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Melatonin Production in Healthy Infants: Evidence for Seasonal Variations

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ABSTRACT

The objective of this study was to determine the normal range of nocturnal urinary excretion of the major melatonin metabolite, 6-sulfatoxymelatonin (6SMT) in a large sample of healthy full-term infants (8 and 16 wk old) and assess whether the endogenous production of melatonin changes with season. 6SMT was assessed in urine samples extracted from disposable diapers removed from full-term, 8- ($n = 317$) and 16-wk-old ($n = 93$) infants over the nocturnal period (19:00–08:00 h). In addition, 6SMT was assessed in 8-wk-old ($n = 35$) healthy infants over the entire 24-h period. 6SMT was determined by an ELISA assay. 6SMT excretion at 8 wk of age exhibited diurnal variations with (mean ± SD) 61 ± 18% of the daily production excreted during the nocturnal period regardless of season. The nocturnal 6SMT values in the entire cohort (at 8 as well as 16 wk of age) were found to significantly depart from normal distribution (Kolmogorov-Smirnov test). A normal distribution was obtained using a natural base logarithmic (ln) transformation of the data. The normal range (2.5–97.5 percentile of the ln 6SMT excretion per night) was thus defined as 4.66–8.64 (106–5646 ng/night) for 8-wk-old and 5.19–9.67 (180–15,820 ng/night) for 16-wk-old infants. A significant effect of the month of birth on 6SMT production at the age of 8 wk was found (ANOVA, $p < 0.002$) with maximal levels produced by infants born in June (summer solstice) and minimal excretion in infants born in December (winter solstice). Short-photoperiod-born infants excreted on average about threefold less 6SMT compared with long-photoperiod-born infants (t test, $p = 0.01$). The seasonal variations were no longer present at 16 wk of age. No effect of breast-feeding at the time of sampling on seasonality of 6SMT was found. Normal ranges for the nocturnal urinary excretion of 6SMT in full-term infants at 8 and 16 wk of age are defined. This enables the evaluation of nocturnal 6SMT excretion as a prognostic and diagnostic factor for child development. The strong effect of season on the normal excretion of nocturnal 6SMT at 8 but not 16 wk of age suggests prenatal influence of the photoperiod on the ontogeny of melatonin. **(*Pediatr Res* 49: 63–68, 2001)**

Abbreviations:
SIDS, sudden infant death syndrome
ALTE, apparent life-threatening event
6SMT, 6-sulfatoxymelatonin
ln, natural base logarithm

The changes in photoperiod are major environmental cues for initiating seasonal acclimatization of thermoregulatory mechanisms and reproduction. In all mammals studied to date, including humans, the nocturnal production of melatonin by the pineal gland reflects the photoperiod (1, 2) and plays a key role in seasonal acclimation. Humans are not considered photoperiod sensitive, although some disorders such as seasonal affective disorders (3) and cluster headache (4) have been associated with a particular season.

Sudden infant death syndrome (SIDS) was shown to occur more frequently during the winter months, during the night, and during the first months of life (5). Some evidence links pineal dysfunction and impaired development with increased prevalence of SIDS (6, 7). A delayed melatonin production was found in infants who had experienced an apparent life-threatening event (ALTE) (6). Nevertheless, there is little information on whether the development of melatonin production in infants is seasonally regulated.

The ontogeny of melatonin production has been extensively studied (7–11). The urinary metabolite of melatonin, 6-sulfatoxymelatonin (6SMT), has been proven to be a very reliable index of melatonin production in humans including infants (11). Using a diaper extraction method, it has recently been shown that daily rhythmic 6SMT excretion appeared at 9 to 12 wk of age in full-term infants and at the corresponding postconception age in premature infants (7, 8). The latter report, which implied that there were no significant seasonal variations in melatonin production at 12 wk of age, has led to the suggestion that the ontogeny of melatonin in infants does not depend on season.

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The evaluation of melatonin production in infants as a clinical and diagnostic marker of child development is, however, limited by the lack of a definition of the normal range of melatonin for a given age group.

The purpose of the present study was to establish the normal range of nocturnal 6SMT excretion in full-term infants at 8 and 16 wk of age using a large sample of healthy infants. In addition, we sought to reassess whether the production of melatonin in infants depends on season. This was achieved using a recently developed method (6) for extraction of the urinary components from disposable diapers and for determination of 6SMT content by ELISA.

