# SEASON'S APPRECIATIONS 2002 and 2003

## Imaging in time: The transyear (longer-than-the-calendar year) and the half-year

**Franz Halberg[1*], with Germaine Cornélissen[1], Alexander Stoynev[2], Ognian Ikonomov[3], George Katinas[1], Mary Sampson[1], Zhengrong Wang[4], Chaomin Wan[4], R.B. Singh[5], Kuniaki Otsuka[6], Robert B. Sothern[1], Samuel B. Sothern[1], Margaret I. Sothern[1]†, Elena V. Syutkina[7], Anatoly Masalov[8], Federico Perfetto[9], Roberto Tarquini[9], Cristina Maggioni[10], Yuji Kumagai[11], Jarmila Siegelova[12], Bohumil Fiser[12], Pavel Homolka[12], Jiri Dusek[12], Keiko Uezono[13], Yoshihiko Watanabe[6], Jinyi Wu[1], Robert Sonkowsky[1], Othild Schwartzkopff[1], Theodor Hellbrügge[1], Novera Herbert Spector[1], Ion Baciu[1], Monica Hriscu[1], Earl Bakken[14]**

[1] Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA
[2] Transport Medical Institute, Sofia, BULGARIA
[3] Wayne State University, Detroit, MI, USA
[4] Sichuan University, Chengdu, CHINA
[5] Medical Hospital and Research Centre, Centre for Nutrition and Heart Research, Moradabad, INDIA
[6] Tokyo Women's Medical University, Daini Hospital, Tokyo, JAPAN
[7] Institute of Pediatrics, Scientific Center for Children's Health, Academy of Medical Sciences, Moscow, RUSSIA
[8] Lebedev Physical Institute, Moscow, RUSSIA
[9] University of Florence, ITALY
[10] University of Milan, ITALY
[11] Kitasato University East Hospital, Sagamihara, Kanagawa, JAPAN
[12] Masaryk University, Brno, CZECH REPUBLIC
[13] Kyushu University, Fukuoka, JAPAN
[14] North Hawaii Community Hospital, Kamuela, HI, USA
† deceased 12.xi.2003

*Correspondence to:* Franz Halberg, MD
Director, Chronobiology Center, University of Minnesota
MMC 8609 · 420 Delaware St. SE · Minneapolis, MN 55455, USA
TEL +1 612.624.6976 · FAX +1 612.624.9989 · EMAIL halbe001@umn.edu

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*Dedicated to Germaine Cornélissen on her 54th birthday, November 22, 2003 and to the memory of her mother Hélène Minne

### There's more to "seasons" than meets the eye

Signatures in us of the alternation of day and night and of the seasons have their non-photic, non-thermal counterparts: a cornucopia of cycles were mapped with their uncertainties during the past 2 years. New aspects emerged for a biological half-week, week and half-year, for 1-, 2- or 5-decadal cycles, along with cycles of even lower frequencies in tree rings, wars and, as far as available to us, in our cosmos. A near-7-day cycle was found in solar (I-42) as in terrestrial (I-23) magnetism. In the perspective of 2,000 or more years, these wobbly, irregular *cycles* can be aligned with less irregular *rhythms,* with a lesser extent of uncertainty in terms of the periods involved. Rhythms and, implicitly, cycles are all qualified by "circa" for reasons not only of biological endogenicity when pertinent and demonstrable in the want of a free-run by non-overlap of 95% confidence intervals, Figure 1 (46, I-95, I-96); in addition, there is the "circa" emphasizing an inferential statistical uncertainty of cycle or rhythm characteristics.

During the past 2 years, further support emerged for the postulate that for each non-photic as well as photic physical environmental cycle one should look for a biological cycle with near-matching length and vice versa. The biological transyear was found, when a cycle with an about 1.3-year period

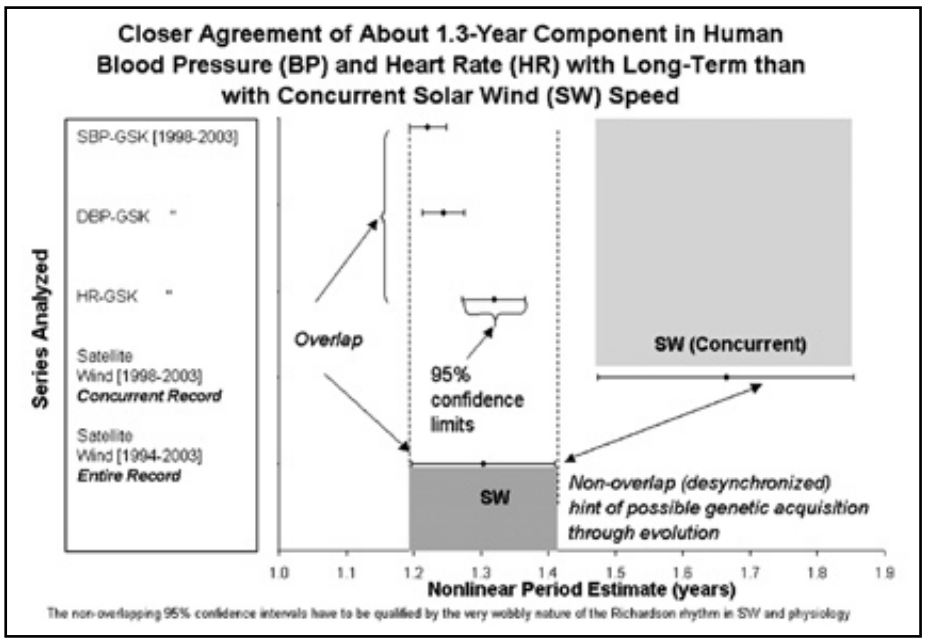



**Figure 1.** The about 1.3-year component of blood pressure and heart rate of GSK (M, 72-77y) recorded during 1998–2003 has a period closer to the solar wind speed period characterizing the entire available record from the Wind satellite than that for the concurrent 5-year span. Physiological variables may resonate with non-photic environmental cycles that may have entered the genetic code during evolution. © Halberg.

was reported in data collected by satellites and a geomagnetic and heliomagnetic near-week was found as a counterpart to a built-in biological week. The speed of the ionized gases ejected by the sun into extraterrestrial space that provides comets with tails – the solar wind – varies; it has a prominent half-yearly and an about 1.3-1.6-yearly component. In biology, a cycle with a length beyond (trans) that of any about-yearly cycle, but shorter than 2 years, was newly mapped. It complements and, when ignored, complicates any effect of the precise alternation of winter and summer outside us and may account, at least in part, for any unexpected changes in "seasonal" variation in us.

The finding of a biological ~1.3-year cycle was made on adult human blood pressure (BP) and heart rate (HR) in all of over 50 time series available to us with a length covering from 5 to 36 years, as a follow-up on Figure 1 (46, I-95, I-96). In adults, the circannual amplitude of systolic or diastolic BP and of HR can be larger or smaller than that of the "transyear". In neonates, on the average, the transannual amplitude is the larger one in each of 6 data pools on systolic and diastolic BP and HR from groups of over 100 premature or at-term babies (I-141). The neonate is not yet synchronized by a decades-long exposure to the seasons and to the solar wind, during which the seasons are superficially more obvious than the solar wind. In this perspective, one can ask why the newborn's spectrum shows a larger transannual than circannual amplitude in a population sampled with serial independence as to individuals. Is the transyear anchored in the gene pool of the population, an inference in keeping with actual data from an adult whose transyear in BP and HR was desynchronized from that in the solar wind, Figure 1? As appendix A shows, there is no numerical correspondence between a spectral peak in magnetic storms and peaks in neonatal BP and HR data, during a given decade and more analyzed.

