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Melatonin Rhythms in Night Shift Workers

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Summary: For some time, it has remained uncertain whether the circadian rhythms of permanent night shift workers are adapted to their night-active schedule. Previous studies of this question have often been limited by "masking" (evoked) effects of sleep and activity on body temperature and cortisol, used as marker rhythms. In this study, the problem of masking was minimized by measuring the timing of melatonin production under dim light conditions. Nine permanent night shift workers were admitted to the Clinical Research Center (CRC) directly from their last work shift of the week and remained in dim light while blood samples were obtained hourly for 24 hours. Melatonin concentrations were measured in these samples using a gas-chromatographic mass-spectrometric method. Sleep diaries were completed for two weeks prior to the admission to the CRC. Overall, the onset of the melatonin rhythm was about 7.2 hours earlier (or 16.8 hours later) in the night workers compared to day-active controls. It was not possible to know whether the phase of the melatonin rhythm was the result of advances or delays. In night shift workers, sleep was initiated (on average) about three hours prior to the onset of melatonin production. In contrast, day-active subjects initiated sleep (on average) about three hours after their melatonin onset. Thus, the sleep times selected by night shift workers may not be well-synchronized to their melatonin rhythm, assumed to mark the phase of their underlying circadian pacemaker. **Key Words:** Shift work—Melatonin—Circadian rhythms—Sleep disorders—Insomnia.

Do the physiological rhythms of night shift workers become adapted to the unconventional hours during which these people work and sleep? In other words, does the circadian pacemaker become "reset" so circadian rhythms are congruent with the inverted sleep and activity schedule? Although a conceptually simple question, it has been difficult to answer experimentally. Initial field and laboratory studies monitoring core body temperature rhythms concluded that there was, at best, partial adaptation (1–5). However, these earlier studies were confounded by the "masking" effects of sleep and activity on body temperature. Sleep, at any time of day, will result in a fall in body temperature (6); thus, a sleep-induced temperature trough can be difficult to distinguish from the circadian temperature minimum. Likewise, vigorous activity can induce a rise in body temperature that is difficult to distinguish from the circadian maximum. Most other marker rhythms (e.g. cortisol, urinary electrolytes, etc.) are likewise confounded by the evoked effects of sleep and activity (7). One way of reducing masking effects is to assess circadian phase with a "constant routine" protocol, used in several recent studies of shift work adaptation (8–10).

In this study, we addressed the question of shift work adaptation by measuring the melatonin rhythm of workers who had been on a night shift for at least six months. In mammals, the melatonin rhythm is driven by the primary circadian pacemaker, located in the suprachiasmatic nucleus (SCN) in the hypothalamus (11). The timing of melatonin production can be determined with a high degree of resolution (±15 minutes), especially the daily onset (12). Recent studies have shown a high degree of correlation between the phase of the melatonin rhythm and other circadian rhythms, measured under constant routine conditions (13,14). Melatonin is minimally affected (masked) by sleep (15) as are core temperature (16) and cortisol (7), two other commonly used marker rhythms in human studies. Stress also appears to have little effect on melatonin (17–21). Although a few recent reports suggest major stress may cause a rise in melatonin (22,23), other studies (in rats) report stress causes a fall in melatonin (24). Our subjects were studied in a low-stress situation. Melatonin production by the pineal is suppressed by bright light (25), but this masking effect can be controlled by keeping the subjects in dim light as blood samples are obtained.

In summary, melatonin was measured as an accurate

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TABLE 1. *Work schedule information*

Subject	Months on night shift	Number of night shifts prior to melatonin determination	Time start shift	Time end shift	Dates of admission to CRC	Time of dawn	Duration of commute (minutes)
N1	55	3	2300	0730	17 Feb	0708	35
N2	60	5	2300	0700	6 Jan	0751	15
N3	15	5	2330	0800	10 Feb	0720	45
N4	32	4	2300	0745	24 Feb	0658	40
N5	38	4	2400	0800	17 Feb	0710	20
N6	10	4	2300	0730	15 Feb	0713	10
N7	7	5	2300	0715	8 Feb	0723	10
N8	14	2	2300	0730	25 Jan	0740	7
N9	15	5	2300	0700	31 Dec	0748	30
Average	23.9	4.3	2304	0730		0725	22.1
Median	15.0	4.0	2300	0730	15 Feb 91	0720	20.0
SD	19.9	1.1	10 min	22 min		18 min	14.3

reflection of the timing of the primary circadian oscillator. The adaptation of the night shift workers was assessed by comparing night workers with day-active controls regarding 1) the timing of melatonin production, and 2) the phase relationship between the melatonin rhythm and the timing of sleep.

