SUPPRESSION OF MELATONIN SECRETION IN SOME BLIND PATIENTS BY EXPOSURE TO BRIGHT LIGHT

Charles A. Czeisler, Ph.D., M.D., Theresa L. Shanahan, B.Sc., Elizabeth B. Klerman, M.D., Ph.D., Heinz Martens, M.D., Daniel J. Brotman, A.B., Jonathan S. Emens, B.A., Torsten Klein, M.D., and Joseph F. Rizzo III, M.D.

Abstract *Background.* Complete blindness generally results in the loss of synchronization of circadian rhythms to the 24-hour day and in recurrent insomnia. However, some blind patients maintain circadian entrainment. We undertook this study to determine whether some blind patients' eyes convey sufficient photic information to entrain the hypothalamic circadian pacemaker and suppress melatonin secretion, despite an apparently complete loss of visual function.

Methods. We evaluated the input of light to the circadian pacemaker by testing the ability of bright light to decrease plasma melatonin concentrations in 11 blind patients with no conscious perception of light and in 6 normal subjects. We also evaluated circadian entrainment over time in the blind patients.

Results. Plasma melatonin concentrations decreased during exposure to bright light in three sightless patients by an average ($\pm$SD) of 69$\pm$21 percent and in the normal subjects by an average of 66$\pm$15 percent.

When two of these blind patients were tested with their eyes covered during exposure to light, plasma melatonin did not decrease. The three blind patients reported no difficulty sleeping and maintained apparent circadian entrainment to the 24-hour day. Plasma melatonin concentrations did not decrease during exposure to bright light in seven of the remaining blind patients; in the eighth, plasma melatonin was undetectable. These eight patients reported a history of insomnia, and in four the circadian temperature rhythm was not entrained to the 24-hour day.

Conclusions. The visual subsystem that mediates the light-induced suppression of melatonin secretion remains functionally intact in some sightless patients. The absence of photic input to the circadian system thus constitutes a distinct form of blindness, associated with periodic insomnia, that afflicts most but not all patients with no conscious perception of light. (N Engl J Med 1995; 332:6-11.)

B LINDNESS afflicts more than 1 million Americans, $\frac{1}{10}$ of whom have no conscious perception of light.[1] The eyes of these blind persons are typically assumed to serve only a cosmetic function. However, besides mediating the perception of images, ocular input of light synchronizes the hypothalamic circadian pacemaker that regulates many physiologic and behavioral processes.[2,3] Given the current understanding that light is the primary synchronizer of the circadian pacemaker, it is not surprising that in most totally blind persons the pacemaker is not synchronized with the 24-hour day. Instead, it oscillates around an intrinsic period of close to 24 hours. Therefore, despite maintaining regular schedules of sleep, work, and social contact, many totally blind people have cyclic bouts of insomnia as their circadian pacemakers move in and out of phase with the 24-hour day.[4-9]

Some totally blind persons, however, remain synchronized to the 24-hour day.[6,7] Nonphotic time cues, once regarded as the principal circadian synchronizer

in humans,[10] have been presumed to be the only cues available to entrain the circadian rhythms of such persons to the 24-hour day.[11] We hypothesized that unrecognized photic input may continue to synchronize the circadian pacemaker in some blind persons with entrained rhythms, even in the absence of conscious light perception and pupillary reflexes to light. To evaluate this hypothesis, we tested the functional integrity of the photic-entrainment pathway in a group of completely blind patients.[12]

The retinohypothalamic tract conveys photic information from the retina to the hypothalamic circadian pacemaker, located in the suprachiasmatic nucleus.[13,14] Such photic entrainment is lost after bilateral transection of the optic nerve or the retinohypothalamic tract, whereas it persists after bilateral transection of the primary optic tract.[13,14] Photic information is conveyed from the suprachiasmatic nucleus to the pineal gland through a circuitous neural pathway,[13,15] resulting in the suppression of melatonin secretion.[16] We reasoned that even in blind persons, we could evaluate the retinal input of light to the suprachiasmatic nucleus by measuring the neuroendocrine response of the pineal gland, the end-organ in this pathway, as has been suggested.[17]

In humans, the pineal gland is the source of circulating melatonin,[18] plasma concentrations of which are higher during the biologic night than during the day. Retinal exposure to light produces short-term suppression of nighttime melatonin secretion in sighted human subjects in an intensity-dependent manner.[19,20] Since the only known photic input governing melatonin synthesis in the mammalian pineal gland is

conveyed through the suprachiasmatic nucleus,[13,15] losing the input of light to this nucleus should preclude the suppression of melatonin secretion.[17] We describe here the use of light-induced melatonin-suppression testing to evaluate the functional integrity of the retinohypothalamic tract in 11 completely blind patients.

