(CNS) arousal that may stimulate respiratory drive in a nonspecific manner. (ii) Respiration during AS is totally a function of diaphragmatic movements, whereas intercostal muscles are additionally involved in QS and W (*12*). (iii) In some adults, compared with QS, AS is characterized by a lower CO_2 threshold and a more sensitive CO_2 response curve (*13*). (iv) Coupling between respiration and heart rate (sinus arrhythmia) is more evident during QS than during AS in infants (*14*), and cat vagal nerves show less spontaneous activity during AS than during QS (*15*). Primitive intrauterine respiratory movements (fetal breathing) are observed regularly only during AS in the fetal lamb (*16*).

The predominant state in both newborn kittens and human infants is AS. Since AS is ontogenetically older than QS or W, neural modulation of the cardiorespiratory function in AS may be correspondingly more mature and stable early in life. During maturation, epochs of QS become longer, more frequent, and more stable: a process termed "coalescence" of the QS state (*17*). Comparison of 10- and 40-day-old control kittens in our study indicated much more developmental change in respiration rate and variability in QS than in AS (Table 1). Mechanisms controlling breathing during QS may mature in parallel with the emergence of that state, and immature respiratory control mechanisms may be more susceptible to hypoxic failure.

On the basis of the infant cat model of chronic hypoxemia, we hypothesize that AS "protects" human infants from SIDS. The predominance and tenacity of the AS state in the newborn period may account for the paradoxical immunity to SIDS in the first month of life. The peak risk period for SIDS coincides with the rapid decrease of AS time between 2 and 3 months of age. By 6 months of age, cardiopulmonary compensatory mechanisms in QS and W are more mature and effectual, and the risk of hypoxemic failure and death is reduced. Experimentally produced hypoxemia in kittens inhibits AS, perhaps by some nonspecific stress effect or by direct interference with metabolic conditions essential for CNS generation of AS. In a complementary manner, QS, W, and T states are prematurely augmented by hypoxia, which often results in abnormally extended intervals of labile cardiopulmonary control. Subsequent siblings of infants that die as a result of SIDS, a population with a higher risk of SIDS, showed less sleep apnea and higher respiration rate than a matched control group (*18*). These similarities to hypoxic kittens may constitute evidence of subclinical hypoxemia in infants with a high risk of SIDS. If AS is suppressed in hypoxemic infants, hypoxemia may progressively worsen, further inhibit AS, and terminate in the irreversible vicious circle of cardiopulmonary failure syndrome.

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7. This 40-day-old kitten and one of the 10-day-old kittens died during periods of hypoxic noncompensation. The three other 10-day-old hypoxic kittens died at night after 1 to 4 days of hypoxic conditioning. Death in these animals was not recorded. However, 12-hour recordings of each animal were made during the night immediately after the last hypoxic conditioning session. One noncompensating kitten experienced respiratory depression and extreme bradycardia (an 80-beat-per-minute drop) during QS several hours after hypoxic conditioning ended. This posthypoxic failure also reversed during AS and W, which suggests that non-AS cardiac and respiratory depression may follow chronic hypoxemia.
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Blind Man Living in Normal Society Has Circadian Rhythms of 24.9 Hours

Abstract. *A psychologically normal blind man, living and working in normal society, suffered from a severe cyclic sleep-wake disorder. Investigations showed that he had circadian rhythms of body temperature, alertness, performance, cortisol secretion, and urinary electrolyte excretion which were desynchronized from the 24-hour societal schedule. These rhythms all had periods which were longer than 24 hours and indistinguishable from the period of the lunar day.*

J.X., aged 28, who had been without light perception from birth owing to retrolental fibroplasia, was an otherwise healthy and active postgraduate student in biostatistics at a major university. For several years he had noticed that for 2 to 3 weeks at a time, insomnia and excessive daytime sleepiness severely interfered with his work and leisure activities. His strenuous but ineffective attempts to adjust to normal society included the cyclic administration of hypnotic and stimulant drugs. A sleep and activities diary suggested that he had a "free-running" circadian rhythm and that he was strongly and symptomatically entrained to a period slightly longer than 24 hours. His Minnesota Multi-phasic Personality Inventory (MMPI) was within normal limits.

