Subject Review

Organic Causes of Mania

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Manic syndromes have many neurologic, toxic, and metabolic causes. It is important for clinicians to be able to distinguish these organic disorders from primary idiopathic mania (bipolar disorder). The cardinal symptom of organic mania is an abnormally and persistently elevated or irritable mood. Organic mania usually develops in patients who are older than 35 years of age, whereas bipolar disorder generally has its onset between late adolescence and age 25 years. In patients with the first episode of mania, the clinician should thoroughly elicit information about current symptoms, recent infections, use of drugs, and past or family history of psychiatric disorders. In addition, a complete medical examination, computed tomography of the head, electroencephalography, and screening for drugs and toxins should be done. Treatment of organic mania includes correcting the underlying disorder when possible.

Manic syndromes, a type of affective illness, are relatively common; the lifetime risk for either sex is about 1%.[1] In addition, many toxic, metabolic, and neurologic disorders have been associated with mania. The practitioner should be able to distinguish these disorders from idiopathic manic-depressive illness or bipolar disorder. In this article, we review the clinical features and differential diagnosis of mania, with emphasis on current information about pathologic anatomic changes and neurochemistry. We also discuss evaluation and treatment strategies. Following standard nomenclature, we use the term "organic" to describe mania secondary to an identifiable medical condition. "Bipolar disorder" is used to describe the primary psychiatric syndrome for which an organic lesion is likely but has not yet been identified. For the purposes of this article, idiopathic bipolar disorder will be distinguished from "organic" mania.

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CLINICAL FEATURES

The diagnostic features of a manic episode are described in Table 1, as condensed from the *Diagnostic and Statistical Manual of Mental Disorders*—third edition, revised (DSM-III-R).[2] The cardinal symptom is an abnormally and persistently elevated or irritable mood, and at least three of the associated symptoms or signs must accompany the mood disturbance. The pronounced increase in energy, impaired judgment, grandiosity, and flight of ideas often lead patients to sexual indiscretions, buying sprees, and foolish business dealings—events that damage relationships and careers. The mood is frequently mercurial, shifting from infectious good humor to irritability or depression, and often the patient lacks insight into the condition. The sex ratios are about equal, although affective disorders as a whole are more prevalent in women than in men.

The diagnostic criteria for organic mood syndrome, manic type (organic mania) are summarized in Table 2. The criteria necessitate only that the patient have a prominent elevated or expansive mood and that, in other ways, the clinical manifestations resemble a manic episode, with no specific number of symptoms present. The

Table 1.—**Diagnostic Criteria for Manic Episode**

A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood
B. Three of the following (or four, if mood is only irritable):
   1. Inflated self-esteem or grandiosity
   2. Decreased need for sleep
   3. More talkative than usual or pressure to keep talking
   4. Flight of ideas or subjective feeling that thoughts are racing
   5. Easy distractibility
   6. Increase in activities or psychomotor agitation
   7. Excessive involvement in pleasurable activities despite risk of negative consequences
C. Substantial impairment in occupational, social, or interpersonal functioning (if this criterion is not present, describe episode as "hypomanic")
D. No delusions or hallucinations lasting as long as 2 weeks in absence of prominent mood symptoms, and not superimposed on a psychotic disorder

Modified from DSM-III-R.[2] By permission of the American Psychiatric Association.

patient must have evidence of an organic cause of the mood disturbance, and the manic symptoms must not occur exclusively during delirium. The manic signs may be the sole manifestation of the organic disorder, or they may coexist with other signs, such as cognitive impairment, hallucinations, and delusions. Some researchers[3] have questioned whether patients with a previous history of depression or mania should be excluded from this group because an organic insult may simply trigger an existing bipolar disorder. This question will remain unanswered until a biologic marker for idiopathic bipolar disorder is identified.

PATHOPHYSIOLOGY

Organic lesions associated with manic syndromes involve the areas of the brain that modulate neurovegetative functions (such as sleep, appetite, libido, and energy) and emotion.[4] These areas include the limbic system, thalamus, and hypothalamus, together with their connections to the midbrain, basal ganglia, and frontal and temporal lobes.[5] Right-sided lesions have been reported more frequently in patients with organic mania, but left-sided and diffuse lesions have also been reported.[3] In a recent study, investigators found that severity of head trauma and presence of a seizure focus (especially temporal lobe epilepsy) correlated with the development of posttraumatic mania.[6] The aforementioned anatomic structures, however, interact in an integrated manner in the perception, internal formulation, and expression of emotion.[7] Consequently, any focal or diffuse degenerative or irritative lesion in these areas could conceivably precipitate a manic episode.

