

# Internal Night

**I**F WE KNEW the physiological cue for the annual change that triggers winter depression, the syndrome of seasonal affective disorder (SAD) would be validated, and there would be a rational basis for designing therapeutic interventions. The depressogenic effect of long winter nights coupled with the antidepressant effect of morning light therapy make for a plausible story line. In this issue of the ARCHIVES, Wehr et al<sup>1</sup> at the National Institute of Mental

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Health (NIMH) report that the melatonin secretion profile, an internal correlate of night length controlled by the hypothalamic biological clock, is linked to emergence and remission of the depression. By aggregating the largest sample size ever for such a study (55 patients and matched controls), they are able to derive virtually noise-free melatonin curves with a set of discrete anchor points: secretion onset and offset as well as final daytime clearance of the hormone from blood circulation.

### ABSOLUTE NIGHT LENGTH VS SEASONAL CHANGE

Patients were distinguished from healthy control subjects by a significant shortening of the secretion episode in the summer of about 37 minutes. The corresponding effect size, *d*, is medium (*d*=0.46). The change in duration was mainly due to an advance in offset of about 26 minutes (*d*=0.29, a small effect size) with a negligible delay in onset of about 11 minutes (*d*=0.13). Whereas these group changes might indicate a pathogenic factor for SAD, the effect sizes show that the response was heterog-

eneous, with many patients deviating from the average trends. Even so, the controls showed no sign of seasonal change in melatonin duration.

Beyond the internal clock signal for melatonin offset, secretion is directly suppressed by retinal illumination.<sup>2</sup> The summer sunrise might trigger earlier suppression than in the winter if we can assume that patients are adequately exposed to the signal in their bedrooms, even while asleep.<sup>3</sup> As a result, the secretory episode would be truncated, and the circadian clock phase-advanced. Indeed, the group difference in the NIMH study occurred solely in the summer, when the patients' melatonin duration was shorter by about 30 minutes relative to the controls, a significant if small effect (*d*=0.36). During the winter, the groups had a nearly identical duration of about 9 hours. Thus, the transition from shorter summer duration to longer winter duration, rather than winter melatonin duration per se, may trigger depression.

Still, it is puzzling that the patients differed from the controls only in the summer, when the depression was in remission. It may be pertinent that 22% of the patients had histories of bipolar II disorder. Might this subgroup have shown early-morning awakening typical of hypomania (also of hyperthymia),<sup>4</sup> thus exposing themselves to earlier light that in turn truncated melatonin secretion? Might the unipolar subgroup, by contrast, have been seasonally stable like the controls? If that were true, the change in melatonin duration would not be a pathogenic factor for SAD but rather a by-product of shorter summer sleep in patients with bipolar disorder, consistent with the small effect size in melatonin offset for the group as a whole.

Melatonin onset has long served as an anchor point for measuring circadian phase shifts to timed artificial light.<sup>5</sup> The onset is delayed after late-evening light exposure and advances after early-morning exposure. Morning artificial light therapy has been interpreted as a surrogate for the antidepressant summer sunrise; the hypothesis has been that both signals act by eliciting phase advances reflected in melatonin onset.<sup>6</sup> By contrast, Wehr and associates now present secretion profiles in which patients' melatonin offset, but not onset, changes seasonally for a net change in duration.

### LIGHT THERAPY VS NATURAL LIGHT

This new interpretation of the seasonal trigger for the switching of mood state needs to be reconciled with the results of light treatment studies and new data showing that melatonin onset can also vary seasonally in SAD. We do not know the NIMH patients' melatonin response to light therapy. It remains to be established whether natural-seasonal and artificial-therapeutic lighting conditions are functional equivalents. Clinical trials<sup>7-9</sup> demonstrate clear phase advances of melatonin onset with morning light therapy. Furthermore, the degree of clinical improvement is proportional to the size of the phase advance. When complete overnight melatonin profiles were obtained after a course of morning light therapy, onset and offset occurred equally earlier with no net change in duration.<sup>9</sup> Such results point to circadian phase shifts more than melatonin suppression or duration of secretion as the therapeutic mechanism of action.

As for the absence of seasonal change of melatonin onset, an ongoing study at Columbia University (New York, NY) provides a counterpoint.<sup>10</sup> Thirty patients have produced saliva samples throughout the evening under dim light conditions, once while depressed in late fall or early winter and again in the spring while euthymic. Melatonin levels were determined by radioimmunoassay, with onset measured at 3 pg/mL. Mean  $\pm$  SD springtime onset occurred  $38 \pm 45$  minutes earlier than fall or winter onset (mean  $\pm$  SD [minutes:seconds],  $20:31 \pm 1:20$  vs  $21:08 \pm 1:35$ ;  $P < .001$ ; 2-tailed *t* test). By contrast, from winter to summer the NIMH patients showed a nonsignificant delay in onset (mean  $\pm$  SD,  $11 \pm 84$  minutes).

### LARKS VS OWLS

A key to reconciling these results may lie in the wide distribution of melatonin onset when patients are depressed, ranging from 6 PM to 12:30 AM in the New York sample. The analysis might be clouded because the authors did not covary baseline phase with phase shift size. Our recent treatment study<sup>9</sup> calculated the circadian time of morning light administration relative to each patient's baseline melatonin onset. Those who received light therapy 7.5 to 9.5 hours after melatonin onset showed twice the remission rate (80% vs 38%) of patients who underwent treatment more than 9.5 hours after onset. The early subgroup also showed significantly larger phase advances.

Similarly, in our winter-spring study,<sup>10</sup> the size of spring phase advances varied with the winter melatonin onset phase ( $r = 0.56$ ;  $n = 30$ ;  $P = .001$ ). The later the winter melatonin onset, the earlier spring sunrise encroaches on the internal night, resulting in a larger phase advance. There were equal numbers of

"larks" and "owls" among our patients, who were chronotyped using a scale of morningness and eveningness.<sup>11,12</sup> This score varied with melatonin onset ( $r = 0.69$ ;  $n = 58$ ;  $P < .001$ ). Owls (with an onset later than 10 PM) showed far greater springtime phase advances than larks (with an onset before 8 PM; mean  $\pm$  SD,  $1.21 \pm 0.89$  hours vs  $0.15 \pm 0.56$  hours;  $P = .02$ ). The effect size for owls was very large ( $d = 1.53$ ), whereas for larks it was negligible ( $d = 0.22$ ). Nevertheless, both chronotypes experience remissions of depression in the spring. From that vantage point, the key to seasonal remission may indeed lie in events occurring at the end of the internal night (melatonin suppression, phase shifting of offset, or both) that are not detectable in melatonin onset at the start of the night.

In winter, both larks and owls benefit from morning light therapy. However, for the larks to experience a phase advance of melatonin onset with an optimum antidepressant effect, they need to receive light far earlier than the owls.<sup>12,13</sup> By contrast, the hour of spring sunrise is the same for everyone, and larks would be less affected because their spontaneous melatonin offset occurs before the dawn signal has a chance to suppress secretion.

If Wehr and associates were to chronotype their patients, separating larks from owls, or use baseline phase as a covariate, they might see a seasonal change in melatonin onset, especially if SAD owls were sufficiently represented in their study. Similarly, the change in melatonin offset may vary with chronotype. If we are lucky, healthy control owls will remain invariant.

Michael Terman, PhD  
New York State Psychiatric Institute  
1051 Riverside Dr, Unit 50  
New York, NY 10032  
(e-mail: mt12@columbia.edu)

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