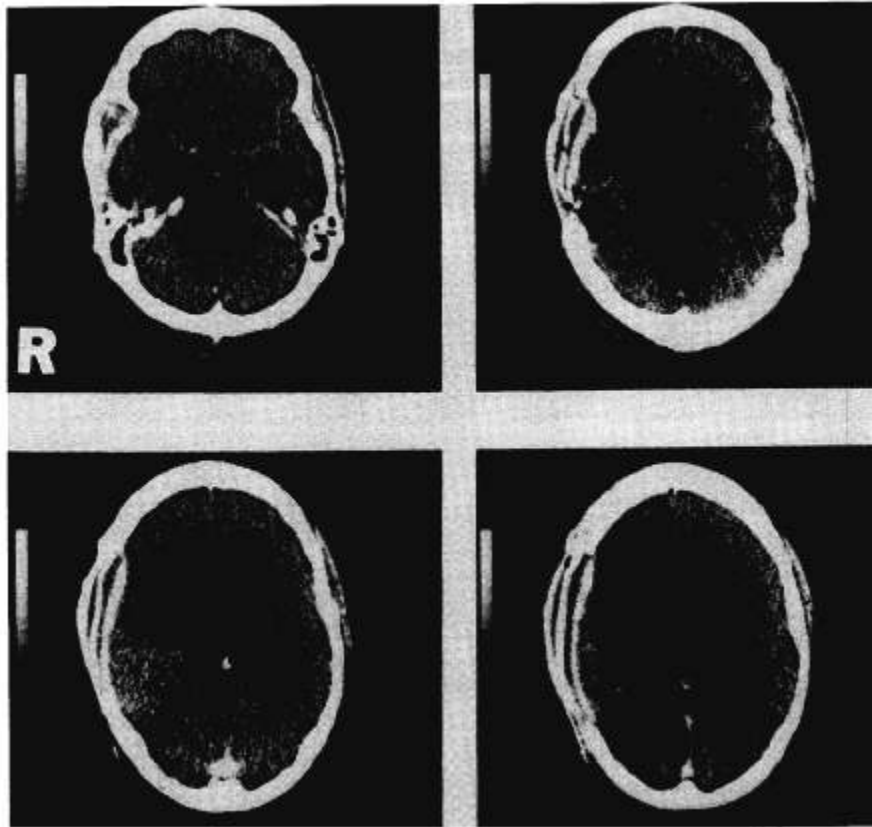


FIG. 6. Enhanced CAT scan showing an enhancing mass occupying the right posterotemporal lobe and causing shift of the septum to the left.

a closed head trauma after a car accident. He remained in a coma for a week and then gradually improved with a residual left hemiparesis. A CAT scan showed diffuse cerebral swelling with several intracranial contusions but without other focal pathology. Although the patient did well at home, he became increasingly suspicious of other people. Eight months later, after a minor car accident without head trauma, he developed agitation and paranoid ideation and had to be admitted to our hospital. A new CAT scan was normal and he did not show endocrine or electrolyte abnormalities. The patient was put on neuroleptics, after which all the symptoms cleared. One year later, he was admitted again with elation, insomnia, increased agitation, demanding behavior, irritability, and pressured speech. Lithium treatment was begun, and over the following weeks the patient showed less agitation and elation and less pressured speech. Six months later, he took several lithium tablets in a suicide attempt. Because he developed a tremor, his medication was changed from lithium to carbamazepine. His mood improved again but he had four more psychiatric admissions in the following 2 years because of manic episodes, even with carbamazepine plasma levels in "therapeutic" range. Manic episodes were characterized by elation, increased energy, decreased sleep, and

grandiose delusions. On one occasion he was very aggressive and was given electroconvulsive treatment, which resulted in dramatic improvement. Considerably less dysphoric, he became calmer and was able to return home.