The noted finding that 95% confidence intervals of period estimates of the transyear, resolved by nonlinear rhythmometry in an adult, did not overlap one year, attests to its representing a component in its own right. In a relatively short (only about 5-year) data series of half-hourly systolic BPs, the about 1-year (circannual) and transyear (transannual) components with non-overlapping 95% confidence intervals, were actually beating – they amplified each other when in phase and cancelled each other out when out of phase. One can thus document at least one reason, a beat, for the vagaries of circannual components in the human circulation in time series covering decades, when analyses are focused on the calendar year only. So much for what is still only basic science. Answers to questions such as whether the transyear also characterizes endocrine variables related to malignant growth are particularly important in this context: they may underlie the onset and recurrence of cancer and possibly of other, notably chronic intermittent disease. A biological half-year, also mapped recently (I-81), must be considered in this context as well, Figure 2.

## Flying blind in dealing with blood pressure

On the clinical side, the longitudinal monitoring of BP around the clock for months or years in both the presence and absence of antihypertensive treatment has revealed that MESOR-hypertension and **c**ircadian **h**yper-**a**mplitude-**t**ension (CHAT or overswinging) can be intermittent, Figure 3. With aging, MESOR-hypertension, albeit very high when first diagnosed, much treatment notwithstanding, may disappear spontaneously. When intermittency of one or several conditions is the case, treatment may be needed when one, the other or both conditions are present but perhaps not when all are absent. This is another argument, apart from good basic science, for longitudinal monitoring

rather than spot-checking, at least as a clinical start once BP abnormality is detected. We recall, perhaps too slowly for many patients receiving alleged "chronotherapy" today, the transience of the enthusiasm for treatment by long-acting insulin for the 24-hour coverage of blood sugar control in type 1 diabetics, which eventually proved to be less desirable than treatment with fast-acting insulin adjusted to the need of each moment. No analogy is perfect, but a 24-hour coverage as the current goal of hypotensive treatment for all with no continued around-the-clock monitoring, even with spotchecks, can miss "escapes" of BP by night, and must be checked for outcomes, before it deserves the label of chronotherapy. Until a causative treatment of BP disorder evolves, if it ever does, there is no alternative to long-term monitoring, e.g., of BP and HR, sooner rather than later, from womb to tomb for health care and science, so that inter-individual differences are accounted for and available treatment is given as needed.

### Strain: blood pressure gauging loads

BP and HR monitoring has, as its invaluable benefit, the detection, treatment and follow-up of MESOR-hypertension and/or of BP overswinging (CHAT). Far beyond uncovering the vagaries of MESOR-hypertension and CHAT as two prominent examples of dynamically changing phenomena, long-term BP monitoring can resolve couplings in everyday physiology. It quantifies the current and past responses to heretofore unidentified or at least unquantified cycles in the past and/or present environment. A great added merit of BP monitoring is the benefit from gauging the

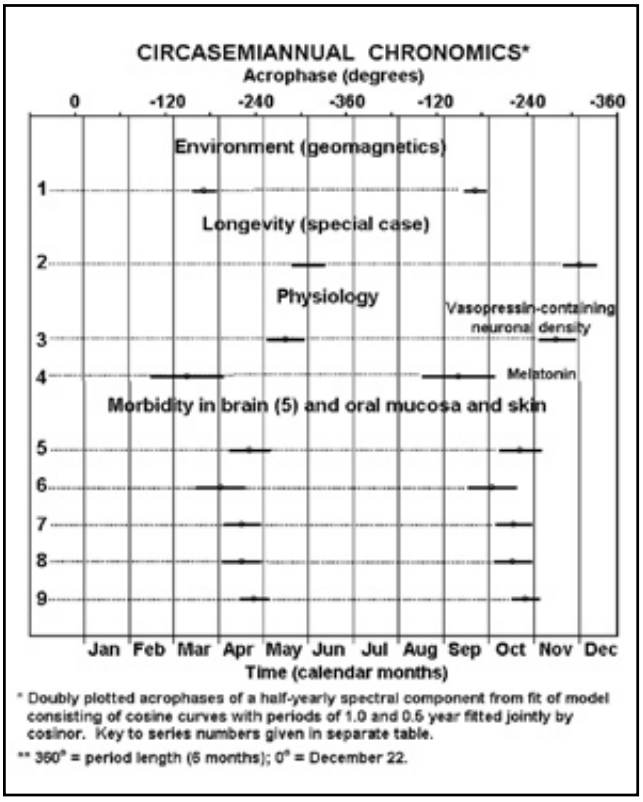
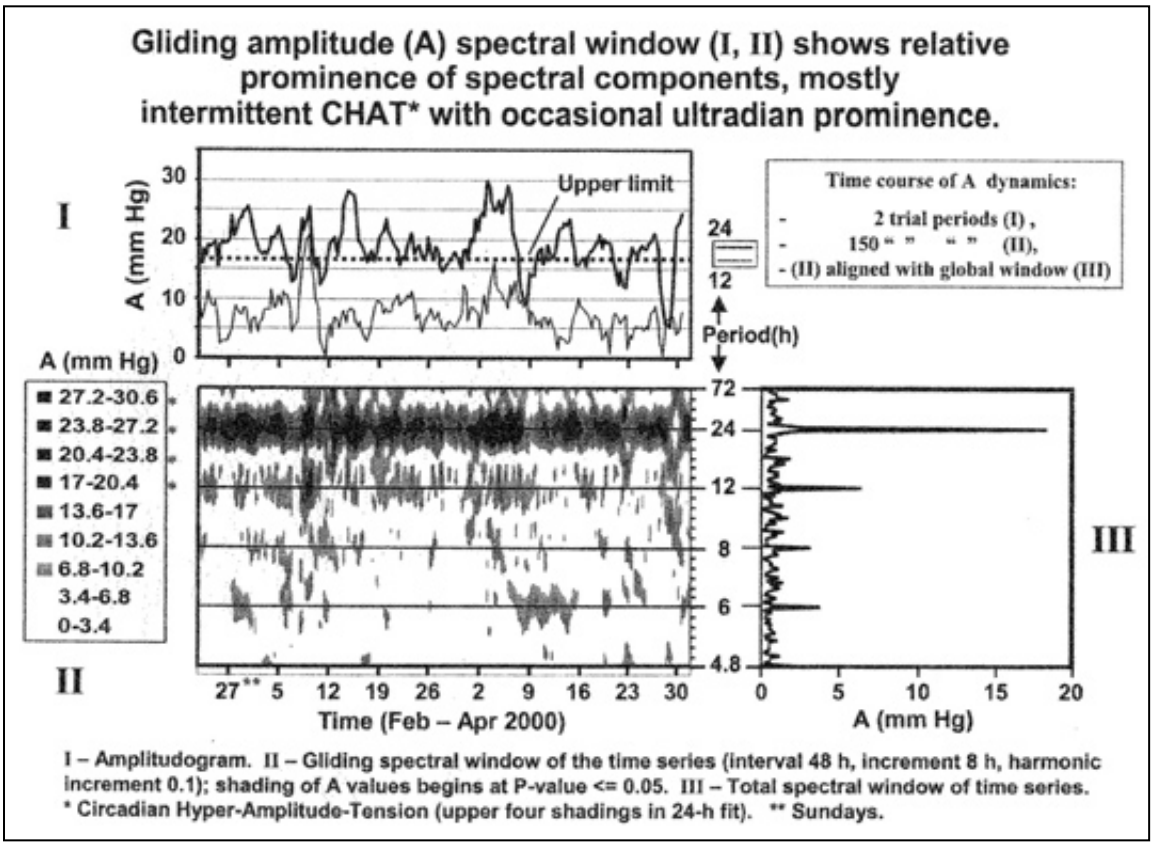



**Figure 2.** Start of a partial circasemiannual acrophase map. © Halberg.

**Figure 3 (below).** A gliding spectral window on the left (II) aligned with a global spectral window on the right (III) for a 2-month section from the 5-year series of GK confirms a diagnosis of intermittent CHAT. The key on the left side of the figure shows the shading grades that correspond to CHAT for GK. © Halberg.



