Peak of circadian melatonin rhythm occurs later within the sleep of older subjects

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Duffy, Jeanne F., Jamie M. Zeitzer, David W. Rimmer, Elizabeth B. Klerman, Derk-Jan Dijk, and Charles A. Czeisler. Peak of circadian melatonin rhythm occurs later within the sleep of older subjects. Am J Physiol Endocrinol Metab 282: E297–E303, 2002; 10.1152/ajpendo.00268.2001.—We investigated the relationship between sleep timing and the timing of the circadian rhythm of plasma melatonin secretion in a group of healthy young and older subjects without sleep complaints. The timing of sleep and the phase of the circadian melatonin rhythm were earlier in the older subjects. The relationship between the plasma melatonin rhythm and the timing of sleep was such that the older subjects were sleeping and waking earlier relative to their nightly melatonin secretory episode. Consequently, the older subjects were waking at a time when they had higher relative melatonin levels, in contrast with younger subjects, whose melatonin levels were relatively lower by wake time. Our findings indicate that aging is associated not only with an advance of sleep timing and the timing of circadian rhythms but also with a change in the internal phase relationship between the sleep-wake cycle and the output of the circadian pacemaker. In healthy older subjects, the relative timing of the melatonin rhythm with respect to sleep may not play a causal role in sleep disruption.

aging; biological rhythms; chronobiology; constant routine

ACHIEVING A GOOD NIGHT’S SLEEP can become more difficult with age. In survey studies, up to one-third of older individuals report difficulty maintaining sleep on a recurring basis, and more than one-half report occasional problems with their sleep (12, 26–28). The depth and continuity of sleep change with age, with a lower percentage of sleep spent in the deepest stages of non-REM sleep (1, 28, 35), more frequent arousals and awakenings during the sleep episode (1, 8, 28, 35), and often an inability to sustain sleep for the desired duration (28, 35). One of the most prominent changes in sleep with aging is the shift in the timing of the nightly sleep episode to an earlier hour. In addition to sleep timing, the rhythms of core body temperature (47) and plasma cortisol (37, 38, 41) have been reported to occur at an earlier hour in older people. Age-related changes in the amplitude of circadian rhythms of hormone secretion (17, 25, 41, 42, 45) and core body temperature (44) have also been reported.

There may be a causal link between the age-related changes in hormone secretion and core body temperature with changes in sleep. Alternatively, a single mechanism may underlie these changes. Given that the circadian timing system regulates the timing and internal organization of sleep (5, 6, 36, 52) and hormone secretion (3, 40, 43), age-related changes in this system may underlie both processes (34).

One of the most reliable markers of the output of the circadian pacemaker is the circadian rhythm of melatonin secretion (2). The central circadian pacemaker, the suprachiasmatic nuclei of the hypothalamus (20, 31, 33, 39), imposes rhythmicity onto the pineal gland (19, 32) through a well characterized neural pathway (2, 18, 46), thus driving the rhythm of melatonin secretion. Melatonin is also a putative sleep-related hormone. Studies of exogenous melatonin administration have shown that melatonin can facilitate sleep onset at certain times of day (9, 51). It has been hypothesized that melatonin secretion decreases with age and that such a decrease is causally related to the increased sleep disruption in older people (14). Although some older people may secrete less melatonin, we reported recently (49) that nocturnal plasma melatonin concentrations in most very healthy older subjects are not significantly reduced compared with those of healthy young men. Furthermore, we did not find a significant difference in the duration of the nightly melatonin secretion time between young and older subjects. Thus neither decreased plasma melatonin levels nor a shorter duration of melatonin secretion can fully explain the age-related changes in sleep timing and consolidation that we and others (16) have observed in such healthy older individuals.

Using the nadir of the rhythm of core body temperature as a marker of the status of the circadian timing system, we reported recently (11) that, in addition to the advance of wake time and circadian phase of the body temperature rhythm, the phase relationship be-
between the temperature rhythm and usual wake time is significantly shorter in older people. This suggests that older people are not only waking up at an earlier clock hour but are also waking at a different internal circadian time. In another study (7, 8, 11), we found that there are higher levels of sleep disruption in older people, both subjectively assessed and objectively recorded, in particular when the end of the scheduled sleep episode occurs shortly after the nadir of the core body temperature rhythm. These recent findings suggest that an alteration in the relative timing between the circadian system and the nightly sleep episode may occur with aging and raise the possibility that this altered timing may contribute to the increased sleep disruption with age.

