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# A CHRONOPEDIATRIC PIONEER WHO PRACTICES PREHABILITATION: A TRIBUTE TO THEODOR HELLBRÜGGE ON HIS 80TH BIRTHDAY*

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Chronobiology in human childhood started in the early fifties and is closely connected with the name of Theo Hellbrügge. The topics of chronobiology covered a broad range. They included the circadian rhythm in many biological functions such as body temperature, blood pressure, frequency of the heart as well as of the respiration; furthermore and peak expiratory flow and the response of patients treated by corticosteroids and other drugs.

This contribution notes the significance of this field for human development and underlines the main tasks for further scientific researches.

*Keywords*: Chronobiology; Circadian rhythm; Prehabilitation

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## INTRODUCTION

With this laudatio, we honor Theodor Hellbrügge, the leading pediatrician in the German speaking world; the founder of social pediatrics; the author of the basic elements of social pediatric developmental rehabilitation; and above all the pioneer in the chronobiology of the human fetus, of the newborn, and of the developing child. To many, his social pediatrics is the cornerstone of mushrooming institutes after the model of his endeavor realized in bricks and mortar in Munich. To a few of us, his name is associated with his first scientific love affair, chronopediatrics, and, we hope, "on revient toujours à ses anciens amours" [1–12].

One of us (FH) met Theo in the late 1950s, first on the dance floor and then in the conference room of a hotel on the Semmering near Vienna, at a meeting of the International Society for the Study of Biological Rhythms (now the International Society for Chronobiology).

## OUR INTERESTS CONVERGED IMMEDIATELY

At the same meeting, while Theo, with his wife Jutta, not only obeyed the high-frequency rhythms of dance but described the rhythms in early human life as well, FH reported on periodicity in RNA and DNA, in the substances that transmit information in the developing individual and from generation to generation.

## OVER THE FOLLOWING DECADES, WE ESTABLISHED A LINK BETWEEN THE UNIVERSITIES OF MUNICH AND OF MINNESOTA

Thanks to Theo's advice, a series of doctoral theses by medical and other students matriculated at the University of Munich were written in Minneapolis. The topics covered a broad range. They included the objective cosinor-validated phase response curve of patients with asthma treated by corticosteroid at different times, gauged by the circadian rhythm in peak expiratory flow, contributions by Alain

Reinberg with Karl Reindl. Wolfgang Maerz described blood pressure dynamics in the human newborn, while Bernhard Kleiser published on DHEA and DHEA-S in health and schizophrenia. A biometric-inferential statistical thesis was written by Bernhard Arbogast. Bernd extended the chronobiological serial section; his routine provided information concerning the changes with time of the rhythm characteristics obtained by the first fit of a cosine curve with a given frequency, such as that approximating a circadian rhythm. For this purpose, he developed second-order serial sections, involving, after the original fit of a cosine curve with a given frequency, the fit of cosine curves with lower and lower frequencies that modulated the parameters obtained originally. Methods were of interest to Theo, as were applications to problems in real life. On the basis of circadian variation in performance, he sought applications by scheduling classes in secondary schools, by the rhythms of the students rather than according to the popularity of teachers.

An early contribution by Theo is shown in Table I [6]. He wrote:

> Little is known about the physiological functions before birth. One of the few data available is the heart rate. We checked twelve healthy pregnant women. From the eighth to the tenth month of pregnancy the pulse frequency and the fetal heart sounds were checked every two hours during daytime and every three hours during the night.
>
> The results are shown in Figure 1. The pulse frequency of the pregnant women showed a typical 24-hour rhythm. There are two peaks at nine A.M. and at seven P.M., and a low night value

TABLE I Circadian rhythm of heart rate of mother and fetus during 8th to 10th month of pregnancy*

| | *PR* | *P* | *Double amplitude ± SE (% of 24-hour mean)* | *Acrophase (degrees) (95% CI)* |
|---|---|---|---|---|
| fetus | 75 | < 0.001 | 2.0 ± 0.3 | −212(−194, −233) |
| mother | 48 | 0.011 | 9.8 ± 2.6 | −197(−168, −227) |

* PR, percent rhythm (proportion of overall variation accounted for by fitted 24-hour cosine curve); P, P-value from test of zero-amplitude (no-rhythm) assumption; Double amplitude, measure of extent of predictable change within a cycle; Acrophase, measure of timing of overall high values recurring in each cycle, expressed in (negative) degrees, with 360° equated to 24 hours; 0° 00:00. CI = confidence interval. Analysis of normalized data (individual 24-hour means equated to 100%) averaged across 12 healthy pregnant women, taken off published graphs (Hellbrügge, T.: The development of circadian rhythms in infants. *Cold Spr. Harb. Symp. quant. Biol.*, 1960; **25**, 311–323).

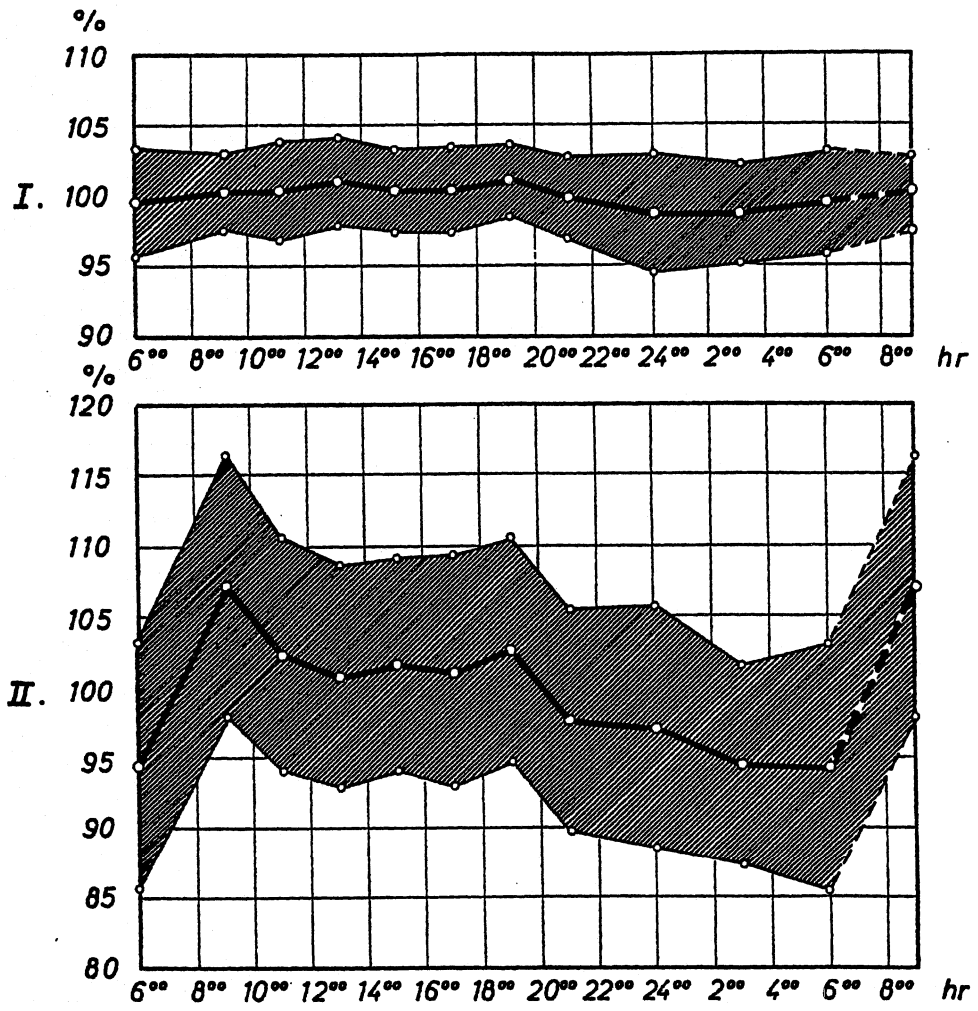



FIGURE 1 Changes along the 24-hour scale in the heart rate of the fetus (top) and mother (below) during the last months of pregnancy [6].