METHODS

Study Subjects

We studied 11 blind patients with no conscious perception of light (Table 1) and 6 normal men ranging in age from 20 to 25 years. With the exception of disturbed sleep in some of the blind patients, no subjects had medical or psychiatric disorders, as determined by history taking, physical examination, chest radiography, electrocardiography, psychological questionnaires, and biochemical and toxicologic screening tests. None had worked at night in the past three years. Their sleep histories were evaluated in a structured interview and a sleep-disorders questionnaire[21] modified to assess sleep disorders in blind patients. The possibility that sleep apnea and nocturnal myoclonus were the basis of the patients' difficulty in sleeping was excluded by polysomnography. All the subjects were instructed to

maintain regular sleep–wake schedules and to record their bedtimes and awakening times for at least two weeks before the studies. The protocol was approved by the Human Research Committee of Brigham and Women's Hospital, and all subjects gave written informed consent.

Ophthalmologic Testing

The blind patients underwent a complete neuro-ophthalmologic examination that included observation of their behavior. Pupillary reflexes to light were evaluated with the brightest light of an indirect ophthalmoscope and were examined with a slit lamp. Complete electroretinographic testing, including narrow-band filtering,[22] was performed in all eight blind patients with eyes; only electroretinograms for which there were control recordings, in which opaque filters shielded the eyes from the white 30-Hz stimulus, are discussed here. Visual evoked potentials were tested in six of the eight blind patients with eyes.

Ambulatory Evaluations

The subjects' wrist activity and core body temperature were monitored on an ambulatory basis (PMS-8 Recorder, Vitalog, Redwood City, Calif.) for at least one week before hospital admission. The sleep–wake schedules during the studies represented an aver-

Table 1. Characteristics of the Blind Patients.

PATIENT NO.	AGE (YR)/ SEX	CAUSE OF BLINDNESS	AGE (YR) AT LOSS OF LIGHT PERCEPTION	OCULAR EXAMINATION	PUPILLARY LIGHT REFLEXES	ELECTRORETINO-GRAPHIC RESPONSE	VISUAL EVOKED POTENTIALS	MELATONIN-SUPPRESSION TEST*	HISTORY OF INSOMNIA	CIRCADIAN ENTRAINMENT AT TIME OF STUDY
1	18/M	Both eyes: Leber's congenital amaurosis	Congenital	Both eyes: funduscopic evidence of retinopathy	Not detectable	Not detectable	Both eyes: abnormal response	Positive	No	Yes, early phase
2	23/M	Both eyes: juvenile retinoschisis	17	Right eye: very mitotic pupil, cataract Left eye: enucleated	Not detectable	Not detectable	Not tested	Positive	No	Yes
3	75/F	Both eyes: optic neuropathy	~50	Both eyes: diffuse pallor of optic nerves, mild nuclear sclerotic cataracts	Not detectable	Both eyes: normal for age	Not detectable	Positive	No	Yes
4	63/M	Both eyes: congenital glaucoma Right eye: penetrating trauma	15	Right eye: enucleated Left eye: phthisis bulbi, opaque cornea	Pupil not observable	Not detectable	Not tested	Melatonin not detectable	Yes, cyclic	No
5	70/M	Both eyes: congenital glaucoma	8	Both eyes: opaque cornea, slight atrophy of globe	Pupil not observable	Not detectable	Not detectable†	Negative	Yes, cyclic	No
6	32/M	Both eyes: motor vehicle accident	22	Both eyes: enucleated	—	—	—	Negative	Yes, cyclic	No
7	38/F	Both eyes: retinopathy of prematurity	Perinatal	Both eyes: phthisis bulbi, opaque cornea	Not detectable	Not detectable	Not detectable†	Negative	Yes, cyclic	No
8	41/M	Both eyes: retinopathy of prematurity	Perinatal	Left eye: cataract Right eye: band keratopathy	Not detectable	Not detectable	Not detectable	Negative	Yes, cyclic	Yes, late phase
9	32/M	Both eyes: bilateral retinopathy	8	Both eyes: opaque cornea, occluded pupils	Pupil not observable	Not detectable	Right eye: poorly defined response Left eye: not detectable	Negative	Yes, cyclic	Yes
10	60/M	Left eye: birth trauma Right eye: sympathetic ophthalmia	14	Both eyes: enucleated	—	—	—	Negative	Yes	Yes, late phase
11	32/M	Both eyes: retinoblastoma	<1	Both eyes: enucleated	—	—	—	Negative	Yes	Yes

*Positive denotes a decrease in the average plasma melatonin concentration during the final hour of the bright-light exposure to 33 percent or more below the average concentration 24 hours earlier.