Patient L was a 20-year-old right-handed man without previous family history of psychiatric disorder. Two years before his admission, he suffered a closed frontal head trauma after a car accident and remained in a coma for several weeks. He recovered consciousness later but continued to have multiple neurological deficits such as unsteady and uncoordinated gait, right hand ataxia, dysarthria, and diplopia. After the accident, the patient underwent a marked personality change. His behavior was coarse and he showed hypersexuality. He felt full of energy, had decreased sleep, and began to spend money without restraint. Despite his marked cerebellar signs, he insisted on playing the guitar and practicing tennis. He affirmed that, with enough training, he would be able to play the guitar better than any professional guitar player and would be able to win tennis tournaments. Two years later he was admitted to our hospital because of elated mood. On physical examination he showed a mild dysarthria, right-sided hand and leg dysmetria, and a wide-based gait. The patient was elated and

hyperactive, showing grandiose delusions, hypersexuality, and a decreased need for sleep. He was put on neuroleptics but developed a marked lethargy, even with small doses. After 2 weeks he was discharged. At that time he was less elated and slept more hours, but continued to have grandiose delusions.

Discussion

We presented 12 patients who developed mania after brain injury. Demographic data and clinical symptoms are summarized in Tables 1 and 2, respectively. Every patient met DSM-III criteria for organic affective syndrome manic episode, and none of them had a known personal history of affective disorder before the brain lesion. Age at onset of mania ranged from 20 to 83 years. Six of our patients had tumors, four had strokes, and two had traumatic closed head injury (Table 3). Lesion location was as follows: five patients had frontal lobe involvement (the orbitofrontal cortex was damaged in four patients), three patients had temporal lobe damage (in two of them damage was localized in the basal portion of the temporal lobe and extended to the diencephalon), two patients had thalamocapsular lesions, one patient had a pituitary tumor and surgery near the diencephalic region, and one patient had a frontal head trauma with cerebellar signs. Although seven patients had lesions restricted to the right hemisphere, four patients had midline or bilateral involvement, and only one patient had a restricted left hemisphere lesion.

The majority of our patients developed secondary mania immediately after (in the cases of strokes or closed head injuries) or concomitant to the brain lesion (in the cases of tumors); two patients (patients A and K) developed secondary mania several months after the brain injury, however. In their comprehensive review, Krauthammer and Klerman (1978) suggested that to be considered "secondary" the onset of manic symptoms should be in close temporal prox-

imity to the brain lesion. Nonetheless, secondary mania has been described in patients who developed manic symptoms years after the brain lesion (Table 4). Because the mechanisms implicated in the pathogenesis of secondary mania have not been established, there is no clear reason for setting a fixed cutoff point after which the appearance of mania would be considered "independent" from the brain injury. For instance, a lesion may not be able to produce secondary mania by itself but may predispose the "triggering" of secondary mania after a second lesion, a stressful life event (Ambelas and George, 1986), or the aging process.

One of our patients (patient C) developed secondary mania shortly after receiving treatment with nortriptyline for a poststroke depression. Krauthammer and Klerman (1978) do not consider manic episodes after tricyclic treatment "true" secondary mania. We believe, however, that the brain lesion rather than the nortriptyline treatment was probably responsible for the production of secondary mania in our patient because manic episodes have never been reported after the treatment of poststroke depression with tricyclic antidepressants (Fogel and Sparadeo, 1985; Lipsey et al., 1984; Reding et al., 1986; Ross and Rush, 1981).

In the case of patient B, it might be argued that the presence of a positive familial psychiatric history was more important than the brain lesion in the production of the patient's bipolar disorder, so that the brain lesion might have acted only as a nonspecific triggering event. If that were the case, in all of our secondary manic patients with positive family history of affective disorder, brain lesion location would be expected to be randomly distributed. In terms of lesion lateralization and intrahemispheric location, however, the previous literature on secondary mania and our present cases demonstrate a specific neuropathology for secondary mania. Still, genetic factors may also play a role, and their involvement in secondary mania should be investigated in future studies.

TABLE 1
Demographic Data

Patient	Age	Race	Sex	Handedness	Psychiatric Family History	Education (yrs)
A	66	White	Male	Right	+	
B	27	White	Male	Right	+	19
C	83	Black	Female	Right	?	5
D	36	White	Female	Right	+	
E	63	White	Male	Right	-	
F	61	White	Female	Right	+	
G	48	White	Female	Right	+	8
H	54	Black	Female	Right	+	8
I	28	White	Male	Left	-	15
J	74	White	Male	Ambidextrous	-	
K	24	White	Male	Right	-	15
L	20	Black	Male	Right	-	9

TABLE 2
Manic Symptoms

Symptoms	A ^a	B	C	D	E	F	G	H	I	J	K	L
Elation	+	+	+	+	+	+	+	+	+	+	+	+
Irritability	+						+					+
Hyperactivity	+	+		+	+	+	+		+	+	+	
Pressure of speech	+	+				+	+	+	+	+		+
Flight of ideas	+	+						+	+	+		
Grandiose delusions	+		+	+	+			+	+			+
Insomnia	+	+	+	+	+	+		+		+	+	+
Distractability			+					+				
Excessive involvement in social activities	+			+	+		+			+	+	+
Depression	+	+	+	+	+		+	+		+		+

^a Letters refer to patient designations.