Because human milk contains some melatonin and, in addition, a pronounced circadian rhythm in melatonin content in human milk has been reported (12), we examined whether melatonin production in the infants was influenced by their being breast- or bottle-fed at the time of assessment.

Due to practical reasons (ease of implementation in the clinic and better compliance of the caregivers), we have concentrated on the determination of nocturnal values of 6SMT excretion. This would be meaningful only if the 6SMT excreted during the nocturnal period out of the entire 24-h period is a constant fraction. To examine this hypothesis, we performed a control study on the diurnal rhythm of 6SMT excretion in a group of 35 8-wk-old infants and determined the ratio of the nocturnal to 24-h 6SMT excretion during both the winter and summer periods.

METHODS

Subjects. The nocturnal urinary excretion profile of 6SMT over a 13-h period (19:00–08:00) was assessed in 317 full-term infants at the age of 8 wk (176 males and 141 females) and in 93 infants (55 males and 38 females) at the age of 16 wk. In addition, the 24-h daily rhythm of urinary excretion of 6SMT was studied in 35 full-term healthy infants at the age of 8 wk (16 males and 19 females). The study infants were recruited from the infant population that visited the well-baby clinics in the city of Tel Aviv for routine periodical medical examination and immunizations. The study was approved by the local institutional review board and informed consent was obtained from all parents following a detailed explanation of the nature of the study. Forty-seven percent (149/317) of the 8-wk-old study group infants and 43% (15/35) of the control group were breast-fed at the time of assessment. The percentage of the breast-fed infants did not significantly differ in the 35 and 317 infant groups [chi ($df = 1$, $n = 352$) = 0.22, $p = 0.65$, χ^2 test].

Protocol. Parents were instructed to retain all diapers used by the infant during the nighttime (19:00–08:00) (410 infants) or a 24-h period (35 infants), remove fecal matter, wrap each diaper in a separate, numbered zip-lock bag that was supplied to the parents, and mark the time each diaper was changed. In this study, we focused on determining the total amount of 6SMT excretion during the night. Therefore, it was unnecessary to enforce fixed diaper exchange intervals during the night, hence, the rate of diaper change was habitual. The diaper-containing bags were transferred to the laboratory within 20 h of collection.

To enhance compliance, no instructions were given to the parents regarding the lighting conditions for the infants while sleeping at night. Some variability may exist in lighting conditions in individual homes that may have increased the variability in individual 6SMT excretion values. Nevertheless, it was assumed that the variability in lighting conditions in individual homes would average across a large study cohort, because lifestyle of families with small babies is not very variable, especially during weekdays. In addition, it is customary for the light intensity in homes in Israel to be dim, less then 10 lux. To minimize the influence of lifestyle changes due to weekends, all studies were performed between two working days (Mondays to Thursdays) in the subjects' homes and no diaper collections were performed during the weekend.

Measurements. 6SMT content of each diaper was determined as described (6). Briefly, on receipt in the laboratory, the diapers were weighed and net urine weight calculated from the difference between the total weight and the weight of an unused diaper of the same brand. Samples of the wet diaper pulpy lining were removed by forceps, weighed (approximately 100 mg each) and macerated in 1 mL methanol. The suspensions were centrifuged (10^4 g/min), the extracts collected and then stored at −20°C until assayed, and the residual resins dried and then weighed. The urine content of the sample was calculated from the difference between the weight of sample and the dry resin weight.

The urine extracts were further diluted with buffer to obtain values readable from the standard curves and the 6SMT content determined on a double-blind basis, by an ELISA assay (Neurim Pharmaceuticals Ltd., Tel Aviv, Israel). The sensitivity of the assay was 3 fmol/tube and the intra-and interassay coefficients of variance were 8.1% and 15.5%, respectively. The validity of this method has been described elsewhere (6).

To assess the uniformity of 6SMT recoveries from the diapers, samples were collected from six distinct loci in each of four different infant wet diapers. 6SMT was extracted from each sample and assayed as described. Mean 6SMT content of each diaper was calculated from the results of the six sampling loci. The coefficient of variation values of the 6SMT content of each diaper were 11%, 13%, 17%, and 15% (mean CV = 12.7%), indicating an even distribution of 6SMT in different loci of a diaper.

Urinary 6SMT is stable for at least 2 d stored at room temperature, for at least 1 wk at 4°C and at least 2 y at −20°C (13). To assess the stability of 6SMT when absorbed in the diaper, the content of 6SMT was assessed in diapers ($n = 3$) immediately at 1 and 2 d after being removed. The diapers were kept at room temperature during this period. The results of these studies indicated that the 6SMT content of the diaper at these times (7.80 ± 1.2, 7.31 ± 1.7, and 7.65 ± 0.9 μg/diaper, respectively) was stable for at least 2 d on the diaper.