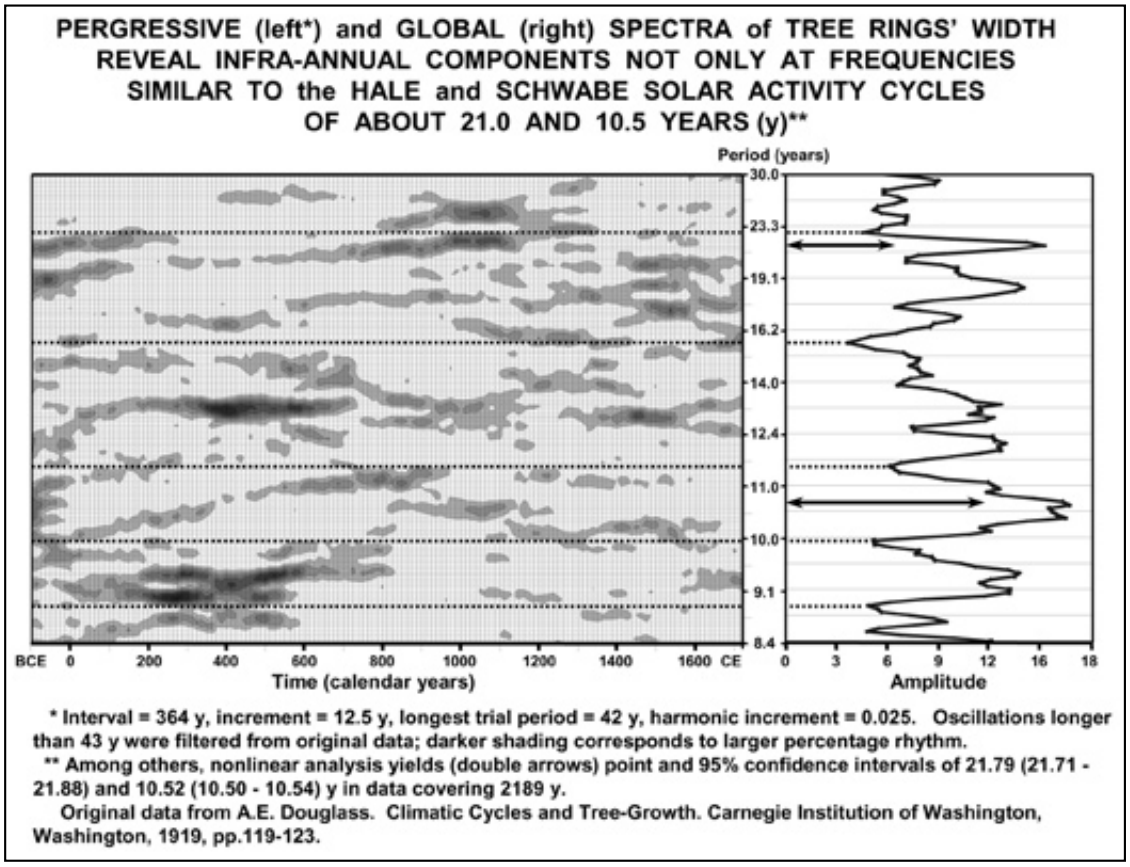



**Figure 4.**
Combined gliding (left) and global (right) spectral window of the average tree ring width of 11 sequoias, computed from original data by Douglas.
© Halberg.

wear and tear of life – stress and strain – notably in the military climate, but also in everyday conflict and grief along the scale of days, where circadian characteristics such as an amplitude or phase, and only subsequently the MESOR, are useful. The former two characteristics constitute sensitive endpoints of strain (I-99). Words like "pervasive" and "subtle", hiding our ignorance of what kinds of phenomena may be involved in the effect of distant drummers, will eventually be replaced by time-varying coherences and multiple phase-synchronization with different strengths at widely differing frequencies, a highly desirable step in the search for mechanisms, a legacy of the late Bärbel Schack, in dealing with human myocardial infarctions (I-89).

## Cherchez le contrôle

Around us, the proceeding study of already-mapped genes requires more than a time-unqualified functional genomics, a discipline which gains from a welcome accelerating focus upon variability (V), that in HR in particular (1). HRV and BPV include, in addition to phenomena labeled as high, low, very low and "ultra-low" frequencies along the scale of seconds or minutes, rhythms with much longer cycles (2–7, I-30, I-146). With informally communicating and cooperating investigators, mostly in the project on The Biosphere and the Cosmos (BIOCOS), since 2001 we have continued mapping chronomes (time structures) of HR, BP and other biological and physical environmental variables, finding further associations between the cosmos and the biosphere. Circadecadal variabilities, superficially pertinent only to scholars of aging and of other long-term phenomena, will seem far-fetched to those interested in changes along the scale of seconds. These circadecadals, however, deserve more general immediate interest once they modulate circaoctohorans, circadians or circasemiannuals that in their turn affect life vs. death within seconds (7, 8). We face the task of assessing the dynamics as a function of both genes and the cosmoi. We are resonating with the latter now and perhaps we have already coded some resonances of the past. Many problems of aliasing from inappropriate sampling on many new cycles can lead to wrong diagnoses, even when the time of day or calendar date of measurements is fixed (I-144).

### Gliding "cosinor windows" based on a method successful in 1801

Curve-fitting by least squares started with the discovery of the asteroid Ceres by Giuseppe Piazzi of Palermo, in keeping with Bode's prediction and the loss of Bode's letter addressed to, but never received by, Piazzi notwithstanding. Piazzi found Ceres where Bode had anticipated it to be and observed its changing position for several weeks. Eventually, though, Piazzi fell ill for several days; he recovered and spotted Ceres once more before it moved into the glare of the sun and its track was lost. The eyes of Europe were now focused on the search for Ceres. The loss of Ceres led to the development of the least-squares method by the young Carl Friedrich Gauss in order to compute Ceres' location based on Piazzi's incomplete data. Already then, prior information (from Johannes Kepler) was critical, namely that on the elliptical movements of celestial bodies. Over ~1.5 centuries later, Gauss' least-squares method became a basis of the cosinor involving tests of the "no-rhythm" assumption at anticipated repeatedly documented frequencies in unequally spaced data (8, 9).

## Table 1: Outcomes of chronobiological screens of blood pressure and heart rate*

| N of patients (ref) | N at follow-up | Sampling | N measurements: Total (outcomes) | Finding |
|---|---|---|---|---|
| 10 | 10 (up to 5 years) | 5/day daily | Up to 9,125 (only partially analyzed) | Among P. Scarpelli's patients, the 4 who died with malignant hypertension had a larger circadian BP amplitude than the 6 who were still alive (SBP: t=1.84; P=0.103; DBP: t=2.99; P=0.017). |
| 63 (1) | 21 after 28 years | 5/day for 2 days | 756 (252) | 9 of 10 subjects without CHAT are alive while 7 of 11 subjects with CHAT are dead 28 years later (chi-square=6.390; P<0.01). |
| 56 | Concomitant LVMI | q15 min for 24 h | 5,376 (5,376) | Classification by Y. Kumagai of patients by LVMI (<100; 100-130; >130 g/m$^2$) reveals elevation of circadian amplitude at LVMI in 100-130 range whereas MESOR elevation occurs only at LVMI >130. |
| 221 | 221 (time of delivery) | q1 h/48 h in each trimester of pregnancy (336 profiles) | 16,128 (16,128) | In addition to an 8 mm Hg difference in mean value between women who will or will not develop complications (gestational hypertension, preeclampsia) already observed during the first trimester of pregnancy, the occurrence of complications is also associated with BP profiles characterized by an elevated circadian BP amplitude. In particular, one case (JK) of CHAT where warning was not heeded, was followed 8 weeks later by severe pre-eclampsia, premature delivery and 26 months of hospitalization of offspring at a cost of about $1 million. |
| 297 (2, 3) | 297 after 6 years | q15 min for 48 h | 57,024 (57,024) | CHAT or a reduced circadian standard deviation of heart rate, or an excessive pulse pressure (>60 mm Hg) are large risk factors (larger than hypertension) for cerebral ischemic events, nephropathy and coronary artery disease, even when the blood pressure is within acceptable limits. |
| 2039 (3) | Concomitant LVMI | Hourly averages for 24 h | 48,936 (48,936) | In C.H. Chen's subjects, LVMI is increased in patients with CHAT, a reduced circadian standard deviation of heart rate, or an elevated pulse pressure. The relation between LVMI and the circadian endpoints is nonlinear. |
| 23 (1) | 12 after 7 years | q15 min for 9 days | 19,872 (10,368) | 10 of 20 patients with no consistent BP abnormality are alive and well; 2 of 3 patients with consistent BP abnormality reported an adverse vascular event (P=0.015 by Fisher's Exact Test). |
| 80 (4) | Response to treatment administered 2 h before daily BP peak vs. control group treated 3 times a day | q4 h for 24 h before and on treatment | 960 (960) | With smaller doses of medications, BP was lowered by R. Zaslavskaya to a larger extent and treatment was accompanied by fewer complications.<br>Treatment: propranolol, clonidine, or alpha-methyldopa (P<0.05 for each effect). |
| 18 (5) | 18 (12 weeks) | q30 min (≥24h) on 3 regimens | ≥2592 (≥2592) | Treating CHAT may prevent adverse vascular events: As compared to placebo, nifedipine (1 mg b.i.d. at 08 & 20) increases and benidipine (4 mg/day at 08) decreases the circadian amplitude of blood pressure. The resulting increase vs. decrease in the incidence of CHAT on nifedipine vs. benidipine may account for the corresponding difference between the number of stroke events of 7.6 vs. 3.5 and the total number of cardiovascular events of 20.4 vs. 8.8 per 1,000 person-years. |
| Totals:<br>2,586 | 2,533 | | 144,641 (>125,508) | |

