LORD OF TIME
FRANZ HALBERG

on the 90th anniversary
of his birth,
on 5 July 2009

CONTENTS

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TOWARD A CHRONOUSPHERE*
(from Gk *chronos* = time, Attic Gk *nous* = mind and Gk *sphairos* = sphere, globe)

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*We used "no**u**s" in the portmanteau'd "nousphere" to credit Vladimir Ivanovich Vernadsky, Pierre Teilhard de Chardin and Edouard le Roy, who, i.a., used the derivation of "noosphere" from "noos", recognizing the need for a sphere of the human creative mind or broader culture, courageously extrapolating beyond the sphere of available data (Hagemeister M. In: Rosenthal BG, ed. The Occult in Russian and Soviet Culture. Ithaca, NY: Cornell University Press; 1997. p. 185-202; cf. Ertel S. Studia Psychologica 1996; 38: 3-22). Cosmism's pioneers as yet did not have the means (computers and satellites) for detecting and documenting the pervading transdisciplinary spectrum of solar, interplanetary, geo- and biospheric cycles and the consequences in the human mind of the aeolian disappearance and/or reappearance of non-photic rhythms, e.g., in Figures 4 and 5 herein.

Update in July 2011 on Franz Halberg's studies, prepared for International Congress "Natural Cataclysms and Global Problems of the Modern Civilization", 19-21 September, 2011, Istanbul, Turkey, with an appendix reprinted from Alexander Sidorin's "Lord of Time", published by the Schmidt Institute of the Physics of the Earth of the Russian Academy of Science in 2009.

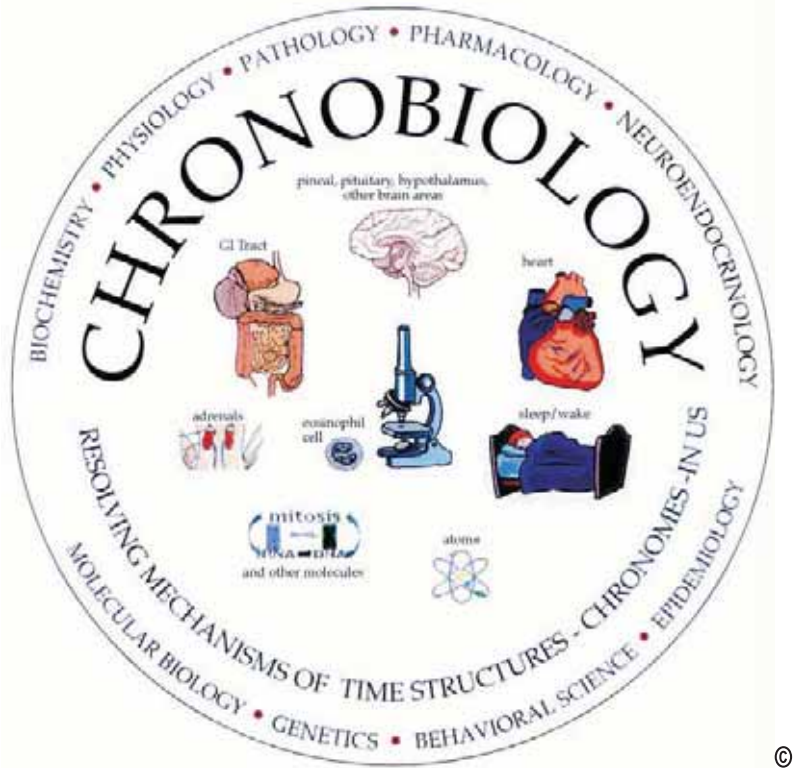
Dedicated to the memory of Frank A. Brown Jr. (1908-1983), who had asked the senior author (FH) to cooperate; FH tried to do so in 3,432 titles, with help from a project on The BIOsphere and the COSmos, BIOCOS.

Introduction

Cardio-cerebro-vascular diseases (CVDs) and cancer are not only personal but also global disasters. Data collected for CVD prevention and treatment as a start also serve to investigate means to avoid or evade social disasters, whether they are human-made like crime, terrorism and war, or natural like earthquakes. To be meaningful, all investigative endeavors need indispensable controls. Time structures consisting of chaos, trends and cycles are controls as complementary systems for anything investigated. Here, we describe first what we learned about cycles from our experience along the 24-hour scale that led to chronobiology as a tool, if not discipline in its own right. Next, neonatal data had to be reinterpreted as they accumulated along the scale of decades, as a result of geo- and heliochange. They led to chronomics, chronobioethics and chronoastrobiology, a apparent from the figures summarizing the bibliography that follows.

*Three tools – chronobiology, Figure 1; chronomics, Figure 2; and chronobioethics, Figure 3 – serve a unified science, including a nascent chronoastrobiology, Figures 4 and 5, all contributing toward a chrononoosphere, or, rather, chronousphere as the fount of human culture, including a unified science, illustrated in its transdiscipinary diversity by the last set of titles in a bibliography in press for this meeting on cataclysms.

Figure 1: A computer-implemented virtual "microscope" (chronobiology) resolves cycles in ourselves, revealing, in different stages, different, sometimes opposite effects of the same stimulus*

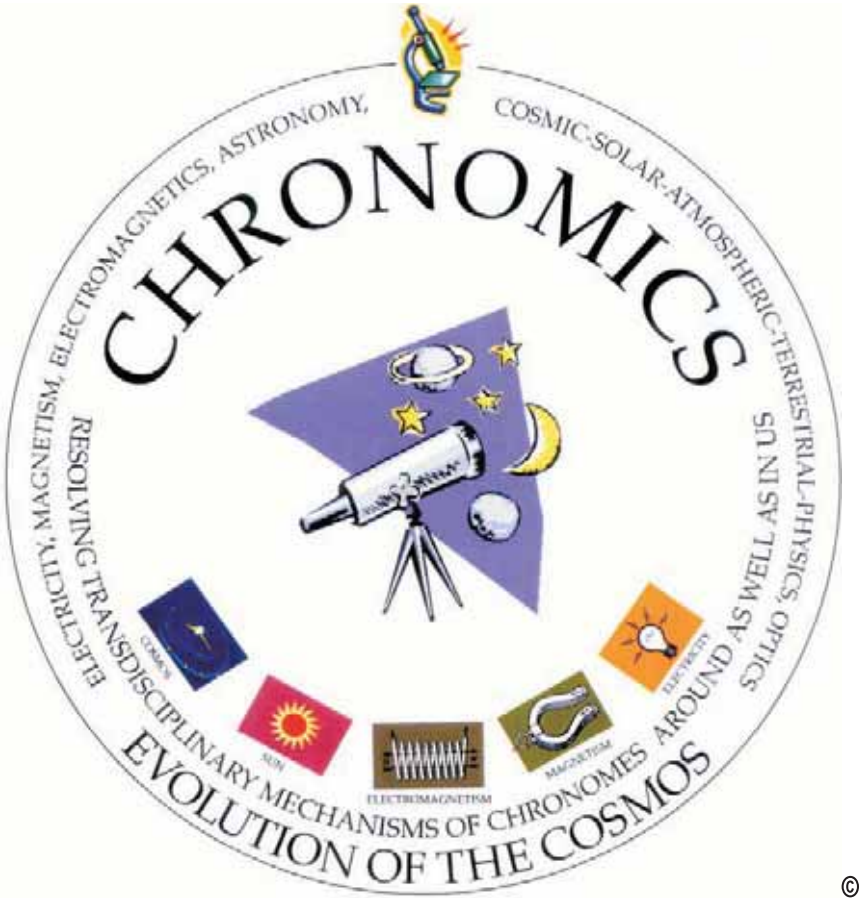


*Such as a hypotensive drug that can harm or yield benefit at different cycle stages, prompting marker rhythm-guided chronotherapy (1) that also applies to X-ray irradiation, that doubled the 2-year disease-free survival rate of patients with perioral cancer (2). Broadly, chronobiology replaces fictitious "baselines" in the life sciences, as the CONTROL information in BIOSCIENCE

1. Halberg F, Cornélissen G, Wilson D, Singh RB, De Meester F, Watanabe Y, Otsuka K, Khalilov E. Chronobiology and chronomics: detecting and applying the cycles of nature. Biologist 2009; 56 (4): 209-214.