Data Analysis. Kolmogorov-Smirnov test (14) was used to assess the normality of distributions of 6SMT values in the two age groups of infants.

The percentage of 6SMT excreted during the nocturnal period was calculated individually for each infant for whom urine was collected over the entire 24-h period ($n = 35$). The mean ± SD percent was then calculated for the entire group and for subgroups of infants born during the winter and the summer months.

To describe the periodic phenomena in quantitative terms, periodic (cosine) functions were fitted for the mean 6SMT excretion over the 24-h day/night cycle as well as for the mean nocturnal 6SMT in infants born in each of the 12 annual months:

$$y(t) = M_{24} + A_{24} * \cos[2\pi/24(t - \phi_{24})] \quad \text{and}$$

$$y(m) = M_{12} + A_{12} * \cos[2\pi/12(m - \phi_{12})]$$

respectively, where t represents the time of day (in hours), M_{24} the mean of data points over the daily period (mesor), A_{24} the amplitude of the daily rhythm, ϕ_{24} the daily acrophase (time of crest), and $y(t)$ the predicted value of the variable at time t, m represents the month of year (by number), M_{12} the mean of data points over the annual period (annual mesor), A_{12} the amplitude of the annual rhythm, ϕ_{12} the annual acrophase (month of crest), and $y(m)$ the predicted value of the variable at month m. The results of the best fit regressions are presented as solid lines in the figures and the values of parameters are given in the text.

ANOVA analysis was performed for testing the possible relation of the infants' month of birth and 6SMT excretion. The difference between the amount of 6SMT excreted nocturnally by infants born during months of short (October through March) and long (April through September) days and between infants assessed at winter (December through March) and summer (May through September) time was assessed using t tests for independent samples. In addition, the interaction between breast-feeding at the time of sampling and seasonal effects on nocturnal 6SMT excretion was analyzed by ANOVA.

RESULTS

Figure 1 represents the 24-h urinary excretion of 6SMT in 35 healthy full-term infants aged 8 wk. 6SMT excretion exhibited a daily rhythm that could be fitted into a cosine function with a mesor value of 99 ng/h, an amplitude of 33 ng/h, and an acrophase in the dark phase (04:00 h). The percentage of 6SMT excreted during the nocturnal period, calculated individually for each infant, was 61 ± 18% (mean ± SD) of the total 24-h excretion. Individual urinary excretion rates of 6SMT over 24 h in five full-term infants born between February and March and five full-term infants born between August and September are shown in Figure 2. The mean percentage of 6SMT excreted during the nocturnal period (19:00–08:00) was found to be similar for those two groups (58 ± 12% *versus* 58 ± 30%, respectively) indicating that the nocturnal excretion represents approximately 58% of the diurnal excretion at this age regardless of season of birth. No significant differences were observed in this group between 6SMT levels in breast-fed and non-breast-fed infants (Mean + SD; 3092 + 3094 and 3102 + 2596 ng/night, respectively, $p = 0.99$, t test) and between male and female infants (3321 ± 2904 and 2909 ± 2729 ng/night, respectively, $p = 0.66$, t test).

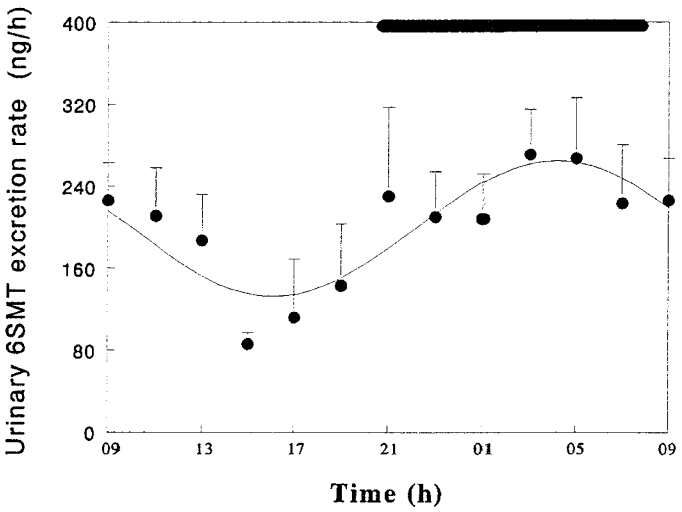

Figure 1. Average excretion rate of 6SMT over 24 h in urine collected from 35 full-term healthy infants at 8 wk of age (ng/h; mean ± SEM). *Line* is a cosine function only used for the purpose of outlining the distribution. The *black bar* represents the phase used for the assessment of nocturnal 6SMT production.

