Int. J. Prenatal and Perinatal Psychology and Medicine Vol. 12 (2000) No. 2, 275–303

From Theodor Hellbrügge to Prehabilitation, Chronopediatrics and Chronomics

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Keywords: chronobiology, chronopediatrics

Abstract: Chronobiology in human childhood started in the early fifties and is closely connected with the name of Theo Hellbrügge. His topics of chronobiology covered a broad range. He and his school described the circadian rhythm in many biological functions, such as body temperature, blood pressure, heart rate, respiratory rate, peak expiratory flow, and the response of patients treated by corticosteroids and other drugs. We here review the significance of chronobiology for human development and outline some tasks for further research and for prehabilitation: the recognition of invisible disease risks by physiological monitoring and the computer-aided resolution of time structures, chronomes, for this purpose and many others, basic and applied, is the task of pediatric chronomics, that complement chronobiology as genomics and proteomics complement genetics.

Zusammenfassung: *Theodor Hellbrügge – Prähabilitation, Chronopädiatrie und Chronomen.* Die Chronopädiatrie, also die Chronobiologie des Kindesalters, ist vom Anfang der 50er Jahre des vorigen Jahrhunderts an eng mit dem Namen von Theodor Hellbrügge verknüpft. Die Themen seiner Schule der Chronobiologie umfassen ein weites Gebiet. Sie betreffen circadiane Rhythmen vieler physiologischer Funktionen wie Körpertemperatur, Blutdruck, herzfrequenz, Atemstoß und auch die Empfindlichkeit der Patienten gegenüber Corticosteroiden und anderen Medikamenten. Der in der Chronobiologie führende Pädiater widmete sich später einer von ihm begründeten sozialen Pädiatrie und erarbeitete die Grundla-

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Another abbreviated laudatio will be published shortly in "Pediatrics and Related Topics".

gen dieses Spezialfaches zur Entwicklungsrehabilitation. Die Bedeutung Hellbrüggescher Beiträge ist somit eine Voraussetzung für die Entwicklung einer zur Vorbeugung dienenden Chronopädiatrie, die er erstmalig geschaffen hat. Die Aufgabe vorzubeugen, betrifft sowohl die REhabilitation bei Erfassung sichtbarer Behinderungen als auch eine PRAEhabilitation, welche es erlaubt, unsichtbaren, aber durch Überwachungen erfaßbaren Risiken durch frühzeitige Erkennung und rechtzeitigem Eingreifen zu begegnen. Wenn auch schon öffentliche Gelder für die Rehabilitation vielerorts verfügbar sind, so sollte es einmal möglich werden, die breite Öffentlichkeit eben auch für die PRAEhabilitation zu interessieren. Aber von der medizinischen PRAEhabilitation und REhabilitation abgesehen, hat die Schule Hellbrügges, welche schon vor einem halben Jahrhundert bei einem internationalen Treffen in Cold Spring Harbor die Chronopädiatrie vertrat, sich zu einem Wissenskreis sui generis entwickelt, der auch zur Grundlagenforschung beigetragen hat, eben durch die Erkenntnis der in uns eingebauten biologischen Woche, die wir mit einer Alge, die schon vor 500 Millionen Jahren auf der Erde gewesen sein soll, früh nach der Geburt teilen. Auch bei Süßwasserkrabben, Ratten und Ferkeln geht die Prominenz der biologischen Woche in frühen Stadien der Entwicklung dem biologischen Tag, also dem circadianen System, voran. Dann aber schon am Ende des ersten Lebensmonates beim Menschenkind, wie es Theo Hellbrügge quantifizierte, erreicht der biologische Tag seinen Gipfel im Spektralelement von Zeitstrukturen, Chronomen. Dann übertrifft in ihrer Amplitude die Circadine andere Komponenten beim Erwachsenen, bis zum fortgeschrittenen Alter, aber nicht bis zum Lebensende. Wir wünschen Theo gesunde Jahre zum weiteren Schaffen an Chronomen, so daß, wie die Genetik die Genomik und Proteomik gebar, er zur Entwicklung der Chronomik sein wichtiges Scherflein beitragen kann.

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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 curves of patients with asthma treated by corticosteroid at different times (Figs. 1–3), gauged by the circadian rhythm

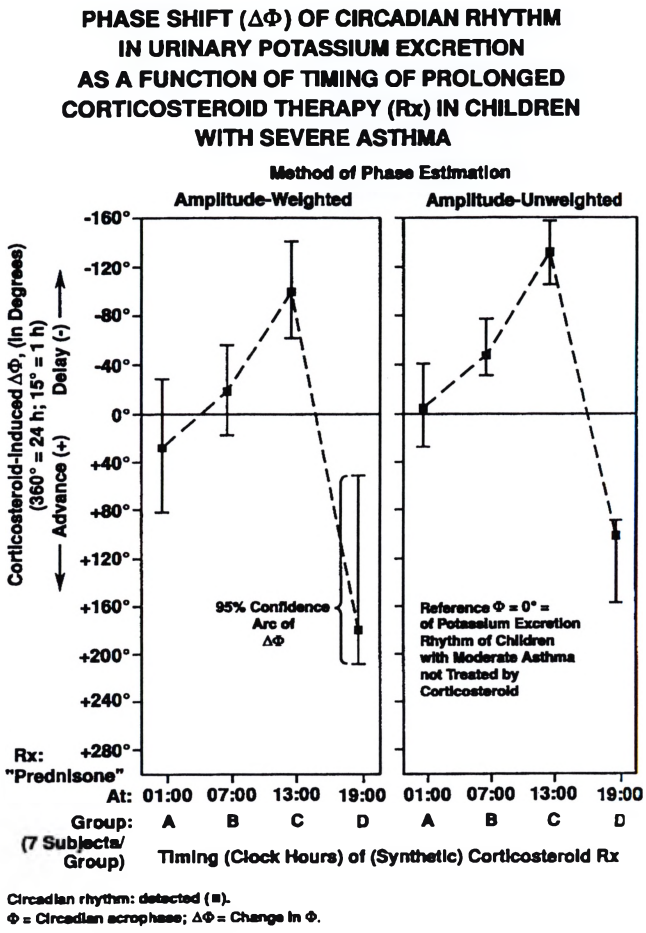


Fig. 1. Cosinor-assessed uncertainties of circadian acrophase response to prednisone of urinary potassium excretion.

in peak expiratory flow, contributions by Alain Reinberg with Karl Reindl. Wolfgang März 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.