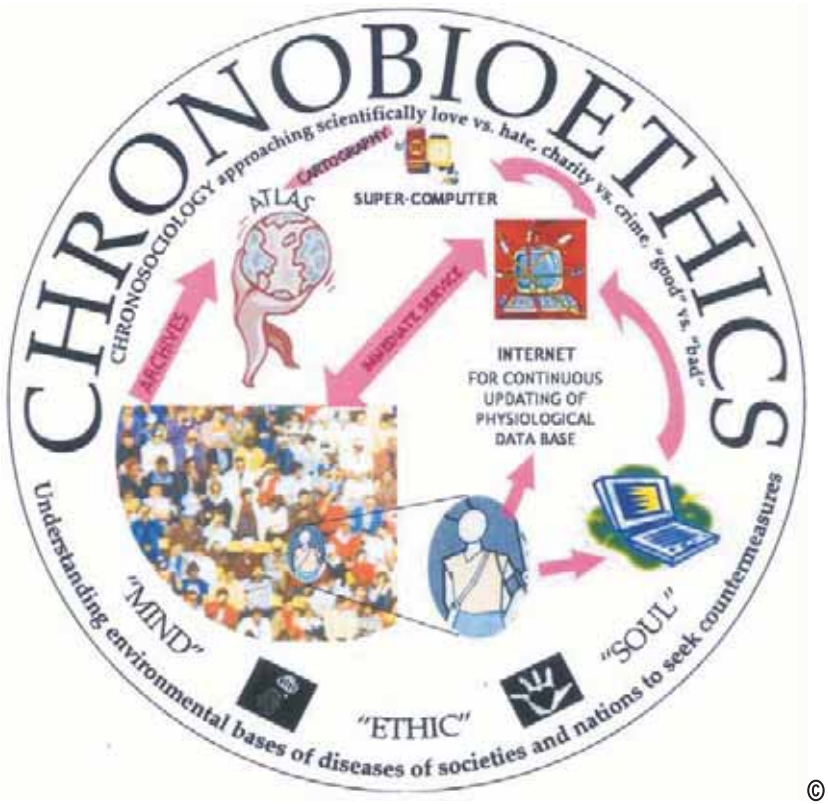
2. Halberg F, Cornélissen G, Wang ZR, Wan C, Ulmer W, Katinas G, Singh Ranjana, Singh RK, Singh Rajesh, Gupta BD, Singh RB, Kumar A, Kanabrocki E, Sothern RB, Rao G, Bhatt MLBD, Srivastava M, Rai G, Singh S, Pati AK, Nath P, Halberg Francine, Halberg J, Schwartzkopff O, Bakken E, Shastri VK. Chronomics: circadian and circaseptan timing of radiotherapy, drugs, calories, perhaps nutriceuticals and beyond. J Exp Therapeutics Oncol 2003; 3: 223-260.

Figure 2: A computer-implemented virtual "telescope" resolves associations among reciprocal cycles in and around us that represent control information replacing fictitious "baselines" in any scientific or other human endeavor



*Halberg F, Cornélissen G, Sothern RB, Katinas GS, Schwartzkopff O, Otsuka K. Cycles tipping the scale between death and survival (= "life"). Invited presentation, Nishinomiya-Yukawa International & Interdisciplinary Symposium 2007, What is Life? The Next 100 Years of Yukawa's Dream, Yukawa Institute for Theoretical Physics, Kyoto University, October 15-20, 2007. Progress of Theoretical Physics 2008; Suppl. 173: 153-181.

Figure 3: Toward mapping and analyzing mechanisms of societal and nations' diseases while caring for individuals*

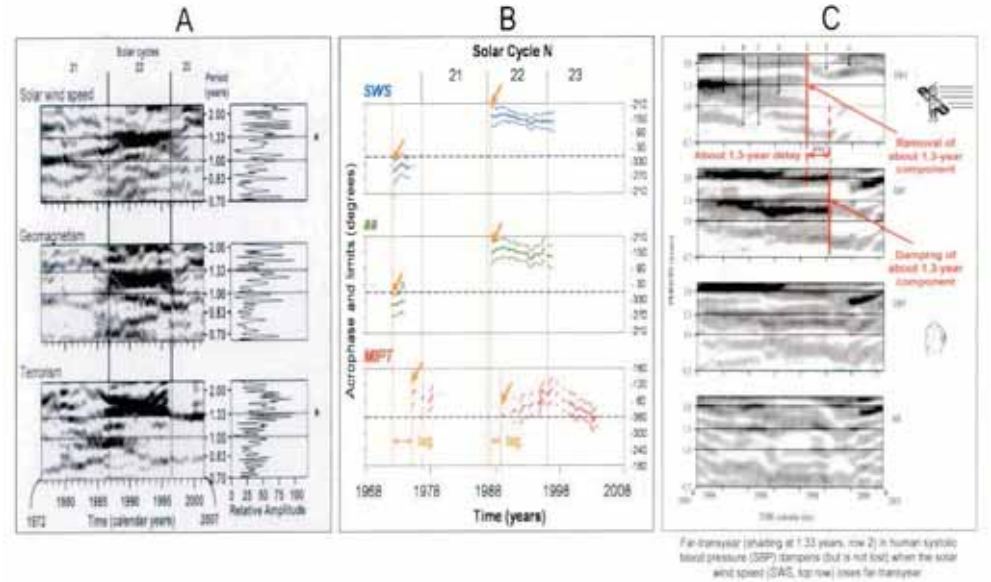


*as a basis for timely and timed countermeasures

1. Starbuck S, Cornélissen G, Halberg F. Is motivation influenced by geomagnetic activity? Biomedicine & Pharmacotherapy 2002; 56 (Suppl 2): 289s-297s.
2. Halberg F, Otsuka K, Katinas G, Sonkowsky R, Regal P, Schwartzkopff O, Jozsa R, Olah A, Zeman M, Bakken EE, Cornélissen G. A chronomic tree of life: ontogenetic and phylogenetic 'memories' of primordial cycles - keys to ethics. Biomedicine & Pharmacotherapy 2004; 58 (Suppl 1): S1-S11.

Figure 4: Additions and Subtractions (loss and replacement) of Spectral Components in and around us. Based on 14,579 Cases of Terrorism in 39 years (B and A, row 3) and Systolic Blood Pressure (C, row 2)

Aeolian behaviors of solar wind speed (SWS), geomagnetism (aa), and terrorism (MIPT) reveal a far-transyear in the absence of a dominant calendar year (*); about 1.33-year component in terrorism lags with intermittent statistical significance behind SWS and aa



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We carry subtraction studies to the cosmos against the background of remove (1-3) and replace (4) studies on the adrenal that demonstrated a loss upon gland removal of the circadian rhythm in circulating eosinophils, i.e., cells that stain with a pink dye, with a persisting but altered rhythm in serum iron (3). The earlier work could be completed on each subject within 24 hours. It takes longer when the interplanetary system decides to remove (or replace) a 1.3-year component of the solar wind, in order to examine the extent of change (amplitude) of the about 1.3-year (transyear) component found to globally characterize the incidence of international terrorist acts (MIPT database). The data were analyzed locally by gliding spectral windows (A-left, bottom). This time structure is compared with that of solar wind speed (A-left, top) and of the antipodal index of geomagnetic disturbance aa (A-left, middle) in the same frequency range. The transyear is observed to be particularly prominent in all three variables during solar cycle 22, as seen from the darker shading at a

frequency of one cycle in about 1.33 years (5). Changes with time of the phase of the transyear component, estimated at the average global period (B as a whole) indicate further that statistical significance for terrorism relatively shortly follows (with only a lag) that in solar wind speed and geomagnetism and that it may persist after statistical significance is lost for the two environmental variables. Despite some expected wobbliness, the transyear appears to be relatively stable in all variables during most of solar cycle 22. A transyear is also detected in the blood pressure and heart rate of men and women of different ages (not shown). In particular, it is illustrated for a man (FH) monitored around-the-clock for 23 years, with interruptions (C-right, rows 2- 4) (6). The transyear in systolic blood pressure (C-right, row 2) is dampened but persists when this component is lost in solar wind speed, suggesting that the transyear may be partly built-in while also amenable to resonance with environmental transyears (6). The fact that a predictable cycle characterizing the incidence of terrorism is also present in the physiology of individuals renders it amenable to monitoring by a population marker rhythm for further scrutiny and for the eventual design of rational countermeasures against undesirable effects of the cosmos. Gliding spectra prepared by Prof. George S. Katinas.

1. Halberg F, Visscher MB, Flink EB, Berge K, Bock F. Diurnal rhythmic changes in blood eosinophil levels in health and in certain diseases. Journal-Lancet (Minneapolis) 1951; 71: 312-319.