*SBP and DBP: Systolic and Diastolic blood pressure; HR: heart rate; CHAT: Circadian Hyper-Amplitude-Tension, a condition defined by a circadian amplitude exceeding the upper 95% prediction limit of acceptability (in healthy peers matched by gender and age); LVMI: left ventricular mass index. By comparison with several classical studies, the number of measurements in chronobiological work completed thus far is likely to be larger, and confounding by inter-subject variability smaller.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The importance of prior information was again critical. The original single component, e.g., 24-hour cosine fit of the linear cosinor method was soon extended on the one hand to the fit of several components to assess the waveform and to a combination of linear and nonlinear least squares to identify the uncertainties of the periodicities or of the less regular cycles involved by the original zero-amplitude (no-rhythm) test. Concomitantly, the chronobiologic serial section evolved and proved its value with or even without reliance on the outcome of the hypothesis testing for determining both circadian and circaseptan desynchronization (10). It was the model for an extension of the cosinor to a gliding spectral window, preferably aligned with a global window, programmed by Sylvain Nintcheu-Fata with guidance by George Katinas (I-120).

Sylvain and George provided a 6-piece set of complementary 3D gliding spectral windows, usually on filtered data, and extended the scope of what before us Ivanka Charvatova and Jaroslav Strestik; A.M. Alpatov; and S.I. Aleksandrov and A.G. Gamburtsev had begun to use as contour maps, toward a transdisciplinary atlas. As a function of time (*x*-axis) and reciprocal period (frequency; *y*-axis), 3D windows display (on the *z*-axis), changes in 1. amplitude, in 2. prominence (percentage rhythm) or in 3. probability (P-values, testing the zero-amplitude assumption, qualified as ordering since they are obtained without correction for multiple testing). These three endpoints were each displayed in a side view for the study of main features and in 3 more windows viewed from above, for the scrutiny of detail.

Wobbly decadals, multidecadals and cycles with even lower frequencies (longer periods) were thus mapped and found in over 2,000 years of tree rings, Figure 4 (I-120), and in 2,556 years of international battles (I-96). These analyses reveal transdisciplinary similarities and differences of chronomes in life and in its cosmoi, in broad frequency *regions* that harbor unsteady unsynchronized components rather than bands or sharp lines. The gliding spectral windows' sometimes spectrally distant clear minima delineated by dotted lines in Figure 4, rather than the multiple irregular spectral maxima (see double arrowed continuous horizontal line in Figure 4), should interest physicists as well as biologists. The windows serve to delineate, in biological data covering 2,000 or more years, the behavior of non-photic solar activity, as a signature in climate, extending by far what observations of the aurora and the relative sunspot number revealed for such solar activity during the past few hundred years and what satellite-collected data show us as coronal mass ejections, as yet for a few decades only.

We also mapped economic and other social, e.g., demographic and psychophysiological cycles in time series, covering, longitudinally, decades, sometimes in the same individual, and centuries on populations. Non-overlapping 95% confidence intervals of near-matching periods in us and in our cosmos are in keeping with some degree of endogenicity. Methods of "subtraction", associated with damping, and "addition", associated with amplification, applied without our control but with our recording by the cosmos (rather than intentionally by surgically removing a gland and replacing its hormone), speak for current resonance at several frequencies. Time-varying spectral windows were aligned with corresponding global spectral windows in 3D to reveal what the global window may hide. Likewise, time-varying coherence and phase-synchronization served to examine couplings among variables at vastly different frequencies, providing a mathematical basis for what the intuitions of Alexander Chizhevsky, Düll and Düll, Arthur Jores and Frank A. Brown Jr. referred to as pervasive or subtle effects (6). We have become able to specify the time-varying frequencies and intensities involved in the way we are modulated by our cosmoi, using the term "modulation" in its physical sense (I-89).

By these extended cosinor windows, we mapped, in different system times, enlarging time horizons by including more decadals and multidecadals, far beyond tree rings and wars. In so doing, we learned about the indispensability rather than only the desirability of pergressive, i.e., gliding spectra as a critical part of the cosinor approach, Figures 3 and 4. Pergressive windows reveal details otherwise lost by reliance on the global spectral windows (of time series analyzed as a whole) and complement a serial section on a serial section. Gliding spectral windows, according to the cosinor algorithms, not only of amplitude but complementary windows of percentage rhythm and probability, as noted (best viewed both from sidewise and above, for focus on main features and on detail, respectively, whenever a time series is of sufficient length and density) have become precious tools of the transdisciplinary cartographer.

## Toward an atlas

Pergressive spectral windows are a beginning toward an atlas of chronomics. The latter is intended as a reference base for the transdisciplinary inferential statistical study of mechanisms underlying variability around us, in us and in external-internal interactions. The view of asking whether a given cycle, if not rhythm, is biological or sociological can be extended to include the search for contributions by the cosmos in a truly transdisciplinary way (6, 11, 12). Chronome maps constitute the *indispensable control information* for experiments or surveys, along any time scale in any investigation of data containing ubiquitous time structures. Proper sampling for any new endeavor, including clinical trials, benefits from the opportunity of taking into account the already-mapped chronomes. Only thus can we prevent a misinterpretation of the aliases, leading to false inferences as to treatment or other action associated with too sparse and/or too-short sampling (I-96). It is a common misconception that sampling at a fixed, convenient but physiologically arbitrary clock-hour and/or day of the week and/or calendar date can "control" or "eliminate" any effect of rhythms. The dangers of such a "fixed" design are not generally realized, notably when there is a chance that a treatment changes the phase of a rhythm or its frequency as well, as discussed earlier for circadians (I-93). The same reasoning applies to all rhythms, irrespective of their frequency as a formidable source of variation, when the cycles are not recognized and accounted for in a sampling design (I-144). By contrast, when evaluated, the cycles constitute new information that provides invaluable basic and applied endpoints in their own right, as in the case of the transyear and the circadian amplitude, respectively (I-95).

## Much more than reference standards

Chronomics provides new kinds of theoretically and/or practically invaluable information such as that of outcomes in Table 1. Outcomes in the system time of any one research or routine diagnostic endeavor, e.g., along the scales of seconds, minutes, hours or days, can depend upon the stage of cycles with still lower frequencies, like one cycle in about one or several decades. These cycles cannot usually be resampled. The need for maps of chronomics as a time horizon for every variable is self-explanatory and highly desirable or even indispensable, as the given case may be.

