esotropia is uncorrectable, at least in terms of the development of cortical binocularity (*14*).

Our primary conclusion is that the sensitive period for the development of binocularity begins several months after birth, and peaks between 1 and 3 years of age. In cases of congenital esotropia, early corrective surgery appears to be indicated for the development of cortical binocularity, which is presumably a prerequisite for fusion and stereopsis. Our data are consistent with several clinical reports that success in managing esotropia is more likely if surgery is performed early (*15*). In contrast, our findings suggest that immediate corrective surgery is not necessary to maintain cortical binocularity when the esotropia is of late onset (approximately 4 years and over).

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5. The tilt aftereffect may be defined in the following way. After prolonged adaptation to a high-contrast grating tilted slightly from vertical, a vertical test grating appears to be rotated slightly in the opposite direction. If the adapting grating is viewed with one eye and the test grating with the other, interocular transfer is defined as the amount of transfer of the aftereffect from the adapted eye to the unadapted eye.
6. D. E. Mitchell and C. Ware, *J. Physiol. (Lond.)* **236**, 707 (1974); J. A. Movshon, B. E. I. Chambers, C. Blakemore, *Perception* **1**, 483 (1972).
7. Concomitant esotropia refers to a convergent deviation that is essentially equal for all directions of gaze. Esotropia with an accommodative component is one in which the angle of deviation varies with the accommodative state of the crystalline lens.
8. The apparatus and procedure are described more fully in M. S. Banks, R. N. Aslin, R. D. Letson, in preparation.
9. Congenital esotropia is defined as an esotropic deviation present at birth. However, ocular alignment in normal infants is variable until 4 to 6 months of age. Thus congenital esotropia is commonly defined as a measurable deviation first detected prior to 4 months [P. E. Romano, *J. Pediatr. Ophthalmol.* **8**, 88 (1971)] or 6 months [F. D. Costenbader, *Am. Orthopt. J.* **18**, 5 (1968)] after birth.
10. The function used to describe the relative importance of different periods for the development of binocularity was:
$$f(t) = e^{-(t-d)/\tau_1} - ke^{-(t-d)/\tau_2}$$
where t represents age, and τ_1, τ_2, k, and d are constants. The integral of this function is used to estimate the cumulative normal binocular experience encountered by a subject. For a subject with a history of esotropia from age A to age B the estimate of NBE is given by
$$\mathrm{NBE} = \frac{\int_0^C [e^{-(t-d)/\tau_1} - ke^{-(t-d)/\tau_2}]dt}{\tau_1 - k\tau_2} \Big/ \frac{\int_A^B [e^{-(t-d)/\tau_1} - ke^{-(t-d)/\tau_2}]dt}{\tau_1 - k\tau_2}$$
where A is the subject's age at the onset of esotropia; B, the age at the end of esotropia; and C, the age when we tested the subject. With a computer program, we systematically varied τ_1, τ_2, k, and d to find the values which yielded the highest correlation between NBE and interocular transfer. The optimum values were $\tau_1 = 1.6$, $\tau_2 = 1.2$, $k = 1.0$, $d = 0.3$ for the congenital esotropes.
11. It can be argued that the reported onset of esotropia is an inaccurate index of when the strabismic deviation first began, especially in view of the difficulty of reliably diagnosing esotropia during the first 6 months of life [F. D. Costenbader, *Trans. Am. Ophthalmol. Soc.* **59**, 397 (1961)]. To test whether such an inaccuracy affected our findings, we performed the data analysis with all onsets less than 6 months set to age zero. The resultant best-fitting function was nearly identical to the function obtained when reported onsets were used. Thus, the use of reported onsets did not appear to lead to artifactual findings.
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13. The NBE values were obtained by setting age at testing to a large value and by setting age at strabismic onset to zero such that NBE is equal to
$$\frac{1 - \int_0^B [e^{-(t-d)/\tau_1} - ke^{-(t-d)/\tau_2}]dt}{\tau_1 - k\tau_2}$$
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16. We thank P. Salapatek and J. D. Pettigrew for helpful comments. Supported by NICHD grant HD-00098 to the Center for Research in Human Learning and by NICHD grant HD-05027 to the Institute of Child Development.

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Apneas During Sleep in Infants: Possible Relationship with Sudden Infant Death Syndrome

Abstract. *Several types of apnea are described in premature infants and in infants who have survived breathing-stoppage episodes which may be related to the sudden infant death syndrome. Upper airway apnea appears to induce the greatest changes: oxygen desaturation is more pronounced than in a central apnea of similar duration, and secondary cardiac changes are observed earlier and are more severe.*

It has been hypothesized that sleep apnea is involved in certain cases of sudden infant death syndrome (SIDS) (*1, 2*). There is also evidence that premature infants with prolonged apneas and "near-miss" infants—infants that survived episodes of prolonged cessation of breathing like those leading to crib death—have a much higher risk of subsequently dying of SIDS (*3*). In order to better understand the relationship between apneic episodes and sleep and the possible involvement of the two in cases of SIDS, we conducted polygraphic recordings during sleep and wakefulness in a population at risk, that is, near-miss infants and premature infants who presented long apneic episodes after birth.