†Visual-evoked-potential testing was performed after the completion of the study.

age of the clock times recorded in the weekly diaries and were verified by ambulatory monitoring.

Constant Routines

Two-day constant routines consisted of enforced wakefulness with the subject in a semirecumbent position, with daily intake of nutrition and electrolytes evenly distributed throughout the day and night. This procedure attenuates the physiologic responses evoked by periodic behavioral and environmental stimuli, such as sleeping, eating, changing posture, and changing the intensity of ambient light, thereby permitting assessment of the endogenous circadian cycles of body temperature and melatonin secretion.[3,23]

Evaluation of Photic Input with the Melatonin-Suppression Test

During a constant routine, the normal subjects and blind patients were exposed to bright light for 90 to 100 minutes, with the exposure timed to coincide with the expected peak in plasma melatonin concentrations (Fig. 1). The midpoint of the bright-light exposure occurred 22 to 23 hours (mean [±SD], 22.6±0.4) after the fitted temperature minimum (as defined below under Statistical Analysis), which has a consistent phase relation with the fitted peak of the melatonin rhythm.[24] The test results were defined as positive when the
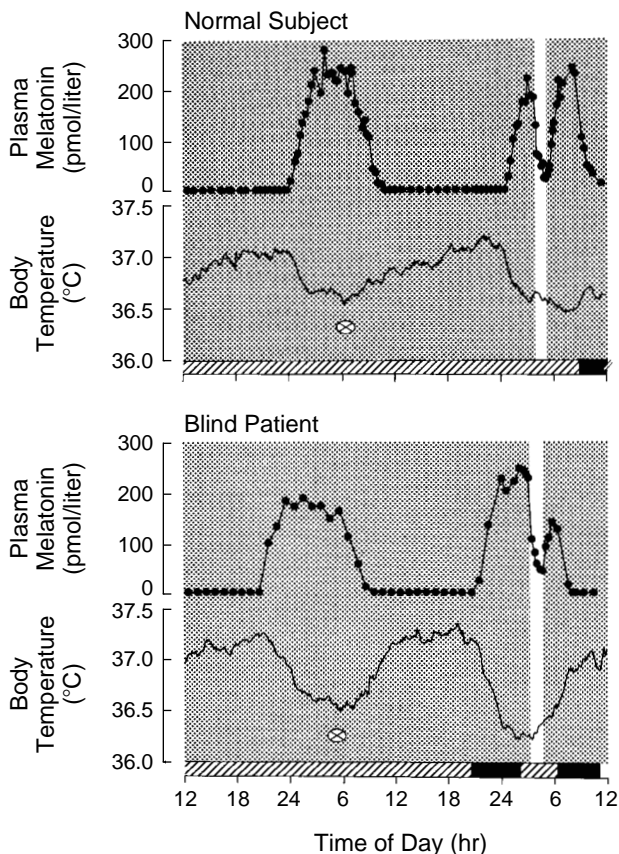

Figure 1. Melatonin-Suppression Test in a Normal Subject (Upper Panel) and a Blind Patient (Patient 2, Lower Panel).

Plasma melatonin and temperature were measured repeatedly during a constant routine (hatched bars) and subsequent episodes of sleep (solid bars). The light intensity was less than 0.02 lux during the sleep episodes, 10 to 15 lux during the constant routine, and approximately 10,000 lux during 90 to 100 minutes of exposure to bright light (open columns) 22 to 23 hours after the initial temperature minimum (crosses). In both subjects, plasma melatonin concentrations decreased markedly in response to bright light and then increased after the return to dim light.

average plasma melatonin concentration during the final 60 minutes of the bright-light exposure was 33 percent or more below that during the corresponding 60-minute interval 24 hours earlier. On two occasions Patients 1 and 2 were exposed to bright light for three hours; on one of those occasions opaque patches were used to shield their eyes from the light.

