# Sleep Reduction as a Final Common Pathway in the Genesis of Mania

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*Diverse psychological, interpersonal, environmental, and pharmacological factors that appear to trigger the onset of mania could act via their capacity to cause sleep deprivation, a mechanism that has been shown in experiments with bipolar patients to induce transient or sustained switches into mania. Since mania in turn causes insomnia, the development of mania is potentially self-reinforcing and could become autonomous after being initiated by precipitating factors. The sleep reduction model is based on experimental evidence and is a parsimonious explanation for the precipitation of manic episodes by a wide variety of factors. Furthermore, this model has clear implications for the prevention and treatment of mania and provides a conceptual focus and an experimental paradigm for psychological investigations of the causes of mania.*

(Am J Psychiatry 1987; 144:201–204)

> Frequently . . . insanity originates indirectly . . . from the psychical causes . . . . A mediator . . . of especial importance and frequency in connection with mental diseases is continued sleeplessness, which often accompanies the depressing emotions, which overexcites the brain . . . . It presents, therefore, in the preliminary stages of insanity, a symptom which may be often effectually combatted by therapeutic measures.
>
> Wilhelm Griesinger
> *Mental Pathology and Therapeutics* (1985)

A variety of factors have been implicated as causes of manic episodes. These include external events, such as disruptions in routine due to job change, travel, or moving (1–7), and stressful or emotionally charged experiences connected with interpersonal relationships, such as infatuation, separation, and loss (1, 3–5, 8–18). The incidence of mania increases during the postpartum period (19), when many environmental, psychological, interpersonal, and hormonal changes occur. Administration (20, 21) and withdrawal (22–24) of various drugs and hormones have also been implicated as causes of mania. The validity of the concept of precipitating factors has been questioned by some investigators (25, 26), but the issue of validity is beyond the scope of this paper.

Many of the factors believed to play a role in inducing mania interfere with sleep. Disruptions of routine connected with travel or various types of emergencies may preclude sleep. Emotional reactions to people and events, such as excitement, anxiety, fear, grief, and despair, commonly cause insomnia. Sleep is often disrupted in the postpartum period by the demands of feeding and caring for a newborn infant. Drugs, such as amphetamines and monoamine oxidase inhibitors, and hormones, such as thyroxine, reduce sleep. Sleep is also disrupted during withdrawal from alcohol and from various drugs used to treat bipolar patients, including antidepressants, neuroleptics, lithium, minor tranquilizers, and sedatives (23, 27).

We propose that many of the diverse psychological, interpersonal, environmental, and pharmacological factors that appear to trigger the onset of mania could do so through their capacity to cause sleep deprivation. In experiments in which sleep has been manipulated as an independent variable, partial or total sleep deprivation for one night has been shown to induce transient or sustained switches into mania or hypomania in bipolar patients. For example, using methods and subjects described elsewhere (28), we deprived 12 depressed bipolar patients of sleep for one night; nine (75%) switched into mania or hypomania during that night or the following day, three switched back into depression after recovery sleep, and six remained manic for days or weeks. Others (29–36) have also reported that sleep deprivation can induce mania.

Although sleep reduction causes mania, mania also causes sleep reduction. In fact, the onset of mania is sometimes accompanied by alternate nights of total insomnia (28). The results of the sleep deprivation experiments strongly suggest that the insomnia caused by mania in turn exacerbates or sustains the mania. Thus, the causal relationship between sleep loss and mania is bidirectional and results in a vicious circle that could spiral out of control because of its self-reinforcing properties. In this way, sleep loss arising from a variety of causes could set in motion a manic process that is capable of becoming autonomous (see figure 1). Because of the clear experimental evidence that sleep deprivation induces mania, it seems reason-