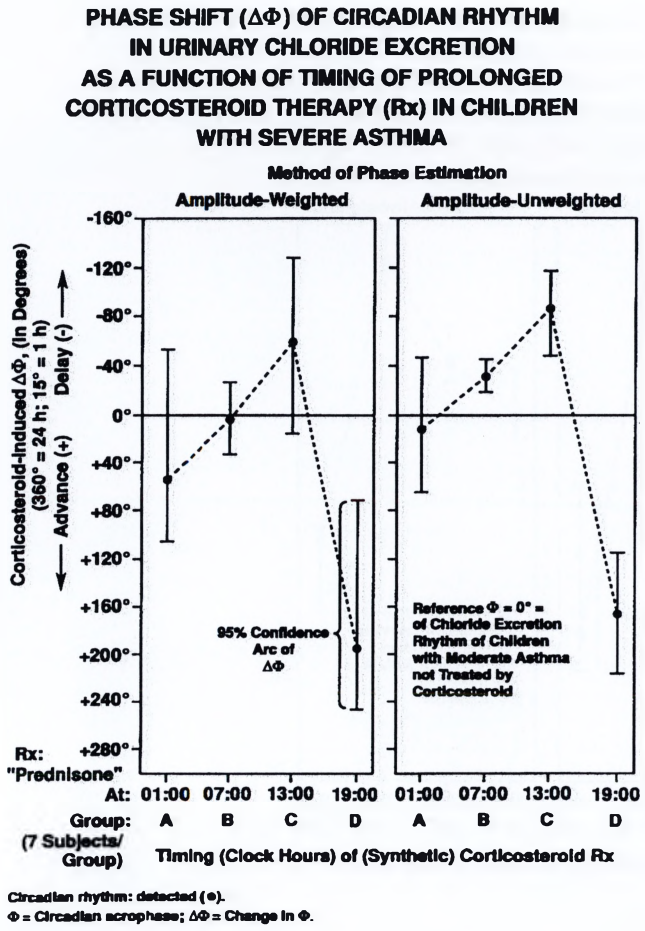


Fig. 2. Cosinor-assessed uncertainties of circadian acrophase response to prednisone of urinary chloride excretion.

An early contribution by Theo is shown in Table 1 [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 Fig. 4. 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 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 (±5)/min. during the eighth and ninth months and 129 (±6)/min. during the tenth month.

Note the time-microscopic amplification from Table 1. The data on fetal heart sound, which time-macroscopically appear to be more or less constant in Fig. 4, allow a statistically significant rejection of the "zero circadian amplitude" or "no circadian rhythm" assumption. The 24-hour cosine curve actually provides a bet-

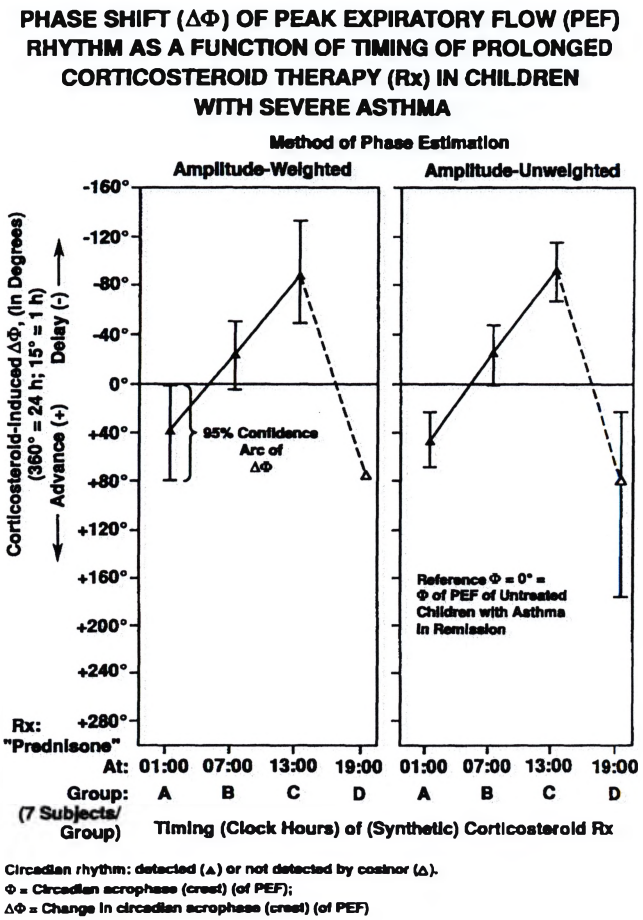


Fig. 3. Acrophase response to prednisone of peak expiratory flow assessed by cosinor with its uncertainty except for last timepoint examined.

ter fit for the data from the fetus than for those of the mother as seen by the 75% versus 48% of variance accounted for by the fitted model (Table 1), 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 2 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

Table 1. Circadian rhythm of heart rate of mother and fetus during 8th to 10th month of pregnancy*

	PR	P	Double amplitude ±SE (% of 24-h 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° ≡ 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).

Table 2. 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 (95% CI)
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° ≡ 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).

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, Fig. 5. As Table 2 also shows in later weeks and months, the circadian group rhythm of heart rate is again detected.

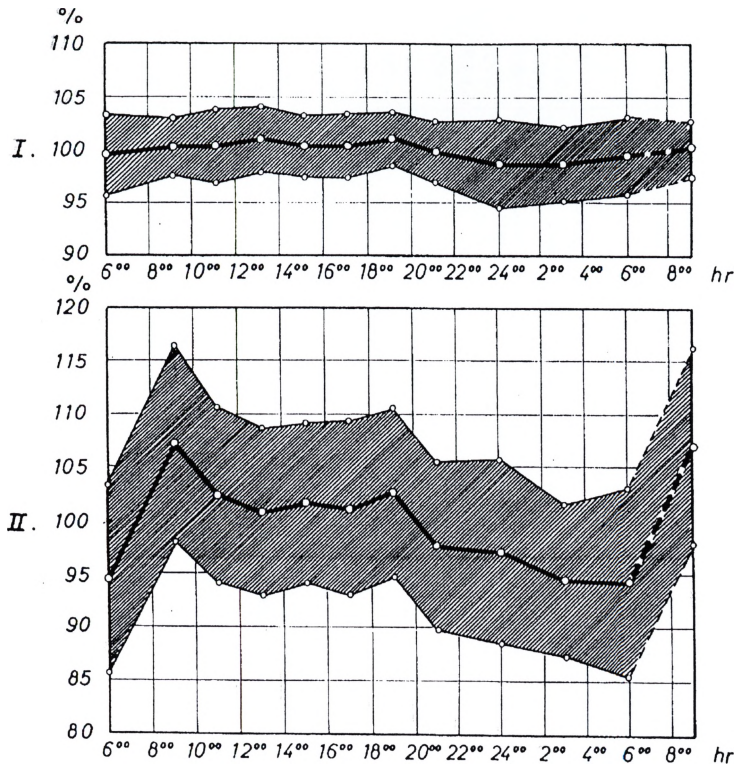


Fig. 4. Changes along the 24-hour scale in the heart rate of the fetus (top) and mother (below) during the last months of pregnancy [6]. (c) Halberg.