To explore our previous findings further, we wanted to examine the internal phase relationship between sleep-wake timing and the timing of another marker of circadian phase. The timing of the plasma melatonin rhythm is considered to be a more accurate marker of the status of the circadian timing system than that of core body temperature, because it is less affected by changes in posture and sleep-wake state. Therefore, in the present analysis, we investigated the relationship between the timing of the rhythm of plasma melatonin secretion and the timing of the habitual sleep-wake episode in healthy young and older adults.

METHODS

Subjects. Included in the present analysis were data from 15 older men and women (mean ± SD: 67.8 ± 3.1 yr) and 33 young men (23.4 ± 3.3 yr) who had participated in studies in our laboratory between 1980 and 1996. These subjects are a subset of those included in our two recent reports (11, 49) and included all of those who met the screening criteria and whose studies included the conditions outlined below. They were recruited from newspaper and radio advertisements, flyers, and notices posted in the Boston area.

Each was in good health, as determined through medical history, clinical biochemical screening tests on blood and urine, an electrocardiogram, a physical examination, and chest radiograph (older subjects only). Subjects were also in good psychological health, which was determined using the Minnesota Multiphasic Personality Inventory, the Beck Depression Index or Geriatric Depression Scale, and, for some subjects, an interview with a clinical psychologist. Subjects were drug free upon admission to the laboratory, as verified by a comprehensive toxicological analysis of their urine. All subjects were without significant sleep complaint by history and questionnaire, and older subjects underwent an overnight polysomnographic sleep screening examination before the study to rule out those individuals with clinically significant sleep apnea and/or periodic limb movements.

To ensure that the circadian timing system of each subject was adapted to his or her daily routine, only subjects who denied a history of night shift work within the past 3 yr and transmeridian travel (>1 time zone) within the past 3 mo were studied. Furthermore, each subject maintained a regular, self-selected sleep schedule (8 h/night) for ≥3 wk before study, recorded their bed and wake times each day during this time in a sleep diary, and had this regularity verified for ≥1 wk before study with an ambulatory wrist activity monitor.

The protocols used in the studies were approved by the Human Research Committee of the Brigham and Women’s Hospital, and each subject gave written, informed consent before study.

Protocol. Each study began with three baseline days and nights, with 8-h sleep episodes scheduled at the subject’s habitual times as determined from the sleep logs from the week immediately before study. The baseline segment was followed by a constant routine (CR) to assess the endogenous phase and amplitude of the subject’s circadian rhythms of plasma melatonin and core body temperature. In this CR, the subjects were kept awake in a semirecumbent posture in dim light (<20 lux) and fed equicaloric snacks each hour. The CR was designed to eliminate or distribute evenly across the 24-h day those factors (light, postural changes, activity, sleep-wake state changes, food intake) known to mask the endogenous circadian component of the plasma melatonin and core body temperature rhythms (10, 29). The CRs varied in length from 31.6 to 52.8 h, depending on the requirements of the remainder of their study protocols; only the data collected during the CRs considered here.

Plasma samples were collected hourly throughout the CR via an indwelling intravenous catheter that was inserted into a forearm vein on the second or third baseline day. The catheter was connected to a 12-ft tubing and manifold apparatus so that samples could be collected from outside the room to minimize disturbance of the subject. Samples were transferred to tubes containing EDTA and kept on ice for ≤1 h before being centrifuged. The plasma was then pipetted and frozen for later radioimmunoassay (assay sensitivity 22 pmol/l, intra-assay coefficient of variation 8%, interassay coefficient of variation 13%; DiagnosTech, Osceola, WI).

Only those subjects from whom we successfully collected hourly plasma samples throughout the CR and whose CR continued for ≥10 h after the minimum of their core body temperature rhythm were included in the present analysis. This duration criterion was imposed to ensure that the entire nightly episode of melatonin secretion, including the return of plasma levels to baseline, was included for all subjects. The present analysis includes data from 15 older men and women (of a larger group of 44 older men and women) and 33 young men (of a larger group of 101 young men) who met all of the criteria outlined above.