between nine P.M. and seven A.M. In contrast to this the fetal heart sounds were more or less constant during daytime and nighttime, showing a medium value of 133 ($\pm$ 5)/min. during the eighth and ninth months and 129 ($\pm$ 6)/min. during the tenth month.

Note the time-microscopic amplification from Table I. The data on fetal heart sound, which time-macroscopically appear to be more or less constant in Figure 1, allow a statistically significant rejection of the "zero circadian amplitude" or "no circadian rhythm" assumption. The 24-hour cosine curve actually provides a better fit for the data from the fetus than for those of the mother, although the circadian amplitude is much larger in the mother's data than in those

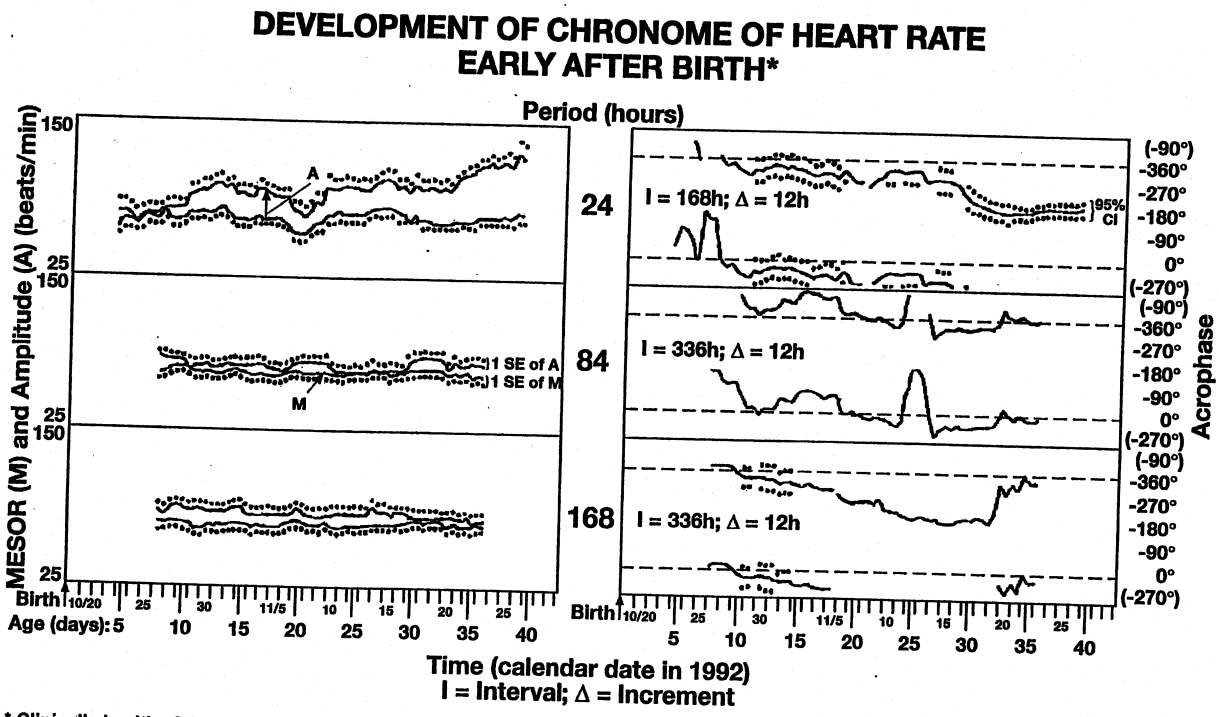
of the fetus. Note also the relatively close agreement in acrophase between the two data series, with a full overlap of their 95% confidence intervals (CIs) during the eighth month of pregnancy and thereafter.

Note from Table II that the circadian rhythm of heart rate is expressed on Day 2 with an acrophase of −290° (−257° to −323°) different from that of the fetus (−212°; 95% CI; −194° to −233°), as attested by the non-overlap of 95% CIs. The later failure to detect a circadian variation could possibly be due to a damping of the circadian in the first 5 weeks, an interpretation that cannot be ruled out; but it seems more likely that the lack of a group rhythm demonstration is associated with inter-individual differences in the possibly free-running circadian periods. The presence of a circadian rhythm well before the sixth week of life is supported by the demonstration of a rapidly increasing circadian amplitude and its initial free-running is seen from a drifting acrophase of heart rate in clinical health in a boy studied longitudinally at half-hour intervals for the first 6 weeks of life, Figure 2. As Table II also shows in later weeks and months, the circadian group rhythm of heart rate is again detected.

TABLE II Circadian rhythm of heart rate during early human development*

| *Age* | *N of infants* | *N of profiles* | *PR* | *P* | *Double amplitude ± SE (% of 24-hour mean)* | *Acrophase* |
|---|---|---|---|---|---|---|
| Day 2 | 49 | 49 | 73 | 0.010 | 6.8 ± 1.6 | −290(−257, −323) |
| Day 4 | 49 | 49 | 11 | 0.664 | 2.4 ± 2.7 | −292( , ) |
| Day 6 | 39 | 39 | 4 | 0.858 | 1.7 ± 3.0 | −228( , ) |
| Day 8 | 26 | 26 | 27 | 0.336 | 5.8 ± 3.6 | −260( , ) |
| Week 1 | 56 | 268 | 24 | 0.381 | 3.3 ± 2.2 | −273( , ) |
| Week 2 | 26 | 67 | 18 | 0.506 | 2.6 ± 2.1 | −257( , ) |
| Week 3 | 7 | 28 | 24 | 0.382 | 2.4 ± 1.7 | −331( , ) |
| Weeks 1−3 | 58 | 369 | 12 | 0.639 | 2.0 ± 2.0 | −238( , ) |
| Weeks 6−18 | 16 | 74 | 55 | 0.028 | 8.5 ± 2.6 | −152(−108, −195) |
| Mos. 5−8 | 4 | 35 | 49 | 0.050 | 10.6 ± 3.6 | −160(−110, −211) |
| Mos. 11−21 | 9 | 71 | 71 | 0.004 | 24.9 ± 5.3 | −186(−158, −215) |

* PR, percent rhythm (proportion of overall variation accounted for by fitted 24-hour cosine curve); P, P-value from test of zero-amplitude (no-rhythm) assumption; Double amplitude, measure of extent of predictable change within a cycle; Acrophase, measure of timing of overall high values recurring in each cycle, expressed in (negative) degrees, with 360° equated to 24 hours; 0° 00:00. Analyses of normalized data (individual means equated to 100%) averaged across infants in different age groups summarizing 627 24-hour profiles provided by 96 children during first 2 years of life; data taken off published graphs (Hellbrügge T., The development of circadian rhythms in infants. *Cold Spr. Harb. Symp. quant. Biol.*, 1960; **25**, 311−323).