TABLE 3
Anatomical Findings, Cognitive Status, and Treatment Responses

Patients	Etiology	Lesion Location	Lesion Side	Minimental	Treatment Response
A	Infarction	Temporooccipital	Right	28	Good
B	Infarction	Frontal	Left	29	Good
C	Infarction	Thalamocapsular	Right	17	
D	Bleeding	Thalamocapsular	Right		
E	Meningioma	Frontal	Bilateral	29	Good
F	Meningioma	Temporoparietal	Right		
G	Meningioma	Frontal	Bilateral	26	
H	Meningioma	Frontal	Right	28	Good
I	Astrocytoma	Temporal	Right		
J	Adenoma	Pituitary	Medial	27	None
K	Head trauma	Frontal	Right		Good
L	Head trauma	Frontal and cerebellum			

One of the significant methodological issues in this study is the process of patient selection. Because we identified patients by the existence of mania, it might be argued that we could have overlooked patients with hypomania or mania whose diagnosis was complicated by the existence of aphasia. This possibility cannot be excluded and our conclusions from this study are therefore tentative. Our findings will need to be evaluated along with those obtained from patients who were systematically examined because of the existence of brain injury rather than mania. It should be pointed out, however, that for several years we have been examining a consecutive series of stroke patients, excluding only those with severe comprehension deficits. After reviewing more than 700 evaluations, we have found only three cases of poststroke mania. Thus the identification of mania after brain injury based on evaluating a consecutive series of brain-injured patients is a formidable task. In addition, although some mild forms of mania might have been missed, the existence of aphasia with intact comprehension has not limited our ability to identify depression even in its mild form (Robinson et al., 1984).

Thus, although selection bias is a potential problem, we believe this case report study can shed some light on the relevance of certain brain structures in the

pathogenesis of secondary mania, because for the first time we have collected enough patients in one study to examine whether there is any unifying finding in the diverse lesions associated with mania. Only 19 cases of secondary mania after focal brain lesions have been described to date in the literature (Table 4). Diencephalic structures were involved in nine patients, four patients had temporal lobe lesions, two patients had frontal lobe damage, and the rest had more extensive brain involvement. In our study, whereas five patients had lesions primarily involving the frontal lobes, five had damage to areas that project strongly to the frontal lobes, such as the temporal cortex and thalamus. The remaining two patients had lesions involving the diencephalic and posterior fossa regions.

The question then is how these diverse lesion sites might be construed to provide a unified theory for the etiology of mania. Lesions of either the frontal lobe or limbic system have frequently been invoked in the explanation of affective changes after brain lesions. In order to establish a basis for the possible role of frontal cortex in secondary mania, a brief review of frontal lobe involvement in affective syndromes is helpful.