METHODS

Ten subjects (2 men, 8 women) were recruited via informational posters and announcements in employee newsletters. One subject dropped out, leaving nine for data analysis. In order to qualify for the study, subjects had to be in good general health and not taking any drugs that would affect melatonin production (e.g. clonidine, tricyclic antidepressants). They must have been working a regular night shift for at least six months. Most of the subjects worked in health care-related occupations, but several were industrial workers. Like most shift workers, they were relatively young [average age = 34.4 ± 8.5 (SD) years old]. For demographic information, see Table 2.

Subjects were admitted to the general Clinical Research Center (CRC) at Oregon Health Sciences University for a 24-hour period following their last shift of the week in order to collect blood samples for the measurement of their melatonin rhythm. Four of the night workers had worked five nights prior to their admission, three had worked four nights, one had worked three nights (due to a variation in her "day-off" schedule) and one had worked two nights (due to some time off because of illness). The studies were all conducted during the winter months (i.e. from January 6 to February 25).

Subjects were kept in a dim-light environment (ambient light less than 50 lux) and were allowed to sleep and nap ad libitum. An intravenous catheter was placed in a forearm vein, and blood samples (5 cc) were obtained hourly, on the hour, for 24 hours. These samples were analyzed for melatonin concentrations using the highly sensitive and specific gas-chromatographic mass-spectrometric method developed by Lewy and Markey (26). The time at which melatonin concentrations rose above a 10 pg/ml threshold was used as the primary marker for circadian phase.

Comparison data for melatonin profiles were also obtained from a group of day-active volunteer subjects, who were participating in a study of the variability of the melatonin rhythms over the four seasons of the year. Procedures for obtaining melatonin profiles were essentially the same as for the night shift workers, except that blood sampling was limited to the overnight period (1700 to 1000 hours). These subjects were in good general health (taking no medications), of similar ages [6 women, 2 men, age = 31.6 ± 12.9 (SD) years old] and maintained a day-active schedule. They had no sleep-related complaints, and no restrictions were placed on their bedtimes. Because time-of-year might affect the timing of the melatonin onset, we used data from only the winter season sampling so it would be comparable to the data from the shift worker subjects. Menstrual cycle data were not collected for either night shift workers or controls, but available data suggest that phase of the menstrual cycle does not affect the timing of melatonin production (27).

For two weeks prior to their admission to the CRC, all shift work subjects kept a daily diary of sleep times (bedtime hour, estimated sleep latency, estimated time of final awakening, hour of leaving the bed) and sleep quality on a scale of 1 to 5. One of the control subjects (C8) failed to fill out sleep diary forms, but his sleep times were quite conventional. Normative data for the relationship between the melatonin onset and sleep