*** Clinically healthy full-term boy (FW), studied around the clock for first 40 days after birth with automatic instrument; analysis of residuals after detrending by 5th-order polynomial; CI = confidence interval. Data of Y. Watanabe.**

FIGURE 2 Amplitudes (left) and acrophases (right), measures of the extent and timing of change during the development of a healthy boy.

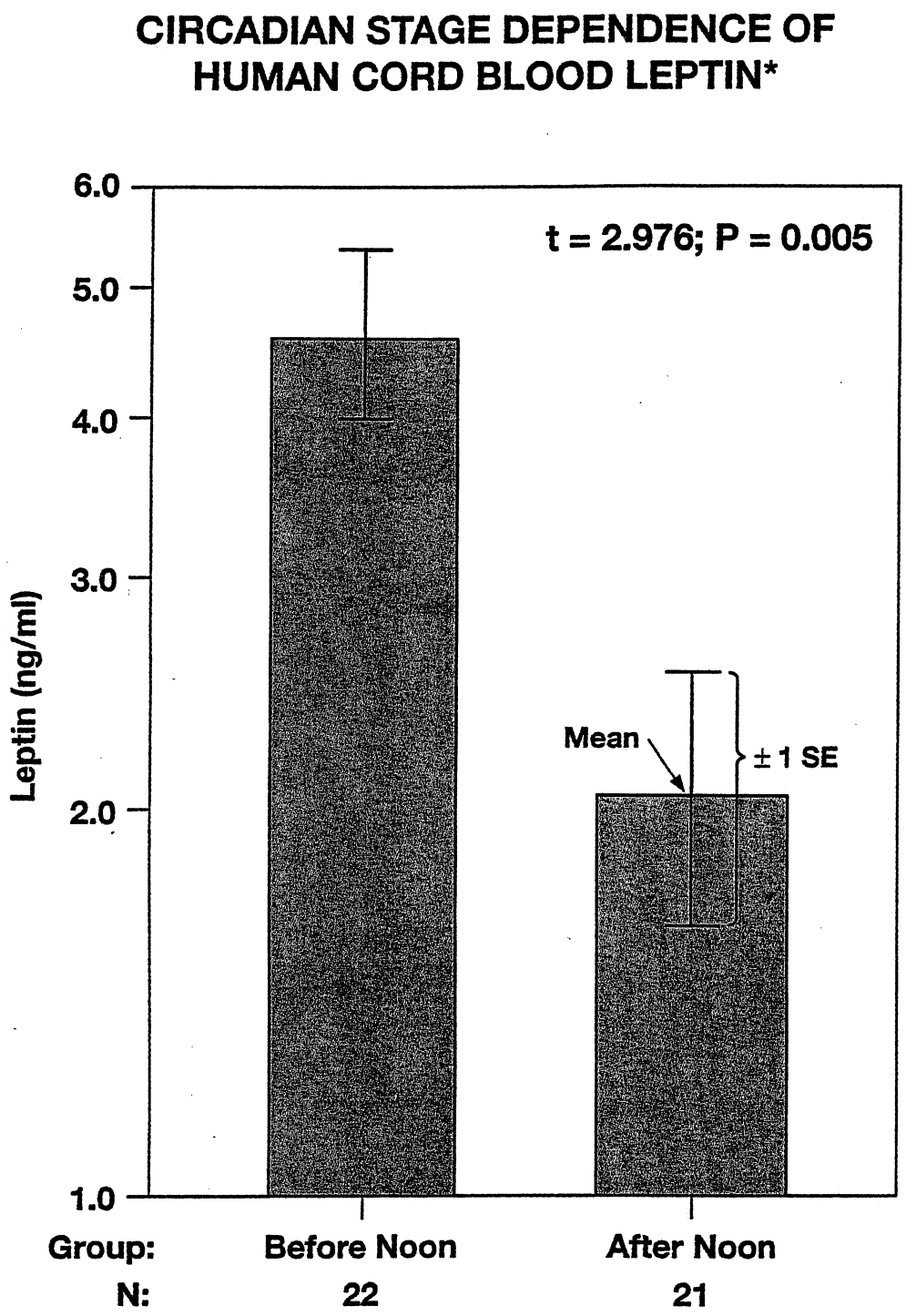



FIGURE 3 Circadian population rhythm along the 24-hour scale of leptin in cord blood [13].

FIGURE 2 Amplitudes (left) and acrophases (right), measures of the extent and timing of change during the development of a healthy boy.

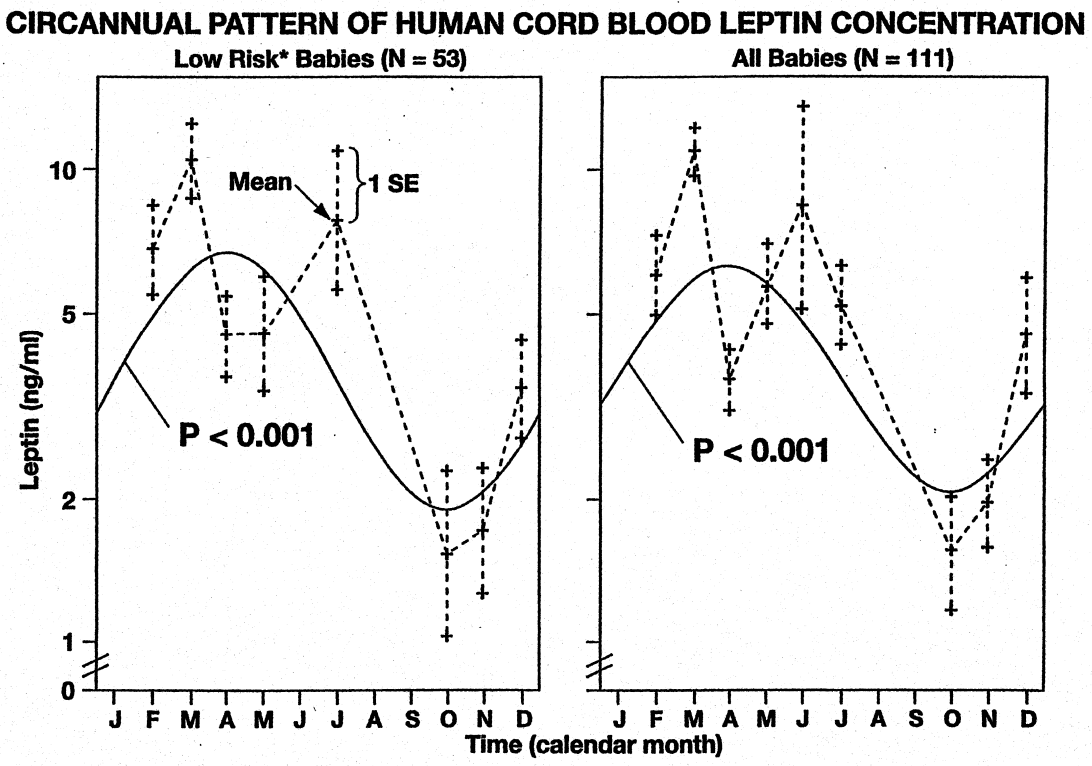



FIGURE 4 Circannual population rhythm of leptin in cord blood (13). © Halberg.