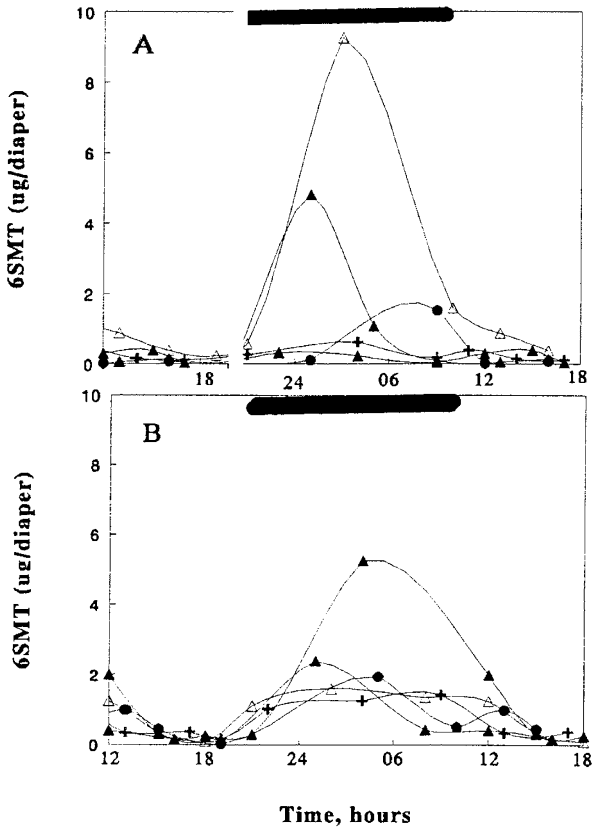

Figure 2. Individual excretion of 6SMT over 24 h in urine collected from five full term infants born in February or March (*panel A*) and five full-term infants born during August or September (*panel B*). The *black bars* represent the nocturnal phase.

The nocturnal excretion of 6SMT in infants aged 8 or 16 wk exhibited a major interindividual variability. For the two age

groups, the distribution of nocturnal 6SMT excretion showed patterns that significantly departed from normality [Kolmogorov-Smirnov test for normality; K-S $z = 3.30$, $p < 0.0001$ ($n = 317$) and K-S $z = 1.45$, $p < 0.05$ ($n = 93$), respectively]. A natural base logarithmic transformation (ln) on the data resulted in a normal distribution for both the 8- and 16-wk-old groups (K-S $z = 0.64$, $p = 0.81$ and K-S $z = 0.91$, $p = 0.38$, respectively) (Fig. 3). Normal 6SMT excretion, defined as 2.5–97.5 percentile of the ln (6SMT) excretion, was 4.66–8.64 (corresponding to 106–5646 ng 6SMT/night) for 8-wk-old infants and 5.19–9.67 (180–15,820 ng 6SMT/night) for infants aged 16 wk. No gender differences were found for 6SMT excretion in infants at wk 8 ($t_{(309)} = -0.11$, $p = 0.91$) and at wk 16 ($t_{(89)} = 0.43$, $p = 0.66$). A significant rise in ln 6SMT from age 8 to 16 wk was observed (6.69 ± 1.04 and 7.84 ± 1.00, respectively, $t_{(64)} = 7.34$, $p < 0.001$; *t* test for dependent samples).

The nocturnal 6SMT in infants aged 8 wk as a function of month of birth is shown in Figure 4. 6SMT excretion at 8 wk was lower in infants born between the September and March equinox than in those born between the March and September equinox, with minimum levels in infants born around the winter solstice and maximal levels in infants born around the summer solstice. On average, there was a threefold difference between the mean values of the populations born around the summer and winter solstices. 6SMT excretion exhibited seasonal variations that could be fitted into a cosine function with a mesor value of 990 ng/night, an amplitude of 490 ng/night, and an acrophase in June-born infants.