Fifteen premature infants were studied. Group A included 11 premature infants continuously recorded for 6 to 8 hours, at 3 to 9 weeks of age. All weighed less than 2000 g at the time of study (range, 1000 to 1900 g; mean, 1650 g). Group B included four premature infants continuously recorded for approximately 20 hours, at 6 to 14 weeks of age. These infants weighed between 2400 and 3500 g.

Eight full-term babies who had been taken to the emergency room or to their pediatricians for "stop-breathing" episodes were also studied. These episodes reportedly occurred during sleep and required stimulation to terminate; stimulation ranged from shaking to mouth-to-mouth resuscitation. When found, the babies were described by the parents as cyanotic or white, unconscious, and not breathing. Complete pediatric examination failed to explain the sudden loss of consciousness during sleep in these infants. However, upper airway infections were present in five infants when hospitalized. A complete work-up, including cultures, was systematically performed to identify possible infections. All these infants were seen between October and March. Those in group C were three males (patients A to C), mean age 45 days, who were recorded for 6 to 8 hours. Infants in group D (patients D to H), mean age 108 days, were recorded continuously for a minimum of 18 hours. Several follow-up recordings were also made on near-miss infants. Three low-risk (control) infants were also monitored (group E).

The family histories of patients B and H indicated a similar problem in a sibling. Patient B's half-brother (same mother), who is now 6 years old and apparently healthy, was hospitalized for two stop-breathing episodes at 13 and 14 weeks of age. Patient H's brother was found dead during a daytime nap 3 days after developing symptoms suggestive of a mild upper respiratory infection. Final diagnosis in this case was SIDS.

Patients were studied during sleep and wakefulness. Electroencephalograms (C_3/A_2-C_4/A_1 and usually O_2/O_1), elec-

trooculograms, and chin electromyograms were recorded by standard methods (*4*). Respiration was monitored by two mercury-filled strain gauges—one abdominal and one thoracic—and two thermistors positioned in front of the mouth and in front of the nostrils. In some near-miss cases, an intraesophageal pressure transducer was positioned through the mouth to give continuous recording of intraesophageal pressure, which has been correlated with intrathoracic pressure (*5*). Groups C and D were also monitored during sleep with an ear oxymeter to obtain a continuous oxygen saturation curve. An electrocardiogram lead was also continuously monitored. Behavioral criteria were systematically checked by an observer and noted on the record during the entire monitoring.

For premature infants and those less than 3 months old, sleep was scored as suggested for newborn infants (*6*); for older infants, it was scored as described for adult sleep (*4*). Respiration was scored in accordance with criteria established in our population of adults and older children with sleep apnea. Apnea was defined as a cessation of air exchange lasting 10 seconds or longer; a cessation of air exchange lasting 3 to 9 seconds was called a respiratory pause. The term "periodic breathing" was used to describe successive respiratory pauses as described by Parmelee *et al.* (*7*). Three types of apnea were defined in infants. Central or diaphragmatic apnea was scored when flat tracings were obtained from the two mercury strain gauges and the two thermistors. The endoesophageal pressure transducer, when inserted, also showed an absence of change in pressure (flat tracing). An upper airway apnea was scored when mercury strain gauges exhibited continuous deflections but no air exchange was recorded with the two thermistors. To avoid uncertainty in scoring upper airway apnea, we relied on the observations of the experimenter at the time of the apnea as well as the continuous curve from the ear oxymeter which showed oxygen desaturation concomitant with the apneic episode. When the endoesophageal pressure transducer was inserted, it showed a progressive increase in pressure with each diaphragmatic movement during an upper airway apnea. A mixed apnea was scored when a central apnea followed by an upper airway apnea was noted during one cessation of air exchange; we have never observed the reverse order.

Infants were stimulated when an apneic episode reached 20 to 30 seconds, depending on the intensity of the bradycardia noted on the recording by the experimenter. Bradycardia was scored when the cardiac rhythm dropped by at least 20 beats per minute during the apnea compared to the previous minute's mean heartbeat rhythm.

Table 1. Data for patient A.