Not only the circadian heart rate rhythm is expressed early in life, as Theo's data suggest upon chronometa-analysis, Table II. Figures 3 and 4 document circadians and circannuals for the hormone leptin, demonstrable as group phenomena, already in cord blood [13]. With respect to Figure 2, Theo's data are invaluable. They show that on day 2 there is a demonstrable circadian heart rate rhythm for a group as a whole if one averages over a sufficient number of individuals, presumably because on the second day of life the rhythms are still reasonably inter-individually synchronized. By contrast, in a given individual whose data are analyzed separately, as in Figure 2, the circadian heart rate rhythm after birth is not readily demonstrable, albeit relatively rapidly it becomes sufficiently pronounced to be documented on an individual basis. The use of population rhythms in actual clinical applications emerges from studies on the effect of betamimetics that have been noted by two of us (CM and ES) in the human newborn and adolescent, respectively. Others among us then documented that the betamimetic effect results in an amplification of the circadian swing in blood pressure as well as in an increasing left ventricular mass index that persists into human adolescence [14]. Concern for "first do no harm" could thus prompt the use of treatments other than betamimetics in the case of premature labor.



FIGURE 4 Circannual population rhythm of leptin in cord blood (13). © Halberg.

## THEO HELLBRÜGGE HAS INTRODUCED BEHAVIORAL SCIENCE INTO PEDIATRICS, AND IN SO DOING PROVIDED ETHOLOGICAL MEASURES FOR DIAGNOSIS AND TREATMENT, FOR WHAT HE CONCEIVES OF AS DEVELOPMENTAL REHABILITATION

Initially, Theo's interest was very broad and led him to become editor of the Fortschritte der Medizin, wherein he sought to cover progress in all areas of medicine. But his real concern remained pediatrics and thus children. Theo has written or edited 51 books, including the volumes "Diagnosis", "Therapy", and "Social Pediatrics" of the 12-volume Handbook of Pediatrics, published by Springer. He contributes to various textbooks and has more than 1,000 publications in national and international journals. He has founded 5 pediatric journals (der kinderarzt [The Pediatrician], Sozialpädiatrie/Kinder-

und Jugendheilkunde [Social Pediatrics/Child and Adolescent Health Care], Video-Forum Kinderarzt [Pediatrician's Video Forum], Kindergesundheit [Child Health] and Kinderkrankenschwester [Pediatric Nurse]). His books on functional developmental diagnostics, including a book for parents on "The First 365 Days of a Child's Life", were translated into 30 languages and spread further to other languages.

Literally as well as figuratively, Theodor Hellbrügge's most spectacular contribution is the Kinderzentrum in Munich, a model of an interdisciplinary institute for early diagnosis, early treatment and social integration of children with disabilities. Against the resistance of all authorities, he founded the first kindergarten in the world in which children with and without handicaps learn and interact jointly, in a continuation of the physiological pedagogy of the French physician Eduard Seguin and of the Italian educator Maria Montessori. Also, more than 30 years ago, Hellbrügge founded "Aktion Sonnenschein" ("the Sunshine Project") in Munich to benefit children with multiple disabilities, a model for Sunshine organizations in various countries. His Kinderzentrum in Munich today has 80 centers in Germany and over 50 first- and second-generation spin-off centers worldwide that spread his ideas on early diagnostics, therapy and social integration to prevent children with disabilities from facing lifelong handicaps. He has been honored with many awards, honorary doctorates and honorary professorships.

In this light, he can turn back to what was to become chronobiology, his first love, which thereafter led him to make his contributions to social pediatrics. These two fields may seem remote, but are actually united by a common theme of prevention of obvious handicap in rehabilitation and, we add, of high risk syndromes that may prompt prehabilitation, *i.e.*, concern for risk reduction, as early in life as possible, in order to reduce the risks of the diseases in the second childhood by action pre- and perinatally.

Theo views social pediatrics as comprising three large fields. Primary prevention then includes preventive measures for healthy children, such as vaccination, health education, input into the construction of school buildings, group accommodation, hygiene and studies of workload. Secondary prevention screens for existing or developing disorders. What he then refers to as "tertiary prevention",

in his words, attempts to reduce or eliminate existing disorders by early psychosocial or other therapy, a field which he calls "developmental rehabilitation". He then promptly emphasizes that these tertiary endeavors should be called "developmental habilitation", since this action precedes the development of adult functional areas. He chose "developmental rehabilitation" intentionally because rehabilitation is a worldwide concept laid down by law, and material and financial help is available.

## BY LINKING THE TYPICAL BIOLOGICAL PHENOMENON OF "DEVELOPMENT" WITH "REHABILITATION", CONCEPTUAL AS WELL AS LEGAL CHANCES FOR A NEW FORM OF HELP FOR CHILDREN EVOLVED

Theo Hellbrügge amplifies that his developmental rehabilitation utilizes those abilities for adaptation and reorganization in early developmental stages that can help children with innate or early-acquired disorders or damage, so that they do not become handicapped. As examples, he seeks to prevent deaf children from becoming mute; children in the early stages of cerebral palsy from developing the full clinical form; or neglected children developing what he calls "sociosis". Along this line, the task of his first love, chronopediatrics, consists of developing the means for detecting risk elevations in the physiological range for earliest prehabilitation [15]. In so doing, more than circadian focus is required. The longitudinal pH data of a premature boy taken during the first 33 days of life reveal over 4 about-weekly cycles with an amplitude much greater than that of the also-approximated about-daily swings (Fig. 5). Actually, an about-monthly change is further apparent, and has an even greater amplitude when it is approximated by stacking in the case of heart rate and blood pressure (Fig. 44 in [16]).