Evaluation of Entrainment by Repeated Phase Assessments

The blind patients were asked to return for repeated phase assessments of body temperature and melatonin secretion during a constant routine to evaluate the entrainment of their circadian pacemakers to the 24-hour day. Since Patient 1 was unwilling to undergo a second constant routine, blood samples for the plasma melatonin assay were collected in dim light (approximately 10 to 15 lux) with the patient kept in a semirecumbent position, to evaluate entrainment.[7,19]

Lighting Conditions

The intensity of ambient light, provided by ceiling-mounted "cool white," high-output fluorescent lamps (North American Philips Lighting, Bloomfield, N.J.), was approximately 150 lux (equivalent to ordinary indoor artificial light) during the base-line day, approximately 10 to 15 lux (equivalent to dim indoor light) during the constant routines, 6000 to 13,700 lux (equivalent to ambient outdoor light just after dawn) during the exposure to bright light in the melatonin-suppression tests (both the 90-to-100-minute and the 3-hour tests), and 0.02 lux or less (equivalent to total darkness) during sleep. Light levels during the melatonin-suppression tests were recorded every 5 to 10 minutes by photometers (International Light, Newburyport, Mass., and Sper Scientific, Tempe, Ariz.) placed on the forehead and directed toward the angle of gaze.

Physiologic Measures

Core body temperature was continuously recorded by a rectal thermistor (Yellow Springs Instrument, Yellow Springs, Ohio). Blood samples were collected every 10 to 60 minutes through an intravenous catheter in the subject's forearm. Plasma melatonin was measured with radioimmunoassay kits (Elias USA, Osceola, Wis.; assay sensitivity, 7 pmol per liter; intraassay and interassay coefficients of variation, 8 and 15 percent, respectively) or (in the case of Patients 4 and 5) by the method of Arendt et al.[25] All the samples collected from a subject during a single assessment were analyzed in the same assay.

Statistical Analysis

The fitted minimum of the body temperature and the fitted maximum of the plasma melatonin rhythms were used as markers of the phase of the endogenous circadian pacemaker.[3,24] Nonlinear least-squares harmonic-regression analysis[26] was used to fit a dual-harmonic model with correlated noise (for body temperature) or a one-harmonic model (for melatonin secretion) to the data. The results from the first five hours of the constant routine were excluded to eliminate masking effects produced by the preceding episode of sleep.

RESULTS

Ophthalmologic Evaluation

Neuro-ophthalmologic examination revealed multiple causes of blindness in the 11 patients (Table 1). All the patients reported that they had no conscious perception of light, and when they were observed at length, their behavior was consistent with that of a completely blind person. The brightest light of an indirect ophthalmoscope did not elicit pupillary constriction, although corneal opacification precluded examination of the pupils in three patients. No electroretinographic responses to flashes of bright light were detectable within the limits of sensitivity (0.05 to 0.10 μV),[22] except in Patient 3. Patients 3, 5, 7, and 8 had no detectable occipital visual evoked potentials.

Patient 1 had no visual evoked potentials to patterns of any size at the age of 18 years, a finding consistent with his medical records from the age of 6; but the stimulus of a diffuse strobe flash elicited an abnormal but reproducible occipital evoked potential (not present in the control recordings, when the eyes were shielded from the stimulus) in both eyes at the age of 18 (when he entered the study) and in one eye at the age of 21. Similarly, Patient 9 had an abnormal occipital evoked potential in one eye in response to a diffuse strobe flash.

History of Sleep–Wake Disturbances

Patients 1, 2, and 3 reported no difficulties with sleep (Table 1). Patients 4 through 9 reported cyclic difficulties, with bouts of insomnia or excessive daytime sleepiness alternating with periods of remission. Patients 10 and 11 reported intermittently severe sleep disturbances, with months or years of inadequate sleep and poor daytime alertness followed by long periods of remission.

Melatonin-Suppression Test

All six normal subjects had decreases in plasma melatonin concentrations in response to bright light (Fig. 1, upper panel). Their plasma melatonin concentrations during the final 60 minutes of bright-light exposure were an average ($\pm$SD) of 66 ± 15 percent below the corresponding concentrations 24 hours earlier. Thirty to 90 minutes after the return to dim light, the melatonin concentrations increased to 35 ± 6 percent below the corresponding base-line values.