Not only the circadian heart rate rhythm is expressed early in life, as Theo's data suggest upon chronometa-analysis, Table 2. Figures 6 and 7 document circadians and circannuals for the hormone leptin, demonstrable as group phenomena, already in cord blood [13]. With respect to Fig. 5, 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 interindividually synchronized. By contrast, in a given individual whose data are analyzed separately, as in Fig. 5, 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. The exposure to betamimetic drugs 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.

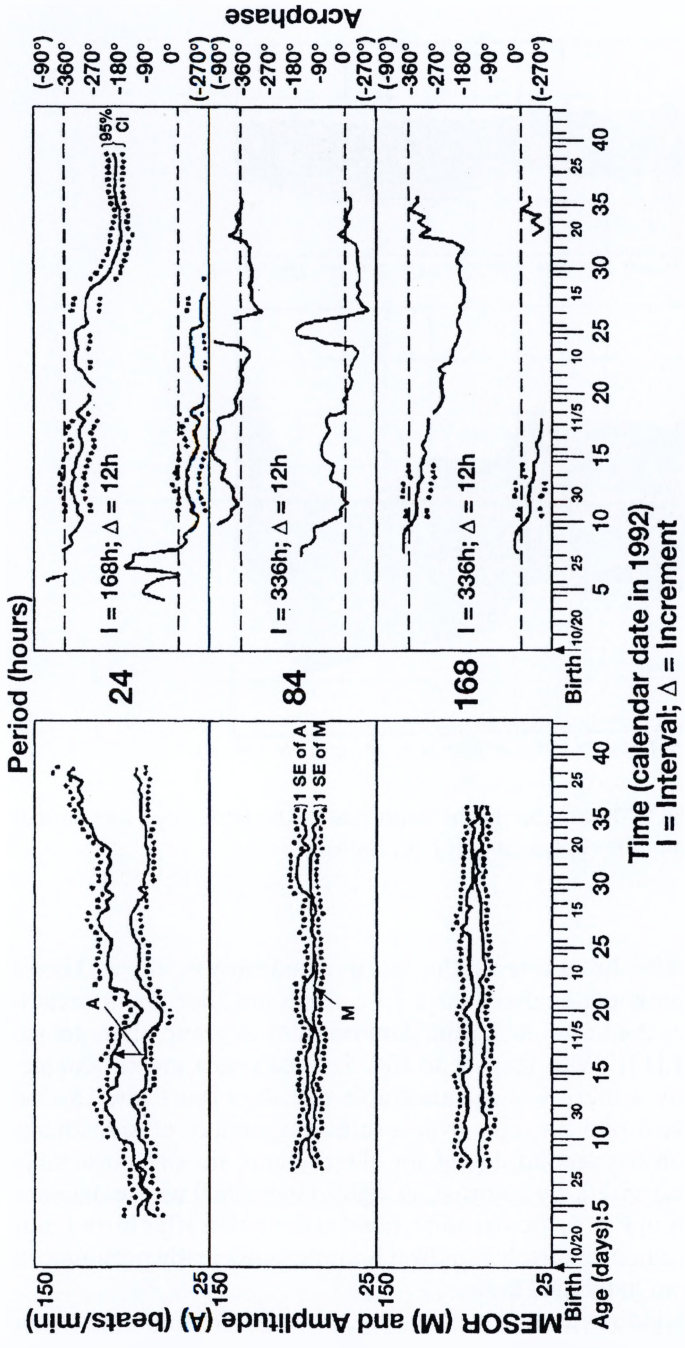


Fig. 5. Development of chronome of heart rate early after birth. Clinically healthy full-term boy (FW), studied around the clock for first 40 days after birth with automatic instrument; analysis of residuals after detrending by 5th-order polynomial; CI = confidence interval (data of Y. Watanabe). Amplitudes (left) and acrophases (right), measures of the extent and timing of change during the development of a healthy boy. (c) Halberg.

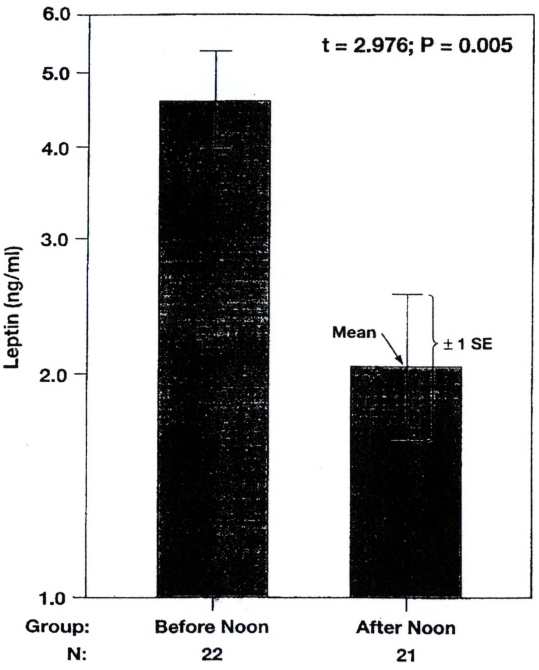


Fig. 6. Circadian population rhythm along the 24-hour scale of leptin in cord blood [13]. 43 babies appropriate or large for gestational age with negative history of non-insulin dependent diabetes mellitus and obesity. (c) Halberg.

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 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.