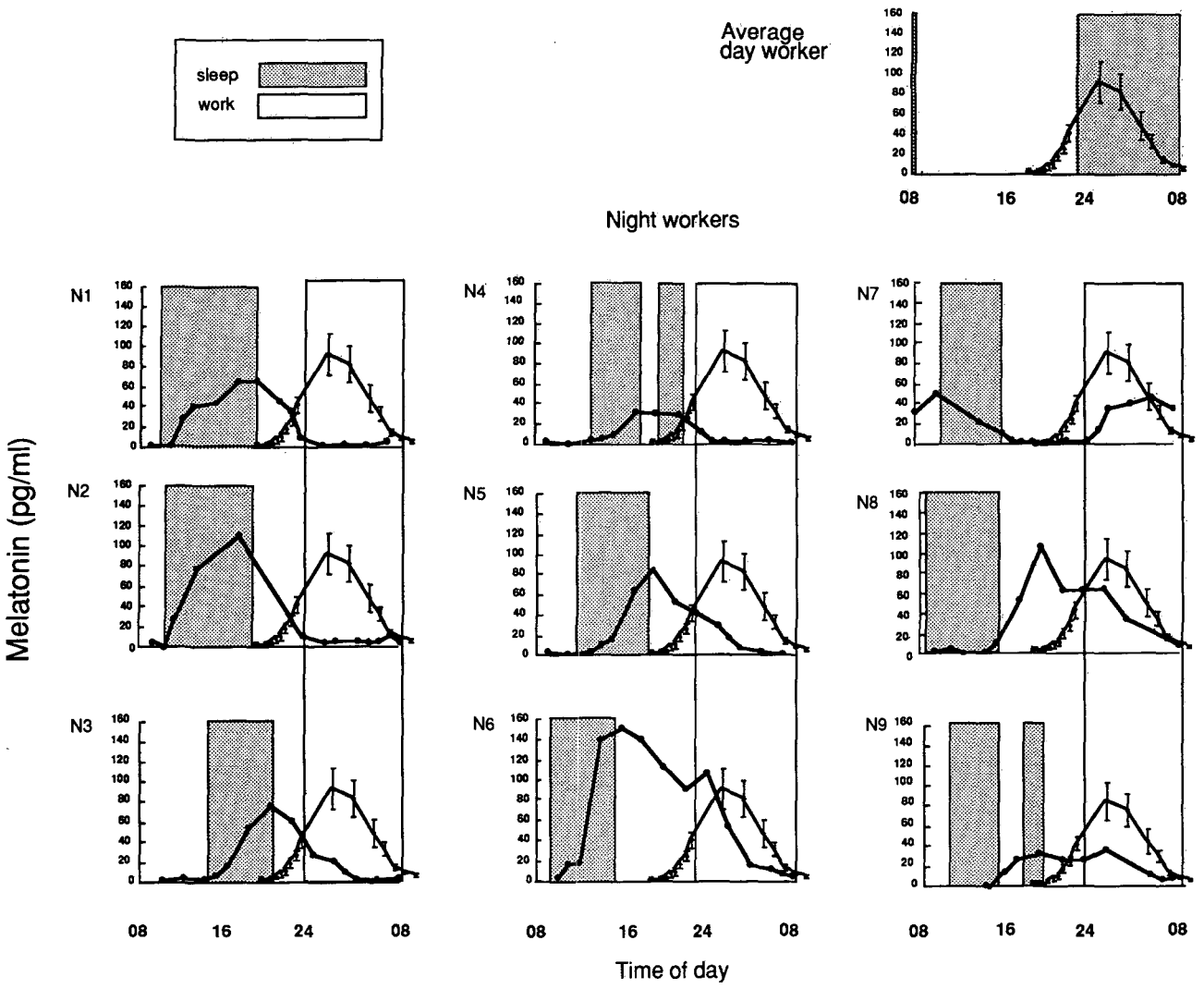

FIG. 1. Melatonin profiles for nine night shift workers are plotted in separate panels. The average melatonin curve derived from a matched group of the day-active subjects is superimposed on each of the nine night worker's graphs. The darkly shaded area represents the time of sleep and the lightly shaded area represents the time spent working on the previous day. Although there is considerable variability in the melatonin profile among the night shift workers, most appeared to be shifted from the typical phase observed in day-active subjects. Thus, there is evidence of partial adaptation to the night work (day sleep) schedule. Furthermore, the night workers appear to be initiating sleep prior to the onset (rise) in circulating melatonin, in contrast to day-active people, who typically initiate sleep after the melatonin onset. For some night workers, elevated melatonin is overlapped with a large portion of their night shift duty.

onset were calculated by obtaining averages from the control subjects.

RESULTS

All results are reported as the median score and range of scores unless otherwise specified. All times given are in military time. Preliminary results of this study have been presented previously (28).

Melatonin rhythms

The melatonin rhythms for each night shift worker are plotted in comparison to the averaged melatonin rhythm for the control group in Fig. 1. Because we were interested primarily in the timing of melatonin production indicated by the onset and offset times, some samples, occurring between these times, were not assayed. Composite data for the two groups are shown in Fig. 2.