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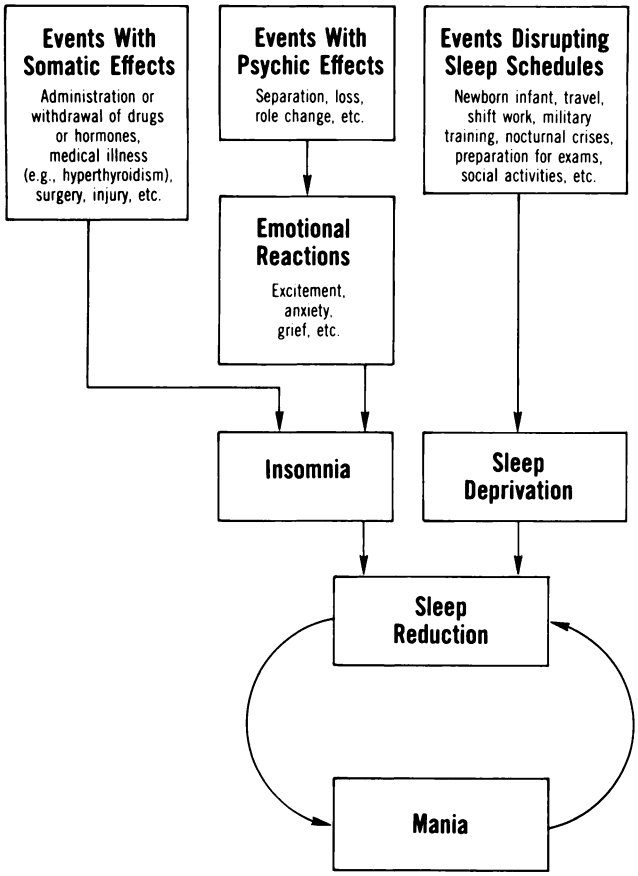
**FIGURE 1. Diagram of Hypothesis of Sleep Reduction as Final Common Pathway of Diverse Factors Thought to Precipitate Mania**




able to postulate that factors which both interfere with sleep and appear to induce mania do so through the mechanism of sleep deprivation. The postulated relationship of precipitating events, sleep loss, and mania is illustrated by the following examples.

## CASE REPORTS

*Case 1.* Dr. A, a 25-year-old bipolar patient on maintenance lithium carbonate treatment, had been mildly depressed during his last year of medical school. During the first 2 months of his internship, he was on call at the hospital every third night. When on call, he was unable to obtain more than a few hours of sleep during the night. Each day after the on-call night Dr. A became hypomanic; he became euthymic on the second day and mildly depressed on the third. Thus, he developed a rapid-cycling course of manic-depressive illness that was driven by external factors regulating his sleep schedule. Because of his hypomanic behavior, he was encouraged by supervisors to seek a consultation regarding the management of his illness. He responded to an increase in the dose of lithium carbonate, which attenuated the severity of his hypomania.

*Case 2.* For the past 2 years Mr. B, a 28-year-old bipolar patient, drove 800 miles to spend the Christmas holidays with his family. Impatient to return home and unable to find a motel room, he drove through the night without stopping until he reached his parents' house. By the time of his arrival, Mr. B, who had been euthymic, became hypomanic. The first year the mania escalated and required his hospitalization; the following year it was possible to attenuate the severity of his mania through early treatment with adjunctive neuroleptic medications.

*Case 3.* Mr. C, a 20-year-old college student, became romantically involved with a girl from a college in a neighboring city. She invited him to visit her in her home town during spring vacation. After pleasurable anticipation of the visit, he arrived and discovered that she had become interested in someone else and did not wish to see him. Lonely and dejected, he passed a sleepless night in an unfamiliar hotel. The following day he began to exhibit signs and symptoms of his first manic episode. He failed to return to college and began to engage in a variety of bizarre activities. Ultimately, he was arrested for operating an illegal radio station, was hospitalized, and responded to lithium carbonate.

*Case 4.* Ms. D, a 50-year-old woman who had been depressed for several months, took an overnight transatlantic flight from the United States to Europe to visit her family. Like many passengers, she slept very little (if at all) during the flight and by the time of her arrival the following morning had switched into her first hypomanic episode. The hypomania continued unabated for several weeks and did not require treatment. Ultimately, she relapsed into depression. Maintenance treatment with lithium carbonate failed to prevent depressive relapses. Having inferred that her switch into hypomania resulted from sleep deprivation, she periodically used it successfully to treat her recurrent depression.