After being without medication for 3 weeks, J.X. entered a hospital for a 26-day study in which he was allowed normal contact with society and access to all time cues except light perception. Facilities were provided so that he was able and encouraged to work, eat, sleep, and interact with others as he felt necessary or inclined. While awake, consecutive 90-minute urine samples were collected, and on five different occasions integrated 6-minute plasma samples were obtained by 24-hour continuous blood withdrawal through an antithrombogenic catheter.

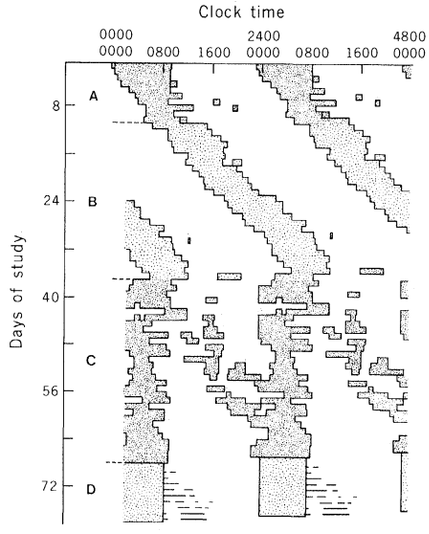

Fig. 1. Sleep-wake pattern of blind subject J.X. The shaded area denotes sleep. (A) In home environment with use of alarm clock. (B) Ad-lib sleep-wake, work, and meal schedule, without time isolation. (C) Return to usual home, work, and drug environment. (D) Entrainment attempt, with strict schedule of nocturnal sleep, meals, and activity. The small trailing lines in (D) show episodes during the entrainment attempt in which the Stanford Sleepiness Scale was greater than 3.

Regular observations included 15-minute measurements of alertness [Stanford Sleepiness Scale (*1*)], 30-minute performance tests, and 90-minute temperature, pulse, and respiration measurements. Standard polygraphic sleep recordings were obtained.

His pattern of sleep and wakefulness during this study (which we will call the "ad-lib sleep" study) is shown in a conventional double plot (Fig. 1B). Under these conditions, J.X. spontaneously adopted a sleep-wake cycle of about 24.9 hours and was asymptomatic for the first time in many years. Furthermore, the sleep-wake cycle during the 10 days before admission (Fig. 1A) had the same "free-running" tendency, despite his habitual arousal at 0900 by means of an alarm clock.

On the 37th day J.X. returned home and attempted to readjust to a 24-hour day, but his fragmented sleep (Fig. 1C) appeared to closely maintain the phase and period of his "free-running" cycle.

A 10-day attempt to entrain J.X. to a nycthemeral (24 hour) rhythm was begun on day 69 (Fig. 1D) because the acrophase of his body temperature then occurred at the normal time, and his sleep phase coincided with normal nocturnal sleep. During this trial we instituted a strict schedule of bedtime, meals, and activity. At 2300 hours he was put to bed with instructions to sleep. His watch, radio, and books were removed and the light was turned off. He was not allowed up except to urinate, until 0700 hours, when he was aroused and made to leave his bed. No sleep was allowed during the day.

On this regime his sleep-wake cycle showed evidence of unabated "free-run," so that his nocturnal sleep became progressively disrupted and his daytime became progressively invaded by sleepiness and deteriorating performance. During the ad-lib sleep study (Fig. 1B) his sleep parameters were essentially normal. During the "entrainment" study (Fig. 1D) J.X. showed an increase in wake time after sleep onset ($P < .2$) and a significant increase in sleep latency ($P < .05$) and total wake time ($P < .05$), whereas total sleep time ($P < .01$), sleep stage 4 (slow-wave sleep) ($P < .01$), and sleep stage REM (rapid eye movement or "dream" sleep) ($P < .001$) showed significant decrease.