Research during the past decades has revealed a time structure or chronome in many variables of early extrauterine life, of the newborn infant and child and in conditions such as sudden infant death syndrome, SIDS [17]. An age of higher susceptibility for SIDS may be

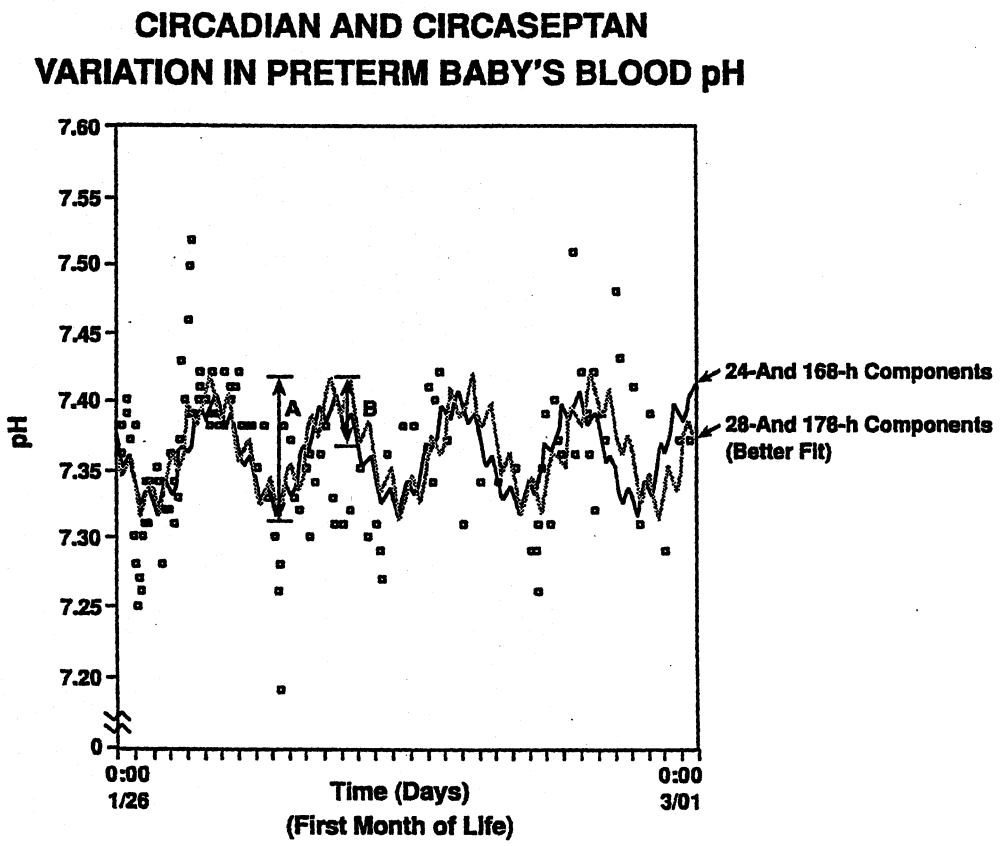



FIGURE 5 As compared to children, premature babies can be more easily monitored longitudinally; their circaseptan component has an amplitude often larger than the circadian, as illustrated for blood pH. Original values during the first five weeks of life are shown as quadrangles. Two curves are fitted to these data. The lighter curve, representing a model consisting of a 28- and a 178-hour component, fits the data better than the continuous curve corresponding to a model consisting of a precise 1-day and a 7-day component [16]. During very early human life, the circaseptan (with 1 cycle in about 7 days) can predominate over the circadian [17]. In this graph, the latter is represented by the smaller ripples superimposed on the (nearly five) cycles of larger amplitude recurring with a period of about 7 days.

programmed or set by the time of birth (Fig. 6); it is present congenitally, genetically or epigenetically. The ensemble of temporal features leading to SIDS may constitute an inopportune set of phase and amplitude relations among the congenitally programmed multi-frequency rhythms and age trends, rather than necessarily a gross deviation of the chronome-adjusted mean, *i.e.*, MESOR, in any one variable. If so, and if these deviations relate to infradians (components with a frequency lower than one cycle in 28 hours) as well as to circadians and ultradians (components with a frequency higher than one cycle in 20 hours), chronobiologic methods will be indispensable

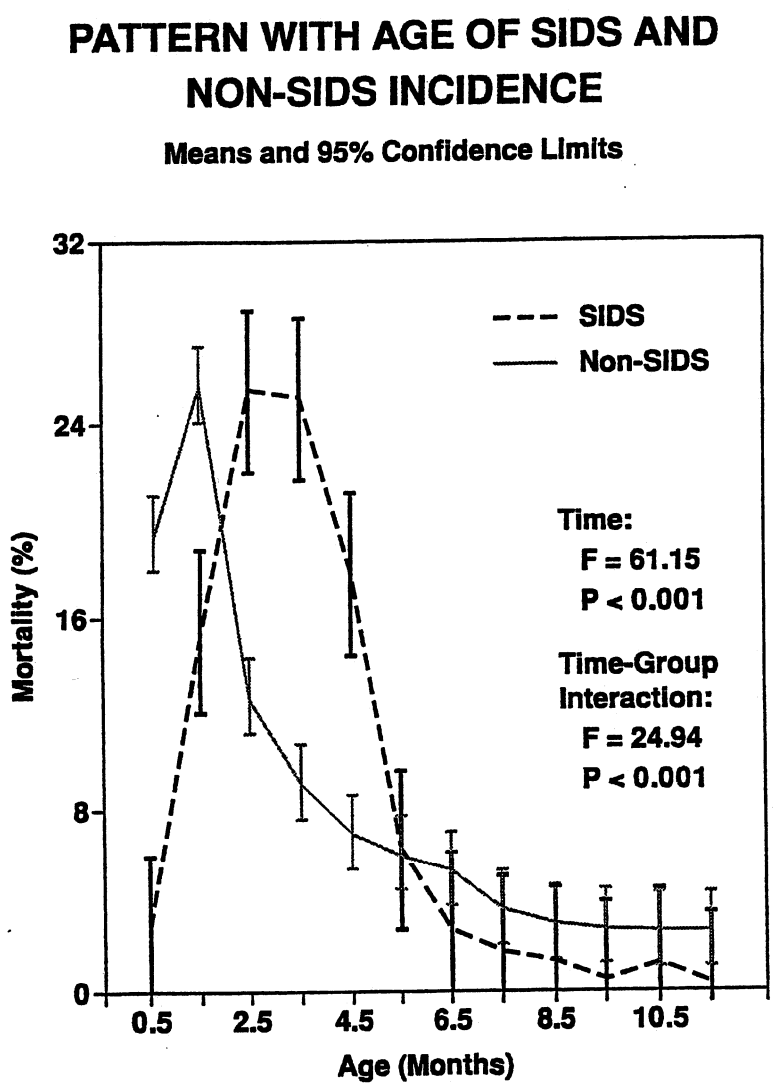
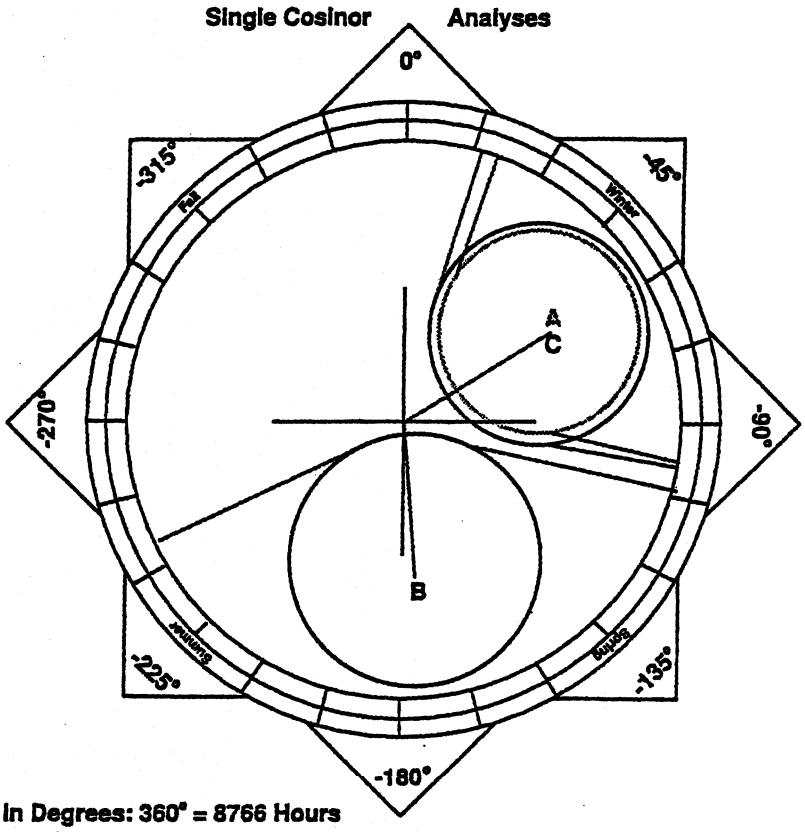