## Pre- (rather than only re-)habilitation

Variabilities along the scale of a day have already proved to be diagnostically useful, Table 1, revealing risks greater than hypertension in association with an over-threshold circadian BPV, an under-threshold HRV, an over-threshold pulse pressure and probably with an odd circadian BP timing. By its applicability to pre-habilitation, i.e., by service in risk detection and in the validation of the merits of preventive treatment, one of its long-term aims, chronomics becomes much more than the ubiquitously needed control. Eventually, current endeavors in rehabilitation may be replaced by endeavors for pre-habilitation (13, I-95). The ongoing detection of the high risk conditions summarized in Table 1 constitutes a halting step toward the goal to reduce if not forestall the need for rehabilitation. During the past two years, BIOCOS continued to be implemented routinely, in several locations, as a preferably 24-hour/7-day BP and HR monitoring for stroke and other serious disease prevention (14–17). We analyzed all comers' data, whether they covered one or seven days or one or several decades (I-80), and learned that the choice of a fixed clock-hour of measurement can still bias a diagnosis based on 26 years of weekly measurements in the morning (I-144).

## Continued free world-wide service

Routine 7-day series for chronobiological analyses continued to be collected in Brno, where, on the initiative of Jarmila Siegelova, Pavel Homolka complements the chronobiologic legacy of Gregor Mendel, and in Brussels by the private practice physicians Alain Delcourt and Guy Toussaint. Dissemination of the 24-hour/7-day approach in the city of Urausu, Japan, continued, thanks to Kuniaki Otsuka of Tokyo and Shoki Yano of Sapporo. Seven-day series were also collected in Moradabad, India, by R.B. Singh (I-138); in California by Balasasikumar Sundaram and Daniel Holley, and in Michigan by Katarina Borer (I-4, I-5). Seven-day series, and hundreds of shorter series covering several days, also came from Salvador Sanchez de la Peña and Clicerio Gonzalez of Mexico City (I-21), with emphasis on diabetes; Ziyan Zhao of Jinan, China, provided hundreds of series routinely covering one or two days for a study of aging. Series of 2 to 3 days on pregnant women were provided by Noubar Aslanyan of Yerevan (I-3). Monitoring has also been resumed in Florence, Italy, by Federico Perfetto and Roberto Tarquini, and by Andi Weydahl in Alta, Norway.

## Newborns' chronomics

The challenge of monitoring the healthy human newborn as well as the sick (I-140, I-141) was emphasized by Theodor Hellbrügge, a pioneer of chronopediatrics (I-84) and by Dietrich Reinhardt, head of pediatrics at the University of Munich. In their behalf, Germaine Cornélissen organized a meeting, supported by the Deutsche Forschungsgemeinschaft, on "Time structures, chronomes, in child development" on November 29–30, 2002. Germaine also contributed maps of chronomes for obstetricians and pediatricians to the meeting in Munich and to one in January 2002 in Brno, Czech Republic, in honor of the 60th birthday of Jarmila Siegelova, and to another meeting in Brno on November 3, 2003, honoring the 60th birthday of Bohumil Fiser, who, after serving his country as minister of health, has now joined the executive board of the World Health Organization. *Carpe diem*. Othild and Franz contributed to the same meetings in the historical contexts of Jan Evangelista Purkinje's self-experimentation and Gregor Mendel, the chronobiologist's concern for meteorology, more often than for the hybrids' "dialogue of hereditary particles", respectively.

### Other events

We appreciated invitations by R.B. Singh with Daniel Pella to lecture at an international cardiology meeting in Kosice in April 2002 (I-28, I-50) and in Bratislava on experimental design (I-7, I-29), and an invitation by Miroslav Mikulecky to provide an update on blood pressure also in Bratislava and Upice (I-24). Othild's birthday in May 2002 was an occasion for celebration by her long-time friends from her pediatric and other clinical practice. In 2003, we visited and I lectured in Hong Kong, where cooperation is planned with our BP analyses of a study by Brian Tomlinson. In India, we visited R.B. Singh, R.K. Singh, Adarsh Kumar and B.D. Gupta, opening an international meeting on antioxidants, contributing to a national blood pressure conference and giving grand rounds in internal medicine in Lucknow, and lecturing further in Moradabad, Chandigarh and Amritsar, regretting only that in the limited time we had, we could not accept other greatly appreciated invitations. Cooperation along biochemical lines was begun with Weihong Pan and Abba Kastin in New Orleans (I-53), on tree rings with Henry Michael of Philadelphia, on her method of phase-synchronization with Barbara Schack, intensified in chronomolecular biology with Zhengrong Wang in Chengdu (I-151), and resumed on antioxidants and free radicals with R.K. Singh and his daughter Ranjana in Lucknow, India. There Othild and Franz were guests of Shri Vishnu Kant Shastri, the governor of the province of Uttar Pradesh, who said that he and his scholarly brother are ready to set an example by monitoring themselves 24 hours a day for 7 days and have readied funds for the purchase of instruments.

Gen Mitsutake, Yoshihiko Watanabe, and Takashi Yamanaka visited, and cooperation with Kuniaki Otsuka continued. George Kachukhashvili came to renew cooperation with the Republic of Georgia, begun earlier with Lev Gheonjian, Tamar Paatashvili and Avtandil and Vazha Amiranashvili (I-1) and continuing with Lev. Plans for a clinical facility to be built in Tbilisi for manipulations such as shielding from, and/or compensating for changes in geomagnetic activity did not materialize but remain desirable in view of many new reports that all point to the need for complementing the remove-and-replace approach by the cosmos in an experimental facility.

Erwin Schaffer, emeritus dean of dentistry at the University of Minnesota, and we welcomed Hisashi Shinoda of Tohoku University, Sendai, Japan, whose data revealed circaseptans in the dentin of murine teeth (I-59, I-134). With Otto Appenzeller of Albuquerque, New Mexico, we studied fossilized teeth by comparison to current teeth, finding a different multiseptan time structure in the phase-weighted amplitude spectra of the thickness between the striae of Retzius in enamel, then as compared to now (I-2). This (spectral) difference in time patterns complements a spatial difference – greater thickness – of the bioweek's signature again then vs. now found by Otto himself.

## Challenge

In a day when garages are monitored to prevent crimes against persons, supermarkets to prevent theft, and experimental animals as small as mice for research notably on drugs, the monitoring of human

health gains at least equal importance. In view of the ongoing telemetering of EEGs, ECGs and BP on mice, the current, still slightly cumbersome 24-hour/7-day human BP and HR monitoring to us appears to be an anachronism, while to the vast majority this still looks like utopia. The merits of overcoming the vagaries of the conventional approach by single measurements at the outset, still advocated in guidelines (18, 19), are extensively documented in the bibliography on our website and summarized in a (2-part) recent review, mainly from a circadian viewpoint (I-34, I-35). This review also outlines the extent of the engineering and governmental challenge for stroke and other severe disease prevention set by the opportunities for vascular monitoring with currently available instrumentation for ("research" in) good practice. The 90 or 80% reductions in price for slightly heavier or lighter instruments, respectively, are practically a gift by the A&D company (Tokyo, Japan) for as long as the offer lasts, with the slightly larger instrument preferred since it has rechargeable batteries and hence its use is more cost-effective and its memory stores half-hourly BP and HR measurements for 17 consecutive days. With this unobtrusive instrumentation, analyses are also available from corne001@umn.edu, provided by computer methods in the light of data bases accumulating in Minnesota. Available outcomes, Table 1, suggest that 24-hour/7-day monitoring is an important step toward stroke and other vascular disease prevention and thus for the optimization (from the viewpoint of vascular disease) of health-related life quality. In the long term, the development of preferably implanted un-cumbersome instrumentation for BP and HR monitoring and for automatic data interpretation is recommended to meet the dreams of opinion leaders such as Theodore C. Janeway, Howard Levine and Frederic C. Bartter (20–22).

**Nearly a century ago, Janeway presciently wrote (20):**

… *it is essential* that a record of the pressure be made at frequent intervals *at some time previous* [presumably to an examination], to establish the *normal level* and the *extent of the periodic variations*. When this is done, it may be possible to demonstrate changes of small extent, which, lacking this standard for comparison, would be considered within the limits of normal variation.