ANOVA showed a main effect of month of birth on the 6SMT excretion for the 8-wk-old infants ($F_{(11, 299)} = 2.74$; $p < 0.002$) but not for the 16-wk-old group ($F_{(11, 81)} = 1.87$; $p = 0.055$). At 8 wk of age, short-photoperiod-born infants (months October to March) had significantly lower 6SMT levels than long-photoperiod-born infants (months April to September) [mean ln (6SMT) ± SD; 6.70 ± 0.90 *versus* 6.98 ± 0.97, respectively, $t_{(302)} = -2.61$, $p = 0.01$, *t* test). Therefore, separate normal values (2.5–97.5 percentile of the ln 6SMT excretion) were defined for 8-wk-old infants born in long and short photoperiods. At 8 wk of age, normal 6SMT excretion for short photoperiod infants was 5.04–8.47 (corresponding to 154–4766 ng 6SMT/night) and for long photoperiod infants the normal range was 5.14–8.77 (170–6412 ng 6SMT/night).

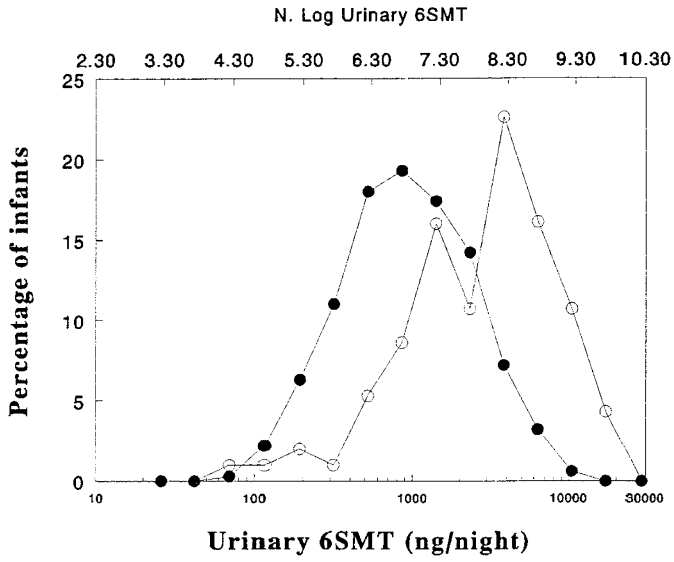

Figure 3. Frequency distribution plots of nocturnal 6SMT (ng/night) excretion in 8-wk-old (●) and 16-wk-old (○) infants. *Lines* are functions only used for the purpose of outlining the two distributions.

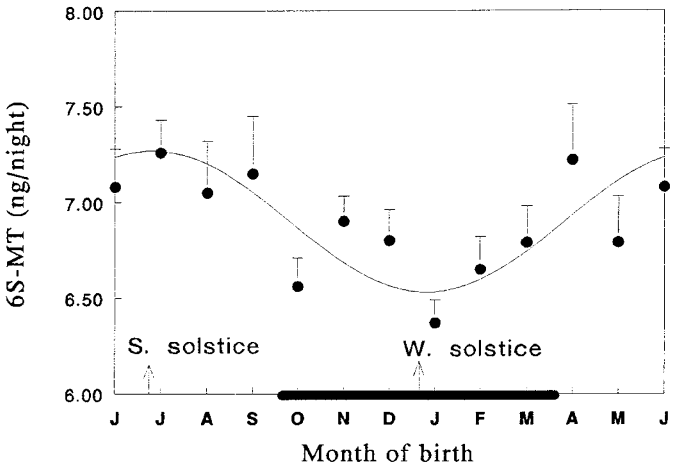

Figure 4. Natural base logarithm nocturnal 6SMT excretion in 317 8-wk-old infants by month of birth (mean ± SEM). *Line* is a cosine function used for the purpose of outlining the distribution. The *black bar* represents the winter phase; winter and summer solicits are shown as *arrows*.

At 16 wk of age there were no significant differences between 6SMT levels in long- and short-photoperiod-born infants ($t_{(89)} = -0.59$, $p = 0.56$).

To examine a possible effect of the ambient season on 6SMT production, a *t* test was performed comparing 6SMT levels in infants assessed during the winter (December through March in Israel) to infants assessed during the summer (May through September in Israel). At 8 wk of age, winter 6SMT levels were significantly lower than summer values [mean ln (6SMT) ± SD; 6.67 ± 0.89 *versus* 7.04 ± 0.99, respectively, $t_{(278)} = 3.28$, $p = 0.001$]. No significant difference was obtained for measurements performed at age of 16 wk. No significant interaction was found between breast-feeding and season ($F_{(1, 294)} = 2.30$, $p = 0.13$, ANOVA): comparing breast-fed with the non-breast-fed infant groups, short-photoperiod-born infants had lower levels (6.80 ± 0.97 *versus* 6.63 ± 0.91) than long-photoperiod-born infants (6.87 ± 1.02 *versus* 7.00 ± 1.03) for both groups, respectively.