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 reportedly first kindergarten in the world in which children with and without handicaps learn

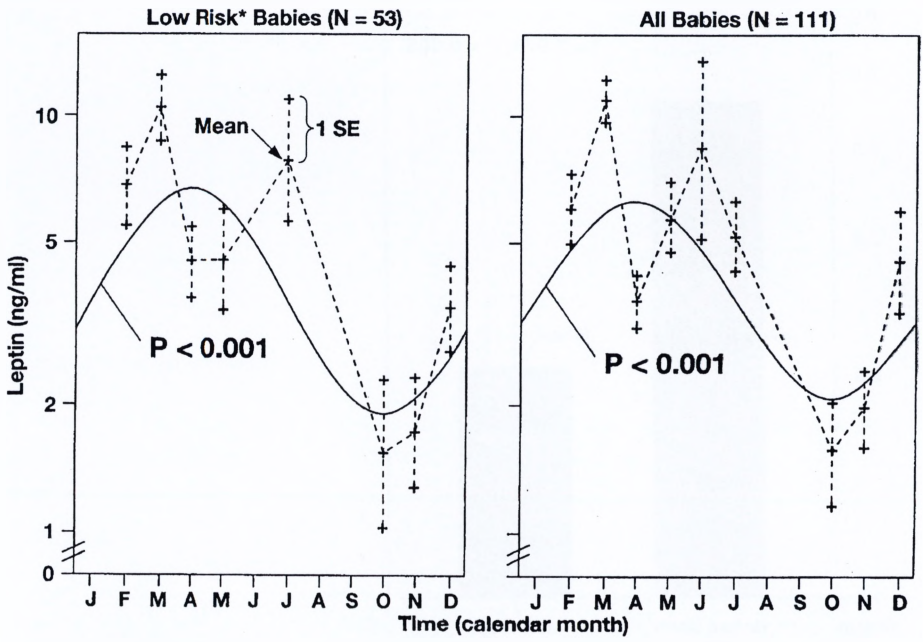


Fig. 7. Circannual population rhythm of leptin in cord blood [13]. Babies appropriate or large for gestational age with no familial antecedents of obesity or diabetes. (c) Halberg.

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, by the need for the detection 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 "developmen-

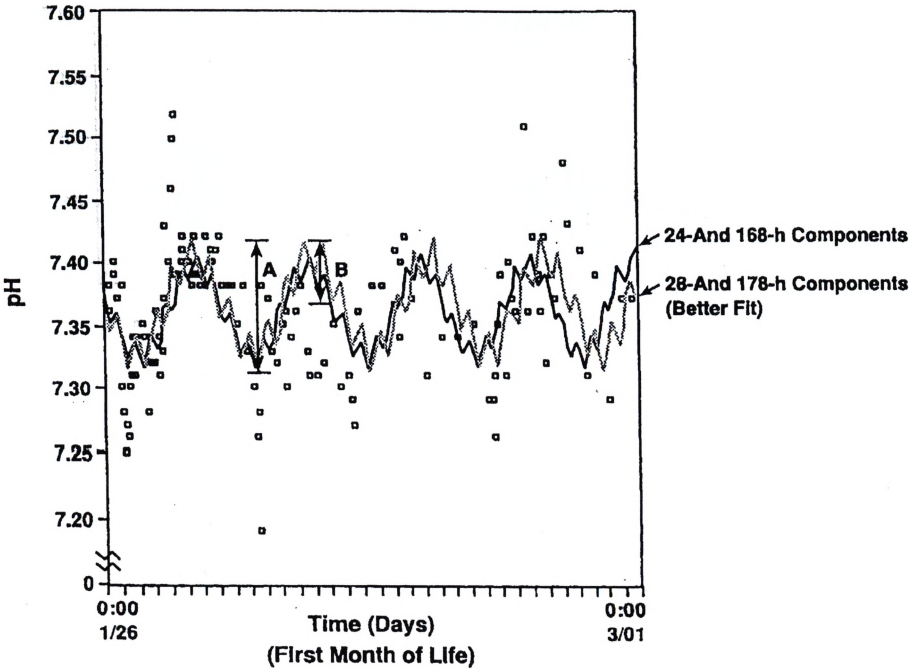


Fig. 8. Circadian and circaseptan variation in preterm baby's blood pH. As compared to children, premature babies can be more easily monitored longitudinally; their circaseptan component has an amplitude often larger than the circadian, as illustrated for blood pH. Original values during the first five weeks of life are shown as quadrangles. Two curves are fitted to these data. The lighter curve, representing a model indicating 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. (c) Halberg.

tal 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

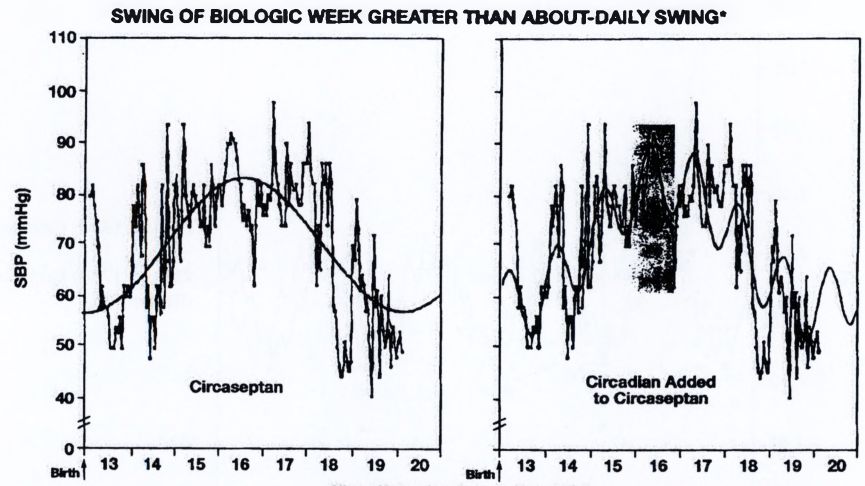


Fig. 9. About-weekly changes in blood pressure and heart rate are invariably found to predominate over circadians on a group basis in human babies, whether they are healthy and full-term or premature and sick. In the systolic blood pressure of the high-risk infant shown here, both components can be detected with statistical significance by non-linear least squares. The about-weekly amplitude is about twice as large as the circadian variation. Width of shaded area shows span of 1 day.

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. 8. Actually, an about-monthly change is further apparent, and has an even greater amplitude when it is approximated by stacking (Fig. 44 in [16]). In the case of blood pressure and heart rate also, circaseptans are often more prominent than circadians in early extrauterine life, as illustrated in Fig. 9.