2. Halberg F. Some physiological and clinical aspects of 24-hour periodicity. Journal-Lancet (Minneapolis) 1953; 73: 20-32.

3. Halberg F, Howard RB. 24-hour periodicity and experimental medicine. Example and interpretations. Postgrad Med 1958; 24, 349-358.

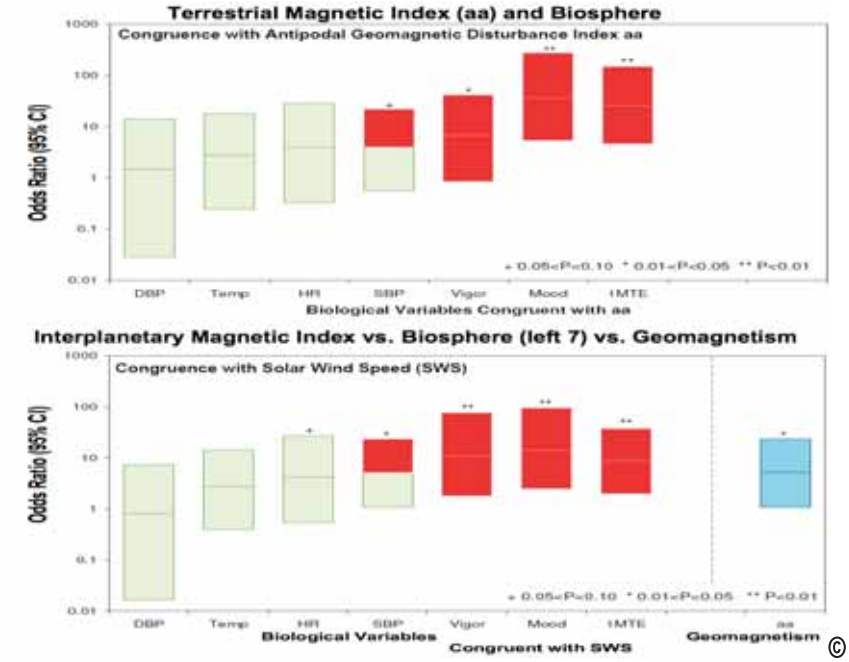
4. Kaine HD, Seltzer HS, Conn JW. Mechanism of diurnal eosinophil rhythm in man. J Lab Clin Med 1955; 45 (2): 247-252.

5. Halberg F, Cornélissen G, Sothern RB, Katinas GS, Schwartzkopff O, Otsuka K. Cycles tipping the scale between death and survival (= "life"). Invited presentation, Nishinomiya-Yukawa International & Interdisciplinary Symposium 2007, What is Life? The Next 100 Years of Yukawa's Dream, Yukawa Institute for Theoretical Physics, Kyoto University, October 15-20, 2007. Progress of Theoretical Physics 2008; Suppl. 173: 153-181.

6. Halberg F, Cornélissen G, Katinas G, Tvildiani L, Gigolashvili M, Janashia K, Toba T, Revilla M, Regal P, Sothern RB, Wendt HW, Wang ZR, Zeman M, Jozsa R, Singh RB, Mitsutake G, Chibisov SM, Lee J, Holley D, Holte JE, Sonkowsky RP, Schwartzkopff O, Delmore P, Otsuka K, Bakken EE, Czaplicki J, International BIOCOS Group. Chronobiology's progress: season's appreciations 2004-2005. Time-, frequency-, phase-, variable-, individual-, age- and site-specific chronomics. J Applied Biomedicine 2006; 4: 1-38. http://www.zsf.jcu.cz/vyzkum/jab/4_1/halberg.pdf.

Figure 5: Toward chronoastrobiology

Alexander Leonidovich CHIZHEVSKY (1897-1964): "Peut-être même nos sentiments et nos pensées ne sont-ils qu'un faible écho de ces vibrations du cosmos .... Involontairement, une antique idée nous vient à l'esprit: notre connaissance des phénomènes de la nature ne serait pas autre chose qu'un écho, reçu par nos organes, des processus réels de l'univers" ("Perhaps even our feelings and thoughts are just a weak echo of the vibrations of the cosmos .... Involuntarily an old idea comes to mind: Our knowledge of natural phenomena will not be different from an echo, received by our organs, of the real processes of the universe")



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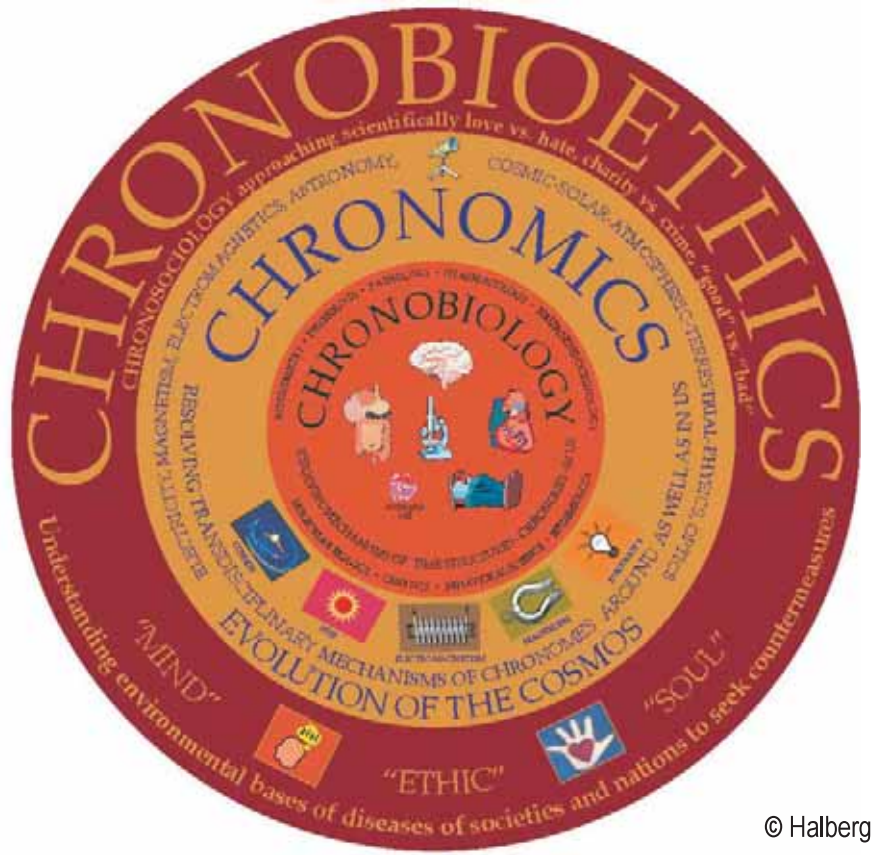
Anticipated influence of the antipodal index of geomagnetic disturbance aa (top) and of the non-photic solar system environment (gauged by solar wind speed, an approximation of interplanetary magnetism) on human psychophysiology was assessed by means of the congruence of periods, τ, of their spectral components (defined by overlap of the 95% confidence intervals of the τs) in the frequency range of one cycle in 2.5 years

to 3 cycles per year). The biological data stem from 40 years of self-measurements of oral temperature (Temp), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) and of ratings of mood and vigor and the estimation of 1-minute by counting (1MTE), performed about 5 times a day by a clinically healthy man, Dr. Robert B. Sothern (1, 2). Congruences (assessed by means of odds ratios based on the noncentral hypergeometric distribution) found for 1MTE and for several other variables more than equal that of the known association of helio- and geo-magnetism (bottom, last column on right of dashed vertical line in blue). Mental functions (full red) show higher congruence than somatic functions (green). Among the latter, systolic blood pressure (SBP) is responsive, perhaps constituting a seemingly acceptable proxy for the mental functions. P-values are based on the non-central Fisher hypergeometric distribution, with 95% confidence intervals computed using Fisher's exact test, used since the null hypothesis was rejected in some, yet not all cases.

1. Cornélissen G, Grambsch P, Sothern RB, Katinas G, Otsuka K, Halberg F. Congruent biospheric and solar-terrestrial cycles. J Appl Biomed 2011; 9: 63-102. DOI 10.2478/v10136-009-0023-7.

2. Halberg F, Cornélissen G, Grambsch P, McCraty R, Beaty L, Siegelova J, Homolka P, Hillman DC, Finley J, Thomas F, Kino T, Revilla M, Schwartzkopff O. Personalized chronobiologic cybercare; other chronomics' progress by transdisciplinary cycles' congruences: Season's Appreciations 2009. J Appl Biomed 2011; 9: 1-34. DOI 10.2478/v10136-009-0022-8.