There is considerable variability in the timing of melatonin between night shift workers with their melatonin onsets ranging between 1028 and 2430 hours. However, it is apparent that for all but one of the night shift workers (N7), the melatonin rhythm was in a distinctly atypical phase. The median melatonin onset for the night shift workers was at 1428 hours (range = 14.48 hours), statistically different from the dayworkers' median onset of 2142 hours (range = 2.24 hours) ($p \leq 0.007$, Mann Whitney *U*). It is not possible to

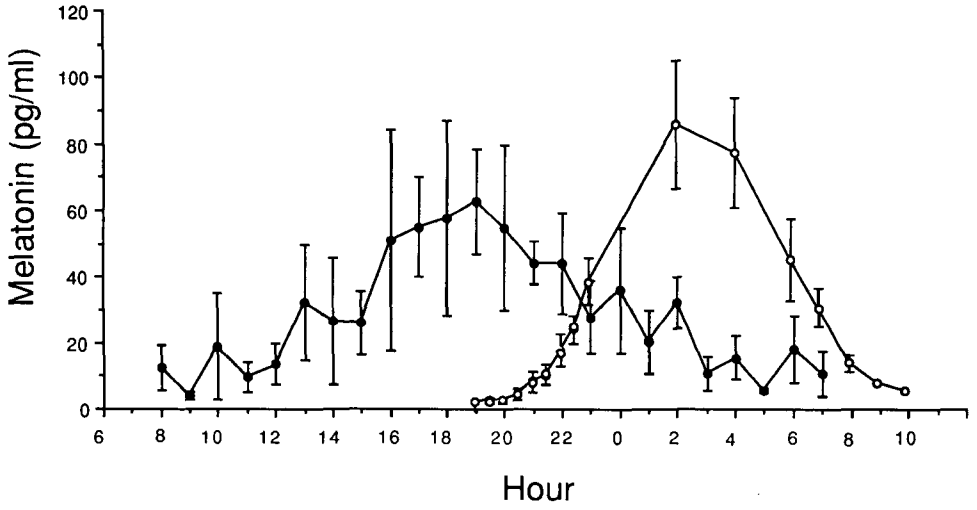

FIG. 2. A composite melatonin profile for the night shift group (closed circles) is superimposed on a melatonin profile from day-active control subjects. There is much more variability in the timing of melatonin production in the night workers than in the day-active subjects. Also, the peak in average melatonin production occurs in the late afternoon and early evening, even though the self-selected sleep times usually occurred in the morning.

conclude whether this circadian phase was the result of delays or advances (to be discussed more later). Furthermore, for a number of subjects (N3, N5–N9) elevated melatonin levels continued well into the work shift.

There is also variability in the peak concentrations of circulating melatonin. This variability may be explained by the age of the subject because age is the most important demographic variable influencing total melatonin production (29). Two of the three shift workers with low melatonin production were older (N4 and N7), and the subject with the notably elevated levels was the youngest (N6). There was no statistically significant relationship between melatonin amplitude and phase.

In summary, the timing of melatonin production was distinctly different in this group of permanent night workers compared to the day-active controls.

Work and sleep schedules

Work hours were very similar for each subject (Table 1). There was no significant relationship between time leaving the job (average = 0730 hours; range = 0700 to 0800), nor time commuting home (average: 24 minutes, range = 7–45 minutes) and melatonin phase. Also there was no relationship between the number of prior days on the night shift (average = 4.1 days; range = 2–5 days) and melatonin phase. Considering the small numbers of subjects, the lack of correlation is not surprising. Studies of larger samples may reveal an effect of one of these variables.

Sleep times obtained from diary data are present in Table 2. As has been reported in most previous studies (30,31), the night shift workers were in bed significantly less (median = 6.03 hours, range = 5.00 hours) during their primary sleep period than the dayworkers (median = 8.17 hours, range = 3.20 hours) ($p \leq 0.05$, Mann-Whitney U). However, if night workers' naps were included in the totals, there was no significant difference in the 24-hour total time in bed (median = 7.00 hours, range = 4.24 hours), although sleep efficiency could not be assessed. Night workers appeared to make up sleep with significantly longer sleep bouts on their days off (median = 9.00 hours, range = 8.06 hours; $p \leq 0.05$, Wilcoxon's t) suggesting they had accumulated a sleep debt during their work week.

More striking than total time in bed were the highly variable and inconsistent sleep patterns of many of the night shift workers. None of the night shift workers maintained an orientation of daytime sleep and nighttime wakefulness on days away from work. They tended to make up sleep either by napping in the afternoon or by sleeping extra hours in the evening. Figure 3 shows the percentage of night workers in bed at any given time during an average 24-hour period for both work days and days away from work. Thus, we conclude these regular night shift workers rotated to a day-active schedule on their days off, a pattern followed by most night workers surveyed (32). Furthermore, there was great variability in the times chosen for sleep and the degree to which sleep was broken into multiple sleep bouts.