FIGURE 6 There is a statistically highly significant difference of over one month in the age of peak incidence of SIDS *vs.* infant deaths from all other recorded causes.

for both the prediction of SIDS and, what is more important, for a rational prevention. Some of these unfavorable time and amplitude relations may be specific for SIDS, just as the distribution of SIDS along the age scale seems to be characteristic of this condition (Figs. 7–11 and Tab. III).

The chronome of SIDS incidence suggests that by the time of birth (and perhaps by that of conception; this point remains to be clarified), there is a program for increased risk along several time scales. This chronorisk depends critically on the organism and much less on the environmental stimulus, often referred to as the trigger. A precedent

# CIRCANNUAL CHANGE IN INCIDENCE OF SIDS AND LIVE BIRTHS IN NORTHERN IRELAND[1]




| Key | P | N | PR | MESOR ± SE | Amplitude* | Acrophase (ϕ) * |
|---|---|---|---|---|---|---|
| C SIDS ** | 0.006 | 12 | 68 | 1.01 0.09 | 0.56 (0.19 0.94) | -58° (-16 -99) |
| A SIDS (monthly incidence) | 0.004 | 12 | 70 | 12.71 1.05 | 6.88 (2.54 11.21) | -58° (-19 -97) |
| B Live Births (x 1000) | 0.037 | 12 | 52 | 5.58 0.08 | 0.34 (0.02 0.66) | -173° (-104 -242) |

P = Probability of Hypothesis: Amplitude = 0; N = Number of Observations
PR = Percent Rhythm (Percentage of Variability Accounted for by Cosine Curve)

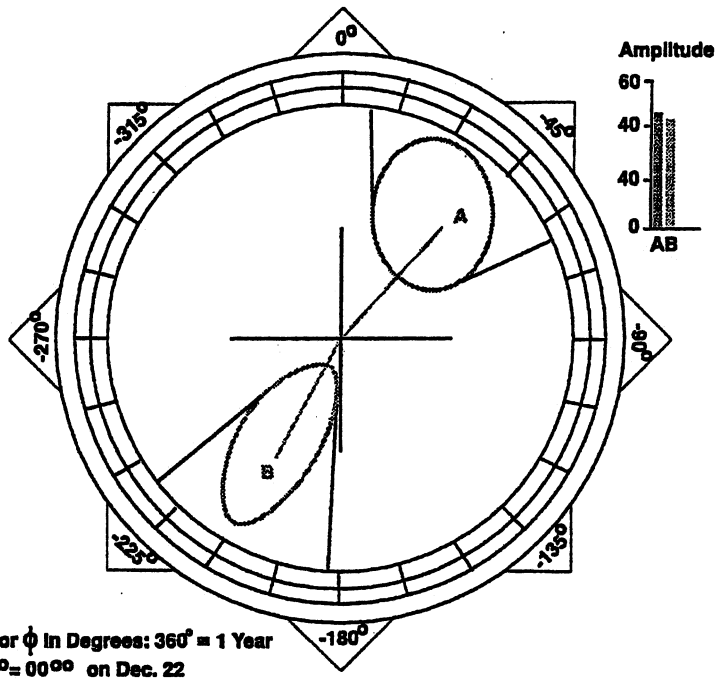
* Conservative 95% Confidence Limits (Parentheses) Derived from Cosinor Ellipse

** Relative Incidence, After Correction for Difference in Number of Days in Each Month

1 Data from Froggatt et al., Br J Prev Soc Med 25: 119 - 134, 1971

FIGURE 7 Incidence of live births in Northern Ireland follows a circannual pattern peaking in late spring and early summer. In this cosinor display, the circular scale on the rim represents one cycle, with 360° equated to 1 year and the reference time chosen as December 22. The circannual amplitude and acrophase of the fitted curve are represented as a directed line (vector). The ellipse shown around the tip of the vector is the 95% confidence region for the joint estimation of the amplitude and acrophase. A statistically significant difference in the circannual timing of the highest incidence of SIDS *vs.* stillbirths is shown by the non-overlap of the corresponding elliptical confidence regions. There is thus a time of higher susceptibility specific to SIDS along the scale of the calendar year just as there was one as a function of age (Fig. 6).