Welt (1888) suggested that injuries to the medial

TABLE 4
Secondary Mania after Brain Focal Lesions—Review of the Literature

	Age	Sex	Etiology	Location	Laterality	Familial History	Interval	Depression	Response to Treatment
Tumors									
Stern and Dan- cey (1942)	31	Female	Glioma	Dienceph- alon	Right	+	Concomitant	-	
Oppler (1950)	29	Male	Meningioma	Frontopa- rietal	Right	-	Concomitant	+	
Alpers (1937)	39	Male	Teratoma	Intraven- tricular (third ventricle)	Midline		1 yr	-	
Malamud (1967)	53	Male	Cranio- pharyn- gioma	Hypothal- amus	Midline		Concomitant	-	
Bourgeois and Campagne (1967)	25	Male	Bone tumor	Subtemporal	Left	-	15 yr	+	+
Jamieson and Wells (1979)	45	Male	Metastases	Parieto- temporo- occipital	Right	+	Concomitant	+	+
Guttman and Herrman (1932)	27	Female	Neoplasm	Intraven- tricular (third ventricle)	Midline		Concomitant	-	
Oyewumi and Lapierre (1981)	21	Male	Neoplasm	Brainstem	Midline	-	5 yr	+	+
Greenberg and Brown (1985)	55	Male	Metastases	Brainstem and thala- mus	Right	-	Concomitant	-	+
Binder (1983)	40	Female	Meningioma	Intraven- tricular (lateral ventricle)	Right		Concomitant	-	+
Vascular lesions									
Cohen and Niska (1980)	59	Male	Hematoma	Temporal	Right	-	3 yr	-	+
Jampala and Abrams (1983)	25	Male	Infarction	Temporo- parietal	Left	-	10 mo	-	+
Jampala and Abrams (1983)	35	Male	Infarction	Fronto- temporo- parietal	Right	+		+	+
Cummings and Mendez (1984)	63	Male	Infarction	Thalamus	Right	-	Immediate	-	
Cummings and Mendez (1984)	61	Male	Infarction	Thalamus	Right	-	Immediate	-	+
Surgical lesions									
Forrest (1982)	31	Male	Hemide- cortica- tion	Hemispheric	Right	?	23 yr	+	+
Foerster and Ga- gel (1933)			Surgical traction	Hypothal- amus	Midline	?	?	?	?
Trauma									
Rosebaum and Barry (1975)	57	Male	Surgical trauma	Temporo- polar	Right	-	2 mo	-	+
Cohen et al. (1979)	12	Male	Traumatic contu- sions	Frontopa- rietal	Right	-	Immediate	-	+

orbital surface of the frontal lobes might cause a change in character expressed by restlessness, euphoria, and overtalkativeness, as well as lowering of ethical and moral standards. Jastrowitz (1888) described several patients with frontal lobe tumors. Although some became depressed, others appeared euphoric or elated, showing pressure of speech and a tendency to pun and use obscene language. He coined the term "moria" in reference to the above disturbances, and Oppenheim (1890) referred to these symptoms as "witzelsucht." Binswanger (1917, cited in Rylander, 1939) described the case of a patient who, after a right frontal lobe trauma, showed extreme irritability, hot temper, and a tendency toward asocial behavior. After much of that lobe was surgically removed, however, he became good-humored, euphoric and even-tempered. Not only euphoria but decreased fatigability has also been reported after frontal lobe damage (Poppelreuter, 1915, 1918). Kleist (1931) considered that the frontal convexity might be associated with psychomotor and intellectual activities, so that lesions of this area would induce a lack of motor and psychic initiative. On the other hand, he considered the orbitofrontal area to be the center of emotional life, so that lesions of this area would induce euphoria, puerility, and moral insanity. These hypotheses were later supported by the findings of Poetzl (1924, cited in Rylander, 1939), who described two patients with frontal lesions, one with a frontal convexity lesion and an akinetic syndrome, and one with orbitofrontal damage and euphoria. Blumer and Benson (1975) described two syndromes associated with frontal lobe damage. One syndrome they termed "pseudodepression." It was characterized by slowness, indifference, and apathy and was produced by prefrontal convexity lesions. They labeled the other syndrome "pseudopsychopathic." It was characterized by slowness, lack of social restraints, hyperactivity, and paranoid or grandiose thinking and was frequently associated with damage to the orbitofrontal cortex.

Surgery on restricted frontal lobe lesions has also provided some insight into the role of the frontal lobe in emotion. Ackerley (1937) reported the case of a patient whose right frontoparietal cortex had been removed because of an olfactory meningioma. A few months after surgery the patient developed a marked euphoria, was overtalkative, constantly moving, hyperenergetic, and overactive. She was in a constant state of sexual excitement and showed pathological decrease in fatigability. From the above description, this patient might meet DSM-III criteria for mania. After frontal lobe surgery, symptoms like hers have not infrequently been described in the literature (Brickner, 1936). Reitman (1946) described a triad of symptoms that can develop after orbitofrontal leu-

kotomy, including extroversion, increased motor activity, and euphoria. In a landmark study, Rylander (1939) described the personality changes sustained by 32 patients after frontal lobe surgery. Euphoria developed in 20 patients (18 of whom had their orbitofrontal region removed), which was of a marked degree in 12. Hyperactivity was observed in 17 patients and hypersexuality in 10.