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 programmed or set by the time of birth (Fig. 10); 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 multifrequency 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 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

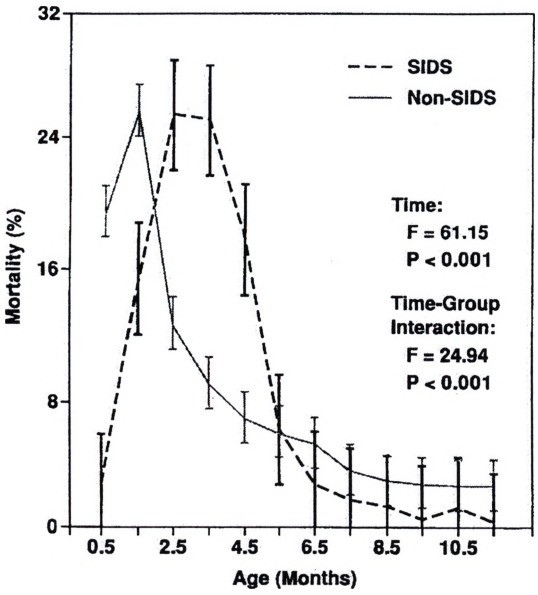
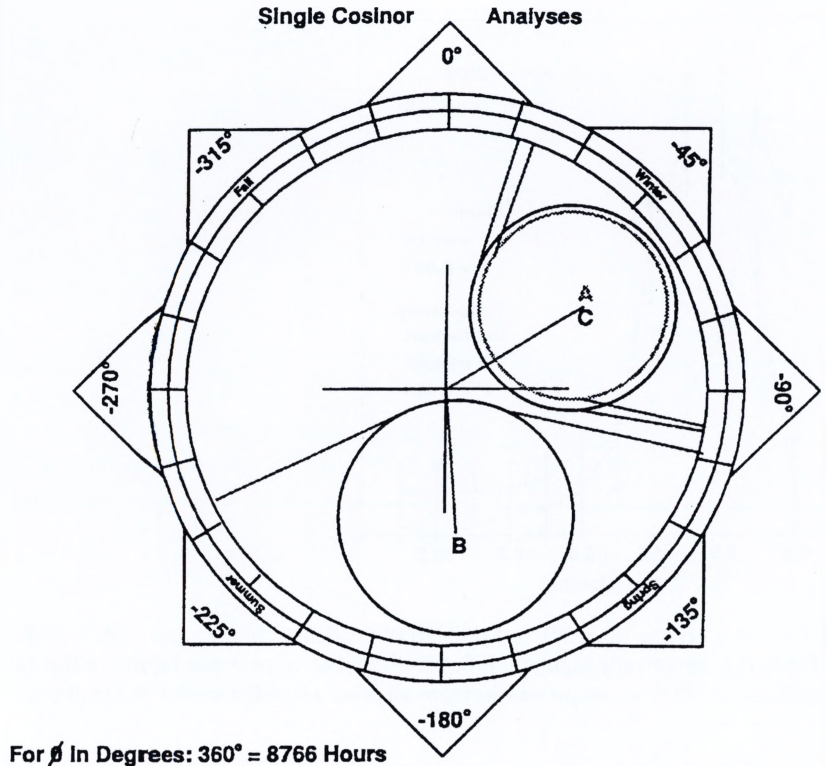


Fig. 10. Pattern with age of SIDS and non-SIDS incidence. Means and 95% confidence limits. There is a statistically highly significant difference of over one month in the age of peak incidence of SIDS vs. infant deaths from all other recorded causes. (c) Halberg.

as the distribution of SIDS along the age scale seems to be characteristic of this condition, Figs. 10–15 and Table 3.

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

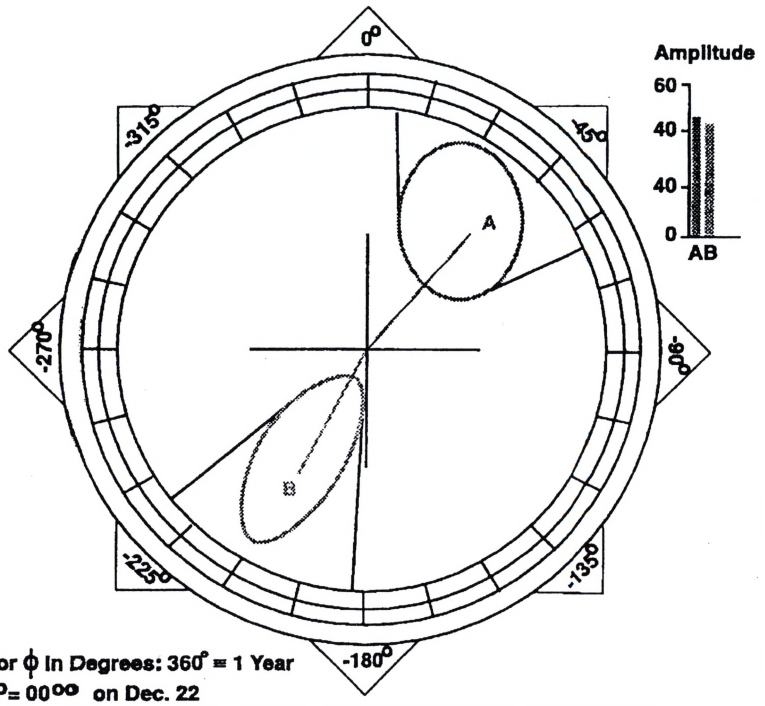
This hypothesis is further supported experimentally by the fact that the timing of peaks and troughs in the incidence of audiogenic convulsion and death can be shifted by manipulating external factors, such as the lighting regimen [19]. In other words, the timing of the circadian rhythmic system, as 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



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 the cosine curve.
* Conservative 95% confidence limits (parentheses) derived from cosinor ellipse.
** Relative incidence, after correction for difference in number of days in each month.