Figure 6: Chronobiology (center) spawned transdisciplinary tools, chronomics and yet-to-be-developed chronobioethics, concomitantly aiming to serve the health of individuals and the well-being of humanity*

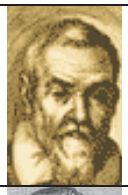
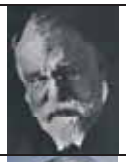


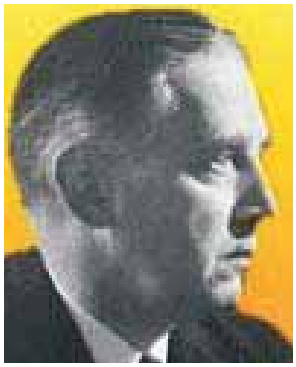
*By the avoidance of personal and population disasters, such as massive strokes or earthquakes, and for the development of measures for the prevention or evasion from human-made or natural cataclysms

Chronoastrobiology is as yet missing in this diagram, has milestones in Figure 4, introducing remove-and-replace experiments (cf. 1), and Figure 5, documenting an association of human mood with interplanetary and earth magnetism. This may open a chapter in the care of global health problems of populations to avoid personal and natural environmental cataclysms.

1. Cornélissen et al., Resonance of about-weekly human heart rate rhythm with solar activity change. Biologia [Bratislava] 1996; 51: 749-756.

Figure 7: Atavars of chronoastrobiology for monitoring and eventually for attempting to maintain the integrity of the cosmos

	Santorio Santorio (1561-1636) Introduced self-monitoring for decades
	Giovanni Battista Riccioli (1598-1671) Linked sunspots to terrestrial weather
	Sir William Herschel (1738-1822) The sun can be "ill-disposed" and crops suffer
	Sir J. Norman Lockyer (1836-1920) "Surely in Meteorology, as in Astronomy, **the thing to hunt down is a cycle**, and if that is not to be found in the temperate zone, then go to the frigid zones or to the torrid zone to look for it, and if found, then above all things, and in whatever manner, lay hold of, study it, record it and see what it means" (1874).
	Eduard Brückner (1862-1927) Paratridecadals (broadly near 30-40-year cycles) influence human migration
	Vladimir Ivanovich Vernadsky (1863-1945) Proponent of a noosphere with life (biosphere of Eduard Suess) shaping the earth as a geophysical force
	Pierre Teilhard de Chardin (1881-1955) Developed noosphere further as the sphere of human thought
	Alexander Leonidovich Chizhevsky (1897-1964) The biosphere is an echo of the sun



Sir Edward Victor Appleton (1892-1965)

"There are simple and fundamental reasons why collaborative effort is necessary in studying the influence of the sun's emanations on our own planet. First of all, the earth is round, and not flat. The result is that solar radiations do not impinge with equal effect on all regions of the earth's surface. The second reason is that the earth is constantly rotating; and, since interesting solar features may occur at any time, it is necessary to have observers at different terrestrial longitudes, in order that none of these interesting events may be missed. The third important fact is that the earth itself is a great magnet, and, because of this magnetic influence, electrified particles of solar origin are constrained to travel, not in straight lines, but along curved tracks. Sometimes the curvature of these tracks is so great that such charged particles impinge on the side of the earth's atmosphere which is further from the sun. In other words, we get solar effects at night. Moreover such effects occur with unequal intensity at different terrestrial latitudes because of the earth's magnetic qualities." (1947)

Frank Arthur Brown Jr. (1908-1983)

Documented subtle, including lunar effects in the biosphere. The last two decades of titles in the following bibliography are dedicated to his memory as the cooperative endeavor he wanted.

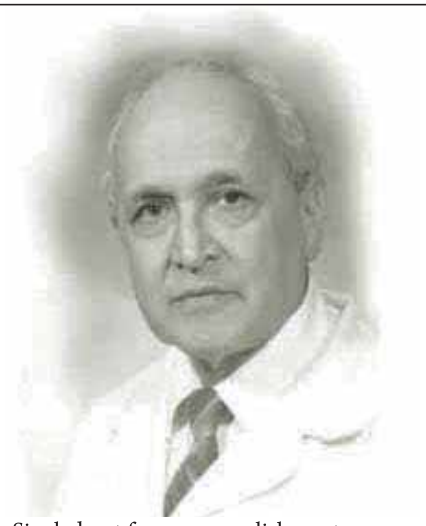
Celebration of a lifetime's achievements by Franz Halberg

This jubilee volume is published in honor of Franz Halberg, for his foresight in recognizing the merits of a transdisciplinary approach where physical and biological data can by their integration shed new light onto life on earth, in the tradition of Chizhevsky and a long list of Russian investigators.

By adding TIME to the existing body of knowledge in all of biology and medicine, and by recognizing the crucial role this new element was to play in all matters of life, Franz Halberg developed the new science of chronobiology. By insisting on an inferential statistical foundation, a microscopy in time was born. He later added a telescopy in time by his methodical scrutiny of non-photic as well as photic environmental influences on biota, from which chronomics flourished.

Born on July 5, 1919 in Romania, Franz Halberg studied the adrenal as a university assistant in post-World War II Innsbruck, Austria. He did so at Harvard Medical School, where he held a World Health Organization fellowship in clinical endocrinology in 1948. In 1949, he moved to the University of Minnesota, which saw his breakthrough experiments that led to the important discovery that circadian rhythms are partly endogenous and can be manipulated by environmental synchronizers. His results were published in 1969 in a citation classic (1). By 1958, Franz had recognized the important role played by the cell's RNA and DNA cycles, which he was first to demonstrate as complementing the hypothalamic-pituitary-adrenal system as mediator of photic inputs, and subsequently he added pineal feedsidewards to form a network responding to the cosmos.

His work earned him numerous awards. Apart from holding professorships in Laboratory Medicine and Pathology, Physiology, Biology, Bioengineering and Oral Medicine at the University of Minnesota, he received honorary doctorates from the University of Montpellier (France), Ferrara (Italy), Tyumen (Siberia), Brno (Czech Republic), L'Aquila (Italy), and most recently People's Friendship University of Russia (Moscow, Russia). At near 90 years of age and still active 7 days a week in the Center named after him at the University of Minnesota, he is one of the last two recipients of a lifetime career award from the National Institutes of Health.



Singled out from accomplishments summarized in over 3,000 published titles in cooperation with colleagues from all five continents are the following highlights. First, rhythms are not trivial as they can tip the scale between health and disease and even between life and death. Second, after suggesting the hypothalamus mediated light information, Franz fought from the start the idea that the suprachiasmatic nuclei were "the" master clock. After a debate that lasted more than a decade, Franz's view has been vindicated now that modern molecular biological techniques have shown the presence of oscillators in practically every cell, in the brain as well as in the periphery. Third, as the crowning of a distinguished career, Franz's early vision that rhythms were not trivial but rather constituted the founding block of life itself is being unveiled by findings that alterations in clock genes are not only responsible for alterations in circadian rhythms but are fundamentally involved in a host of diseased conditions from addiction and cancer to cardiovascular disease. Last but not least, his mapping of a much broader time structure includes cycles with frequencies covering 10 orders of magnitude, aligned between biology and physics by means of an armamentarium of analytical procedures, including a remove-and-replace approach extended from endocrinology to a true transdisciplinary endeavor. Franz's most recent work addresses wide-ranging applications from the optimization of individualized health care to concerns for the health of societies. Toward this goal, the monitoring of vital signs such as blood pressure and heart rate serves the double purpose of advancing both the biomedical field and physics, enlarging the scope of Humboldt's purely physical monitoring into a transdisciplinary endeavor.

Young Franz Halberg

Graduation

Budapest (1942)

Young Franz Halberg
in the mountains (Alps)

Contributions by Franz Halberg, leading to the birth of two new scientific disciplines: chronobiology and chronomics

Germaine Cornélissen

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Much of the history underlying the development of **chronobiology** as a discipline in its own right was published in a *laudatio* prepared on the occasion of the 70th birthday of Franz Halberg (1, cf. 2). Whereas the discovery of important physiological problems and their mechanisms is certainly one of Franz's major achievements, the science itself would not have developed without his changing the very fundamentals of medicine and biology still prevailing today. It was his recognition that variability and not homeostasis is the essence of life (3–8) that put **chronobiology** on the map. True to his motto to "measure in time (hence meaningfully) what is measurable and render measurable what as yet is not", Franz unveiled a new lawfulness that applies within the physiological range, thereby opening new horizons for a better and more positive definition of health by a rigorous assessment in inferential statistical terms of multi-frequency rhythms and other endpoints of a broad time structure with a measure of uncertainty of all pertinent parameters. Alterations of these parameters then become a gauge of increased risk even when all measurements are still residing within the range of acceptable values, thus yielding new opportunities for the institution of primary prevention before the onset of overt disease. By investment into education and monitoring of vital signs interpreted chronobiologically, Franz offers means to achieve a better health care at a reduced cost without having to compromise on the quality of care.