The three blind patients who had no difficulties with sleep (Patients 1, 2, and 3) also had sharp decreases in plasma melatonin concentrations in response to bright light (Fig. 1, lower panel; Fig. 2D; and Table 1). The average values in Patients 1, 2, and 3 during the final 60 minutes of bright-light exposure were 93, 61, and 53 percent, respectively (or an average of 69 ± 21 percent), below the values 24 hours earlier. Thirty to 90 minutes after the end of the bright-light stimulus, the concentrations increased to 58, 54, and 10 percent below base line in Patients 1, 2, and 3, respectively.

Plasma melatonin concentrations did not decrease during bright-light exposure in Patients 5 through 11, all of whom had histories of sleep disturbances (Fig. 2B). Plasma melatonin was undetectable in Patient 4.
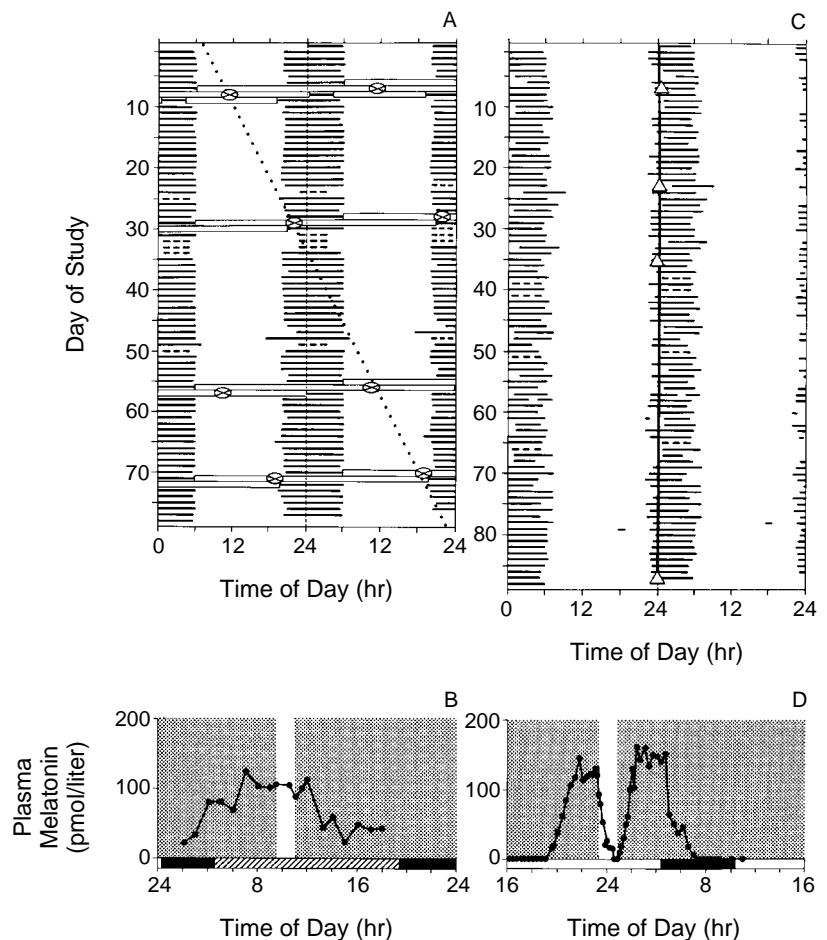

Figure 2. Sleep–Wake Patterns and Plasma Melatonin Concentrations in Two Blind Patients.

Panel A shows the sleep–wake pattern reported by a 70-year-old blind patient (Patient 5) during 78 consecutive days of study. The results are double-plotted, with successive days shown both next to and beneath each other. Clock time is shown on the horizontal axis. The solid horizontal lines indicate episodes of sleep as recorded in the patient's diary kept at home, the dashed lines represent missing data, and the open bars signify constant routines during laboratory evaluations. The slope of the regression analysis (dotted line) through the fitted temperature minimums (crosses) represents the estimated period of the endogenous circadian temperature cycle (24.5 hours).

Panel B shows the results of a melatonin-suppression test in Patient 5. The light intensity was less than 0.02 lux during scheduled sleep episodes (solid bars), 10 to 15 lux during the constant routine (hatched bar), and approximately 10,000 lux during exposure to bright light (open column). The plasma melatonin concentrations remained elevated despite the bright light.