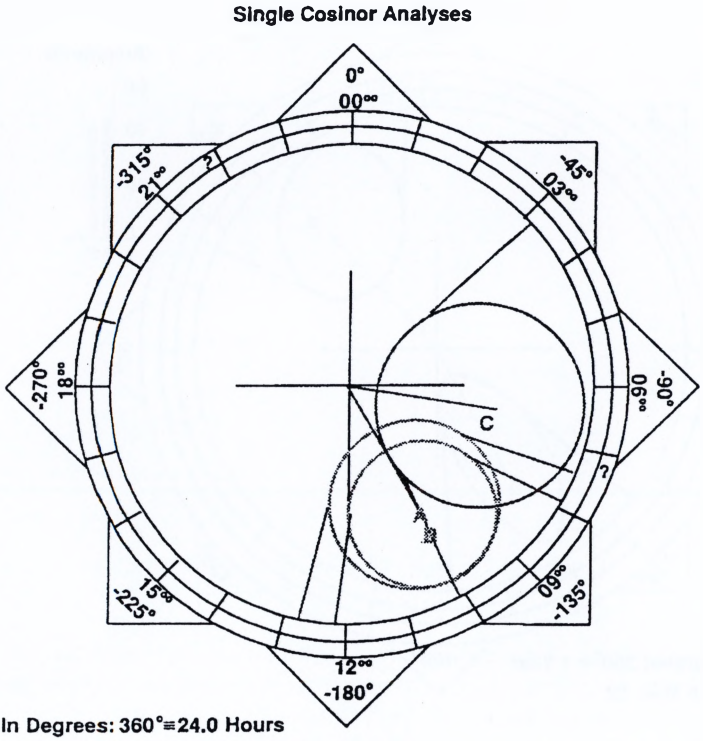
Fig. 11. Circannual change in incidence of SIDS and live birth in Northern Ireland (data from Frogatti et al., Br J Prev Soc Med 25: 119–134, 1971). Incidence of live births in Northern Ireland follows a circannual pattern peaking in late spring and early summer. In this cosinor display, the circular 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. 10).



Population - Mean Cosinor

Hemisphere	P	N	PR	Amplitude*	Acrophase (ϕ)°
A Northern	<.001	20	63	36 (22 50)	-29° (-8 -50)
B Southern	.020	5	69	42 (12 72)	-207°(-181 -234)

Fig. 12. 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, 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 in keeping with the evidence in the following figures.



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)

Fig. 13. 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.

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 among internal chronome components and in their relations to 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

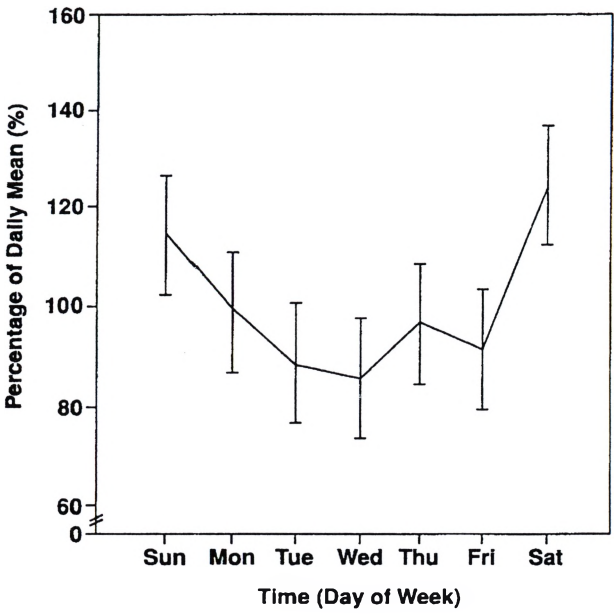


Fig. 14. A most surprising and only superficially environmental effect is the distribution of SIDS along the scale of a week. Lack of medical attention can hardly play a critical role in sudden infant death, although it has been invoked as a factor. That a social phenomenon is not necessarily involved 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 (Table 3).

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, OS, GC & EH) owe him our acquaintance with social pediatrics, 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 by 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 editor of this journal [20, 21].

Epilogue

In a recent literature search concerning "Chronobiology in childhood", carried out by a librarian for Theo Hellbrügge, 598 titles were found in English, 20 in French and about 10 in German, an indication of Theo's worldwide impact in pediatrics (and of English being at this time the *lingua franca*). Also important is the

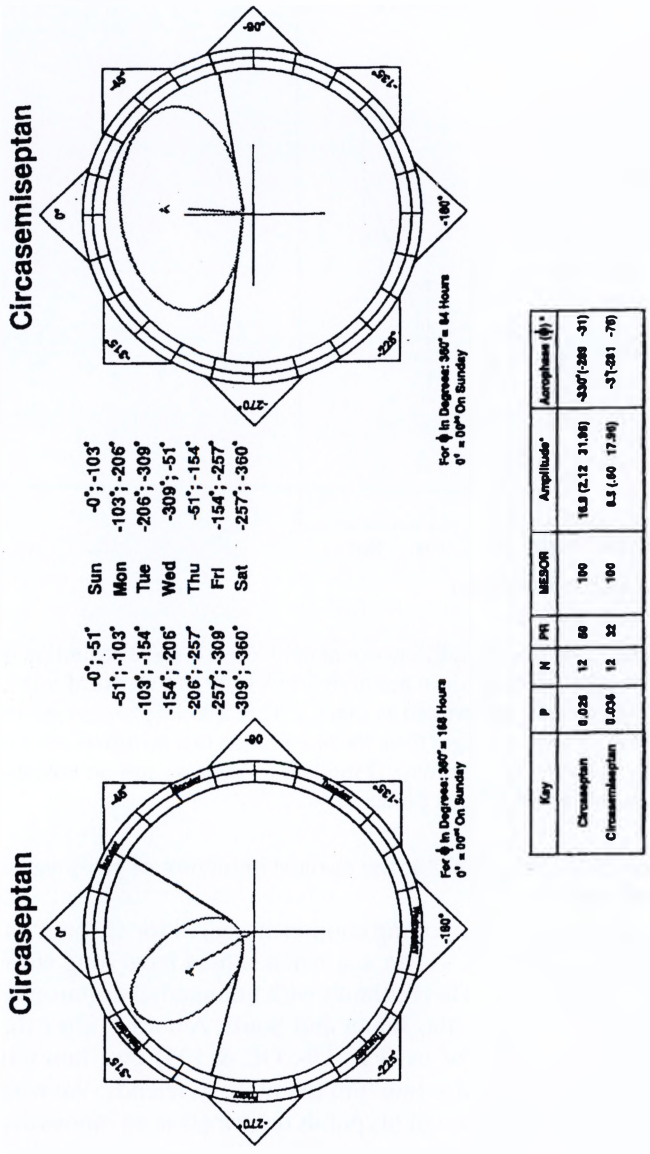


Fig. 15. There is also a circasemiseptan (3.5-day) aspect to the incidence of SIDS with a secondary peak on Thursdays. This about-3.5-day component may be a major feature to SIDS in a state such as Minnesota: the circasemiseptan component is more prominent than the circaseptan one. Two peaks during the 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.