DISCUSSION

The determination of 6SMT in urine using the diaper extraction method has been shown to be a reliable and practical method for the assessment of melatonin physiology in infants (8). Using this technique, a recent report has shown delayed ontogeny of 6SMT excretion in infants who had experienced an apparent life-threatening event (ALTE) (6). Because a whole daily (24-h) diaper collection is technically more difficult than overnight collection and requires individual parental cooperation also during the daytime, it is likely to be associated with decreased parental compliance. We, therefore, concen-

trated on the part of day that may be more informative on the one hand and practically applicable on the other. Using a large sample of healthy infants (8 and 16 wk old) the normal range of nocturnal urinary excretion of 6SMT has been defined. The results show that the nocturnal 6SMT values are consistent with the 24-h values, thus enabling us to use the nocturnal values for practical diagnostic purposes.

Low melatonin levels in infants and children were shown to be linked to prematurity (8), blindness (15), myoclonus (16), epilepsy (17), abnormal sleep (18), colic (19, 20), ALTE (6), and SIDS (21, 22). Melatonin production increases at about the same time when rapid eye movement (REM) abundance decreases in infants (7, 23); the latter may reflect cerebral maturation (23). The present study, which characterizes the early nocturnal urinary 6SMT production, may enable the use and application of this variable in the evaluation of pediatric neuropathologies (24) already during early infancy. The mean peak in daily 6SMT excretion rate found in our study for 8-wk-old infants (132 ng/h) is compatible with that reported by Kennaway *et al.* (7) for 12-wk-old infants (115 ng/h).

The present study shows for the first time that early in life (postnatal wk 8) nocturnal 6SMT production exhibits seasonal variations. Surprisingly, the nocturnal excretion of 6SMT was found to be significantly lower in infants born during the short photoperiod portion of the year than in infants born during the long photoperiod portion. This finding is surprising because, theoretically, melatonin production, which is inhibited by light, is expected to be higher during the short photoperiod. One possible explanation is that the percentage of 6SMT excreted between 19:00 h and 08:00 h differs between long and short days with prolonged melatonin production during the short photoperiod into daytime. However, no significant differences in the percent nocturnal 6SMT excretion out of the total 24-h excretion cycle was found in infants born in August or September (long days) compared with infants born in February or March (short days).

Another possible explanation is that during the winter months, infants are more exposed to artificial light, especially during evenings and nights, because they spend more time indoors. This explanation assumes that the ambient light schedule on day of testing is responsible for the seasonal differences. This however may not be the case inasmuch as outdoor light in Israel is of greater intensity than indoor light and, therefore, longer photoperiod should result in less melatonin excretion, contrary to what has been found. In addition, infants born a short period before the equinox (*e.g.* August) would be facing the opposite photoperiod at the time of assessment, 8 wk later (*e.g.* in October), and should thus exhibit values that resemble those of the short photoperiod. As shown in Figure 4, infants born close to the equinox (*e.g.* August) and tested in October have 6SMT levels similar to those born in July (long photoperiod). Moreover, we did not find a similar seasonal effect in the 16-wk-old infants, although those would be exposed to similar variations in ambient lighting schedules.

Our data indicates annual variations in 6SMT excretion in 8- but not 16-wk-old infants. The fact that Kennaway (8) reported a lack of seasonal effect on 6SMT production might be explained by the fact that they have studied older infants aged 12 wk. Thus, the photoperiod modulation of 6SMT excretion that occurs early no longer exists later in infants. There are two main explanations for the transient nature of this phenomenon. One explanation is that the pineal gland is sensitive to photoperiod during the first months of life. The human embryonic pineal gland exhibits two distinctive types of cells, a photoreceptor cell and a neuroendocrine cell eventually transforming into a melatonin-secreting pinealocyte (5). At the end of the third month of life, the photoreceptor cell type begins to lose its structure and finally vanishes during the fifth month (25). The size of the pineal gland is also affected by the season. Accordingly, Sparks has observed larger pineal glands in infants during the summer months (5).