Panel C shows the sleep–wake pattern reported by a 21-year-old blind patient (Patient 1) during 88 consecutive days of study; the symbols are as in Panel A. The slope of the regression analysis (heavy vertical line) through the fitted plasma melatonin maximums (Δ) represents the estimated period of the endogenous circadian melatonin cycle (24.0 hours)

Panel D shows the results of a melatonin-suppression test in Patient 1, with the patient kept in a semirecumbent position in dim light (open bars). The symbols and light intensity are as in Panel B. The plasma melatonin concentrations decreased in response to bright light and returned to the nighttime values on the patient's return to dim light.
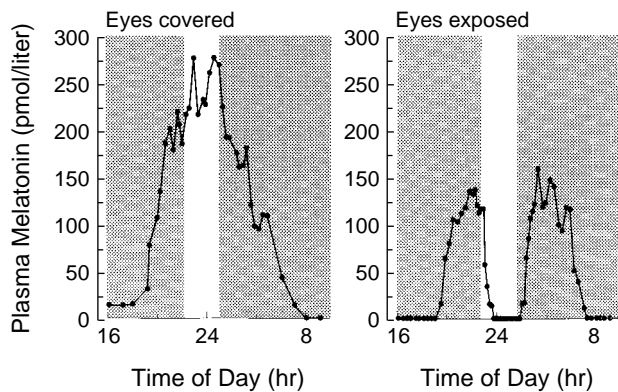
Figure 3. Results of Melatonin-Suppression Tests with and without a Blindfold in Patient 1.

The symbols and light intensity are as described in the legend to Figure 1. The plasma melatonin concentrations did not fall during the bright-light exposure when the blindfold was in place (left-hand panel), but they fell abruptly during the exposure when the patient's eyes were not blindfolded (right-hand panel).

Plasma melatonin concentrations did not decline in Patients 1 and 2 during a three-hour exposure to the bright-light stimulus when the eyes were shielded from the light (Fig. 3).

Evaluation of Entrainment

Repeated assessments of the phases of plasma melatonin and core body temperature in Patients 1 (Fig. 2C), 2, and 3 revealed stable entrainment to the 24-hour day for 12, 4, and 18 weeks of study, respectively. Endogenous circadian body temperature and, when measured, melatonin phases drifted to progressively later hours (by approximately 10 to 30 minutes per day) in four of the remaining eight patients (Patients 4, 5, 6, and 7; Fig. 2A). Repeated phase assessments in Patients 8, 9, 10, and 11 suggested entrainment during the study period, despite a history of disrupted sleep. Details of these data are available elsewhere.*

DISCUSSION

Our finding that ocular light exposure caused a robust neuroendocrine response in some blind patients challenges the presumption that the loss of conscious perception of light and pupillary reflexes to light indicates a complete loss of ocular function.[7] Despite severe retinal disease and the apparently total lack of pupillary light reflexes and conscious light perception, three blind patients had light-induced suppression of plasma melatonin concentrations that was indistinguishable from that of normal subjects.[19,20] The absence of light-induced inhibition of melatonin secretion during ocular shielding in the two patients

*See NAPS document no. 05172 for two pages of supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance (in U.S. funds only) $7.75 for photocopies or $4 for microfiche. Outside the U.S. and Canada, add postage of $4.50 ($1.75 for microfiche postage). There is a $15 invoicing charge for all orders filled before payment.

so tested indicates that the eyes mediated this inhibition, despite their negative electroretinograms. To our knowledge, this photic response has not been previously noted in blind patients; presumably, it was assumed that ocular damage sufficient to eliminate conscious perception of light and pupillary reflexes to light precluded the input of light to the hypothalamus and pineal gland.

Melatonin-suppression testing can thus determine the functional integrity of the neuroanatomical pathways that pass through the suprachiasmatic nucleus, linking the retina to the pineal gland.[17] Our demonstration that the photic pathway used by the circadian system is functionally intact in some blind patients supports the hypothesis that in these patients light may synchronize the circadian pacemaker, and thus the sleep–wake cycle, to the 24-hour day.

Data obtained in studies of animals support our hypothesis of photic entrainment in some blind patients. Light-induced shifts in circadian phase that require the eyes are undiminished in a strain of mutant mice with retinal degeneration,[27,28] despite the complete loss of light perception, negative electroretinograms, and histologic verification of widespread retinal degeneration.[27,28] Similarly, ocular exposure to light entrains circadian rhythms in blind mole rats, in which projections from the retina to the suprachiasmatic nucleus are preserved despite complete blindness, an atrophic subcutaneous eye, and the widespread degeneration of central visual structures.[29] These results suggest that the mammalian eye subserves at least two photic systems: the occipital cortex, which mediates the conscious perception of light and the recognition of images, and a subcortical system that mediates light-sensitive synchronization of the circadian pacemaker.[2,14,27-30]