Neurochemical abnormalities associated with idiopathic bipolar disorder involve the ascending monoaminergic pathways (Fig. 1)[8] and are likely to be involved in organic mania as well.[9] These pathways begin in the midbrain and interconnect the limbic system, basal ganglia, and cerebral hemispheres.[8,10] Increases in the functional output of dopamine, norepinephrine, and serotonin

Table 2.—**Diagnostic Criteria for Organic Mood Syndrome (Manic Type)**

A. Prominent and persistent elevated or expansive mood
B. Evidence from history, physical examination, or laboratory tests of one or more specific organic causes of the disturbance
C. Manic symptoms not occurring solely during delirium

Modified from DSM-III-R.[2] By permission of the American Psychiatric Association.

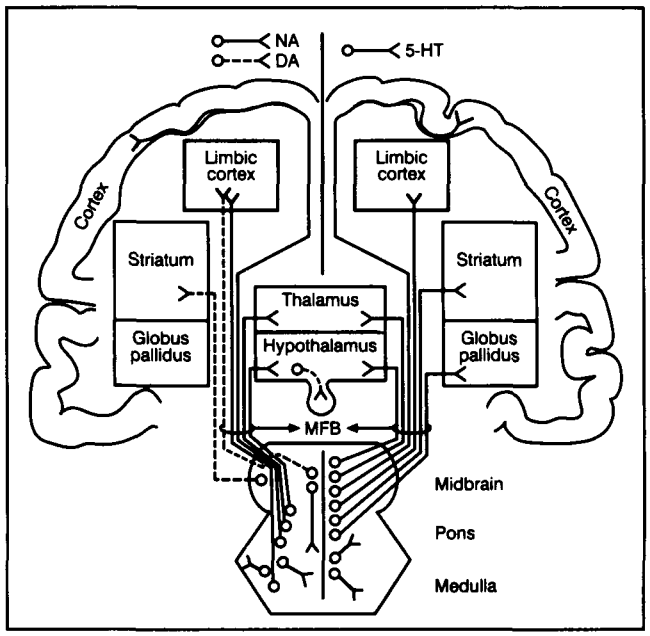

Fig. 1. Schematic diagram of major monoamine pathways in the human brain. *DA* = dopamine; *5-HT* = 5-hydroxytryptamine (serotonin); *MFB* = medial forebrain bundle; *NA* = noradrenaline (norepinephrine). (Modified from Andén and associates.[8] By permission of the Scandinavian Physiological Society.)

have all been reported in patients with mania,[9,11] and current evidence favors a hyperadrenergic or hyperdopaminergic state.[11] Mania has also been diagnosed in patients using or withdrawing from baclofen,[12-14] a structural analogue of γ-aminobutyric acid, which is a major inhibitory neurotransmitter that interacts with dopamine in the mesolimbic system. A specific neurochemical abnormality in mania remains elusive; it probably involves complex interactions among neurotransmitters or multiple abnormalities converging on a final common pathway of adrenergic or dopaminergic tracts.

ORGANIC ETIOLOGIC FACTORS

Method of Identification.—We conducted a MEDLINE search for all English-language references published from 1965 through 1987 in which organic or medical conditions were associated with mania. Further references dating back to 1892 were gathered from the articles cited in MEDLINE. The organic conditions listed as being associated with mania (Table 3) were compiled from cases that were judged to meet the DSM-III-R criteria for organic mood syndrome, manic type. In cases of multiple references to the same conditions or patient, the earliest or most clinically descriptive references are cited. Cases of organic mania in patients with past or family histories of psychiatric disorder are included, along with a specific notation of past or ongoing psychiatric disorder. In this review, however, we omitted cases of mania associated with tricyclic antidepressants,[3] monoamine oxidase inhibitors used as antidepressants,[3,15] and elctroconvulsive therapy[16] because of the clear risk of unmasking a primary bipolar illness by antidepressant therapy for unipolar depressive illness.[3]