Data analysis. Habitual wake and bed times were determined for each subject by averaging the wake and bed times from the sleep diary for the seven nights immediately before the study began.

The phase of the melatonin secretion pattern was defined as the midpoint between the upward and downward crossing of the 24-h mean value. This 24-h mean value was calculated beginning 5 h after the start of the CR (when the influence of waking, changing posture, and beginning of the CR had dissipated); thus all samples collected between hours 5 and 29 of the CR were used in determining this average. The exact upward and downward mean crossing times were determined by linear interpolation between adjacent points. The time at which the midpoint occurred was then calculated as the time halfway between the upward and downward crossing times, and this time was defined as the phase of the melatonin secretion pattern, MELmid. Duration of melatonin secretion was defined as the interval between the upward and downward mean crossing.

To further explore potential age-related changes in the sleep-melatonin phase relationship, we analyzed the plasma melatonin rhythm in four additional ways to examine the timing of plasma melatonin onset and offset. We defined plasma melatonin onset in two ways: 1) the dim-light mela-
MELATONIN, AGING, AND SLEEP

Table 1. Timing of sleep-wake cycle and circadian melatonin rhythm in young and older subjects

<table>
<thead>
<tr>
<th></th>
<th>Older Subjects</th>
<th>Young Subjects</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wake time</td>
<td>06:54 ± 0:53</td>
<td>08:17 ± 0:46</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Bedtime</td>
<td>23:08 ± 0:47</td>
<td>24:16 ± 0:53</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Midpoint of melatonin rhythm (MELmid)</td>
<td>03:14 ± 1:01</td>
<td>04:04 ± 1:15</td>
<td>P = 0.928</td>
</tr>
<tr>
<td>Dim-light melatonin onset (DLMO)</td>
<td>21:55 ± 1:09</td>
<td>23:08 ± 1:28</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Melatonin onset (MEL25%up)</td>
<td>22:30 ± 1:12</td>
<td>23:29 ± 1:29</td>
<td>P = 0.041</td>
</tr>
<tr>
<td>Melatonin offset (MEL25%down)</td>
<td>07:56 ± 1:08</td>
<td>08:32 ± 1:18</td>
<td>P = 0.184</td>
</tr>
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Values are clock hour means ± SD.

Melatonin onset (DLMO), defined as the time at which plasma levels reached 10 pg/ml (23), and 2) the time at which melatonin levels rose to 25% of the nightly peak (MEL25%up). This alternative method for determining melatonin onset time was used to account for the wide variation in plasma melatonin levels between individuals and to be able to determine onset in “low secreters” (22), who are more likely to be older subjects (49). The nightly melatonin peak was determined by fitting a three-harmonic waveform to the data from the CR (after eliminating the initial 5 h, as described), determining the magnitude of the fitted waveform (maximum − minimum of fitted waveform), calculating 25% of that magnitude, and then interpolating between adjacent plasma samples, if necessary, to determine the minute at which the plasma levels rose to MEL25%up. Plasma melatonin onset was defined as the time at which melatonin levels fell to 25% of their nightly peak (MEL25%down). An alternative method of calculating the duration of melatonin secretion used MEL25%up to MEL25%down.

The phase angle, or time interval, between habitual wake time and circadian phase was calculated by subtracting the time of MELmid, DLMO, MEL25%up, or MEL25%down from habitual wake time for each subject.

Because of the greater than 10-fold variability in nocturnal melatonin concentrations among individuals (49), average waveforms of the melatonin data from the entire CR were compiled by first normalizing each individual’s data with respect to their mean and standard deviation from the samples collected during the CR (z-score, mean = 0, SD = 1). Each melatonin z-score value was then assigned an elapsed time with respect to the subject’s habitual wake time, and an hourly mean was calculated for each subject. Mean data for the young and older groups were then averaged per hour, and a mean and standard error for each group per hour were calculated.

Statistical analyses were carried out using the SAS system (SAS Institute, Cary, NC). Data are presented as means ± SD unless otherwise noted. Student’s t-tests were used to compare data from older and young subjects after verification of variance homogeneity. In cases in which the variance between the two groups was significantly different, an approximate t was calculated. Correlation analysis was performed using Pearson’s correlation coefficient.