It is the privilege of only very few to have an impact in science, not only by original findings but primarily by a vision of their implications, that lead beyond a scientific breakthrough to a new way of thinking. By his deep sense of humility and his ability to sit in front of the facts without preconceived ideas, Franz has made a lasting dent in the history of medicine. In an era when RNA and DNA were considered to be the most stable and constant entities in biology, Franz showed that both underwent a circadian variation and that it was RNA that led DNA in the sequence of events within the cell cycle. Realizing the implications of this finding for cancer treatment, Franz proceeded to demonstrate that both tumor regression rate and disease-free survival could be improved two-fold by timing the administration of radiotherapy in accordance to the circadian rhythm in tumor temperature used as marker rhythm (9). In large studies in the laboratory and in the clinic with investigators around the world, Franz continued to demonstrate the gains to be had from chronotherapy

(timed treatment) in almost every field of medicine. His discovery that circadian rhythms are partly endogenous and not effects of daily loads ("stress") transformed the field from mere curiosity to a discipline in its own right.

Another tribute prepared on the occasion of Franz's 85th birthday (10) attempted to present a synthesis of the new field of **chronomics** that he had developed in the intervening 15 years (11). Central to the new discipline is the concept of chronomes, broad time structures in us and around us. During the last 5 years, the alignment of spectral components shared between physiology (living matter) and physics (environment) has led to the concept of congruence when the 95% confidence intervals of their respective nonlinearly-assessed periods are overlapping or overlying (12). Franz's most recent endeavor consists of longitudinally monitoring physiological variables for the double purpose of health surveillance and maintenance and the study of how health may be affected by the broad environment, recognizing that organisms being open systems, they cannot be fully understood without paying equal attention to their environment. Toward this goal, Franz had to break **transdisciplinary** barriers, bridging two major disciplines, physiology and physics.

As part of the process of evolution, prominent cycles characterizing the environment, such as the alternation of light and darkness, have become integrated in the genome. Clock genes, first identified in Drosophila (13), then in hamsters (14) and now also in humans (15), have not only been related to the integrity of a biological time structure but they have also been shown to underlie health much more broadly (16–18). These findings fully vindicate Franz's original discovery that circadian rhythms were at least partly endogenous, assuming a period slightly but statistically significantly different from exactly 24 hours in the absence of synchronizers such as light, temperature and/or food availability (3–8). In the presence of environmental synchronizers cycling every 24 hours, the biological circadian system resonates with its environmental counterpart. These facts underlie the essence of **chronobiology**.

Also an integral part of the evolutionary process is the continued influence of the broad environment on life on Earth. Effects of the alternation between day and night and of the changing of the seasons are well-known and are intensively studied in the context of shift-work and the adjustment of rhythms following transmeridian travel (19) on the one hand, or in that of reproduction (20, 21) and the incidence patterns of several conditions such as vascular (22–25) and infectious (22, 26) diseases on the other hand. While already reported in the first part of the last century to affect infectious diseases (27) and a host of other conditions (28), non-photic environmental influences are not quite as obvious, in part because the cycles characterizing them are mostly non-stationary, varying in intensity as well as in frequency as a function of time. To Franz's credit, the rigorous and systematic mapping of these non-photic cycles in both the environment and biota constitutes the foundation of **chronomics**.

Rather than viewing the non-stationarity of non-photic cycles as a hindrance, Franz took it in his stride as a way to further explore which environmental variables may exert their influence on a given physiological component at a given time in a given geographical location, and what may be putative underlying mechanisms. Some lessons have already been learned from his approach. One example relates to a prominent about 21-year cycle found to modulate (religious) motivation in 103 different geographic locations, its characteristics being latitude-dependent (29). Another example is the finding of about 1.3-year (transyear) components in the patterns of incidence of sudden cardiac death in some but not all geographic locations examined thus far (30). In Minnesota, the transyear is present in the absence of a calendar-yearly component, the alternation between hot summers of cold winters notwithstanding. A transyear is also found to characterize natality in the Philippines but not in Italy or Japan (31).

One very attractive method Franz introduced to assess congruence of anticipated components between physiology and physics is known as the remove-and-replace approach, akin to studies in endocrinology. Instead of removing an organ or tissue and replacing it by the hormones it produces, the removal (or subtraction) is done naturally when some non-stationary cycles are present only during part of the time but not always. It then becomes possible to examine whether the counterpart in physiology also changes in intensity toward but not necessarily to the point of no longer being detected when the environmental variable is absent but regains strength when the physical cycle picks up in intensity (replacement or addition).

Such congruence in both time and frequency was first observed in relation to circaseptans, rhythms with a period of about a week. The weekly variation is often dismissed as trivial, thought to result

primarily from the social routine. The fact that, like the circadian system, the week may be partly endogenous was first demonstrated by Franz in his analysis of a 15-year time series of urinary excretion of 17-ketosteroids, the breakdown products of steroids, hormones essential for survival and reproduction, meticulously recorded by a clinically healthy man. Whereas changes in urine volume remained 7-day synchronized, the 17-ketosteroids free-ran with a period slightly shorter than 7 days during the last 3 years of the record, a time coinciding with the self-administration of testosterone (32). Much evidence followed supporting the partly endogenous nature of circaseptans, from their amplification after a single stimulus that carries no time information (such as an organ transplant) (33) to their demonstration in early extra-uterine life when they exceed in prominence the circadian variation (34). When Vernova et al. (35) reported the presence of circaseptans in the rate of change in sunspot area during some study spans but not in others, the longitudinal records of heart rate self-measured for years by several of Franz's associates offered themselves to answer the question whether changes in circaseptan prominence in human heart rate followed those observed for solar activity. Not only was the question answered in the affirmative, both variables were shown to undergo a shared about 11-year cycle (36).

Other examples of congruence followed. On himself, Franz showed that a transyear with a period of about 1.3 years characterizing his systolic blood pressure was dampened when this component was no longer detected in solar wind speed, suggesting that transyears may also be partly endogenous while also responding to the non-photic environmental counterpart (37). A transyear detected in the daily incidence of international terrorist acts, assessed between February 1968 and March 2007, is particularly prominent during solar cycle 22 when this component is also detected more prominently in solar wind speed and in the antipodal geomagnetic index aa (12). In another spectral region, a cis-half-year with a period of about 0.42 year was found in the 15-year record of urinary volume and excretion of 17-ketosteroids referred to above. The time course of the 0.42-year component in 17-ketosteroid excretion was found to mimic that of the planetary geomagnetic index Kp. The cis-half-year in urine volume, globally congruent with both these variables, showed a phase behavior transiently congruent only with relative sunspot numbers, differing in its time course from that of Kp and the excretion of 17-ketosteroids (38).

The above examples illustrate the wide frequency range wherein living matter interacts with its environment and the ubiquity of shared time structures between physics and physiology. Following the example of cartographers, Franz deserves enormous credit for starting a systematic mapping of the biological chronomes to be aligned with their environmental counterparts. In doing so, Franz not only contributed to most biomedical fields but extended their scope toward a chronobioethics to favor the good and avoid the bad (39).

Much of the knowledge gained from this transdisciplinary approach was derived from longitudinal records of physiological variables monitored around the clock for days, weeks, months, years, and even decades by some dedicated chronobiologists, including Franz first and foremost and members of his personal and scientific families. The endeavor of continuous health surveillance by means of physiological monitoring, long advocated by Franz in schools, at home and the work-place (40, 41), attempts to revolutionize health care by changing it from an art to a science that relies on time series (rather than single samples) interpreted by inferential statistical tools developed to serve the individual patient rather than imaginary average patients.

Franz devoted much effort particularly in the field of blood pressure and heart rate monitoring. From a series of outcome studies, it became clear that current practice relying on single samples is associated with too many misdiagnoses and that concern for an elevated blood pressure ignores many other vascular variability disorders that can carry a vascular disease risk higher than a high blood pressure itself (42). At variance with current guidelines that advocate the same limits for all adults 18 years of age and older (43), an international project on the BIOsphere and the COSmos (BIOCOS) coordinated at the Halberg Chronobiology Center of the University of Minnesota has derived time-specified reference values qualified by gender and age to interpret data from ambulatory (or manual) monitors, collected around the clock, preferably for at least 7 days if not continuously by means of a double-barreled approach consisting of a combined parametric and non-parametric assessment (44–46). His methodology, used worldwide (47), has led to the detection of pre-hypertension (42) and pre-diabetes (48, 49).