Review of Literature.—Neurologic lesions commonly reported in association with mania include tumors[17,18] and vascular lesions[19-21] of the hypothalamus, diencephalon, and frontal cortex and temporal lobe seizures.[22,23] Mania has been the initial symptom in some cases.[17] Thalamotomy[23] and right hemispherectomy[24] have also been linked to mania, although evidence in the latter case is not as clear. Patients with Huntington's chorea,[25] Wilson's disease,[26] idiopathic calcification of the basal ganglia,[27] and postencephalitic parkinsonism[28] have also manifested mania, and in Huntington's chorea, mania has been reported as the single initial manifestation. Other neurologic syndromes that may produce mania include posttraumatic encephalopathy,[6,29] multiple sclerosis,[23,30] syphilitic,[31] viral,[32-34] and cryptococcal[35] central nervous system infections, Pick's disease,[36] Kleine-Levin syndrome,[37] and Klinefelter's syndrome.[38]

Mania has been reported in patients with hyperthyroidism[39,40] and has been induced by starvation in a hypothyroid patient.[41] In another case, a severely manic patient with bipolar disorder was refractory to lithium treatment until her primary hypothyroidism was diagnosed and corrected.[42] Hemodialysis[43] and uremia with progressive dialysis encephalopathy[44] have been reported to produce mania. Although no 20th century accounts have been reported, Osler[45] described uremia alone as a precipitant of mania,

Table 3.—**Organic Conditions Associated With Mania**

Neurologic conditions	
Focal lesions	Other
Tumors (hypothalamic, diencephalic, frontal)	Posttraumatic encephalopathy
Cerebrovascular lesions (temporal, hemispheric)	General paresis
Temporal lobe seizures	Multiple sclerosis
Thalamotomy	Viral encephalitis
Right hemispherectomy	Cryptococcal meningoencephalitis
Huntington's disease	Pick's disease
Wilson's disease	Klinefelter's syndrome
Postencephalitic parkinsonism	Kleine-Levin syndrome
Idiopathic calcification of basal ganglia	
Systemic conditions	
Hyperthyroidism	Q fever
Hypothyroidism with starvation diet	Infectious mononucleosis
Uremia	Niacin deficiency
Hemodialysis	Vitamin B_{12} deficiency
Uremia with progressive dialysis dementia	Carcinoid
Puerperal psychosis	Use of hyperbaric chamber
	Postoperative excitement
	Premenstrual psychosis
Drugs	
Levodopa	Corticosteroids
Bromocriptine	Thyroid preparations
Metoclopramide*	Baclofen
Cocaine	Bromides
Sympathomimetics	Procainamide
Isoniazid	Metrizamide
Procarbazine	Procyclidine
Cyclobenzaprine*	Phencyclidine
Yohimbine*	Alprazolam*
Cimetidine	Triazolam*

*Mania occurred in patients with histories of affective disorders.
Modified from Cummings.[4]

characterized by restlessness, talkativeness, noisiness, and sleeplessness. Q fever,[46] infectious mononucleosis,[47] carcinoid,[48] niacin deficiency,[49] vitamin B_{12} deficiency,[50] and even use of a hyperbaric chamber[51] have also been associated with manic symptoms. In 1934, "postoperative excitement"[52] was cited as a cause of mania, but no more recent cases have been reported. Puerperal[53] and premenstrual psychoses[54] have been linked to mania, but substantiation in the latter case is less clear.

Many drugs have been reported to produce mania; most of them modulate central monoaminergic metabolism. These agents include the dopamine agonists levodopa[3] and bromocriptine[55] and the dopamine antagonist metoclopramide,[56] although in the last case the patient had had recurrent unipolar episodes of depression. Over-the-counter sympathomimetic agents[57] and cocaine[58] have been linked to florid manic psychoses. The monoamine oxidase inhibitor derivatives isoniazid[59] and procarbazine[60] have been associated with mania in patients without histories of affective disorders. Cimetidine, a histamine H_2 antagonist, has produced mania.[61] Cyclobenzaprine,[62] a structural analogue of amitriptyline, and yohimbine,[63] an α_2-adrenergic antagonist, have been cited as producing mania, but these occurrences were in patients with previous manic episodes.

Many other classes of drugs have induced well-documented cases of mania, including corticosteroids,[3] thyroid preparations,[64] bromides,[65] baclofen,[12-14] and procainamide.[66] Mania has occurred spontaneously after metrizamide myelography.[67] The anticholinergic procyclidine[68] and the dissociative anesthetic phencyclidine[69] have produced mania in patients with histories of polydrug abuse but not affective illness.