Synchrony between melatonin and sleep times

The sleep times for night workers for the day prior to measurement of the melatonin rhythm are also shown in each panel of Fig. 1. The prior night's sleep was plotted with the assumption that if sleep had an

TABLE 2. *Study results for night shift workers and control subjects*

Subject	Age	Gender	Time of melatonin onset	Average estimated sleep onset	Average estimated time of awakening	Average estimated total sleep	Time of estimated mid-sleep	Average self-rated sleep quality
Night workers								
N1	39	F	1117	0942	1645	7.01	1308	1.5
N2	34	F	1028	0933	1521	6.03	1234	1.5
N3	42	M	1518	1345	2030	6.07	1734	1.8
N4	42	F	1428	1124	1630	5.06	1357	2.3
N5	29	F	1343	1012	2015	10.03	1513	2.4
N6	22	F	1200	0920	1500	5.34	1207	1.5
N7	47	F	2430	0851	1413	5.36	1139	1.9
N8	27	F	1448	1231	1822	5.27	1515	3
N9	28	M	1440	0830	1504	6.30	1145	2.3
Mean	34.4		1434	1025	1653	6.23	1341	2.0
Median	34		1428	0942	1630	6.03	1308	1.9
SD (decimal)	8.5		4.10	1.76	2.32	1.48	1.98	0.5
SD (hours and min)			0406	0146	0219	0129	0159	
Control subjects								
C1	27	F	2000	2310	0915	10.04	0412	1.4
C2	25	F	2204	0146	0834	6.49	0510	1.4
C3	30	F	2120	2312	0757	8.44	0334	1.6
C4	25	M	2215	2310	0651	7.40	0300	1
C5	25	M	2240	2446	1000	9.30	0515	1
C6	62	F	2208	2334	0733	7.59	0334	1.8
C7	23	F	2032	2301	0719	8.17	0310	1.3
C8	36	M	2115	–[a]	–	–	–	–
Mean	31.6		2131	2346	0812	8.26	0359	1.4
Median	26		2142	2312	0757	8.17	0334	1.4
SD (decimal)	12.9		0.91	1.00	1.12	1.10	0.90	0.3
SD (hours and min)			0055	0100	0112	0106	0054	

[a] Missing data.

influence on the melatonin rhythm (either directly or by structuring the light–dark cycle), the sleep bout from the preceding day would have the greatest influence. A very similar picture is obtained if sleep from the previous three nights is averaged. Sleep on the day of the melatonin sampling was assumed to be atypical because of the novelty of the environment and the interuptions from blood sampling, and thus was not monitored.

If we assume the melatonin rhythm was in a comparable phase on the night preceding admission to the CRC, then the relationship of sleep time to the timing of melatonin production is quite different in the night shift workers, compared to the day-active subjects. In day-active people, melatonin almost invariably rises several hours prior to bedtime. The control subjects in this study had average melatonin onset at 2131 hours (±0.91 hour, SD) and an average sleep onset at 2346 hours (±1.0 hour, SD), leaving an average of 2.22 ± 0.96 hours (SD) between the onset of melatonin production and subsequent sleep onset. In contrast, the average night shift worker's melatonin onset was at 1434 hours (±4.1 hours, SD) and the overall average sleep onset was at 1025 hours (±1.8 hours, SD). Thus, the night shift workers typically initiated sleep an average of 3.3 hours (±2.4 hours, SD) hours prior to the onset of melatonin production. If the one subject (N7) who had a relatively normal melatonin phase (and, thus, is an outlier compared to the rest of the group) is left out, the difference for the remaining subjects is 2.71 hours (±0.57 hours, SD).

This conclusion about the relationship of the timing of sleep to the phase of the melatonin rhythm must be considered preliminary because of the following deficiencies in the available data: 1) sleep time and melatonin phase were not assessed on the same day, and 2) we are not sure of the night-to-night variability in the phase of the melatonin rhythm, especially in night shift workers, who may be exposed to irregular and atypical episodes of bright light exposure. However, the data suggest that night workers may be initiating sleep earlier in their circadian cycle, compared to the day-active controls.