The orbitofrontal cortex constitutes an important area of the limbic system and the frontal lobe is known to be the only cortical structure to have connections to the subcortical limbic region known as the septo-hypothalamomesencephalic continuum (Nauta, 1971). This region is regarded as one of the main limbic efferent channels to the hypophysial complex and the visceral motor system (Nauta, 1971). By way of its projection to the septohypothalamomesencephalic continuum, the frontal cortex might not only affect the functional status of the limbic system, but also modulate the effect of the limbic system discharge upon hypothalamic areas (Nauta, 1971). The two other cortical areas that also project to the limbic system are the rostroventral region of the temporal cortex and the inferior parietal lobe (Nauta, 1971). Major corticocortical efferents connect the frontal lobe with the anterior temporal cortex, with the inferior parietal lobe, and with the cingulate and parahippocampal gyri.

All except one of the lesions that have been associated with secondary mania have demonstrated connections to the frontal lobe. Thus the frontal lobe is a unifying structure that might mediate mania after brain injury and explain the diverse sites that are associated with mania because of their connections to the frontal lobe (Figure 7).

Another important finding from this study was that 10 of 12 patients had right hemisphere injury (in seven the lesion was exclusively in the right hemisphere). In the literature on mania, 12 of 19 patients had lesions localized to the right hemisphere, although only two patients presented restricted left hemisphere damage. Sackeim et al. (1982) reported pathological laughing associated with right hemisphere damage and euphoric mood after right hemispherectomy. These findings suggest a strong association between secondary mania and lesions to the right hemisphere.

What might account for these findings? In laboratory research, we have demonstrated that, in rats, unilateral right hemisphere cortical infarction will induce hyperactivity whereas a comparable left hemisphere lesion will not (Robinson, 1979). A similar type of behavioral lateralization can be elicited by subcortical electrolytic lesions of the nucleus accumbens (Kubos et al., 1987). In addition to this behavioral asymmetry, we have also reported that the biochemi-

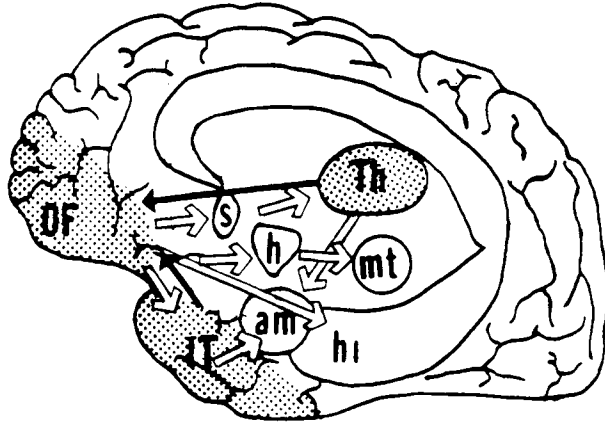


FIG. 7. Schematic diagram showing the main areas of lesion involvement for the secondary mania patients (shaded areas) and the central role the orbitofrontal cortex plays as a common locus for the interaction of these lesion sites. Black arrows, afferents to the orbitofrontal cortex; white arrows, orbitofrontal main efferents to the limbic system; Th, thalamus; OF, orbitofrontal cortex; IT, inferior temporal cortex; s, septum; h, hypothalamus; am, amygdala; hi, hippocampus; mt, mesencephalic tegmentum.

cal response of the brain varied with the site of hemispheric injury. After right middle cerebral artery ligations in rats, depletions of norepinephrine (NE) concentrations were observed within the ipsilateral and contralateral cerebral cortex and locus coeruleus (Robinson, 1979). On the other hand, after left middle cerebral artery ligation, there were no postoperative changes in brain catecholamine concentrations (Robinson and Coyle, 1980). We have also reported a lateralized response to ischemic brain lesions in humans. Stroke lesions of the left anterior brain region, either cortical or subcortical, were associated with major depression; right-sided lesions were associated with undue cheerfulness and apathy (Starkstein et al., 1987).

Based on these findings, we have suggested that the association between poststroke mood disorders and lesion location might be a consequence of damage to the ascending biogenic amine pathways, with injury to one hemisphere producing a different biochemical and hence emotional/behavioral syndrome than injury to the opposite hemisphere.