Data	12 hours after admission	48 hours after first recording
Sleep time (minutes)		
Total sleep	231	160
Quiet + indeterminate	172	120
Active (REM)	59	40
Number of episodes		
Total apneas	35	8
Central apneas	4	7
Mixed + obstructive apneas	31	1
Total respiratory pauses	55	38

For premature infants in group A, a mean of 29 apneic episodes were recorded in the four infants of very low birth weight (less than 1400 g) compared to a mean of 19 apneic episodes in the other seven prematures in this group. Sixty-eight percent of the apneic episodes appeared during quiet and indeterminate sleep, and 5 percent appeared within minutes after feeding while the infant was still awake or in a transitional (drowsy) state. The longest apneic episodes were always associated with quiet or indeterminate sleep. All apneic episodes were of the central type.

For group B premature infants, no apneic episodes were observed when the infants were awake. A mean of 130 respiratory pauses per infant (3 to 9.9 seconds) occurred, 53.8 percent (mean, 70) during active [rapid eye movement (REM)] sleep. A mean of 18 apneic episodes was observed (range, 3 to 56); 61.1 percent (mean, 11) appeared during quiet and indeterminate sleep. Of these apneic episodes, 68.5 percent were classified as central apnea, 9 percent as upper airway apnea, and 22.5 percent as mixed apnea. Bradycardia followed a mean of 11 apneic episodes in each infant. The most severe bradycardia was always noted when an infant had a mixed or upper airway apnea. One patient (D.C.), recorded shortly after a dramatic near-miss event, had 103 respiratory pauses and three upper airway apneas.

Group C infants were recorded within 36 hours after admission. At their first recording, the three infants had a mean of 37.5 respiratory pauses and 24 apneic episodes (range, 10 to 35). The apneas were classified as central (mean, 8.8; range, 4 to 14) and upper airway and mixed (mean, 13.6; range, 2 to 31). Two of the three infants had nasopharyngeal infections when admitted. Patient A, who had a nasopharyngeal infection when hospitalized, was rerecorded within 48 hours after the first recording (Table 1). In this patient, (i) bradycardia was associated with all apneic episodes during the first recording, but with only one in the second; (ii) clinically, the nasopharyngitis greatly improved between the first and second recordings; and (iii) there was a shift from a predominance of upper airway apnea to central apnea within 48 hours.

Three of the five group D infants had upper airway infections when referred to the Neonatology Division. They were recorded within 10 days of the initial near-miss incident. No apneic episode was recorded during wakefulness. A mean of 167 respiratory pauses occurred (range, 21 to 355), with 58.7 percent (mean, 98) of these pauses during active (REM) sleep. There was a mean of 5.25 apneic episodes (range, 0 to 10), of which 76 percent were central apnea and 24 percent were upper airway and mixed apnea.

Patient D, who had two near-miss episodes within 48 hours, was recorded twice, 24 hours and 5 days after the second episode. Total sleep times were 453 minutes in the first recording and 571 minutes in the second, active sleep times were 111 and 194 minutes, respectively, and 21 respiratory pauses were recorded in each session. Only one central apneic episode occurred, although ten episodes of bradycardia (sudden decreases from a mean of 120 to 70 heartbeats per minute) occurred in each recording session. These episodes lasted more than 15 seconds, were seen only during sleep, and were not related to apnea. In infants G and H, episodes of bradycardia during sleep did not follow apnea but occurred simultaneously with the onset of some apneic episodes.

In follow-up recordings, near-miss infants recorded at 3 months (cases B and H) and 4 months of age (cases E and F) showed similar numbers of respiratory pauses and apneic episodes. In infants 6 months of age, a marked decrease in any type of stop-breathing episode was observed. However, infant H at 6 months of age developed an upper airway infection with a runny nose, followed by a stop-breathing episode during sleep which necessitated resuscitation. A 12-hour nocturnal sleep recording performed when the upper airway infection was subsiding, compared to one executed 10 days before the appearance of infection, showed an increase of sleep-related respiratory pauses from 40 (four during REM sleep) averaging 5.3 seconds to 84 (21 during REM sleep) averaging 5.7 seconds.

Patients A and B were rerecorded when nearly 15 months of age for a mean of 20

hours. Patient A had three central apneic episodes during sleep (average, 11.2 seconds); one occurred during active sleep and was associated with rapid eye movements, and two occurred during stage 2 non-REM (NREM) sleep. Six respiratory pauses (average, 6.5 seconds) were also recorded. Patient B had 33 sleep-related apneic episodes (average, 12 seconds), of which 30 were of the central type; 30 were seen during stage 2 NREM sleep and were followed by bradycardia. Sixty-one sleep-related respiratory pauses (average, 7 seconds) were also recorded.