In five recent reports, the triazolobenzodiazepine compounds alprazolam[70-73] and triazolam[74] were associated with precipitation of mania. All patients, however, had histories of bipolar disorder, depression, or anxiety disorders, and in the case of triazolam, the manic symptoms were coincident only with the duration of action of the drug. One patient who became manic while taking alprazolam was switched to lorazepam therapy, a standard benzodiazepine, and the manic syndrome resolved.[73] In contrast to other benzodiazepines, alprazolam has been reported to have antidepressant efficacy[75] and neurochemical similarities to antidepressants.[76] It remains to be seen whether alprazolam can cause mania in a patient with no history of a psychiatric disorder.

Finally, in a patient with bipolar disorder who had hydrochlorothiazide-induced lithium toxicity (serum level, 3.9 meq/liter), manic-appearing agitation occurred.[77] Had the physician not determined her serum lithium concentration, the dosage of the drug may have been increased to a fatal level.

Comment.—Although organic mania has been reported to be relatively rare,[78] a recent review listed 43 separate conditions or drugs associated with the onset of mania.[4] Many of these reports involved several patients. Amphetamines have been listed as mania-inducing drugs,[4] but in our review, we found references only to euphoria[3,79] and toxic psychosis.[79] The antiparasitic agent niridazole has also been described as precipitating mania;[80] however, the original references describe confusion, hallucinations, delusions, suicidal behavior, and seizures[81,82] but not mania. We included three drugs (metoclopramide,[56] cyclobenzaprine,[62] and yohimbine[63]) that produced mania in patients with histories of depression or mania because these drugs are not antidepressants and may pose a risk to patients taking them for nonpsychiatric reasons. Despite their similarities to antidepressants, alprazolam[70-73] and triazolam[74] are also included because they are used as sedatives and hypnotics. The number of reference citations of organic mania will probably continue to increase as clinicians become more aware of the disorder.

DISTINCTION BETWEEN ORGANIC AND IDIOPATHIC MANIA

Idiopathic bipolar disorder should be diagnosed only after all organic causes have been ruled out. This can be difficult when mania is the solitary initial symptom, as in the aforementioned cases of Huntington's chorea,[25] herpes simplex encephalitis,[34] and cryptococcal meningoencephalitis.[35] In most cases cited, however, other neurologic abnormalities (delirium, dementia, unilateral motor or sensory deficits, or cranial nerve palsies) were present as well. Anosognosia and unilateral neglect have been noted in organic mania,[17] corresponding to the relative preponderance of right-sided[20] or thalamic[83] lesions. Although the dramatic nature of mania may distract the clini-

cian, it should prompt a careful assessment for other medical problems or neurologic signs.

Organic mania generally develops in patients who are older than 35 years of age,[3] whereas patients with bipolar disorder usually have their first episode between late adolescence and age 25 years.[84] Irritability and assaultive behavior were more common than euphoria in a group of patients with posttraumatic mania,[6] although irritability is seen in idiopathic bipolar disorder as well. The literature is divided about whether a family history of affective disorders is more common[79,85] or less common[3,6] in organic mania in comparison with idiopathic mania.

EVALUATION AND TREATMENT

Organic mania can be clinically identical to idiopathic bipolar disorder and may respond similarly to lithium (see subsequent material). Therefore, all patients who have first-onset mania should undergo the following assessment: (1) careful elicitation of the history regarding current medical symptoms, recent infections, use of medications or drugs of abuse, and past history and family history of psychiatric disorders; (2) complete medical examination, in conjunction with a neurologic consultation if unexplained neurologic deficits are present; (3) computed tomography of the head, electroencephalography, and determination of serum thyroxine, vitamin B_{12}, and folate levels; and (4) screening for drugs and toxins. Additional studies should be ordered if abnormalities are found.

Treatment of organic mania involves correcting the underlying disorder when possible (neurosurgical removal of tumors or hematomas, correcting metabolic abnormalities, treating infections, or removing toxins or drugs). Treatment with lithium carbonate has proved to be effective in many patients with fixed or progressive lesions (central nervous system tumors,[18] strokes,[19-21] Klinefelter's syndrome,[38] and temporal lobe epilepsy[22]). Carbamazepine has been successfully used in addition to lithium therapy in a patient who underwent right hemidecortication and subsequently had mania[24] and also in mania attributable to head trauma.[86]

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