Is there any role for the catecholaminergic disturbances in the pathogenesis of secondary mania? Cummings (1986) suggested that lesions producing secondary mania are located close to ascending monoaminergic pathways thought to play a role in affective disorders. Moreover, many of the drugs causing mania are monoaminergic agonists (Krauthammer and Klerman, 1978). NE was the first neurotransmitter considered to be involved in the pathogenesis of mania. An increase of its metabolite 3-methoxy-4-hydroxyphenylethyleneglycol (MHPG) has been found in the urine of manic patients (Post, 1980), and plasma concentra-

tions of MHPG were found to be elevated during the manic phase in two manic-depressive patients (Halari, 1978). Manic swings precipitated by the use of monoamine reuptake inhibitors (antidepressant drugs) have also been reported (Bunney, 1979). Other authors have suggested that overactivity of dopaminergic (DA) pathways may play an important role in the etiology of mania. An increase of the DA metabolite homovanillic acid during the switch from depression to mania has been reported (Bunney et al., 1977). L-Dopa, a precursor of DA, may precipitate mania in patients with a past history of manic episodes (Murphy, 1972) as does bromocriptine, another DA agonist (Vlissides et al., 1978). Post et al. (1976) and Bunney et al. (1979) suggested that lithium, one of the most effective drugs in the treatment of mania, may act by reducing the sensitivity of supersensitive DA receptors in the brain. Lesions of the mesocorticolimbic DA and/or NE pathways can both induce receptor supersensitivity. Thus, if right hemisphere lesions in humans produce a different biogenic amine response than do left hemisphere lesions, perhaps an altered biogenic amine-mediated input to the frontal lobe that modulates mood leads to mania, whereas a different biochemical response after left hemisphere lesions leads to depression.

Although this explanation might be a plausible theory for further investigation of the neural mechanisms of mood, it does not explain why left frontal lesions frequently lead to depression (Robinson et al., 1983) whereas right hemisphere lesions rarely lead to mania. The infrequent occurrence of mania after brain injury suggests that another factor in addition to a right hemisphere lesion is involved. Genetic factors, evident in several of our patients, may play an important role; perhaps perinatal brain damage may predispose some patients to the development of secondary mania after a right hemisphere lesion. Identification of the causal factors in secondary mania will require further research.

Conclusion

We have presented the cases of 12 patients who developed mania after brain lesions (vascular, tumoral, or traumatic). Ages ranged from 20 to 83 years, with a similar number of affected men and women. In almost all patients, manic symptoms (hyperactivity, irritability, flight of ideas, pressure of speech, hypersexuality, grandiose delusions) appeared immediately after or concomitant with the brain lesion. The longitudinal evolution of secondary mania was variable, as some patients developed a bipolar disorder (with cycles of mania and depression) while others only

manifested mania. Five of six patients showed a good response to lithium therapy.

The most significant finding of the present study was that brain lesions in patients who later develop secondary mania were mainly located in limbic or limbic-related areas (orbitofrontal and basotemporal cortex, head of caudate, and thalamus) that have strong connections with the frontal lobes. There also was a side preponderance, with lesions located primarily in the right hemisphere. A review of the literature showed a similar association between secondary mania and right hemisphere lesions of limbic or limbic-connected areas. Further studies of this fascinating but rare condition of secondary mania may provide further insights into both the neural structures that are involved in mood disorders and the differences in the neurophysiological mechanisms of mania *vs.* depression.