## CIRCANNUAL CHANGE IN SIDS INCIDENCE IN DIFFERENT HEMISPHERES



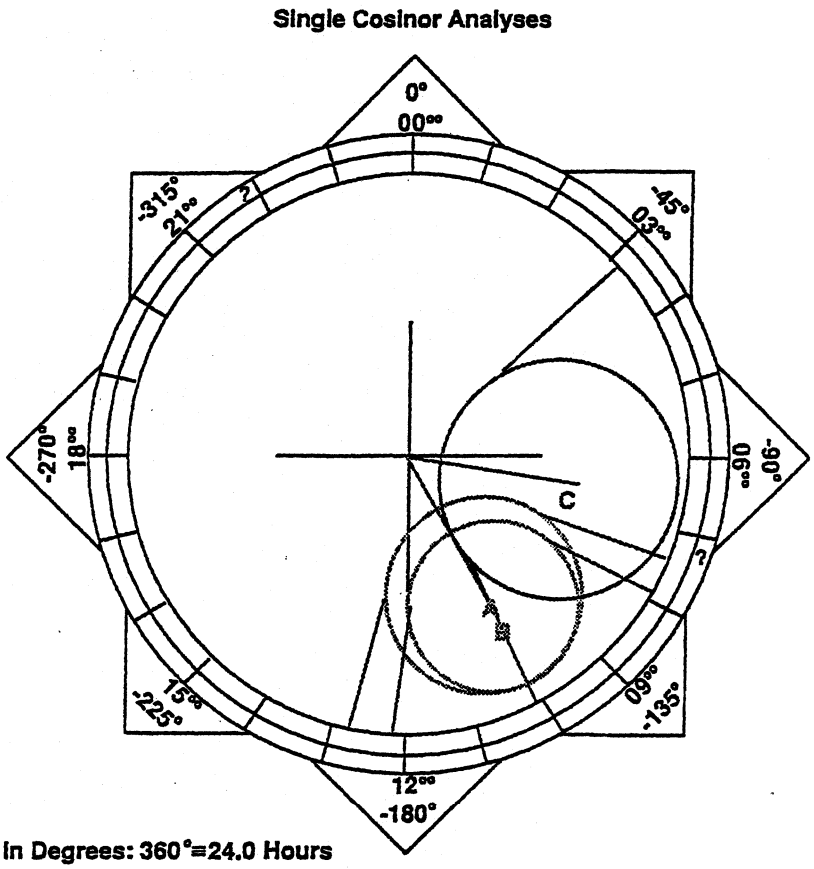

**Population - Mean Cosinor**

| Hemisphere | P | N | PR | Amplitude* | Acrophase (ϕ)* |
|---|---|---|---|---|---|
| A Northern | <.001 | 20 | 83 | 36 ( 22 50) | -29° (-9 -50) |
| B Southern | .020 | 5 | 69 | 42 ( 12 72) | -207° (-181 -234) |

P = Probability of Hypothesis: Amplitude = 0;
N = Number of Series Used by the Mean Cosinor Technique to Find Ellipse
* Conservative 95% Confidence Limits (Parentheses) Derived from Cosinor Ellipse
Amplitudes are Expressed as a Percentage of MESOR

FIGURE 8 A peak incidence of SIDS in the winter is observed both on the northern and on the southern hemisphere. Disturbances in the magnetosphere, gauged by a planetary index such as Kp, or the horizontal component of the geomagnetic field, occur simultaneously on both hemispheres. If SIDS were to be critically determined by geomagnetic disturbances, the peak incidence of SIDS would be similar in both hemispheres. The fact that SIDS incidence is season-associated does not rule out an influence of the magnetosphere, but if there is such a relation it is not direct. The possibility of an indirect influence will have to be studied for SIDS along with the role of environmental factors such as temperature. A multifactorial genesis has been suggested for SIDS. No single environmental factor need play a key role if SIDS is a feature of certain time and amplitude relations within a broad multifrequency rhythm- and age-dependent chronome. If the chronome is the decisive albeit unspecific internal factor, determining the difference between death and survival in the face of ever-present triggers, such as a virus, a vitamin deficiency or environmental temperature or even geomagnetic disturbance, one expects to find in SIDS incidence all other known components of our chronome structure as well. This hypothesis is validated in the following figures.

# CIRCADIAN CHANGE IN INFANT MORTALITY IN SWEDEN [1]




| Key | P | N | PR | MESOR ± SE | Amplitude* | Acrophase (ϕ) * |
|---|---|---|---|---|---|---|
| C SIDS (calculated time) | 0.011 | 24 | 35 | 12.29 1.47 | 6.96 (1.48 12.44) | -99° (-47 -151) |
| B SIDS (time of discovery) | <0.001 | 24 | 55 | 13.75 1.69 | 12.00 (5.72 18.28) | -150° (-118 -181) |
| A Non-SIDS | 0.002 | 24 | 45 | 53.21 1.44 | 8.52 (3.15 13.89) | -151° (-111 -190) |

P = Probability of Hypothesis: Amplitude = 0; N = Number of Observations
PR = Percent Rhythm (Percentage of Variability Accounted for by Cosine Curve)
* Conservative 95% Confidence Limits (Parentheses) Derived from Cosinor Ellipse
1 Data from Norvenius: Acta Pediatr Scand (suppl 333) 1987, 138 pp

FIGURE 9 The incidence of infant mortality in Sweden not related to SIDS follows a circadian pattern peaking between 08:00 and 12:00. The circadian incidence pattern of SIDS in Sweden differs from that of other infant mortality: a sharp peak in the time of discovery around 09:00 accounts for a relative amplitude of 87% *vs.* only 16% for causes other than SIDS. There is thus a SIDS *vs.* non-SIDS difference in circadian amplitude. The circadian peak remains prominent when the estimated time of death is used instead of the time of discovery. The relative amplitude remains large (53%) whereas the peak is slightly advanced to about 05:00, now clearly out of phase with the peak in incidence of non-SIDS deaths.

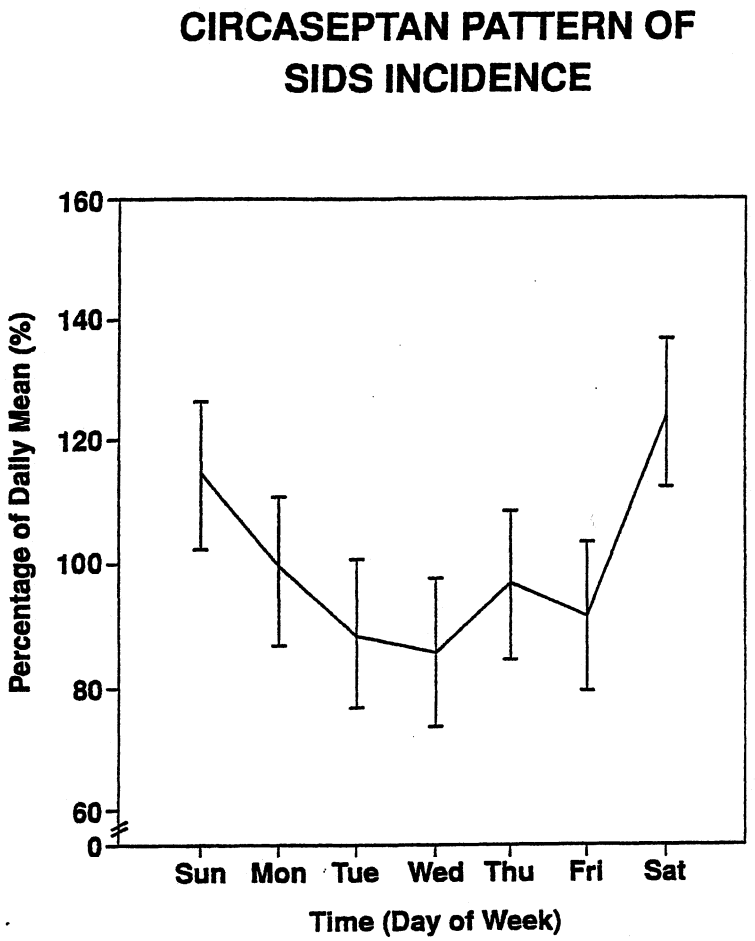



FIGURE 10 A most surprising and only superficially environmental effect is the distribution of SIDS along the scale of a week. Lack of medical attention can hardly play a critical role in sudden infant death, although it has been invoked as a factor. That a social phenomenon is not necessarily involved in a major way emerges from the observation that no difference can be detected between SIDS incidence on workdays (Mondays to Fridays) and on holidays that fall during the Monday–Friday work week (Tab. III).