The following example illustrates the huge benefits that could be derived from the approach advocated by Franz once it becomes fully integrated in clinical practice. In one study of 297 patients with

no history of morbidity at the time of monitoring, including 176 treated hypertensives (50), only 103 had uncomplicated MESOR-hypertension (58.5%). Of these, 9 (8.7%) suffered a morbid event within 6 years of the blood pressure monitoring session. By comparison, among the 55 MESOR-hypertensive patients who had one additional vascular variability disorder (such as an excessive pulse pressure, excessive circadian amplitude of blood pressure, or deficient heart rate variability), 16 (29.1%) had a morbid event. This represents a 3.3-fold increase in risk. Vascular disease risk was even further increased among the 15 patients who had two additional vascular variability disorders complicating MESOR-hypertension. Eight of them (53.3%) suffered a morbid event, corresponding to a 6.1-fold increase in risk by comparison to uncomplicated MESOR-hypertension. The 3 patients who were diagnosed with MESOR-hypertension, excessive pulse pressure, CHAT and deficient heart rate variability all had a morbid event within the 6-year follow-up, a 11.4-fold increase in risk by comparison to uncomplicated MESOR-hypertension. Moreover, among the 121 MESOR-normotensives, 12 had a single vascular variability disorder other than MESOR-hypertension (9.9%), among whom 2 (16.7%) had a morbid event.

These results testify to the merit of blood pressure and heart rate surveillance, the data being interpreted from a chronobiological viewpoint, assessing a number of vascular variability disorders that may exist in the absence or presence of an elevated blood pressure. This approach is cost-effective since the monitoring could be part of a website-based self-help system (42), a physician's advice being sought only after a vascular variability disorder is diagnosed. Once an intervention has been prescribed, it is also cost-effective for the patient to continue surveillance to make sure that the treatment is effective and that it is not associated with undesired effects. Indeed, there is evidence that for some patients treated for MESOR-hypertension, the medication lowers the blood pressure but increases the circadian amplitude above a threshold value, thereby raising the risk of an adverse event, perhaps even above the original risk of an elevated blood pressure itself. Remedies to this situation are available, and sometimes all it takes is to change the timing of treatment administration (38). Clinical data already indicate that following the principle of reducing an excessive circadian amplitude of blood pressure in an attempt to eliminate CHAT is associated with a better than two-fold decrease in the incidence of adverse outcomes (51).

Franz's vision is to use the same data collected within the scope of health surveillance for a biologic monitoring of photic and non-photic solar effects worldwide, thereby to serve physics as well as physicists, and thus provide another facet of a space weather report for the public at large (12). His incredible persistence and intellectual clarity (in the face of entrenched thinking, with established procedures) in fields that transcend disciplinary boundaries, sets him apart as an extraordinary human being and a truly great scientist.

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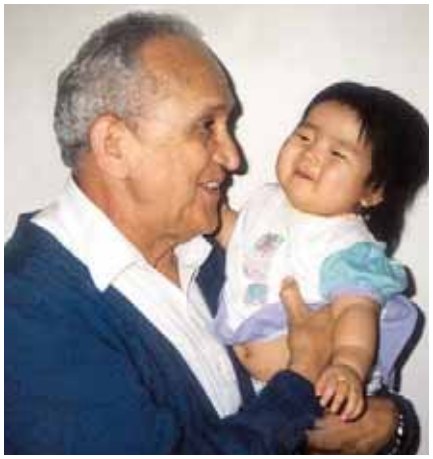
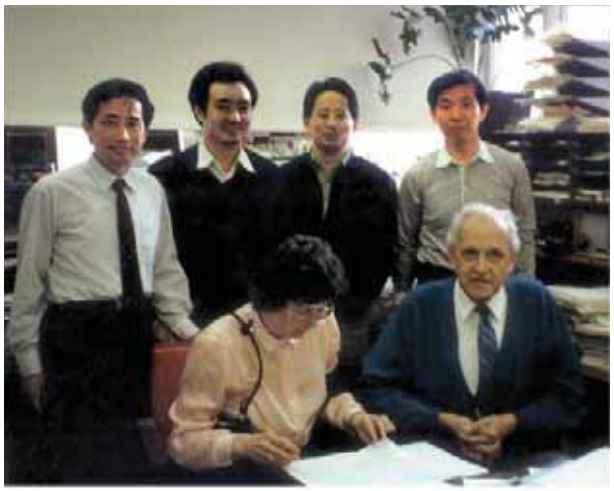
With wife Erna (seated) and Elena Syutkina (standing next to Franz Halberg)

Halberg's daughter Julia



With "Little Erna" (named after Franz's wife), 2nd daughter of Yuji Kumagai

Halberg's daughter Francine

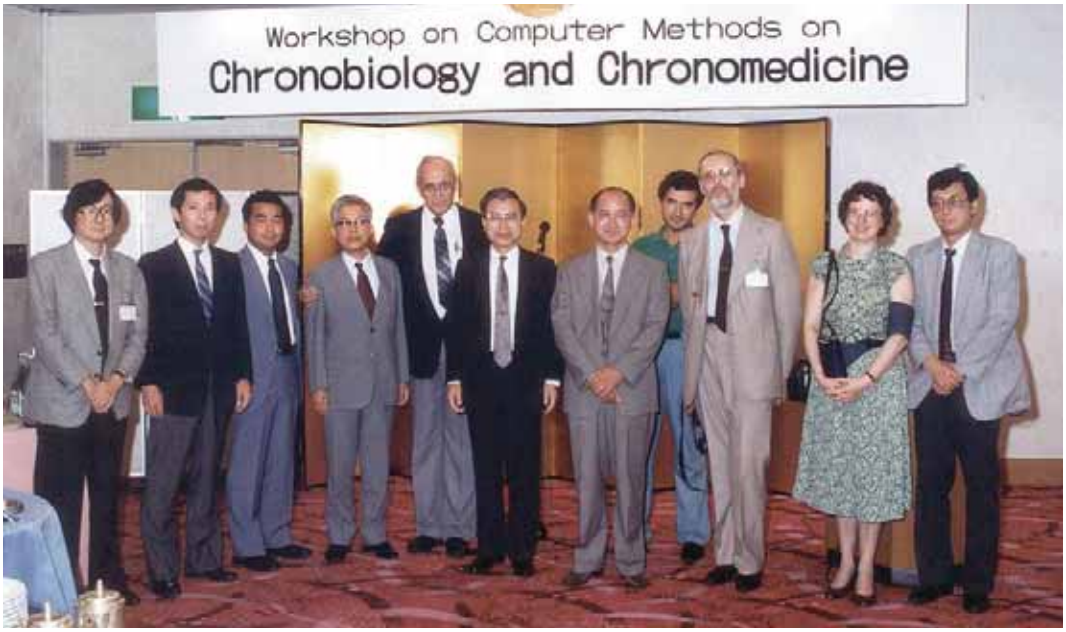


At the lab (University of Minnesota, Lyon Labs) With Germaine Cornélissen (seated), and (standing, left to right) Jinyi Wu, Zenghrong Wang, Saito, Hata

In front of Lake Owasso house With Guenther Hildebrandt (far left), E Haus (left of FH), wife Erna (right of FH), and Alain Reinberg (3rd from right)

In Washington DC, with Terukasu Kawasaki (left)