DISCUSSION

This is the third study in which the melatonin rhythm has been used as a phase marker for circadian rhythms in shift workers. Waldhauser et al. (33) showed phase-advanced melatonin rhythms in two bakers who began

their shifts very early in the morning. Their report was limited to two subjects and did not include any sleep data. Touitou et al. recently showed that melatonin rhythms do not change in workers who are on a quickly rotating schedule (34).

Melatonin was chosen for this study because problems of masking are easily managed. We assume that the melatonin rhythm is a sufficient and accurate reflection of the endogenous pacemaker that controls other circadian rhythms—core body temperature, cortisol and the rest-activity cycle, for example—which have been studied more extensively. Evidence to support the use of melatonin production as a circadian phase marker comes from a variety of animal and human studies (11,13,35). For example, we found that most totally blind subjects have free-running melatonin, temperature, cortisol and sleep propensity rhythms that are phase-locked and are presumably driven by a common oscillator (14,36). Although instances of internal desynchronization between sleep and other rhythms have been documented, there is no evidence that the melatonin, temperature, and cortisol rhythms can become internally desynchronized. Nevertheless, it has not yet been proven that melatonin onset is the most accurate marker for the phase of the endogenous pacemaker.

Our data suggest that most long-standing night workers have melatonin rhythms that are significantly different from those of dayworkers. We infer that their internal circadian clocks have been "reset" to a new time, presumably as a result of their nocturnal activity and daytime sleep. However, this inference must be tempered by the limitations of the study, in which only one measurement of the melatonin rhythm was made and, thus, the day-to-day variability was not measured. Futhermore, data from other marker rhythms were not obtained. A single assessment of circadian phase can only provide a "snap shot" sample of an ongoing rhythm. It is possible that considerable day-to-day variation would be revealed if longitudinal studies were carried out. It is even possible that longitudinal measures might demonstrate free-running melatonin rhythms.

Before conducting the study, we predicted that the melatonin onset would be moderately delayed, in a "compromise" phase position somewhere between the typical phase for day-active people and a phase representing complete adaptation to the night work schedule. This prediction was based on the well-known fact (confirmed in our study) that night workers become day-active on their days off and are, thus, alternating between two sleep schedules. Rather than a compromise phase, these night shift workers had melatonin rhythms that were delayed even more than their workday sleep times.