References

- Ackerley S (1937) Instinctive, emotional and mental changes following prefrontal lobe extirpation. *Am J Psychiatry* 92:717-729.
- Alpers BJ (1937) Relation of the hypothalamus to disorders of personality. *Arch Neurol Psychiatry* 38:291-303.
- Ambelas A, George M (1986) Predictability of course of illness in manic patients positive for life events. *J Nerv Ment Dis* 174:693-695.
- American Psychiatric Association (1980) *Diagnostic and statistical manual of mental disorders* (3rd ed). Washington, DC: Author.
- Babinski J (1922) Reflexes de defense. *Brain* 45:149-184.
- Binder RL (1983) Neurologic silent brain tumors in psychiatric hospital admissions: Three cases and a review. *J Clin Psychiatry* 44:94-97.
- Blumer D, Benson DF (1975) Personality changes with frontal and temporal lobe lesions. In DF Benson, D Blumer (Eds), *Psychiatric aspects of neurologic diseases*. New York: Grune & Stratton.
- Bourgeois M, Campagne A (1967) Maniac-depressive et syndrome du Garcin. *Ann Med Psychol* 125(Suppl 2):451-460.
- Brickner RM (1936) *The intellectual functions of the frontal lobes*. New York: MacMillan.
- Bunney WE (1979) Psychopharmacology of the switch process in affective illness. In MA Lipton, A Di Mascio, and KF Killan (Eds), *Psychopharmacology: Generation of progress*. New York: Raven.
- Bunney WE, Pert A, Rosenblatt J, et al (1979) Mode of action of lithium. *Arch Gen Psychiatry* 36:898-901.
- Bunney WE, Wehr TA, Gillin JC, et al (1977) The switch process in manic-depressive psychosis. *Ann Intern Med* 87:319-335.
- Cohen MR, Niska RW (1980) Localized right cerebral hemisphere dysfunction and recurrent mania. *Am J Psychiatry* 137:847-848.
- Cohn CK, Wright JR III, DeVaul RA (1979) Post head trauma syndrome in an adolescent treated with lithium carbonate. *Dis Nerv Syst* 38:630-631.
- Cummings JL (1986) Organic psychoses: Delusional disorders and secondary mania. *Psychiatr Clin North Am* 9:283-311.
- Cummings JL, Mendez MF (1984) Secondary mania with focal cerebrovascular lesions. *Am J Psychiatry* 141:1084-1087.
- Denny-Brown D, Meyer JS, Horenstein S (1952) The significance of perceptual rivalry resulting from parietal lesions. *Brain* 75:434-471.
- Foerster O, Gagel O (1933) Ein Fall von Ependymeyste des II Ventrikels: Ein Beitrag ane Hirustam. *Z Gesamte Neurol Psychol* 149:312-344.
- Fogel BS, Sparadeo FR (1985) Focal cognitive deficits accentuated by depression. *J Nerv Ment Dis* 173:120-124.
- Folstein MF, Folstein SE, McHugh PR (1975) Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res* 12:189-198.
- Forrest DV (1982) Bipolar illness after right hemispherectomy. *Arch Gen Psychiatry* 39:817-819.
- Gainotti G (1969) Reactions catastrophiques et manifestations d'indifference au cours des atteintes cerebrales. *Neuropsychologia* 7:195-204.
- Goldstein K (1942) *After effects of brain injuries in war*. New York: Grune & Stratton.
- Greenberg DB, Brown GL (1985) Mania resulting from brain stem tumors. *J Nerv Ment Dis* 173:434-436.
- Guttman E, Herrmann K (1932) Ueben psychische Storungen beihiris Stanimerkrakungen und das Automatosesyndrome. *Z Gesamte Neurol Psychol* 140:439-472.
- Halaris AE (1978) Plasma 3-methoxy-4-hydroxyphenylglycol in manic psychosis. *Am J Psychiatry* 135:493-494.
- Jamieson RC, Wells CE (1979) Manic psychosis in a patient with multiple metastatic brain tumors. *J Clin Psychiatry* 40:280-282.
- Jampala VC, Abrams R (1983) Mania secondary to left and right hemisphere damage. *Am J Psychiatry* 140:1197-1199.
- Jastrowitz M (1888) Beitrage zur Localisation im Grosshirn und über deren praktische Verwerthung. *Dtsch Med Wochnschr* 14:81-83.
- Kleist K (1931) Die Storungen der Ichleistungen und ihre Lokalisation inn orbital-, innen und Zwischenhirn. *Monatsschr Psychiatr Neurol* 79:338-350.
- Krauthammer C, Klerman GL (1978) Secondary mania: Manic syndromes associated with antecedent physical illness or drugs. *Arch Gen Psychiatry* 35:1333-1339.
- Kubos KL, Moran TH, Robinson RG (1987) Differential and asymmetrical behavioral effects of electrolytic or 6-hydroxydopamine lesions in the nucleus accumbens. *Brain Res* 401:147-151.
- Lipsey JR, Robinson RG, Pearlson GD, et al (1984) Nortriptyline treatment for poststroke depression: A double-blind study. *Lancet* 1:297-300.
- Lipsey JR, Robinson RG, Pearlson GD, et al (1985) Dexamethasone suppression test and mood following stroke. *Am J Psychiatry* 142:318-323.
- Lipsey JR, Spencer WC, Rabins PV, et al (1986) Phenomenological comparison of poststroke depression and functional depression. *Am J Psychiatry* 143:527-529.
- Malamud N (1967) Psychiatric disorders with intracranial tumors of the limbic system. *Arch Neurol* 17:113-123.
- Murphy AL (1972) L-Dopa, behavioral activation and psychopathology. *Res Publ Assoc Res Nerv Ment Dis* 50:472-493.
- Nauta WJH (1971) The problem of the frontal lobe: A reinterpretation. *J Psychol Res* 8:167-187.
- Oppenheim H (1890) Zur Pathologie der Grosshirngeschwulste. *Arch Psychiatr Nervenkr* 21:560-587.
- Oppler W (1950) Manic psychosis in a case of parasagittal meningioma. *Arch Neurol Psychiatry* 64:417-430.
- Oyewumi LK, Lapiere YD (1981) Efficacy of lithium in treating mood disorders occurring after brainstem injury. *Am J Psychiatry* 138:110-112.
- Poppelreuter W (1915) Über psychische Ausfallserscheinungen nach Hirnverletzungen. *Muench Med Wochnschr* 1:489-491.
- Poppelreuter W (1918) *Die psychischen schadigungen durch kopfschiss im kriege*. Leipzig: Voss.
- Post RM (1980) Biochemical theories of mania. In RH Belmaker, HM van Praag (Eds), *Mania, MTP*. Lancaster, Pa: Lancaster House.
- Post RM, Gerner RH, Carman JS, Bunney WE (1976) Effects of low doses of a dopamine-receptor stimulator in mania. *Lancet* 1:203-204.
- Reding MJ, Orto LA, Winter SW, et al (1986) Antidepressant therapy after stroke: A double blind trial. *Arch Neurol* 43:763-765.
- Reitman F (1946) Orbital cortex syndrome following leucotomy. *Am J Psychiatry* 103:238-241.
- Robinson RG (1979) Differential behavioral and biochemical effects of right and left hemisphere cerebral infarction in the rat. *Science* 205:707-710.
- Robinson RG, Bolla-Wilson K, Kaplan E, et al (1986) Depression