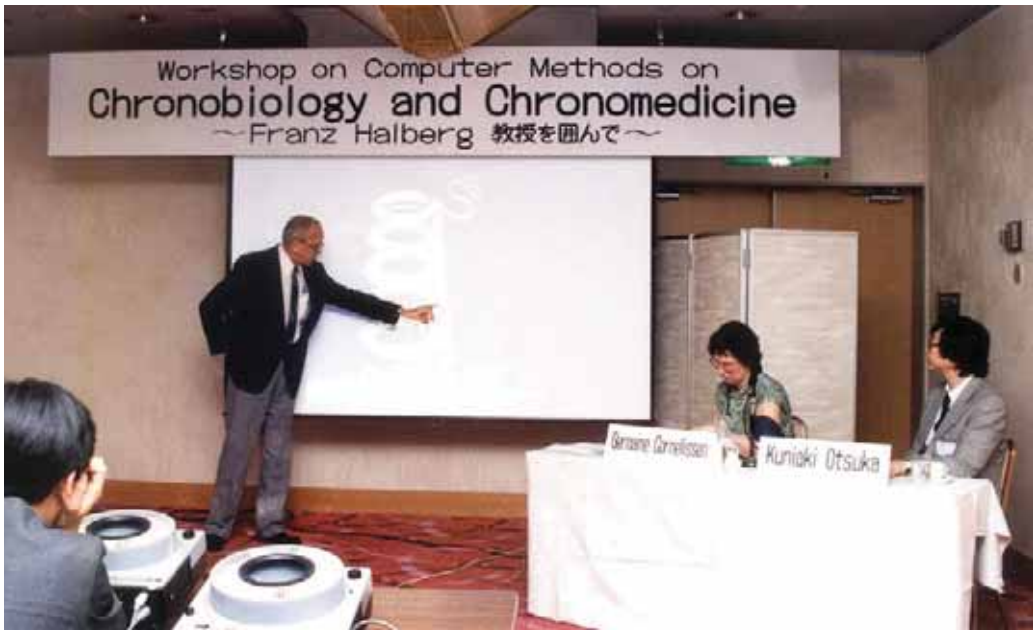
In Washington DC with Keiko Uezono



with (left to right) K. Otsuka, A. Hata, Yu. Kumagai, T. Yanaga, F. Halberg, H. Watanabe,K. Tamura, G. Germano, P. Cugini,G. Cornelissen, Y. Watanabe

In Tokyo, Japan with Kohji Tamura (right)

In Slovakia with Hans Wendt (2nd row, left) and Miroslav Mikulecky (2nd from right)



In Tokyo, Japan

Halberg Hospital and Research Institute in Moradabad, India

Vascular monitoring for physics, physicists and a universal personalized and societal health care, accounting for weather in space

Interview of Franz Halberg by Othild Schwartzkopff

Halberg Chronobiology Center, University of Minnesota, Minneapolis, Minnesota, USA

OS: You started here at the University of Minnesota 60 years ago in the department of physiology. What prompted you to switch your activities from those of a classical physiologist to those of a chronophysiologist, and then to those of a chronobiologist?

FH: My scientific journey was prompted by the need to assess the lawful rather than random variability that takes place within the physiological range in order to avoid blunders (1, 2). As an active scientist, the young Claude Bernard (3) recognized in 1865, as I did 83 years later, that indeed there is an "extreme variability of the internal environment", as he described his major finding at the time. Unfortunately, the aging Bernard interpreted physiology in terms of a relative constancy (4). We must deal with the information derived from a predictable variability rather than with an imaginary steady state, transdisciplinarily in physics as in biology.[1] Once we measure known cycles or, when needed, identify and render them measurable, we open a new realistic domain of critical importance in its own right. A novel perspective records cyclic phenomena, that can surpass in relevance the vicissitudes of the midcontinental climatic changes from harsh Minnesotan winters to hot summers, whether we focus upon the solar wind or upon its signatures in us.

OS: Prof. Jürgen Aschoff, another physiologist who became a chronobiologist, wrote about you 55 years ago: "Halberg's investigations are so important because they are some of the very few experiments available at this time on the endocrine control of 24-hour periodicity ... that consider to a sufficient extent the

1. Variability can play havoc with anything we examine, notably if we take a single measurement for the imaginary baseline or compare cycles differing in phase or period, yielding meaningless opposite results as a function of the times of sampling. I had no choice but to become a chronophysiologist by seeking, finding and quantifying, with uncertainties, the many rhythms with different frequencies in physiology and subsequently in a much broader biology, results that made me later a chronobiologist (1) and eventually led to the cosmos. (The alternative was the possibility of blunders I wished to avoid [2].) Eventually, it became clear that we are in all of our physiology, pathology and even sociology, products of the dynamics of our cosmos, and you could now call me a chronoastrobiologist. Rhythms, not imaginary baselines, are the indispensable control protecting us from blunders only if these somewhat predictable changes are mapped and accounted for.

possible effects of disturbance and have led for the first time to clear results. [Halbergs Untersuchungen sind deswegen so wichtig, weil sie unter den wenigen bisher vorliegenden Experimenten zur endokrinen Steuerung der 24 Std-Periodik (siehe Lewis-Wright) die moeglichen Stoereinflüsse genügend berücksichtigen und zum ersten Mal zu klaren Ergebnissen führten.]" Did he refer to any specific studies?

FH: Yes, his comment was made at the meeting of the German Physiological Society in Homburg/Saar in 1953 (5), after my presentation of the about 24-hour change in eosinophil blood cell counts as an internal bioassay of adrenal cortical hormones) and in body temperature and their partly intrinsic nature documented by circadian desynchronization. To avoid effects of multiply repeated trauma, we cut an animal's tail to draw blood only once: separate groups of comparable animals at different sampling times rendered our approach serially independent as to animals. To establish a marker rhythm, we also measured on another two groups of animals, with and without eyes, the rectal temperature of the same mice every 4 hours day and night for months, to find that each animal without eyes had a built-in rhythm that differed from the environmental 24-hour day, whereas the animals with eyes had a statistically significant rhythm that was 24-hour synchronized. This very study prompted us to coin the term "circadian rhythmicity", then described by my department head as "Halberg's paranoia", a topic of well over 50,000 scientific papers in the world literature now.

OS: Why did you switch further from chronobiology, focusing on biology, to chronomics, studying aligned environmental and biospheric time structures or chronomes?

FH: Living things are open to their environment and depend on whatever they take in from outside. This accounts for shared chronomes (6, 7) (time structures) between biology and physics. After we found the built-in free-running week in the excretion of steroidal hormonal metabolites and then in heart rate, among other biotic variables, we detected its counterparts in the magnetism of the sun, the solar wind and the earth. After Prof. Hans Wendt directed our attention toward the discovery in physics of a 1.3-year component in solar wind speed, we found this cycle with a drifting behavior of its period in both physical and biological data. We dubbed it a far-transyear (1.2 years ≤ [τ {period} - CI {95% confidence interval}] < [τ + CI] < 1.9 years). By "τ - CI" or "τ + CI", we mean the lower or upper limit of the 95% confidence interval of the period, in keeping with the notation that a mean is given ± 1 SE or ± 1SD. The actual length of the uncertainty bar is then 2SE or 2SD. As 95% CIs can be obtained in some cases when a normal distribution can be assumed in the presence of large sample sizes as about 2xSE, the entire width of a 95% confidence interval is 2CI as the period is estimated as τ ± 1CI. An about 1.3-year component was invariably detected in all of several dozen longitudinal time series of blood pressure and heart rate available to us (8). Prof. Miroslav Mikulecky (Comenius University, Bratislava, Slovakia) then greatly extended the scope of what he dubbed "Halberg's transyear" (and had described as "stronger than a year" in the title of his paper [9]) to natality in two geographic locations (10) and in Slovakia to epilepsy (11) and stroke (as Mikulecky put it, to "Halberg's paraseasonality") (12).[2]

Our common ancestors, the cycles of our cosmos eventually gave rise to nucleic acids that in turn coded the same cycles in ourselves. The cyclic atavars of our environs constituted the essence mirrored by self-sustaining features in living matter. The cycles' extrinsic-intrinsic interwoven nature is clear theoretically (25), and is documented experimentally by

2. We then found near-transyears (1.00 year < [τ - CI] < [τ + CI] < 1.20 years) in and around us. Eduard Brückner (13), Alexander Leonidovich Chizhevsky (14, 15) and Suitbert Ertel (16) had already recognized signatures in the biosphere of environmental transtridecadals (13) and decadals, respectively, and we added a long list of biospheric variables (6, 7) to the fruits of their scholarship.
Within the past decade, it became clear, to the point of a rule, and by now, as a law, that cosmic cycles are our true common ancestors, that for each consistent cycle in the biosphere, whether continuous or recurring intermittently, there is one in the environment near or far. In some cases the environmental cycle was not previously viewed as an entity in its own right, as was the case for the week, or it was not recognized at all, as in the case of a near-transyear (27; cf. 17, 18). The biological importance of a weekly cycle was noted by Ladislav Derer (19). We found the week to free-run from the societal 7-day schedule for several years in human steroid excretion, as a feature of its built-in partly endogenous nature (20), and thereafter validated a near-week in terrestrial magnetism (21, 22), where it was confirmed and recognized as intermittent (23) or was subsequently displayed in a spectrum by leading physicists (24).

subtraction and addition maneuvers implemented by the sun. We had used a remove-and-replace approach (18) by surgical removal of the adrenals or of the eyes in chronobiology. In chronomics, i.e., in studies of cosmic relations to the biosphere, the sun does the amplification or damping, if not loss, of one or several of its spectral components, such as a near-weekly cycle. Variability in solar spectra offers the chance to study its biospheric consequences as biotic spectral change (26–28).