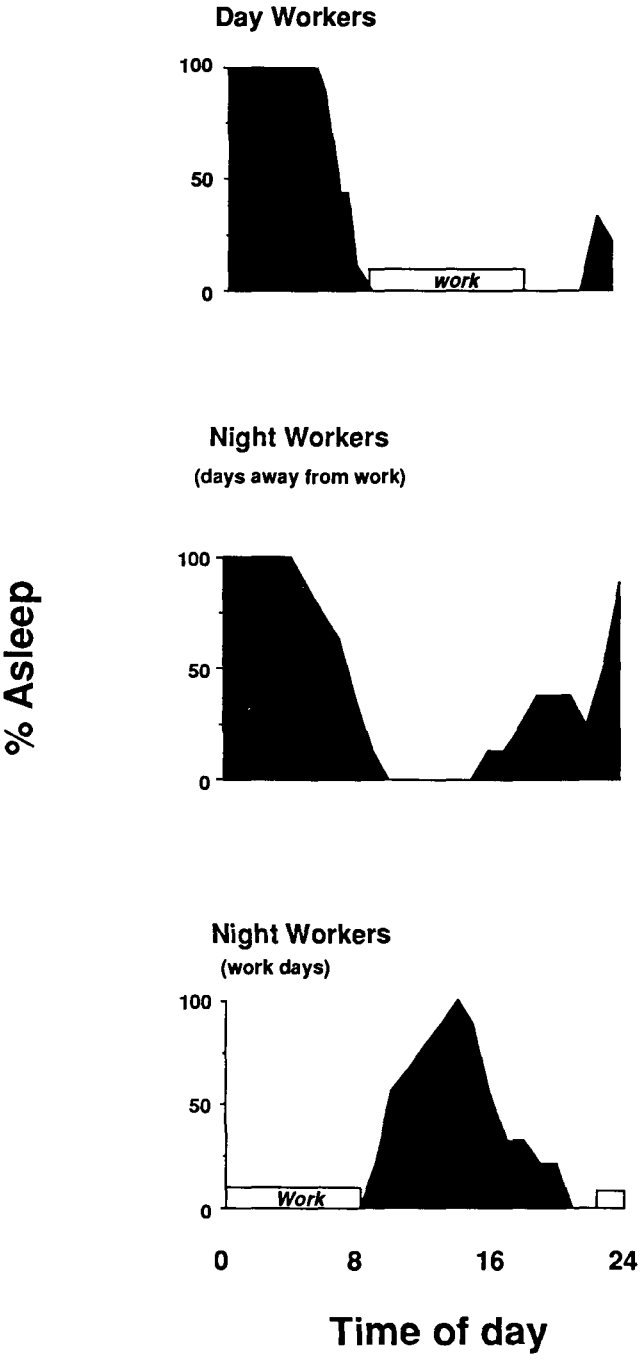

FIG. 3. In all three panels, the percent of people who are in bed at any given hour of the day is represented by the darkly shaded area. On their days off, night workers typically reverted to a pattern (middle panel) that is similar to that of day-active people (upper panel). Most night workers preferred to sleep as soon as they were off work, but some delayed their sleep until the evening hours (lower panel).

Our data not only demonstrate a distinctly altered melatonin secretion pattern in night shift workers, but also suggest a lack of synchronization between the sleep and melatonin rhythms. Thus, our findings are similar to other studies that show incomplete adaptation in chronic night shift workers (1–5). A recent report sug-

gested that untreated night shift workers may make essentially no adaptation (8). In contrast, we found a few subjects (N1, N2 and N4) who had melatonin rhythms that were about 180 degrees out of phase with day-active controls, suggesting better adjustment of circadian rhythms than has been typically reported in the literature. The lack of consistency among studies probably is a result of the many paradigms used to study shift work; that is, laboratory vs. naturalistic, rapidly rotating vs. fixed shifts, as well as the marker used to assess circadian phase. Individual differences in the ability to adapt to night work schedules also contribute to the variability.

Without measurements of transient phase positions, it is impossible to state whether the altered phase of the melatonin rhythm was the result of advances or delays. However, since the human circadian system has a period greater than 24 hours, it is logical to assume that resetting is the result of delays rather than advances. Also, night shift workers typically delay their sleep times. For example, they typically stay up (or take a short nap) on their first day off and sleep later that evening. When starting back to work, they typically further delay sleep until the day after their first night on duty. Thus, their sleep times and concomitant exposure to the light–dark cycle would be expected to promote recurrent delays.

It would not be surprising to find that night shift workers (and perhaps many day-active people) sleep out of phase with their other circadian rhythms. Although sleep propensity ("sleepiness") has a circadian rhythm (37,38), sleep can be resisted for a while by most adults, so that sleep times are often structured by other considerations. A high priority for night shift workers is to maintain their social interactions. Therefore, sleep times are often structured by social constraints. Thus, sleep times may be only loosely coupled to the underlying circadian sleep propensity rhythm. As sleep deprivation builds a sleep "debt", sleep may be governed more by homeostatic than by circadian factors (39,40). It remains to be demonstrated to what extent sleeping out of phase with the circadian sleepiness rhythm exacts a toll in sleep efficiency and daytime alertness.

Surprisingly, daily subjective ratings of sleep quality did not differ either between dayworkers and night shift workers, or between night shift workers' days "on" and days "off" work. The simple rating system used (a scale of one to five) may not have been sensitive to actual differences in sleep quality. Moreover, global ratings of sleep quality are often unreliable. Although the average ratings were not statistically different, two of the subjects expressed distinct dissatisfaction with their sleep and excessive awake-time sleepiness. Future studies should include polysomnographically monitored sleep recordings to evaluate sleep efficiency and awake-time sleepiness.

Data from this pilot study suggest that melatonin rhythms are shifted to a distinctly different phase in permanent night shift workers, indicating a major adaptation of the circadian pacemaker to the atypical schedule for activity, sleep, and light exposure. However, there is a suggestion that adaptation remains incomplete (and perhaps unstable) because the timing of sleep appears to be at an earlier circadian phase than is typical for day-active subjects. However, this conclusion of a relative desynchronization between the rhythms needs to be confirmed by longitudinal measurements of melatonin phase concurrent with precise measurements of sleep.

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