For group E (control) infants, an average of 25 respiratory pauses (average, 3.4 seconds) and one episode of central apnea (average, 10 seconds) were recorded at birth; 109 respiratory pauses (average, 6 seconds) and 0.4 episode of central apnea (average, 10 seconds) were recorded at 3 months of age; and 50 respiratory pauses and no apneas at 6 months of age.

A direct relationship between birth weight and amount of apnea has been reported in premature infants (*8*). It appears from our data that although apneic episodes are primarily central in infants of low birth weight, upper airway and mixed apnea can be recorded in older prematures of higher weight. The distinction between the different types of apnea is important because the most severe and longest episodes of bradycardia were always associated with upper airway or mixed apneas in premature as well as near-miss infants. In addition, our recordings with the ear oxymeter showed greater desaturation during upper airway apnea than during central apnea (mean difference, 7 percent). We hypothesize that the increased muscular effort required during an upper airway apnea may explain this finding. In addition, low-risk infants also have respiratory pauses (central type) which are most frequent near 3 months of age.

Epidemiological data indicate that near-miss episodes in full-term infants or prematures who have outgrown apnea of prematurity frequently occur in combination with a slight upper airway infection. Our data confirm that upper airway apneas occur more frequently in infants with such infection. The results from case A suggest the following hypothesis: Certain infants may spontaneously present a slight regulatory defect of the central mechanism of respiration during sleep, which leads to frequent respiratory pauses or even repetitive episodes of central apnea during sleep. If an upper airway infection is superimposed on the respiratory dysfunctions, hypopneic episodes may become complete upper airway apneas, and some central apneas may become the mixed type as a result of this external factor. There also may be a feedback loop, acting on respiratory command during sleep. An increased number of "respiratory pauses" (RP) (primarily of the central type) and central apneas associated with the upper airway infection may be secondary to the hypoxia, hypercapnia, and mild acidosis normally seen during sleep apnea (*9*). The greater oxygen desaturation produced by upper airway apneas may induce a greater dysfunction of the neuronal network involved in controlling respiration than occurs during central apneas.

During voluntary breath-holding, slowing of the sinusal cardiac rhythm can be observed in normal subjects. This is commonly known as the "diving reflex" and is also observed during central apnea in infants (premature or full-term). Mixed and upper airway apneas induced more severe changes, however. All the changes seen in infants, as well as repetitive arrhythmias and laborious inspiratory efforts, have been documented in both our adult and child populations (*10*). From our data we propose that upper airway apnea at onset of inspiration presents the most serious risk for an infant; inspiratory upper airway apnea with marked bradycardia and severe arrhythmia (such as sequences of ventricular tachycardia that we have recorded during upper airway apnea in our child and adult populations) may lead to sudden death.

Some SIDS infants seem to have suffered episodes of repetitive apnea before their sudden death (*11*). This would support the theory that a similar respiratory dysfunction may be involved in certain cases of SIDS and near-miss episodes. Considering the epidemiologic and anatomic findings, we believe that certain SIDS infants with a dysregulation of respiratory drive may have developed upper airway apnea during an upper airway infection and that the apnea led to severe dysrhythmia, and, depending on the type of dysrhythmia, death.

We emphasize the following points. (i) It has been hypothesized that REM sleep was the "at risk" period. Our recordings, however, indicate that the worst apneic episodes (longest duration, greatest oxygen desaturation; upper airway apnea associated with bradycardia) occurred not during REM sleep but always in quiet or indeterminate sleep. This result is in accordance with our findings in children and adults with sleep apnea in stage 2 NREM sleep and the observations of Parmelee *et al.* in prematures (*7*). (ii) Upper airway infection in some near-miss infants can upset the precarious equilibrium. Thus, we recommend hospitalization and careful evaluation when an upper airway infection occurs in any near-miss infant who has shown a large number of respiratory pauses and apneic episodes during sleep. (iii) Apnea monitors have been recommended in near-miss cases. Our data suggest that if a monitor detects only the presence or absence of thoracic and abdominal movements, it will be ineffective in cases of upper airway apnea, in which respiratory movements increase. In such cases, apnea monitors may have no therapeutic value unless cardiac rate is also monitored. (iv) Steinschneider (*1*) has reported a familial factor in certain cases of SIDS. In our eight near-miss cases, two had a positive familial history.

Finally, in at least one near-miss case we were unable to demonstrate any respiratory irregularity during wakefulness or sleep. We feel that the near-miss and perhaps the SIDS populations are heterogeneous. One segment presents dramatic incidents associated with an upper airway infection. These infants with a slight central respiratory dysfunction developed upper airway or mixed apnea (or both) which induced severe cardiac changes. Another segment seems to have no respiratory involvement but may have a dysregulation of the central control of the heart. At this time, however, we have little data to support the latter hypothesis.

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