## DISCUSSION

In each case, the onset of mania immediately followed external events that induced sleep deprivation directly through interference with sleep schedules or indirectly through emotional responses that disturbed sleep. Although the switches into mania could be attributed to factors other than sleep deprivation, such alternative explanations may be unnecessary in light of the known capacity of sleep deprivation to induce mania. This model does not exclude interpersonal and psychological factors as causes of mania; rather, it provides a plausible mechanism and a final common pathway through which such factors could operate. According to the model, interpersonal and psychological factors are causative when they disrupt sleep (e.g., insomnia caused by grief giving rise to bereavement manias [16]); they may not be causative when they occur in conjunction with sleep loss due to other factors (e.g., sleep loss secondary to changes in routine or travel). Depending on one's training and point of view, one might be inclined to attribute the onset of mania in the case of the all-night driver (case 2) to psychological factors related to his reunion with his family or to an anniversary reaction connected with the holiday season. Sleep deprivation incurred in traveling is a more prosaic explanation, but it is a sufficient

one. The hypothesis of a sleep deprivation mechanism for travel-related mania fits very well the observations of Jauhar and Weller (7), who found an association of west to east (i.e., overnight) flights with hospitalizations for mania among patients from Heathrow airport.

It could be argued that insomnia associated with depression should precipitate mania in bipolar patients. In fact, as many as half of all manic episodes are preceded by depressive episodes (37). In some bipolar patients with decreased sleep during depression, the degree of sleep reduction may be insufficient to induce a switch out of depression into mania; our experiments with partial sleep deprivation suggest that sleep must be reduced to less than 4 hours to elicit a change in clinical state (unpublished data of Sack et al.). On the other hand, many bipolar patients are hypersomnic when depressed (38) and thus are not subject to the effects of sleep reduction.

In experiments with patients, recovery sleep sometimes reverses switches into mania that were induced by sleep deprivation (28). In a similar way, manias induced by sleep loss in the clinical setting sometimes might be short-lived. In these instances, we presume that the level of activation induced by sleep loss on one night produces too little insomnia on the following night to become self-reinforcing.

How does sleep deprivation cause mania? In proposing sleep reduction as a final common pathway for induction of mania in diverse situations, we are not specifying the mechanism through which sleep deprivation exerts its effects. We have previously hypothesized (39) that depression is a sleep-dependent process and that depression might occur when a sleep-sensitive, circadian phase interval normally associated with the first hours of wakefulness is abnormally advanced into the last hours of sleep and interacts with sleep to produce depression. The sleep reduction model is compatible with the phase advance hypothesis in that sleep reduction would be predicted to promote switches out of depression into mania by interfering with the hypothesized interaction of sleep with a sleep-sensitive circadian phase interval. However, the sleep reduction model leaves open other possible mechanisms.

To date, the most dramatic biochemical correlates of sleep deprivation have been found in neuroendocrine systems. Sleep deprivation stimulates thyrotropin (TSH) (40) and cortisol (41) secretion and inhibits prolactin (42) and growth hormone (43) secretion. Sleep deprivation has little effect on plasma metabolites of neurotransmitters such as norepinephrine and dopamine (unpublished data of Sack et al.). In light of evidence that thyroxine or hyperthyroidism can cause mania (44), stimulation of the thyroid axis deserves further investigation as a possible mechanism through which sleep reduction induces switches into mania. The fact that sleep reduction stimulates the thyroid axis and stimulation of the thyroid axis induces sleep reduction indicates that this axis could participate in the vicious circle of sleep reduction and mania. The importance of disruption of REM sleep in patients' responses to sleep deprivation also needs to be considered, since selective REM sleep deprivation has been shown to have antidepressant effects (45).