Table 3. 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 holiday	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.

basic aspect of chronopediatrics, as reflected in neonatal individual and population rhythms with heretofore largely neglected frequencies. For a very long time, the week was regarded as purely social and the rapid eye movement cycle as purely organismic, until the biologist found physical environmental near-matches in geomagnetic disturbance [16, 22, 23]. Likewise, other natural physical environmental cycles in addition to the near-week, such as the half-year, the about 10.5-year and 21-year cycles related to solar activity, were found as signatures in biodata; sometimes, their amplitude compared favorably with that of the corresponding yearly or daily change in the same variable [15, 24–26]. The analyses of data from the late Hans-Georg Schweiger, kindly provided by Sigrid Berger and Lübbo von Lindern of the Max-Planck-Institute of Cell Biology in Ladenburg, near Heidelberg, show in Fig. 16 that the electrical activity of *Acetabularia acetabulum* released into continuous light (upon signal averaging from over 20 cells) has a more prominent circaseptan feature than its circadian rhythm ([26]; cf. [27]). This finding is in keeping with the demonstration of circaseptans in other eukaryotic unicells, including *Euglena gracilis* Klebs [28, 29] and *Gonyaulax polyedra* [30–32].

Till Roenneberg, in Theo's home city of Munich, and David Morse describe multiple circadian rhythms in the unicell *Gonyaulax*, some differing in frequency from each other, proposing "that the glow rhythm is influenced by the relative phase angles between bioluminescence and aggregation, which are controlled by separate but coupled oscillators" [32]. Albeit without inferential statistical estimates of the uncertainties involved in the estimation of periods and phases, Roenneberg and Morse [32] deserve credit for reporting that under certain conditions, two rhythms can run independently in the same cells. Indeed, there need not be a sole master oscillator, even in a single cell, in keeping with the proposition of a collateral hierarchy in the multicellular circadian system [33]. When a circaseptan is found in a unicell or in other species, interpreting it as a beat phenomenon [32], as illustrated in the abstract in Fig. 17 [33, 34] is tempting and was documented with actual human data in Fig. 18 [34]. In the latter case, the circaseptan was a consequence of the superposition of two interacting circadian schedules, one from without, namely a clock-imposed 21-hour day, the other(s) from within,

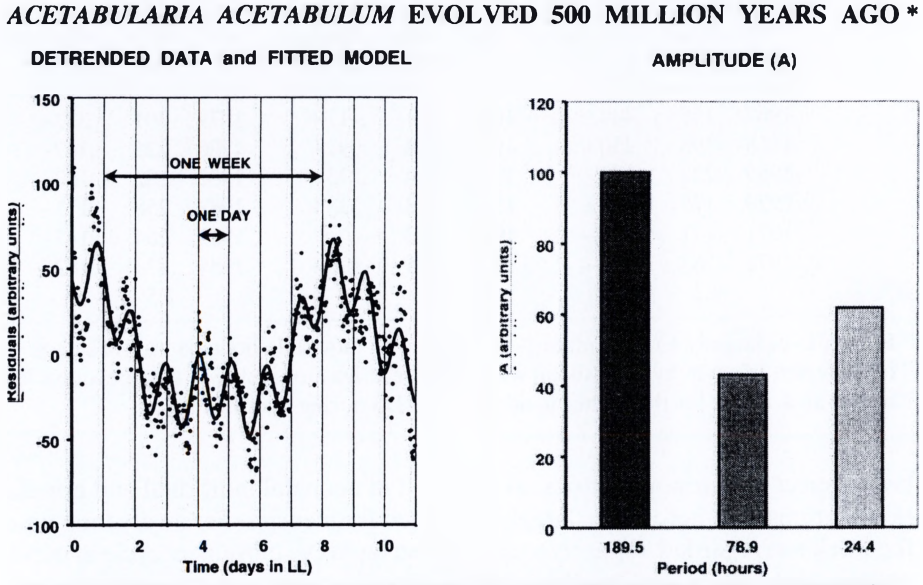


Fig. 16. The about-7-day (circaseptan) rhythm is more prominent than the circadian in the electrical potential of Acetabularia acetabulum, immediately after release into continuous light.

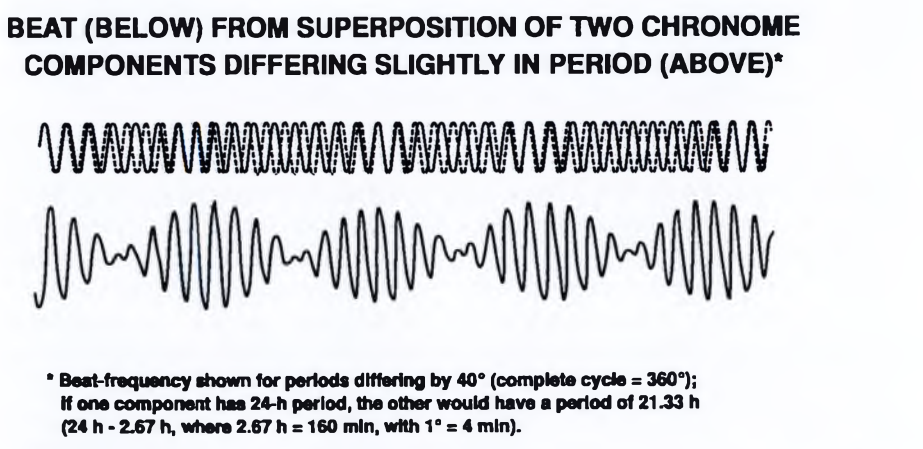


Fig. 17. Beat frequency as a function of the difference in period of two superposed hypothetical periodic mechanisms (34, 35).