In the 1970s, when Bartter treated a patient whose blood pressure was diagnosed differently by two physicians whom he saw at different times of day, he noted (23):

By conventional standards, this patient is clearly normotensive every morning. But the blood pressure determined each day at 6 in the afternoon provides especially convincing evidence that this patient is a hypertensive. …

My plea today is that information contained in [data curves compiled under differing circumstances, such as 24 hours a day/7 days a week] become a *routine minimal amount* of information accepted for the description of a patient's blood pressure. *The analysis of this information by cosinor should become a routine*. It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, to wit, an estimate of M [the time structure or chronome-adjusted mean, or MESOR] … an estimate of [the amplitude] A itself, and finally an estimate of acrophase, $\phi$ [a measure of timing]. In this way, a patient can be compared with himself at another time, or under another treatment, and the patient can be compared with a normal or with another patient.

In an article on "The Forgotten Domestic Crisis" (The New York Times, Sunday, October 13, 2002), Marcia Angell (24) writes that the U.S. "tolerates enormous disparities in income, material possessions and social privilege", and points out that "those disparities should not extend to essential services like education, clean water and air and protection from crime, all of which we already acknowledge are public responsibilities". Along similar lines, we had commented (15):

a Citywide Blood Pressure Monitoring Project can be a first step toward flying through the mountain range of blood pressure and heart rate variation patterns with open eyes. … Some may regard this aim as utopian, or at least as hyperbole. Scrubbing before surgery and antisepsis broadly were once ridiculed. There is nothing ridiculous in the fact that leaders in hypertension-medicine who were hypertensive have self-measured themselves for a lifetime several times each day, with analyses by desk computer. It is so much easier and more efficient today. The health watch aims as a first step not only at clean and safe streets and clean air, but also at as clean and as safe a circulation of blood as one can make it by self-help with education and instrumentation available as a public service, with as few "accidents", such as strokes, heart attacks and kidney disease, as thus possible.

Angell (24) feels that health care should likewise be a public responsibility for those reported by the U.S. Census Bureau in 2002 as nearly 1.5 million Americans who lost their insurance in 2001, and of course for settings with medium and less resources abroad. It need not be utopia, and it is heartening to read that for medium and low resource settings, "WHO will explore the possibility of developing an accurate and inexpensive automatic blood pressure monitoring device for worldwide use" (25, 26). Until such a device is further developed, and preferably rendered implantable, we call attention again to the availability not only of a device but of data analyses now offered through our center worldwide, and used by those mentioned in this report, among others. It was a privilege, in Brno in 2003, to submit to a symposium a set of:

**10 Amendments to Guidelines for Blood Pressure and Heart Rate Care**

Based on the formulated and experimentally validated demonstration that in the pursuit of happiness an education in chronobiology is an immediate fundamental channel in health promotion and universal health care (15), in keeping with an earlier unanimously accepted earlier resolution (27), we note that:

1. Self-surveillance and self-experimentation analyzed for and guided by time structures (chronomics) can be started at all ages, continuing throughout life, providing returns for health care and science (13–16).
2. Self-surveillance is best implemented in time series focusing upon endpoints of *variability* as well as upon averages in manual and preferably automatic blood pressure and heart rate measurements, among other variables (27).
3. Chronomics detects *risks greater than hypertension* as a basis for countermeasures that are possible by relaxation methods and/or medications (27).
4. Chronomics also detects, more reliably than by conventional spotchecks, actual disease such as MESOR-hypertension, and is best used to validate effects of treatment (27).
5. *Clinical significance*, gauged by return to reference values of the individual and/or of gender- and age-matched peers in clinical health, is an indispensable complement to the required, but in itself not sufficient, *statistical significance* of treatment effects.
6. Chronomics can establish whether treatment is beneficial, undesirable, ineffective or unnecessary by as-one-goes sequential analysis available for the individual patient to observe treatment effects and eventually to validate the beneficial effect, all in continuously monitored and time-structure analyzed serial data (27).
7. Literacy in chronomics should be built into an integrated comprehensive *curriculum*.
8. Such literacy is best started from scratch in *developing areas* as a model for the developed world, where modification of

existing programs is more difficult to achieve.

9. Literacy in chronomes and self-help is likely to lead to *higher-quality care,* focusing on prevention, at *less cost* (14, 27).
10. Research standards of hypothesis testing (P-values) and parameter estimation (95% confidence intervals) may thus enter routine health care practice for the first time in the service of the individual patient, as implemented and illustrated by an international consensus meeting (27).

## Tasks remaining

When Roberto Refinetti, the editor of a new online journal on circadian rhythms, invited me to submit an autobiography for the inaugural issue, I gladly complied and alluded to another major task, namely seeking unity in the field, as noted in the title of the article, a goal shared with Roberto (I-93). Any interested reader may forget historical detail related to others or to myself, included in view of Roberto's suggestion. Instead, the reader is asked to turn directly to a few puzzles encountered in the late 1940s and early 1950s, stemming from phase-shifted or phase-drifting rhythms being compared. It was clear half a century ago that variability can be a terrible source of confusion and if unrecognized remains just that in much ongoing research on up and down regulation. In the interim, it has also become clear, with a long list of examples, that risk elevations starts in the normal range of variation, whether we deal along the scales of circadian rhythms, of circannuals, or of aging. The circadian amplitude of melatonin is elevated in association with an elevated risk of developing breast cancer (28) and is reduced in association with actual cancer (29), in each case in the absence of a change in chronome-adjusted average or MESOR (30). The circadian amplitude of melatonin also decreases as a function of aging, even under conditions associated with the absence of a decrease in MESOR (31). The circadian amplitude of aldosterone decreases with aging without a change in MESOR (32). The circannual amplitude of aldosterone changes with cardiovascular disease risk and the circannual prolactin and TSH amplitudes change with the risk of breast and prostate cancer (7).

Most importantly, the Okamoto rat's blood pressure amplitude, a model in which practically every animal will have a stroke after spontaneous hypertension, can increase very greatly before the MESOR increases (33). This phenomenon has its counterparts in humans (34, 35). For a very long time, neuroendocrinologists and others have focused on the hypothalamus and its role in blood pressure elevation as a potential social disease (36) and have tried to reproduce it experimentally (37, 38). The finding in Figure 5 of a disappearance of the circadian rhythm in BP after bilateral ablation of the suprachiasmatic nuclei (SCN) (39) adds to the challenge of focusing on the hypothalamus (27) prompting the question of what a unilateral SCN ablation may do. In the case of the core temperature rhythm, a bilateral SCN ablation lowers the circadian amplitude but does not eliminate the rhythm (40). Again, for the case of core temperature, a unilateral ablation amplifies the circadian amplitude. Seeing whether such a finding, indicating subtractive coupling, also applies to the

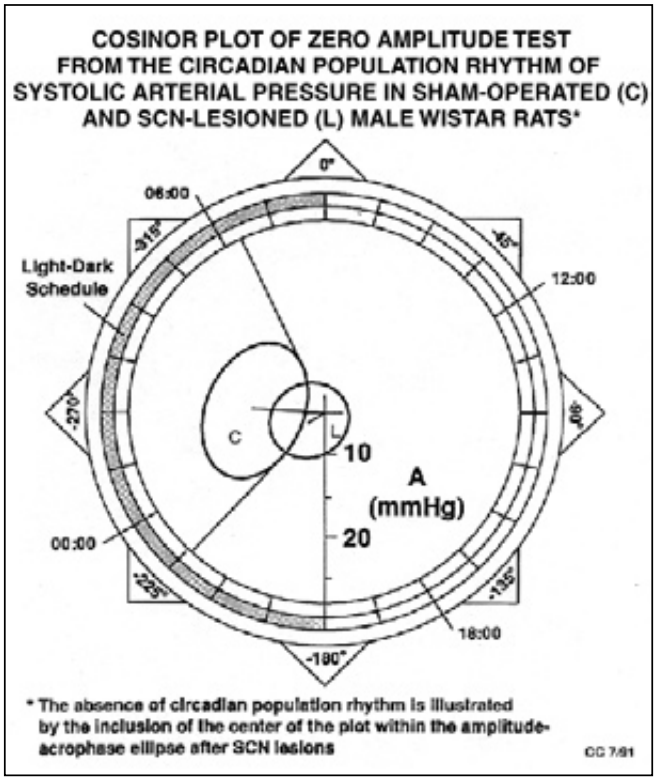


**Figure 5.** Cosinor plots of the zero-amplitude test for a group circadian rhythm of systolic blood pressure (SBP) in rats after a sham-operation (C) ($P<0.05$) and after a bilateral ablation of the suprachiasmatic nucleus (SCN) (L) ($P>0.05$); note overlap of center of graph (pole) by the L, but not by the C group. If there were an increase in circadian amplitude after unilateral ablation, a model would be available for SBP overswinging (such subtractive coupling is demonstrated for core temperature after unilateral SCN ablation) (7, 40). Original data and analyses of A.G. Stoynev et al. (39). © Halberg.

circadian rhythm in BP is an urgent task in the laboratory to seek this or another model for BP overswinging (CHAT), a possibility that as yet is sheer speculation.