The patterns of serum cortisol and growth-hormone secretion were determined throughout days 12, 17, 22, 28, and 35 (during the ad-lib sleep study) and day 78 (last day of entrainment study). The major growth-hormone secretion occurred in association with stage 4 sleep and therefore appeared to "free-run" during the ad-lib sleep study and to be well entrained to 24 hours during the entrainment study. In normal adult humans, cortisol is secreted episodically with a circadian rhythm having an acrophase at about wake onset (0800 hours) and a nadir at about sleep onset (2400 hours). In J.X., the pattern of episodic cortisol secretion appeared normal during the five blood withdrawals of the ad-lib sleep study; however, the acrophase was inconsistent with a circadian period of 24 hours. Values averaged according to clock time showed no circadian trend (Fig. 2a), but when these serum cortisol values were averaged from a 24.9-hour "free-run" reference point, a "smoothed" but otherwise normal circadian pattern was found (Fig. 2b). This pattern was normally related to his sleep-wake cycle.

During the last day of the entrainment study the pattern of cortisol secretion was clearly abnormal (Fig. 2c). The circadian acrophase was displaced to 1530 hours (8.5 hours after wake onset) and was consistent with a cortisol rhythm which continued to "free-run" throughout the entrainment study. The circadian nadir was also displaced and appeared at 0500 (6 hours after sleep onset). The major episodic secretion appeared rhythmic

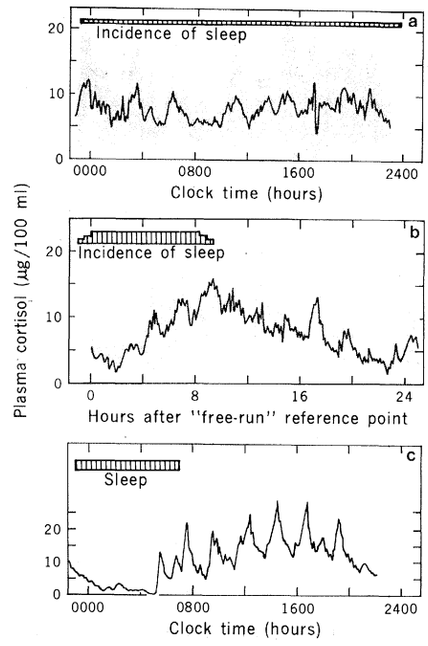

Fig. 2. Plasma cortisol values during the ad-lib sleep study (compare Fig 1B) averaged according to clock time (a) and 24.9-hour "free-run" period (b) and compared with values obtained during the last day of the entrainment study (c) (compare Fig 1D).

(period 2.4 hours) and extended throughout 16 hours, apparently owing to the fact that some secretory activity remains associated with wake onset (0700 hours).

Circadian rhythms of body temperature; urinary K, Na, Cl, Ca, and PO_4; alertness; and performance also had a period of 24.9 hours and continued to "free-run" during the entrainment attempt. All these circadian rhythms "free-ran" despite the fact that J.X. endured extraordinary social pressure to conform to usual nycthemeral behavior.

Normal subjects isolated from all time cues usually revert to circadian rhythms which have a period of about 25 hours (*2*), and this rhythm can be artificially reentrained by regular "zeitgebers" (*3*). As a result, at least two authors have explicitly postulated the existence of the syndrome we have now identified in J.X. In 1968 Halberg (*4*) suggested that such a mechanism might explain single 24-hour physiological profiles obtained during an early study of "late-blind" subjects by Remler (*5*), and might also explain a series of alternate day measurements in one case of manic-depressive psychosis reported by Bryson and Martin (*6*). In 1972 Webb and Agnew (*7*) postulated that "superdian" rhythms might become manifest as sleep-wake disorders in some people. Indeed, they invented a fictional case history which might well be applied to J.X., the subject of our report.