The visual system mediating the conscious perception of light is ordinarily far more sensitive to light[14,18] than the system mediating melatonin suppression, yet three patients could not perceive light of sufficient intensity to suppress their melatonin secretion. This suggests that the photoreceptive system mediating melatonin suppression differs — either quantitatively (i.e., in requiring only a few conventional photoreceptors)[27,28] or qualitatively (i.e., in using a novel phototransductive system with a distinct subgroup of retinal ganglion cells)[31] — from the photoreceptive system that mediates the conscious perception of light.[2,14,27-31] This is consistent with the preservation of circadian-phase–shifting responses in transgenic mice lacking rod photoreceptors and cone outer segments.[32]

Our hypothesis of entrainment by light in Patients 1, 2, and 3 does not preclude the possibility that weaker, nonphotic synchronizers have an influence in other blind patients. Despite a history of insomnia in Patients 8, 9, 10, and 11, their circadian rhythms were entrained to the 24-hour day during the study, notwithstanding bilateral enucleation in two of them and a lack of light-induced melatonin suppression in all four. This may re-

flect entrainment by nonphotic synchronizers in these patients, whose intrinsic circadian period may be nearer to 24 hours.[7] Yet such nonphotic synchronizers were not sufficiently strong to entrain the circadian pacemaker in four other patients (Patients 4, 5, 6, and 7) who lacked light-induced melatonin suppression, despite their regular social and sleep–wake schedules.[5,7-9]

The loss of photic input to the human circadian system may constitute a distinct form of blindness. Such circadian blindness, often associated with insomnia, may afflict many blind patients. Although circadian blindness could occur in a sighted person, as has been reported in another strain of mutant mice,[33] we have not yet identified such a patient. Conversely, the preservation of circadian photoreception in otherwise totally blind patients can escape detection, even by sensitive electroretinographic or visual-evoked-potential testing,[28] as it did in three of our eight blind patients with eyes (Patients 1, 2, and 3). This ability to respond to light may be specific to the type of blindness and may thereby provide insight into the components of the visual system that subserve the circadian system.

Melatonin-suppression testing may contribute to the ophthalmologic care of blind patients. Measures to limit trauma and the further deterioration of apparently blind eyes would be prudent for patients in whom this pathway of light input is intact. Enucleation, sometimes performed for cosmetic reasons or to alleviate intractable pain, should be reconsidered, given its potential for disrupting the photic entrainment of the circadian pacemaker. Before bilateral enucleation is performed, a comprehensive evaluation of residual visual function, including light-induced melatonin suppression, may assist in identifying blind patients at risk of chronic, recurring insomnia and other symptoms associated with the loss of circadian synchronization to the 24-hour day.