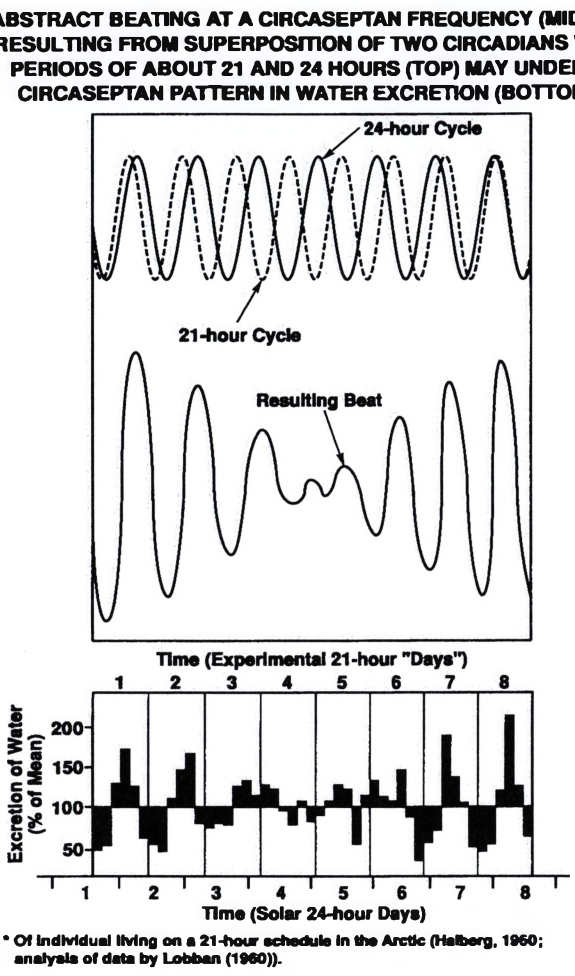


Fig. 18. Beats in physiological circadian data on water excretion data for subject living on a 21-hour schedule in the Arctic (34).

expressed in a circaseptan way [33, 34]. A collateral hierarchy, however, involves with oscillations at or near a given fundamental frequency, a further set of several widely differing frequencies [33], and further deterministic and other chaos and usually trends [35] and, what is the challenge in chronopediatrics, trends also with an increase in the risk of developing disease, often hidden in the physiological range of variation [5].

In early human postnatal life, notably in prematurity [16, 22, 36], Figs. 8 and 9 (as in *Acetabularia*, Fig. 16, a unicell presumably on earth for 500,000,000 years), i.e., relatively early in ontogeny (and phylogeny), the circaseptan can be overwhelmingly larger than the circadian and the circadian can fail the zero-amplitude (no rhythm) test (Fig. 5), sometimes being demonstrable immediately after birth only on a group basis [16, 37, 38]. Whatever their origin, circaseptans can be regarded as components in their own right in early human extrauterine life. Evidence

for their endogenicity is becoming available from studies on twins monitored longitudinally in the neonatal intensive care unit. The circaseptan period of heart rate and diastolic blood pressure, assessed nonlinearly, of twins of the same gender (excluding some but not necessarily all dizygotic twins) have an intra-class correlation coefficient of 0.818 ($P = 0.007$) and 0.821 ($P = 0.004$), respectively. Any beating from the superposition of yet-to-be-identified circadian mechanisms, with a correspondingly different frequency (at least one or both of them free-running), however, also certainly deserves consideration, Figs. 17 and 18.

It has yet to be established by many more data than are now available whether, in the early life of organisms as different as crayfish, rats, pigs and human beings, the circaseptans are a universal design feature: hundreds of human babies ([36]; cf. [37, 38]), but very much more limited data on several other species suggest that this may be so. Circaseptans may be an expression of an internal integrative adaptation, of the need to lock-in with some intermediate frequency for phenomena of growth and regeneration that could not be completed within a day but did not need a month for completion [39]. If, as seems possible in view of the evidence thus far, circaseptans in evolution preceded circadians, it is important to know that they have a geophysical near-match with a period of 6.75 days in geomagnetic disturbance ([16]; cf. [40, 41]). This harmonic of the rotation of the sun around its axis, apart from any lunar influence, may be particularly important for forms of life developed, perhaps at the bottom of the sea or in the earth's interior, away from the 24-hourly alternation of light and darkness at the surface.

In bacteria examined thus far, circaseptans, albeit present, are, however, not more prominent than circadians, and in *Acetabularia* as well, in the same alga, different variables may have circaseptan-over-circadian amplitude ratios that differ in prominence among variables. Thus in an *Acetabularia*, circaseptans may dominate in the electrical potential, with the circaseptan-to-circadian amplitude ratio above unity and, in the same cell, circadians in chloroplast migration, recorded concomitantly, may have an amplitude ratio below unity.

At issue is the broadening of focus, initially from circadians to circaseptans and from there to chronomes [17, 25, 26]. From a broad view of unicellular and human cartography, it is exciting that even the about 10.5-year Schwabe cycle is reflected in *Acetabularia* [26]. This cycle or the about 21-year Hale cycle may represent indices of non-photic solar activity in the weight, length and head circumference of the human newborn and may show cross-spectral coherence with purely physical variables such as the geomagnetic disturbance index, Kp. Archival human natality statistics, notably of morphology, provide both basic and applied lessons. Physiological cartography may lead to the detection of risks heretofore unrecognized by the time of birth [37, 38], so that the prevention of the diseases of old age may start as early as possible. Another challenge for pediatricians focusing upon old age and gerontologists stems from the resurgence of circaseptans in the second childhood [42].

Apart from its basic interest, a broader-than-circadian perspective is critical for human therapy [27] when the circaseptan pattern of drug administration can account for the difference between the enhancement versus the inhibition of a malignant growth by the same weekly dose of an immunomodulator, given in equal vs. sinusoidally changing daily doses [17]. Health care can change focus

from only upon single samples (leaving too much to chance) to the analysis of time series that allow the detection of deviations in circadians, circaseptans and much broader chronomes. Practical applications are in sight, in the detection and timely treatment of disease risk syndromes before catastrophic disease occurs. We have very much to learn from the mapping of human morphology, physiology and pathology, so that the development from Theo's chronobiology leads to broad time structures, chronomes, that are dense enough to reveal deterministic and other chaos as well as long enough to assess a very broad spectrum of rhythms with different frequencies and trends, not only with age but with the increases in the risk of vascular and other diseases. Progress from chronobiology to chronomics may then be the needed integrative complement to the development from genetics to genomics and proteomics.

Support. U.S. Public Health Service (GM-13981), National Heart, Lung, and Blood Institute, National Institutes of Health (HL-40650), University of Minnesota Supercomputer Institute, Dr. h.c. Dr. h.c. Earl Bakken Fund and Mr. Lynn Peterson, United Business Machines, Fridley, MN.

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