RESULTS

The average wake time and bedtime of the older subjects occurred >1 h earlier than did those of the young subjects (Table 1), as we have reported previously (11). The circadian phase of MELmid also occurred at a significantly earlier hour in the older subjects (Table 1 and Fig. 1). When we examined the plasma melatonin rhythm in more detail, we found that the earlier midpoint of the overall rhythm among the older subjects was reflected in a significantly earlier onset of the rhythm (DLMO and MEL25%up, Table 1). Although the offset of the melatonin rhythm also occurred at an earlier clock hour in the older subjects, this did not reach statistical significance (Table 1).

The 24-h mean melatonin values of the older and young subjects were not significantly different (older: 67.72 ± 41.36 pmol/l, range 19.27–157.57 pmol/l; younger: 79.94 ± 49.0 pmol/l, range 21.03–204.7 pmol/l; P = 0.406), nor was the duration of melatonin secretion different (older: 9.03 ± 0.73 h; younger: 9.11 ± 0.71 h; P = 0.735; upward mean crossing to downward mean crossing), as we reported previously in a larger group that included these subjects (49). The duration was also not significantly different when we defined it from MEL25%up to MEL25%down (older: 9.46 ± 0.78 h; younger: 9.26 ± 1.13 h; P = 0.588).

There was a significant correlation between habitual wake time (HW) and melatonin phase (MELmid) in both the older (r = 0.85, P < 0.001) and young (r = 0.63, P < 0.001) groups of subjects. A linear regression fitted to both data sets indicates that the nature of this relationship is different between the two groups, with an earlier wake time associated with an even earlier circadian phase in the older subjects (older subject slope = 0.737; young subject slope = 0.391; see Fig. 2). When we compared the relationship between habitual wake time and melatonin phase between the age

Fig. 1. Clock hour of melatonin rhythm midpoint in young and older subjects. The midpoint of the plasma melatonin rhythm (MELmid) is plotted with respect to age for each of the 48 subjects (c). Means ± 1 SD for each age group.
groups by use of a general linear model, we found a significant effect of age (F$_{1,44}$ = 12.77; P < 0.001), a significant effect of melatonin phase (F$_{1,44}$ = 43.96; P < 0.0001) and a significant interaction between melatonin phase and age (F$_{1,44}$ = 4.15; P < 0.05). The latter observation reflects the steeper slope of the regression line in older subjects (see Fig. 2).

When we examined the phase relationship between the average wake time and the timing of the midpoint of the circadian rhythm of plasma melatonin secretion, we found a significantly shorter interval between these two measures in the older subjects (MEL$_{mid}$-to-wake interval; Fig. 3 and Table 2). When the relationship between the melatonin rhythm and habitual sleep times was examined in more detail, the altered phase relationship in the older subjects was particularly evident when the offset of melatonin secretion (MEL$_{25\%down}$) was considered (Table 2). This altered phase relationship between melatonin secretion and habitual sleep times in the older subjects was also evident when the onset of melatonin secretion (DLMO, MEL$_{25\%up}$) was considered (Table 2), although this did not reach statistical significance. Thus the phase relationship between habitual sleep times and the melatonin secretion pattern in the older subjects was such that they were going to bed earlier with respect to melatonin onset and waking earlier with respect to melatonin offset (Fig. 4).

We also examined whether interindividual differences in the level of melatonin secretion (the 24-h mean level) might contribute to the altered phase relationship between the timing of the melatonin rhythm and sleep-wake timing that we observed in the older subjects. In only one measure of that phase relationship did we find a significant correlation with mean melatonin level (bedtime to MEL$_{25\%down}$), and the relationship was significant for the older subjects only (older subjects: r = 0.68, P = 0.0154; young subjects: r = 0.13, P = 0.5448). When we examined these data in more detail, the significant relationship among the older subjects appeared to be due to the two older subjects with the highest melatonin mean levels (Fig. 5), and the correlation of melatonin mean and the melatonin-sleep/wake phase relationship among the entire group of subjects was not significant (r = 0.24, P = 0.1586).