Orth *et al.* (*8*) briefly reported findings on a blind subject who appeared to have a "free-running" component of cortisol secretion despite a normal sleep-wake cycle. In several other studies, psychologically normal subjects not isolated from time cues, but with varying degrees of blindness, did not show evidence of "free-running" circadian rhythms (*9*). Nevertheless, our subsequent survey of 50 subjects with varying degrees of blindness revealed that 38 complained of a significant sleep-wake disorder. Of these, 20 reported that their symptoms were cyclic or episodic, 14 had no light perception, 18 were blind from birth, and 13 had retrolental fibroplasia (as did J.X.).

The syndrome suffered by J.X. is not necessarily restricted to the blind. When symptoms are less severe, the syndrome would rarely be suspected, and without sophisticated long-term monitoring or autorhythmometry (*10*) the diagnosis will be difficult to confirm. Nevertheless, the disorder might not be uncommon, and the social and economic impact of even minor symptoms might be substantial.

In view of the many publications which have demonstrated that animal (including human) biological systems are influenced by lunar rhythms (*11*), it is notable that J.X. maintains a circadian rhythm that cannot be significantly distinguished from the period of the lunar day (24.84 hours). Furthermore, throughout the ad-lib sleep study, there was a remarkable coincidence between his sleep onset and a local low tide.

Full details of this unusual case are in preparation (*12*).

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Memory Formation: Evidence for a Specific Neurochemical System in the Amygdala

Abstract. *β-Adrenergic antagonists injected into the amygdala complex of rats trained in a passive avoidance task produced time-dependent and dose-dependent decreases in retention of the task. In addition, the effects observed with β-adrenergic antagonists were both stereospecific and reversed by norepinephrine. The results support a role for an amygdala β-adrenergic system in memory processes.*

Clinical observations of retrograde amnesia following brain trauma (*1*), and permanent loss of long-term memory formation capabilities with temporal lobe resection in humans (*2*), have guided investigations with laboratory animals in which attempts have been made to elucidate the neuroanatomical and neurochemical substrates underlying memory formation. Although a wide variety of disruptive agents such as electroconvulsive shock, anesthetics, and protein synthesis inhibitors have been used in these investigations, the results generally agree that the sooner the agent is applied after an experience, the greater is the amnesia for the experience (*3*). This time-dependent retrograde amnesia gradient confirms and extends the earlier clinical findings of retrograde amnesia following human brain trauma. However, owing to the widespread and nonspecific effects of many of these amnesic agents (*4*), our knowledge of the specific neuroanatomical and neurochemical substrates underlying the memory process has not been greatly enhanced by their use.

Researchers have also investigated systematically the neuroanatomical and neurochemical systems involved in long-term memory formation in animals (*5*, *6*). Here we report that microinjections of β-adrenergic blocking agents into the amygdala of rats that have received a single training experience produce retrograde amnesia which is both time-dependent and dose-dependent. Furthermore, the amnesia produced by these agents is demonstrated to be stereospecific and re-

Table 1. Latencies on day 2. The control groups were as follows: 1, no surgery; 2, surgery only; 3, vehicle only.

Group	Dose (nmole)	*N*	Median (seconds)	Interquartile range (seconds)
Control groups				
1		17	268	139 to 576
2		9	279	80 to 411
3		8	216	145 to 315
Propranolol				
4	8.5	9	166	34 to 576
5	17.0	7	113	35 to 291
6*	34.0	9	30	11 to 180
10†	34.0 (6 hours delay)	9	135	87 to 397
12†	34.0 (dextro isomer)	8	235	126 to 322
Alprenolol				
7	8.5	6	155	45 to 297
8*	17.0	8	69	11 to 187
9*	34.0	9	44	8 to 74
11†	34.0 (6 hours delay)	8	246	166 to 414
13†	34.0 (dextro isomer)	6	182	134 to 302

*Mann-Whitney U tests (two-tailed) performed between these groups and the control groups (pooled data from groups 1 to 3) revealed significant differences ($P < .01$). †While each of these groups did not differ significantly from the pooled control data (groups 1 to 3), groups 10 and 12 each differed significantly from group 6. Likewise, groups 11 and 13 differed significantly from group 9.