for this assumption is provided in the experimental animal laboratory. Studies on the inbred DBA strain of mice, among others, reveal a genetically anchored increased susceptibility as a function of age and multifrequency rhythms to audiogenic convulsions and death [18]. The same stimulus, namely noise of fixed intensity, may kill most animals or may be compatible with survival simply depending on when the stimulus is applied, as a function of age and of the stage of the 24-hour synchronized circadian system. Under a chronome hypothesis of SIDS, we are dealing with a phenomenon occurring in a time structure

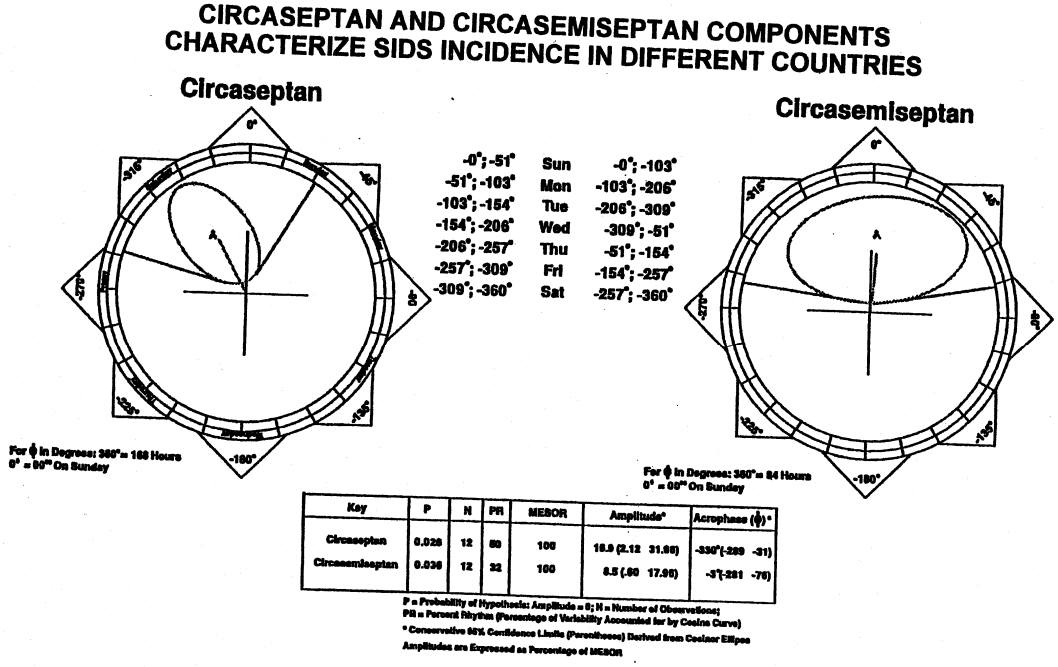



FIGURE 11 There is also a circasemiseptan (3.5-day) aspect to the incidence of SIDS with a secondary peak on Thursdays. This about-3.5-day component may be a major feature to SIDS in a state such as Minnesota: the circasemiseptan component is more prominent than the circaseptan one. Two peaks during the week, rather than one, certainly plead against a purely environmental origin. There is also independent evidence from free-runs of circaseptans in the isolation of a cave or that of an "isolette" in the neonatal intensive care unit in the first few weeks of life, with periods, *e.g.*, of the rhythm in systolic blood pressure differing from precisely 7 days. Eventually, by the age of peak SIDS incidence, activity schedules on the ward or at home have probably synchronized the built-in circaseptan feature into a 7- or a 3.5-day cycle. Both circaseptan and circasemiseptan aspects of SIDS incidence are illustrated in cosinor displays summarizing 12 different studies conducted worldwide.

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TABLE III Yearly comparison of daily incidence of SIDS on workdays *vs.* moveable holidays (Kaada, personal communication)

| *SIDS on:* | *Year* | *Work day* | *Moveable holiday* | *Year* | *Work day* | *Moveable* | *Year* | *Work day* | *Moveable holiday* |
|---|---|---|---|---|---|---|---|---|---|
| | 1967 | .155 | .444+ | 1973 | .181 | .417+ | 1979 | .301 | .333+ |
| | 1968 | .193 | .250+ | 1974 | .164 | .091− | 1980 | .225 | .167− |
| | 1969 | .228 | .182+ | 1975 | .164 | .273+ | 1981 | .192 | .182− |
| | 1970 | .175 | .667+ | 1976 | .183 | .333+ | 1982 | .258 | .111− |
| | 1971 | .151 | .111− | 1977 | .150 | − | 1983 | .264 | .143− |
| | 1972 | .167 | .111− | 1978 | .225 | .500+ | 1984 | .276 | .182− |
| R* | | 3:3 | | | 4:1 | | | 1:5 | |

*R = ratio of larger (+) *vs.* smaller (−) incidence on moveable holidays *vs.* work days. The different lifestyle hypothesis on weekends or at least on holidays thus becomes less likely in an account for the higher incidence of SIDS during the weekend.

built into the organism, dependent upon special internal time relations among constituents of the chronome.

This hypothesis is further supported experimentally by the fact that the timing of peaks and troughs in the incidence of audiogenic convulsion and death can be shifted by manipulating external factors, such as the lighting regimen [19]. In other words, the timing of the circadian rhythmic system, as a component of the chronome, can be moved to any clock-hour; it is not strictly synchronized by any single cosmic factor. Following a manipulation such as an abrupt shift of a 24-hour periodic light-dark schedule, different rhythms shift with different speed. For instance, on the fourth day after the shift of the lighting regimen, when internal time relations among circadian (and other) rhythms are altered, there is an overall change in susceptibility to audiogenic death, in keeping with the assumption of chronorisk, *i.e.*, altered relations within the chronome and in chronome relations to its broad environmental schedules, including planetary and interplanetary ones [15, 16]. When chronorisk is elevated by such alterations, death ensues within seconds, predictably in the experimental animal laboratory. It will take somebody interested in the spectrum of rhythms in human development and in its use for prehabilitation [15] to develop the means for the earliest detection of an elevated disease risk in the human newborn.

For the task of recognizing and developing countermeasures for chronorisk, an active physician-scientist is needed. At an age when others have long since retired, Theo meets this requirement. He continues with unimpeded enthusiasm and is building children's centers in India, Japan and South America, after the model of his center in Munich. Some of us (FH, GC & EH) owe him our acquaintance, and salute him the more as friends. We wish him the opportunity to continue what one of his pupils described as an innovative productivity, adding the notion of prehabilitation to activities in rehabilitation. With all the honors coming his way, he will regard them as a stimulus for further tasks on behalf of children and their families. He will continue, we tract, to focus on the prevention of the diseases of the second childhood already in the earliest stages of intrauterine and neonatal life, in keeping with the position of the co-editor of this journal.

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