But irrespective of what the underlying mechanism may be, the detection and use of early changes for the institution of countermeasures is a challenge second to none when one deals with the BP of the uninsured in the USA or in low- and medium-resource settings. The amendments may constitute a step in the direction of meeting the need for a change from a health care based on the quicksand of single time-unqualified spotchecks to one of time series, self-measured, if there is no other way (I-68, I-79) or cost-effectively implemented by automatic monitoring while following the 10 amendments, with chronomically analyzed time series, interpreted as learned in public early and adult education (15, I-34, I-35, I-99).

## Our partial systems have complementary ones

We always measure a partial system (41, 42) in the pursuit of a given test or problem. Of necessity, we fail to measure whatever is not within our interest, thus leaving unassessed a complementary system (42). Hence, maps of complementary variables' behavior are extremely desirable, and once they are prepared,

they can serve all comers, as long as they are regularly updated as any changes occur. These same maps have to be consulted when one seeks a reference standard at the outset of a study, such as a test. From maps, we can try to estimate the extent of sampling needed for an appropriate pretreatment value.

For instance, in dealing with BP, one cannot take a "baseline" measurement since there is no time-invariant baseline (43). One must refer to circadian MESORs, amplitudes (As), acrophases (ϕs) and waveforms (e.g., [A,ϕ]s of harmonics). For this variable and all others, if our studies have a long-term aim, we cannot measure everything ourselves. There is a need to map cycles and even broader time structures, i.e., the need for an atlas, a broad transdisciplinary set of maps. In short, there is a need for chronomics. Once we make an atlas for what many others and we can resolve in time, a systematic task, we can find in minutes what took half a century to map (I-93). We turn from focusing on the variability in counts of circulating cells that stain with an acid dye, the eosinophils to focus upon the adrenal cycle. Once we find ubiquitous effects of the hormones of this gland's cortex – the corticoids – others and we may also find that these effects may often be triggered by catecholamines from the medulla of the same gland. From focusing on the adrenal, in turn, we are led to the pituitary and the hypothalamus, and eventually to the pineal. From looking at feedbacks and feedforwards, we are also led at inseparable feedsidewards (7) in a very broad network of interactions, involving rhythms with much more than a circadian frequency in much more than a neuro-endocrine-immune network. Each cell is involved with all of the genetically coded apparatus for a chronome (time structure) to be integrated with other chronomes in us and around us.

As satellite data became available (and reveal to physicists cycles in the speed of gases ejected by the sun), we find spectral signatures of the solar wind in the BP and HR of adults and in the same variables of human babies, with an amplitude which exceeded that of the changes recurring from winter to summer. We cannot make our partial systems to be analyzed, such as clinical tests, broader each time we explore them. But we can make maps and eventually an atlas of new findings about a great many cycles that should be available to all users as complementary systems.

This is what chronomics is all about, and this is what students of stimuli in everyday physiology will need, unless one uses words, such as "wear and tear", "stress and strain" (preferably to "stressor/stress") or "allostasis" instead of describing the phenomena of life in the range of everyday physiology. Hans Selye was right in focusing upon the adrenal response to unusual stimuli. He even writes in so doing about daily variations but has to guess that they occur since in the case he explores he has no control (44). His work was based largely on *post hoc ergo propter hoc* reasoning, a line of thought he may have felt to be justified by virtue of the unusual stimuli he applied. But in so doing, he forgot that we not only sleep after waking, but that the eosinophils increase and thereafter decrease, whether or not we eventually fall asleep or continue to stay awake (45).

By his lack of concomitant controls, Selye created, not only a linguistic problem by confusing "stress" with "strain", but also a real problem that transcends linguistics. It has to do with the failure of specification of both stimulus timing and intensity and with the failure of the assessment of effects upon cycles and even broader time structures. These structures yield quantitative endpoints in the form of chronomes with rhythms, the latter both an indispensable control and the basic mechanisms of life. On the practical side, we can make it easy, for general use and compliance, to give a drug at a time for all comers and spotcheck its efficiency at a time of convenience. But there is an alternative to dealing with time-unqualified partial systems such as the measurement of **the** putative true BP. Both the medical and scientific communities can consult and ask maps of variations as they become available, e.g., as we deal with BP amendments for stroke prevention to replace by prehabilitation current approaches that are cost-ineffective, wasteful of life, health and particularly of resources, a luxury of rehabilitation after coronary artery bypasses and transplants that persons and settings with less resources, such as the uninsured in the US, can ill afford.

## Conclusion

Measure, in a **partial system,** everything pertinent that is measurable and render measurable what is pertinent but as yet is not measurable, as simply as possible, but not simpler, in time (tempestive) and hence meaningfully, taking into account chronomic maps, a described and quantified **complementary system.** *[Omnia propria ex* **systemate partiali** *metire quæcumque licet et propria immensa, quam simplicissime sed non simplicius, ad mensuram tempestive et ergo significative redige, reddens rationem tabulae chronomicae ad* ***systema complementare*** *descriptum et quantificatum.]*

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APPENDIX I: PUBLICATIONS BY/WITH MEMBERS OF HALBERG CHRONOBIOLOGY CENTER IN 2002 and 2003

• 2002

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# Appendix A:

## A further example of the usefulness of prior information and of linear-nonlinear rhythmometry

**Anatoly V. Masalov[1] & Elena V. Syutkina[2]**
[1] Lebedev Physical Institute, Moscow, RUSSIA.
[2] Institute of Pediatrics, Scientific Center for Children's Health, Russian Academy of Medical Sciences, Moscow, RUSSIA.

A graph (Figure 1) was omitted from a manuscript by Masalov and Syutkina in a supplement on "Time structures – chronomes – in child development" [1]. This graph accompanied a follow-up investigation on earlier hints that human neonatal blood pressure and/or heart rate may be modulated by the about 10-year solar activity cycle and may resonate with the local index of geomagnetic disturbance in the circaseptan (about 7-day) range. For comparison with data on beginnings and endings of magnetic storms recorded at Troitzk, blood pressure and heart rate data from 232 preterm and 133 full-term babies monitored for 1 to 48 days after birth between January 1990 and April 2002, were pooled and re-analyzed by periodograms with partial results shown in Figure 1. Storms were found to be non-randomly distributed along the 24-hour scale, and a peak in the periodogram at the 1.3-year trial period is noted (p. 113 in ref. 1). Composite series of blood pressure data contributed by all infants showed a response to storms, which was most pronounced 10 hours after the beginning of a storm in full-term infants and about 15 hours prior to the beginning of a storm in preterm infants. Analyses by epoch superposition also indicated an effect of magnetic storms, occurring 10 (preterm babies) or 20–22 (full-term babies) hours after the beginning of a storm, consisting of a suppression of the circadian (and/or circasemidian) component of blood pressure and a shift of 2–3 (preterm babies) or about 10 (full-term babies) hours in acrophase.

*Comment by an editor.*

*F*igure 1 of this appendix shows several spectral peaks in the region between 1 and 2 years, notably in the periodogram of preterm infants, and, to some extent, also in that of full-term infants. The highest amplitudes for magnetic storms are in the 1.3-year period region. There is a trough of the neonatal periodograms at the peak of the magnetic storms. When confronting several peaks that are not predicted, in the absence of prior information, Figure 1 was removed to save space, even though in retrospect it contains critical information. For this, apologies are due, and hence this appendix for the sake of priority.