## TREATMENT IMPLICATIONS

The hypothesis that disruption of sleep is the mechanism through which many factors cause mania in the natural course of the illness was suggested, and is supported, by experiments that show that sleep deprivation induces mania. It provides an inclusive explanation of how diverse psychological, social, environmental, and biological factors may precipitate manic episodes. Moreover, the capacity of reductions in sleep to cause mania and of mania, conversely, to reduce sleep constitutes a self-reinforcing mechanism that, in turn, could explain the tendency of mania to escalate out of control and become autonomous.

The knowledge that sleep reduction can cause mania may be used by patients, their families, and the persons who care for them to help prevent and to alleviate mania. A single night of sleep loss in a bipolar patient could be useful as an early warning of possible impending mania. The risk of mania might be reduced by eliminating or mitigating factors that interfere with sleep. Patients at risk for mania could be counseled to avoid situations likely to disrupt sleep. Psychological management of emotional crises that can disturb sleep could be provided. Drugs known to interfere with sleep could be avoided. Care could be taken to avoid insomnia resulting from rapid withdrawal of drugs, such as antidepressants. Pharmacological treatment of insomnia could be expected to prevent or attenuate manic episodes, as has been reported to occur with the sedative drug clonazepam (46).

Knowledge that sleep reduction can precipitate mania would also provide a conceptual focus and an experimental paradigm (sleep deprivation) for psychobiological investigations of the causes of mania.

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touch with the everyday realities of the students' lives: "Medical students aren't like they used to be; they don't seem as dedicated or tough; they bellyache a lot."

Let me close with excerpts from a letter to the editor of our local newspaper, written by the mother of a medical student at our university who committed suicide (6).

> I am one of those who had an empty chair at the Christmas table because their son or daughter, brother or sister died as a victim of suicide.
>
> She was 25. The entire medical faculty was shaken to the core. At a memorial service, many came to me and said, "But why?" and "Had I known. . . ."
>
> We rush around day by day, our lifestyles hurried and exhilarating—even her classmates didn't notice her missing for two days. We have no time to listen to the needs of others, to the lonely ones.
>
> May her tragic death always remind us that the despair hiding in a heart can become too great to show and too complicated to ask for help.

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6. A tragedy that can strike at any family. Vancouver Sun, Jan 25, 1984

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## Corrections

In the article "Mutism: Review, Differential Diagnosis, and Report of 22 Cases" (November 1986 issue, pp. 1409–1414), by Lori L. Altshuler et al., there was a printing error. The second sentence of the first complete paragraph in the right column of p. 1409 should read ". . . neuroleptic agents (16–19) . . ." rather than "neurologic agents."

In the article "Frequency and Presentation of Depressive Symptoms in Patients With Primary Degenerative Dementia" (January 1987 issue, pp. 41–45), by Lawrence W. Lazarus et al., several words were omitted from a sentence in the final paragraph (p. 45). The sentence should read: "Greater importance might be placed on intrapsychic signs and symptoms and less emphasis placed on endogenous or vegetative symptoms, since the former may be more reliable discriminators of depression in these patients."

In the article "Levels of Emotional Awareness: A Cognitive-Developmental Theory and Its Application to Psychopathology" (February 1987 issue, pp. 133–143), by Richard D. Lane and Gary E. Schwartz, there were several errors. On p. 135, in the third line of the bottom paragraph of the left column, the word "possess" should have been "process." Toward the top of p. 136, left column, the line should read ". . . has been described by Werner and others (26–28). . . ." On p. 138, in the middle of the first paragraph in the right column, the phrase should read ". . . clearly differentiated from one another . . ." rather than "closely differentiated." In the middle of the bottom paragraph on p. 141, the term "double depression" should replace "double expression," and in the final line of that paragraph, "course of the affective disorder" rather than "cause of the affective disorder" is correct.

In the article "Sleep Reduction as a Final Common Pathway in the Genesis of Mania," by Thomas A. Wehr et al. (February 1987 issue, pp. 201–204), an incorrect date was cited for the lead quote by Wilhelm Griesinger. The correct date should be 1855.

The staff regrets these errors.

*Reprints of Letters to the Editor are not available.*