

Cracking the Cycles of Depression and Mania

Some persons with affective disorders appear to be 'out of phase' with the normal 24-hour day. Changing their sleep-wake cycles can trigger dramatic improvements.

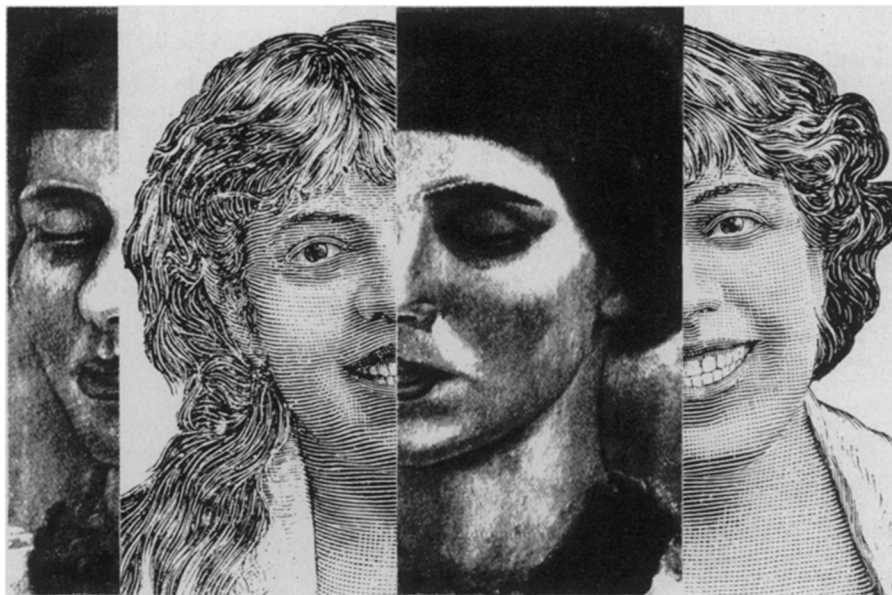
BY JOEL GREENBERG

Despite significant advances in understanding and treating depression and manic-depression, these "affective" disorders still carry with them some of the more curious mysteries in behavioral science. The puzzle involves an apparent cyclic or "up and down" characteristic in certain patients. Many depressives, for example, suffer most in the morning (sleep disturbance is thought to be central to depression); others show some bizarre hormonal activity that appears to be out of synch with normal metabolism; and still others — particularly manic-depressives — seem to function on a daily and annual calendar of their own.

Perhaps shedding some light on affective illness are newly reported research results from the National Institute of Mental Health's Clinical Psychobiology Branch in Bethesda, Md. The findings indicate that slightly abnormal biological rhythms — both long- and short-term — may be key factors in the development of depression and manic-depression. And the results may also hold clues about why certain drugs work or fail to work with different individuals.

In what NIMH investigators term a revolutionary process, the blood metabolites of certain brain chemicals of "normal" persons were measured at various points during the year. What made this type of experiment possible for the first time was the development — by researchers Al Lewy and Sandy Markey — of a "negative ionization" assay procedure that they say provides more than 1,000 times more sensitivity in measuring the hormone melatonin than did previous methods.

They found that melatonin — an indicator of brain norepinephrine activity — seems to run through a cycle in which it peaks in January and July and hits valleys in May and October, while platelet serotonin appears to be on a reverse cycle, with its activity reaching peaks in May and October. Both norepinephrine and serotonin have been implicated in depression; and studies have shown that May and October frequently are "high suicide months," says NIMH Clinical Psychobiology Chief Frederick K. Goodwin, who conducted much of the research with Thomas A. Wehr, chief of the branch's clinical research unit.



"We've known for a long time that there are annual rhythms and seasonal variations in a lot of illness," says Goodwin. "Affective illness is [frequently] a recurrent phenomenon," and the research results suggest "the possibility of some long-term cyclic process." Goodwin is particularly impressed by the melatonin data because scientists know the hormone is produced in the pineal gland and is "specifically under control" of a norepinephrine receptor. This means that, unlike the measurements of some other metabolites, the level of melatonin found in the blood is a direct reflection of brain activity, he says.

In the other portion of the work, Goodwin and his colleagues observed that the *daily* biological rhythms of some persons with affective disorders are slightly out of phase with the standard 24-hour day. In bipolar, or manic-depressive, patients the researchers had noticed that several days before the periodic manic phase set in, the patients would go to bed and wake up somewhat earlier than usual. If such a sleep-wake change was associated with the shift away from depression, the investigators reasoned, perhaps intentionally manipulating the pattern would help depressives — which it did, dramatically, but only for a short period. Still, Goodwin says, "there was *something* going on here."

In the next step, a 52-year-old female manic-depressive patient on a 43-day cycle (from manic to normal to depressed to normal to manic) was found to have a daily biological clock slightly faster than 24 hours. The researchers then isolated and "synchronized" her to a 22-hour day, because that might be closer to her own natural, biological clock, which had

been disturbed by the day-night cycle of the outside world.

This resulted in the shortest depression period the woman had experienced in years. The psychiatrists then deliberately advanced the sleep period by six hours (beginning at 5 p.m., ending at midnight), reasoning that "maybe people [with affective disturbances] were awake when they were supposed to be asleep," Goodwin explains. The results were even more dramatic — the new cycle had an antidepressant effect for about two weeks before the woman relapsed. Sleep was then moved up six more hours, with the same two-week improvement. A third six-hour advance, however (putting her a total of 18 hours out of phase), had no effect.

"Two weeks is a very curious time," observes Goodwin. It also takes about two weeks for tricyclic and lithium drug treatments to take effect after their first dosage, he notes. Moreover, the woman was then placed on tricyclics that produced the *same* two-week improvement and relapse pattern as was found with sleep advance. "The implication is that tricyclics accelerate the bipolar process in manic-depressives," Goodwin suggests.

The results of both the long- and short-term studies may ultimately help explain why drugs such as tricyclics and lithium appear to work sometimes and not others. "Maybe there are differences in the effects of drugs in terms of the phase of the illness or time of year," he says.

"We have to be very careful, because this sounds at first glance like astrology," Goodwin says. "But the recognition of cyclicity has been long overdue in the whole variety of human behaviors." □