The need for invariably providing uncertainties for period estimates, e.g., by added nonlinear analyses, whether or not there is prior information, is a methodologic point. Indeed, nonlinear as well as linear rhythmometry provided interval as well as point estimates for spectral peaks, whereby the transyear was documented with its uncertainties and found to be more prominent than a yearly component in these same neonatal data [2]. *Franz Halberg*

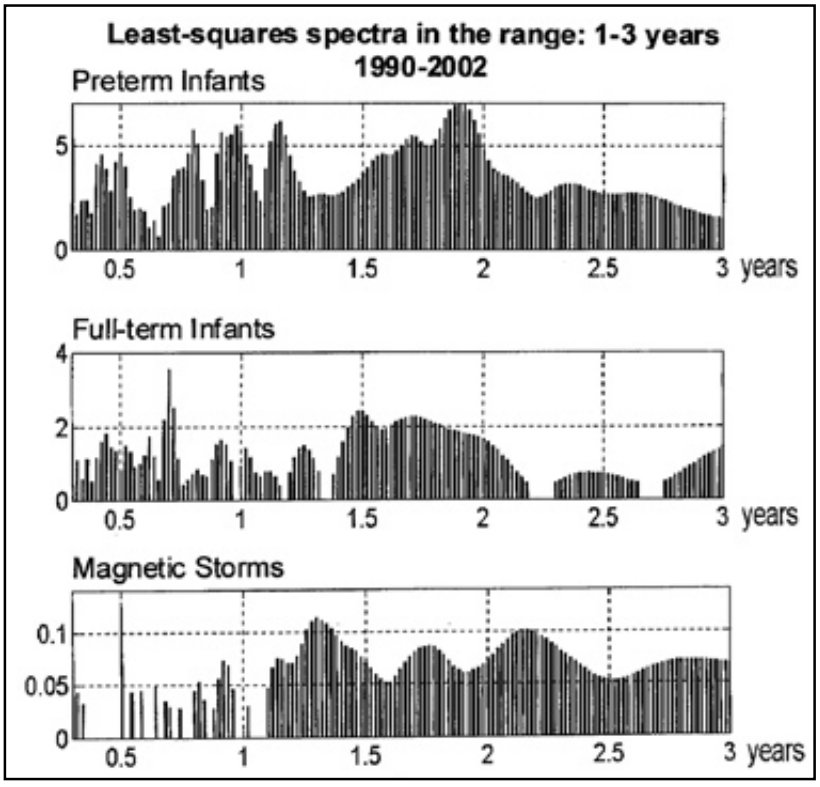


**Figure 1.** Periodogram in the range of trial periods from 1 to 3 years in pooled data collected between 1990 and 2002.

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# Appendix B

## Academician GENNADY D. GUBIN, 75 calendar years, ~58 transyears of age: *Ad multos transannos!*

**Germaine Cornélissen, Franz Halberg, George Katinas, Mary Sampson, Othild Schwartzkopff**
Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA

Changes of a circadian time structure in human and other ontogeny [1] and a broadening to the phylogeny of circadian systems [2] are explicitly associated with the name of Gennady Dmitrievitch Gubin, born in Tyumen on August 20, 1928. By the age of 36 years, he had focused on nucleic acid dynamics [3], and before reaching age 40, he reported on nucleic acid rhythms in liver and brain [4], extending the scope of earlier endeavors [5, 6] that had been contrary to the thinking not only of that time [7], but remain at variance with linear as opposed to cyclic [5, 6] schemes of information transfer in the molecular biology of today. Gennady's doctoral thesis covered the themes of both the ontogeny and phylogeny of rhythms, while his publications cover even broader topics [1–4, 8–13].

Carbohydrate, lipid and protein metabolism, hematological parameters and the buffering capacity of blood were studied repeatedly with serially-independent sampling on several groups of animals of comparable age and gender at 6 different stages of lifespan from several species. Changes around the clock in liver RNA and glycogen were studied in Pisces, Amphibia, Reptilia, Aves and Mammalia to estimate phylogenetic changes of circadian rhythms in hepatic functions.

For the majority of the variables investigated, there was a statistically significantly lower (cosinor-assessed) circadian amplitude in the late stages of ontogeny by comparison to maturity. A decrease in the circadian amplitude as a function of age was demonstrated, among others, for hepatic glycogen, $^{3}$H-cytidine uptake by the hepatocyte nucleus or cytoplasm in mice, erythrocyte counts, relative lymphocyte counts, insulin-containing erythrocyte counts, blood glucose, hemoglobin, pooled serum lipids, $pCO_2$, blood pH, serum 11-oxycorticosteroids and rectal temperature in rats, and for salivary $Na^+$ in humans. Gradual changes with age, consisting first of an increase of circadian amplitude of metabolic variables up to maturity, are followed by the statistically validated decrease in the circadian amplitude of metabolism.

Gennady Gubin initiated his series of transverse studies on phylogenetic and ontogenetic aspects of circadian rhythms in vertebrates in Ekaterinburg in 1959 and resumed them beginning in 1964. They continue through the present time at the Tyumen Medical Academy in Siberia, with his son Denis G. Gubin standing behind him and holding his hand, figuratively [14, 15] and, on the right side of Figure 1, literally. Denis Gubin is an affiliate of the Halberg Chronobiology and Chronomics Center at the University of Minnesota and of the International BIOCOS project [16].

Reviews of the circadian system as a function of age [17, 18] are in keeping with the reduction in amplitude in advanced age documented longitudinally for the Minnesota Sprague Dawley rat by the telemetry of body core temperature during most of its lifetime [19]. They are also in accordance with the above-mentioned results from Tyumen, as is a change with age in the circadian amplitude of circulating aldosterone. The latter occurs in data where a change in time structure (MESOR, or chronome-adjusted average) of aldosterone could not be detected with statistical significance [20]. By contrast, a statistically significant decrease in the circadian amplitude of 17-hydroxyprogesterone, estrone, estradiol, prolactin and DHEA-S occurs invariably with a decrease in MESOR as well, whereas the amplitude of LH increases with advancing age, as does the MESOR of LH. Rules are imperfect and require qualification.

The combined dyschronism of a reduced circadian amplitude and an acrophase advance is the major feature of aging in the telemetered core temperature of the stroke-prone spontaneously hypertensive Okamoto rat (SHR-SP) [19]. With few exceptions in the intestinal tract [21], a circadian amplitude reduction and an acrophase advance are also amply documented for a long list of variables in rats and rodents more generally following histologically-validated bilateral suprachiasmatic lesions [21–27]. Subsequent research on the amplitude provided a mechanism for what Gennady had provided in a comparative physiological approach to the phylogeny and ontogeny of circadian rhythms, a good reason to honor him here in his lifetime, for accomplishments in new disciplinary and transdisciplinary endeavors.

Neuroendocrinology Letters has become an organ for chronobiology, the study of mechanisms underlying circadian and other time structures, and for chronomics, the mapping of these time structures and perhaps someday for chronobioethics [28]. The Gubins are leading contributors to all of these endeavors, Gennady insofar as circadians are concerned [1–4, 8–13] and Denis beyond circadians [14, 15]. As this journal congratulates Gennady, on his 75$^{th}$ birthday, for ex-

tending his interests to polar medicine, a particularly timely endeavor for the study of effects of magnetics upon time structure, it also welcomes the contribution of Gennady's son Denis, who is extending his father's circadian perspective to circaseptans [14] and ultradians [15] and from Tyumen to the polar region. This journal wishes the Gubin team, father and son (Figure 1), many more productive transyears (longer than the calendar year) [29, 30] in good health. Even if this laudatio is premature from a helio-geomagnetic perspective, since Gennady is not yet 58 organismic as well as solar-wind-like "transyears" of age, the dissemination of his results will help readers in molecular as well as integrative research. Again, *ad multos transannos*.

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