Another explanation is that there is a prenatal influence, namely, that the rate of maturation of the pineal gland is modified by the prenatal exposure to maternal factors, perhaps melatonin. In rats, prenatal effects of maternal melatonin have been found to alter the response of the reproductive system in the offspring to the ambient photoperiod (26). In rats, the mother acts as a transducer between the environment and the fetal brain, coordinating the phase of the developing biologic clock to her own clock time (27). Vole infant development is influenced perinatally by maternal photoperiodic history (28). In the latter it was found that information is communicated to fetuses about the length of time dams have been exposed to short day length before mating as well as about the day length prevailing during gestation. Moreover, in humans an interaction between season of conception and incidence of neurodevelopmental disorders in the offspring (29) as well as interaction between season of birth and morningness-eveningness preference (30) has been demonstrated. This possibility is compatible with the fact that the dependency of excretion on the month of birth, not the month of assessment, matched the global change in photoperiod.

Theoretically, the 6SMT values as well as their seasonal variations might be biased by exogenous maternal melatonin supplied to breast-fed infants from their mothers. However, the lack of association in our study between breast-feeding at age of 8 wk and 6SMT excretion or seasonality does not support such a possibility. Non-photoperiod-dependent environmental factors such as seasonal changes in external temperature may also be associated with the seasonal effect of melatonin production (31). The dependency of melatonin production in infants on season of birth is most interesting, especially considering the fact that melatonin is the signal that conveys photoperiodic information to the organism (2). Accumulating evidence about seasonality of birth in individuals with neurologic and psychiatric disorders indicates that the impact of season of birth may extend far beyond infancy (32–34). Epilepsy appears to have an excess of births in winter and deficit in September. Multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and possibly Parkinson's disease appear to have an excess of spring births (33). Schizophrenia and schizoaffective disorder have an excess of winter births, whereas major depression has an excess of spring births (34). The monthly distribution of birth in patients with panic disorder peaks in September to December (35). Winter is associated with seasonal depression in adults (4) and young infants, and it

is apparently associated with colic (19, 20) and possibly SIDS (5). Our finding of lower nocturnal 6SMT production at 8 wk of age during autumn-winter time, a period with an increased rate of SIDS with peak incidence at night may be the basis for an appealing hypothesis for the involvement of melatonin in the etiology of SIDS and seasonality of birth in individuals who develop neurologic and psychiatric disorders later in life.

In conclusion, in this study the normal values for 6SMT excretion are presented for the first time for infants aged 8 and 16 wk, based on a large sample. It is also shown for the first time that 6SMT in young infants is remarkably subject to seasonal influence, with minimal values in infants born around the winter solstice. Further studies are needed to evaluate the physiologic relevance of these findings to child development.