Taken together, these results show that the older subjects were going to bed and waking up at an earlier clock hour, and these earlier bed and wake times were also at an earlier internal circadian phase.

**DISCUSSION**

We found that the timing of the circadian rhythm of plasma melatonin secretion occurred at a significantly earlier clock hour in older subjects than in young adults, a finding consistent with previous reports of earlier circadian rhythms in older subjects in general.

**Table 2. Phase relationships between sleep-wake cycle and melatonin rhythm in young and older subjects**

<table>
<thead>
<tr>
<th></th>
<th>Older Subjects</th>
<th>Young Subjects</th>
<th>Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEL$_{mid}$ to wake time</td>
<td>3.67 ± 0.54 h</td>
<td>4.23 ± 0.96 h</td>
<td>P = 0.013</td>
</tr>
<tr>
<td>DLMO to wake time</td>
<td>8.92 ± 0.88 h</td>
<td>9.21 ± 1.14 h</td>
<td>P = 0.415</td>
</tr>
<tr>
<td>MEL$_{25%up}$ to wake time</td>
<td>8.42 ± 0.65 h</td>
<td>8.86 ± 1.19 h</td>
<td>P = 0.226</td>
</tr>
<tr>
<td>Wake time to MEL$_{25%down}$</td>
<td>1.02 ± 0.75 h</td>
<td>0.17 ± 0.98 h</td>
<td>P = 0.012</td>
</tr>
<tr>
<td>Bedtime to MEL$_{mid}$</td>
<td>4.11 ± 0.59 h</td>
<td>3.79 ± 1.02 h</td>
<td>P = 0.271</td>
</tr>
<tr>
<td>DLMO to bedtime</td>
<td>1.14 ± 0.98 h</td>
<td>1.24 ± 1.13 h</td>
<td>P = 0.784</td>
</tr>
<tr>
<td>MEL$_{25%up}$ to bedtime</td>
<td>0.56 ± 0.8 h</td>
<td>0.89 ± 1.17 h</td>
<td>P = 0.358</td>
</tr>
<tr>
<td>Bedtime to MEL$_{25%down}$</td>
<td>8.87 ± 0.71 h</td>
<td>8.18 ± 1.08 h</td>
<td>P = 0.052</td>
</tr>
</tbody>
</table>

Means ± SD.
There are many reports that melatonin levels decline with age (14, 17, 25, 37, 45, 50). It has also been shown that sleep efficiency declines with age (28, 35). Given the sleep-promoting effects of exogenous melatonin in young adults (9, 51), it has been suggested that there is a causal relationship between melatonin level and sleep quality in aging (14). There have been reports that exogenous melatonin administered to elderly insomniacs may improve sleep quality (13, 15, 48), although those studies used wrist actigraphy to estimate sleep quality. In a polysomnographic study of elderly insomniacs, exogenous melatonin administration did not affect total sleep time, sleep efficiency, or subjective sleep quality, and there was no correlation between endogenous melatonin level and sleep (16). We have reported that endogenous melatonin levels in very healthy older adults are not significantly lower than in young men (49), although sleep efficiency in very healthy older adults is significantly lower (8). Thus there is conflicting information about how melatonin levels in aging are related to sleep quality.

Sleep disturbances in aging are most prominent in the early morning hours and most commonly manifest themselves as early morning awakening and difficulty maintaining sleep (12, 26–28). Our present finding, that older subjects wake at an earlier circadian phase when endogenous melatonin levels are relatively higher than they are in young subjects at wake time, does not support the hypothesis that melatonin plays a causal role in the disturbances of sleep timing associated with aging.

Our present results demonstrate that the overall endogenous circadian rhythm of plasma melatonin secretion is set to an earlier clock hour in healthy older subjects and that the phase relationship between this marker of the circadian timing system and the habitual sleep-wake cycle is such that older subjects also wake at an earlier internal circadian time. When considered in another way, our findings show that the habitual bedtime (x = 0) were z-transformed and an hourly average was computed; data from all subjects in each group were then combined. Dashed lines indicate habitual bedtime (x = −8) and habitual wake time (x = 0).