REFERENCES

1. Chiang YP, Bassi JL, Javitt JC. Federal budgetary costs of blindness. Milbank Q 1992;70:319-40.
2. Rusak B. Neural mechanisms for entrainment and generation of mammalian circadian rhythms. Fed Proc 1979;38:2589-95.
3. Czeisler CA, Kronauer RE, Allan JS, et al. Bright light induction of strong (Type 0) resetting of the human circadian pacemaker. Science 1989;244:1328-33.
4. Miles LEM, Raynal DM, Wilson MA. Blind man living in normal society has circadian rhythms of 24.9 hours. Science 1977;198:421-3.
5. Orth DN, Besser GM, King PH, Nicholson WE. Free-running circadian plasma cortisol rhythm in a blind human subject. Clin Endocrinol 1979;10:603-17.
6. Martens H, Endlich H, Hildebrandt G, Moog R. Sleep/wake distribution in blind subjects with and without sleep complaints. Sleep Res 1990;19:398. abstract.
7. Sack RL, Lewy AJ, Blood ML, Keith LD, Nakagawa H. Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. J Clin Endocrinol Metab 1992;75:127-34.
8. Nakagawa H, Sack RL, Lewy AJ. Sleep propensity free-runs with the temperature, melatonin and cortisol rhythms in a totally blind person. Sleep 1992;15:330-6.
9. Klein T, Martens H, Dijk D-J, Kronauer RE, Seely EW, Czeisler CA. Circadian sleep regulation in the absence of light perception: chronic non-24-hour circadian rhythm sleep disorder in a blind man with a regular 24-hour sleep–wake schedule. Sleep 1993;16:333-43.
10. Aschoff J, Fatranská M, Giedke H, Doerr P, Stamm D, Wisser H. Human circadian rhythms in continuous darkness: entrainment by social cues. Science 1971;171:213-5.
11. Wever RA. The circadian system of man: results of experiments under temporal isolation. New York: Springer-Verlag, 1979.
12. Martens H, Klein T, Rizzo JF III, Shanahan TL, Czeisler CA. Light-induced melatonin suppression in a blind man. In: Program and Abstracts of the Third Meeting of the Society for Research on Biological Rhythms, Amelia Island, Florida, May 6–10, 1992. Charlottesville, Va.: Society for Research on Biological Rhythms, 1992:58. abstract.
13. Klein DC, Moore RY, Reppert SM, eds. Suprachiasmatic nucleus: the mind's clock. New York: Oxford University Press, 1991.
14. Morin LP. The circadian visual system. Brain Res Rev 1994;19:102-27.
15. Li Y, Jiang DH, Wang ML, Jiao DR, Pang SF. Rhythms of serum melatonin in patients with spinal lesions at the cervical, thoracic or lumbar region. Clin Endocrinol 1989;30:47-56.
16. Wurtman RJ, Axelrod J, Phillips LS. Melatonin synthesis in the pineal gland: control by light. Science 1963;142:1071-3.
17. Reppert SM. Circadian rhythms: basic aspects and pediatric implications. In: Styne DM, Brook CGD, eds. Current concepts in pediatric endocrinology. New York: Elsevier, 1987:91-125.
18. Remé CE, Wirz-Justice A, Terman M. The visual input stage of the mammalian circadian pacemaking system. I. Is there a clock in the mammalian eye? J Biol Rhythms 1991;6(1):5-29.
19. Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. Science 1980;210:1267-9.
20. McIntyre IM, Norman TR, Burrows GD, Armstrong SM. Human melatonin suppression by light is intensity dependent. J Pineal Res 1989;6:149-56.
21. Görtelmeyer R. On the development of a standardized sleep inventory for the assessment of sleep. In: Kubicki S, ed. Methods of sleep research. Darmstadt, Germany: Gustav Fischer, 1984:93-8.
22. Berson EL, Sandberg MA, Rosner B, Birch DG, Hanson AH. Natural course of retinitis pigmentosa over a three-year interval. Am J Ophthalmol 1985;99:240-51.
23. Mills JN, Minors DS, Waterhouse JM. Adaptation to abrupt time shifts of the oscillator(s) controlling human circadian rhythms. J Physiol 1978;285:455-70.
24. Shanahan TL, Czeisler CA. Light exposure induces equivalent phase shifts of the endogenous circadian rhythms of circulating plasma melatonin and core body temperature in men. J Clin Endocrinol Metab 1991;73:227-35.
25. Arendt J, Paunier L, Sizonenko PC. Melatonin radioimmunoassay. J Clin Endocrinol Metab 1975;40:347-50.
26. Brown EN, Czeisler CA. The statistical analysis of circadian phase and amplitude in constant-routine core-temperature data. J Biol Rhythms 1992;7(3):177-202.
27. Foster RG, Provencio I, Hudson D, Fiske S, De Grip W, Menaker M. Circadian photoreception in the retinally degenerate mouse (rd/rd). J Comp Physiol [A] 1991;169:39-50.
28. Provencio I, Wong S, Lederman AB, Argamaso SM, Foster RG. Visual and circadian responses to light in aged retinally degenerate mice. Vision Res 1994;34:1799-806.
29. Cooper HM, Herbin M, Nevo E. Ocular regression conceals adaptive progression of the visual system in a blind subterranean mammal. Nature 1993;361:156-9.
30. Takahashi JS, DeCoursey PJ, Bauman L, Menaker M. Spectral sensitivity of a novel photoreceptive system mediating entrainment of mammalian circadian rhythms. Nature 1984;308:186-8.
31. Moore RY, Speh JC, Card JP. The retinohypothalamic tract originates from a distinct subset of retinal ganglion cells. J Comp Neurol (in press).
32. Argamaso SM, Froehlich AC, McCall MA, Nevo E, Provencio I, Foster RG. Photopigments and circadian systems of vertebrates. Biophys Chem (in press).
33. Faradji H, Cespuglio R, Rondot G, Paut L, Jouvet M. Absence of light-dark entrainment on the sleep-waking cycle in mice with intact visual perception. Brain Res 1980;202:41-9.