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REFERENCES

1. Wehr TA 1997 Melatonin and seasonal rhythms. J Biol Rhythms 12:518–527
2. Reiter RJ. Neuroendocrine effects of light. Int J Biometeorol 1991:35:169–175
3. Waldenlind E, Ekbom K, Wetterberg L, Fanciullacci M, Marabini S, Sicuteri F, Polleri A, Murialdo G, Filippi U 1994 Lowered circannual urinary melatonin concentrations in episodic cluster headache. Cephalalgia 14:199–204
4. Sitton SC, Hughes RB 1995 Creativity, depression, and circannual variation. Psychol Rep 77:907–910
5. Weissbluth L, Weissbluth M 1994 Sudden infant death syndrome: a genetically determined impaired maturation of the photoneuroendocrine system. A unifying hypothesis. J Theor Biol 167:13–25
6. Sivan Y, Laudon M, Kuint J, Zisapel, N 2000 Low melatonin production in infants with a life threatening event (ALTE). Dev Med Child Neurol 42:487–491
7. Kennaway DJ, Stamp GE, Goble FC 1992 Development of melatonin production in infants and the impact of prematurity. J Clin Endocrinol Metab 75:367–369
8. Kennaway DJ, Goble FC, Stamp GE 1996 Factors influencing the development of melatonin rhythmicity in humans. J Clin Endocrinol Metab 81:1525–1532
9. Attanasio A, Borrelli P, Gupta D 1985 Circadian rhythms in serum melatonin from infancy to adolescence. J Clin Endocrinol Metab 61:388–390
10. Waldhauser F, Weiszenbacher G, Tatzer E, Gisinger B, Waldhauser M, Schemper M, Frisch H 1988 Alterations in nocturnal serum melatonin levels in humans with growth and aging. J Clin Endocrinol Metab 66:648–652
11. Hartmann L, Roger M, Lemaitre BJ, Massias JF, Chaussain JL 1982 Plasma and urinary melatonin in male infants during the first 12 months of life. Clin Chim Acta 121:37–42
12. Illnerova H, Buresova M, Presl J 1993 Melatonin rhythm in human milk. J Clin Endocrinol Metab 77:838–841
13. Arendt J, Bojkowski C, Franey C, Wright J, Marks V 1985 Immunoassay of 6-hydroxymelatonin sulfate in human plasma and urine: abolition of the urinary 24-hour rhythm with atenolol. J Clin Endocrinol Metab 60:1166–1173
14. Zar JH 1984 Biostatistical Analysis, 2nd Ed. Prentice Hall, Englewood Cliffs, NJ, pp 91–92
15. Davitt BV, Morgan C, Cruz OA 1997 Sleep disorders in children with congenital anophthalmia and microphthalmia. J AAPOS 1:151–153
16. Jan JE, Connolly MB, Hamilton D, Freeman RD, Laudon M 1999 Melatonin treatment of non-epileptic myoclonus in children. Dev Med Child Neurol 41:255–259
17. Fauteck J, Schmidt H, Lerchl A, Kurlemann G, Wittkowski W 1999 Melatonin in epilepsy: first results of replacement therapy and first clinical results. Biol Signals Recept 8:105–110
18. Jan JE, O'Donnell ME 1996 Use of melatonin in the treatment of paediatric sleep disorders. J Pineal Res 21:193–199
19. Weissbluth M, Weissbluth L 1992 Colic, sleep inertia, melatonin and circannual rhythms. Med Hypotheses 38:224–228
20. Weissbluth L, Weissbluth M 1993 The photo-biochemical basis of infant colic: pineal intracellular calcium concentrations controlled by light, melatonin, and serotonin. Med Hypotheses 40:158–164
21. Sparks DL, Hunsaker III JC 1988 The pineal gland in sudden infant death syndrome: preliminary observations. J Pineal Res 5:111–118
22. Wurtman RJ, Lynch HJ, Sturner WQ 1991 Melatonin in humans: possible involvement in SIDS, and use in contraceptives. Adv Pineal Res 5:319–327
23. Cornwell AC, Feigenbaum P, Kim A 1998 SIDS, abnormal nighttime REM sleep and CNS immaturity. Neuropediatrics 29:72–79
24. Cavallo A 1993 The pineal gland in human beings: relevance to pediatrics. J Pediatr 123:843–851
25. Calvo J, Boya J, Garcia-Maurino A, Lopez Carbonell A 1990 Postnatal development of the dog pineal gland. Light microscopy. Histol Histopathol 5:31–36
26. Shaw D, Goldman BD 1995 Influence of prenatal photoperiods on postnatal reproductive responses to daily infusions of melatonin in the Siberian hamster (Phodopus sungorus). Endocrinology 136:4231–4236
27. Reppert SM, Schwartz WJ 1983 Maternal coordination of the fetal biological clock in utero. Science 220:969–971
28. Lee TM, Zucker I 1988 Vole infant development is influenced perinatally by maternal photoperiodic history. Am J Physiol 255:R831–R838
29. Liederman J, Flannery KA 1994 Fall conception increases the risk of neurodevelopmental disorder in offspring. J Clin Exp Neuropsychol 16:754–768
30. Natale V, Adan A 1999 Season of birth modulates morningness-eveningness preference in humans. Neurosci Lett 274:139–141
31. Imai Y, Munakata M, Tsuji I, Ohkubo T, Satoh H, Yoshino H, Watanabe N, Nishiyama A, Onodera N, Kato J, Sekiro M, Aihara A, Kasai Y, Abe K. 1996 Seasonal variation in blood pressure in normotensive women studied by home measurements. Clin Sci (Colch) 90:55–60
32. Castrogiovanni P, Iapichino S, Pacchierotti C, Pieraccini F 1998 Season of birth in psychiatry. A review. Neuropsychobiology 37:175–181
33. Torrey EF, Miller J, Rawlings R, Yolken RH 2000 Seasonal birth patterns of neurological disorders. Neuroepidemiology 19:177–185
34. Torrey EF, Rawlings RR, Ennis JM, Merrill DD, Flores DS 1996 Birth seasonality in bipolar disorder, schizophrenia, schizoaffective disorder and stillbirths. Schizophr Res 21:141–149
35. Castrogiovanni P, Iapichino S, Pacchierotti C, Pieraccini F 1999 Season of birth in panic disorder. Neuropsychobiology 40:177–82