This earlier timing was evident regardless of whether we estimated circadian phase using only the onset or offset of the melatonin rhythm. We also found that the interval between plasma melatonin midpoint and usual wake time was significantly shorter in older subjects, consistent with our earlier report from a larger group of subjects that the core body temperature-to-wake time interval is shorter (11). There was also a correspondingly longer interval between usual bedtime and plasma melatonin midpoint in the older subjects, and this, coupled with our previous report that the duration of melatonin secretion is not different between healthy young and older subjects (49), indicates a difference in the relative timing between the usual sleep-wake cycle and the underlying circadian rhythm of plasma melatonin in older people.

When we examined the phase relationship between the sleep-wake cycle and the plasma melatonin rhythm in more detail, we found that the greatest difference occurred in the morning hours. Although the absolute clock hour at which plasma melatonin levels declined in the morning was not significantly different between the young and older subjects, the usual wake times of the older subjects were significantly earlier. This resulted in the older subjects waking earlier relative to the morning decline in melatonin levels and earlier relative to the overall melatonin rhythm. Thus the older subjects were waking at an earlier circadian phase, when circulating levels of melatonin were at a higher relative value than they were when the younger subjects woke. This finding has important implications for understanding melatonin’s role in the sleep disturbances associated with aging.

Sleep disturbances in aging are most prominent in the early morning hours and most commonly manifest themselves as early morning awakening and difficulty maintaining sleep (12, 26–28). Our present finding, that older subjects wake at an earlier circadian phase when endogenous melatonin levels are relatively higher than they are in young subjects at wake time, does not support the hypothesis that melatonin plays a causal role in the disturbances of sleep timing associated with aging.
circadian rhythm of melatonin secretion occurs later within the habitual sleep episode in older subjects. It would thus appear unlikely that a circadian phase advance of the melatonin rhythm is initiating an advance in sleep-wake timing or an increase in sleep disruption in the latter part of the night.

These findings are consistent with our recent report (11) from a larger group of subjects in which we used the core body temperature rhythm as a marker of the status of the circadian timing system, and they are also consistent with results reported recently by Lewy et al. (21) using a different experimental design. Thus we and others have found that there is a fundamental difference in the relationship between the circadian timing system and the timing of sleep in older subjects. Understanding the cause(s) of this altered phase relationship may aid in the development of strategies for improving sleep in older individuals. On the basis of evidence from other studies conducted in our laboratory, we have suggested that there is an age-related change in the interaction between the circadian and sleep-wake processes controlling sleep timing and structure.

Recently, we reported results from a forced desynchrony study (8) in which young and older subjects were scheduled to live on a 28-h rest-activity schedule for 1 mo, resulting in sleep and wake episodes occurring at all circadian phases after a similar length of prior wakefulness. We found that, when the sleep of older subjects was scheduled at advanced circadian phases, it was much more impaired than the sleep of young adults. From both objective and subjective measures of sleep in that study, we found that older subjects spontaneously woke at an earlier internal circadian phase (8, 11), similar to what we found in the present study. Furthermore, when we examined daytime cognitive performance from those same subjects, we observed an age-related difference in the circadian waveform that paralleled the difference observed in sleep (11). Thus, in that study with a very different design, we found a similar age-related change in the interaction between the circadian timing system and the timing of both nighttime sleep and daytime performance. Those results suggest that the primary change initiating these age-related alterations may be a reduced drive for sleep in older people at particular circadian phases, leading them to awaken early relative to both clock time and internal circadian time. Such early morning awakening would be accompanied by light exposure at a time when the circadian system would be more sensitive to light (4), reinforcing and maintaining the advanced phase of awakening.

In the present study, we found that the phase relationship between habitual sleep-wake timing and the timing of the circadian rhythm of plasma melatonin was altered, such that the older subjects were not only waking at an earlier clock hour, they were also waking at an earlier circadian phase. This altered phase relationship was such that the older subjects were waking at a time when the relative levels of plasma melatonin were higher than were the relative levels in the young subjects at wake time. These findings do not support a causal role for melatonin phase in the sleep disruption associated with aging. Understanding the mechanisms underlying the age-related change in the relative timing between the circadian system and the habitual sleep-wake episode may aid in the development of chronobiological treatments for the sleep disruption and early morning awakening that affect so many older people.

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