- influences intellectual impairment in stroke patients. *Br J Psychiatry* 148:541-547.
- Robinson RG, Coyle JT (1980) The different effects of right versus left hemispheric infarction on catecholamines and behavior in the rat. *Brain Res* 188:63-78.
- Robinson RG, Kubos KL, Starr LB, et al (1983) Mood changes in stroke patients: Relationship to lesion location. *Compr Psychiatry* 24:555-566.
- Robinson RG, Kubos KL, Starr LB, et al (1984) Mood disorders in stroke patients: Importance of location of lesion. *Brain* 107:81-93.
- Robinson RG, Price TR (1982) Post-stroke depressive disorders: A follow up study of 103 patients. *Stroke* 13:635-641.
- Robinson RG, Szetela B (1981) Mood changes following left hemisphere brain injury. *Ann Neurol* 9:447-453.
- Rosenbaum AM, Barry MJ (1975) Positive therapeutic response to lithium in hypomania secondary to organic brain syndrome. *Am J Psychiatry* 132:1072-1073.
- Ross ED, Rush AJ (1981) Diagnosis and neuroanatomical correlates of depression in brain-damaged patients: Implications for a neurology of depression. *Arch Gen Psychiatry* 38:1344-1354.
- Rylander G (1939) *Personality changes after operations on the frontal lobes*. London: Oxford University Press.
- Sackeim HA, Greenberg MS, Weiman AL, et al (1982) Hemispheric asymmetry in the expression of positive and negative emotions: Neurologic evidence. *Arch Neurol* 39:210-218.
- Shukla S, Cook BL, Mukherjee S, Godwin C, Miller MG (1987) Mania following head trauma. *Am J Psychiatry* 144:93-96.
- Starkstein SE, Robinson RG, Price TR (1987) Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. *Brain* 110:1045-1059.
- Stern K, Dancey TE (1942) Glioma of the diencephalon in a manic patient. *Am J Psychiatry* 98:716-719.
- Vlissides DN, Gill D, Castelow J (1978) Bromocriptine-induced mania? *Br Med J* 1:510.
- Welt L (1888) Ueber Charakterveränderungen des Menschen infolge von Läsionen des Stirnhirns. *Dtsch Arch Klin Med* 42:339-390.