OS: What specifically made you become interested in the relation between cycles in and around us, and further in the wider cosmos?

FH: We could not confirm results that we had obtained on relatively large numbers of newborns (29) for years: after the start of neonatal studies, we could separate babies with a positive from those with a negative family history of high blood pressure and/or other vascular disease by the extent of blood pressure change along the 24-hour scale, dubbed the circadian blood pressure amplitude. Thereafter, however, the difference between newborns with a positive vs. negative family history of vascular disease was no longer found (30). The circadian amplitude of blood pressure had undergone secular changes, where "secular" is used often to hide one's ignorance concerning the length of any long cycle with a period up to that of one or several human generations and to hide a lack of information with respect to the underlying mechanisms. An about 11-year cycle was later documented to modulate the circadian amplitude of neonatal blood pressure (31). Further evidence for associations of terrestrial magnetism with neonatal cardiovascular health involved the weekly component as well (32).

OS: You have previously used the term "chronomics". How do you define it?

FH: We had called the study of biological rhythms chronobiology and had given the name "chronomics" (6, 7) to the aligned mapping of time structures (i.e., chronomes) in both biology and the environment. Eventually the results became the subject of a chronoastrobiology (33), as we found more and more reliable signatures of the solar system and thus of the broader cosmos in various important human affairs. Chronobiology is akin to the microscope that provided an opportunity to quantify the partly endogenous biologic rhythms, whereas chronomics has an analogy in the telescope that allows the exploration of environmental influences from the larger cosmos.

OS: How did these discoveries change your subsequent studies?

FH: The cosmos had to be taken into account in work along any time scale. While we investigated about 24-hour changes I had dubbed circadian (34) that led to chronobiology (1), we had tried to keep the local (e.g., laboratory) environment as constant or as standardized as we could, trying to prevent any environmental variation. Unfortunately, with notable exceptions when we recorded calendar dates and could thus fruitfully compare results on days with vs. days without a magnetic storm (35–37), we ignored the cosmos, albeit important information was available as a space weather report. No longer. The more we studied any variable, and the longer the time series became, the more cycles we found (in us and near and far outside us) that were congruent in the sense that they could not be distinguished insofar as the 95% confidence intervals of their periods were overlying or overlapping. We could not standardize or fix the conditions on the sun and in the interplanetary magnetic field. Until we may succeed in manipulating solar activity there is no other way out: like it or not, we need to assess solar and other variability. Thereby, in investigating any biospheric problems, we are now able to find, as did our predecessors (13, 14), the signatures of the environment characterizing various important terrestrial climatic, economic, military or political human affairs (38, 39) and what seems desirable we add measures of uncertainty to their characteristics. We realize that even "conservative" 95% confidence intervals may be too liberal and use them for ordering only.

OS: What do you mean by 'environment'? Do you mean the earth and our solar system?

FH: We mean the environment whose effects can be measured at any given time (39, 40). Even when the most remote time series stem only from the galaxy, as do cosmic rays, the changes may have more remote, to-us as-yet unknown origins. With these qualifications, our major interest is in cosmic cycles that influence the solar system. Many of the cycles we map are intermittent (we have called them aeolian), needing a special methodology, i.e., the equivalents in time of a microscopy and telescopy in space, in order to resolve and quantify the dynamics that may reveal what the cosmos as a whole has to say to us.

OS: Do you have any examples to demonstrate the connection between physio-pathology and the cosmos?

FH: The patterns in time of the electrical potentials of the heart and brain in health and disease reflect the cycles found in the cosmos (6, 7, 39). So we look

for cycles in humans corresponding to the cycles in the solar system and cosmos, find them and study any alterations in us when the cycles outside exacerbate or disappear, an approach equivalent to addition and subtraction. We are especially interested in the variability of the sun, which gives us an opportunity to study living matter, usually ourselves, during spans when the sun is active to the point of magnetic storms and when it is quiet. We then compare our physiology when some components in the spectrum of the sun are present and when they are absent or are not detected because they are buried in noise. This, in its extreme, a remove-and-replace approach, is most helpful in looking for associations beyond the concomitance of events around and in us, in our blood pressure and heart rate (31), in the ECG (35), in our endocrine system (36) and in the cell (37).

OS: You have spent much time in presentations abroad. In which countries have you given lectures?

FH: With advancing age the trips are getting less frequent (only 8 trips abroad during the academic year 2007–2008). Over the years I have lectured, among others, in Austria, Argentina, Azerbaijan, Belgium, Bulgaria, Chile, China, the Czech Republic, Denmark, Finland, France, Germany, the Republic of Georgia, Greece, Hong Kong, Hungary, India, Italy, Japan, Mexico, Kazakstan, Kirgizstan, Nepal, the Netherlands, Norway, Poland, Portugal, Romania, Russia (including Siberia), Slovakia, South Africa, Spain, Sweden, Switzerland, Taiwan, Ukraine, the United Kingdom, Uzbekistan, where I was made an honorary citizen, Vietnam and Zimbabwe. Cooperation is ongoing in quite a few of these countries and in Armenia in the context of a project on The BIOsphere and the COSmos (17).

OS: Given the variability of cycles, cosmic and biotic, did you set a limit to what % they are to be congruent in order to make the results convincing?

FH: To express the extent of congruence, one can refer as 100% to either the total of peaks in a given biological spectral window or use as 100% the total number of peaks found in biological variables and in one or more environmental variables. For human time estimation in a spectral window of para-annual frequencies, the 16 biologic peaks were equated first to 100%; we then find 68.75% of the biologic periods congruent with two aspects of their environment, the speed of the solar wind, SWS, briefly the sun, and/or with the antipodal geomagnetic index aa, briefly the earth. This overall percentage involves 25% congruent with the sun only, 25% with the earth only and 18.75% with both. Thus, when only a single solar or a single terrestrial variable and a single biological variable are considered, there is a lack of environmental congruence in only 31.25 %.[3] When 34 peaks, found in a paraannual window of all 3 variables are equated to 100% (16 biologic peaks + 18 components from sun & earth without a biologic counterpart), congruence drops from 68.75% to a still-respectable 32.34 %. We have reasons from independent evidence, from the remove and replace approach implemented by the sun, to assume that there is a causal relation between the magnetism of the sun and earth on the one hand and that of the body, expressed, among others, as mental performance in the 1-minute estimation, on the other hand (18). Even when there is much more congruence than could be expected by chance alone from random sampling error, a solar-biospheric relation suggested by a subtraction and addition approach, whenever feasible, renders this congruence much more convincing.

OS: Your colleagues, Professors John Pauly and the late Larry Scheving, wrote in 1987 (41):

"... Franz Halberg is the father of modern chronobiology ... responsible for developing and refining the cosinor method for analyzing time-series data ... [He] has provided new reference standards and end points that can be used to screen for elevated risks of developing diseases, for diagnosis and prognosis, and for timed treatment. ... He personally has coined

3. The transdisciplinary congruence based on overlying or overlapping confidence intervals of the periods compared is selective, so that we must specify the frequencies involved for both the environmental and the biospheric variable and the calendar dates during which this relationship is being explored. For a given organism, the congruence can differ in terms of environmental counterpart for heart rate vs. blood pressure or vs. a mental function such as the estimation of 1 minute. For blood pressure and heart rate in the one subject with sufficiently long and dense data, Dr. Robert B. Sothern, the heart rate may match with one of its (congruent) components an ~33-year cycle in Zürich-Brussels-Wolf numbers, whereas the blood pressure is congruent with an ~22-year Hale cycle. For any one variable, there is a global % congruence (based on time series as a whole) with respect to a given environmental counterpart, such as one related to the sun and/or to the earth. It is also documented that congruence can change with time and hence the calendar dates must be specified and when long time series become available, different intervals can be analyzed for the behavior in time of phases of globally congruent periods.

much of the terminology used in modern chronobiology including the term 'circadian rhythms'. ... Halberg served for more than ten years as President of the International Society for the Study of Biological Rhythms and, after the name was changed, as President of the International Society for Chronobiology for another fifteen years. During this time he worked untiringly to develop a 'field of interest' into a recognized integrative discipline of modern biology. The exploration of many of the basic phenomena in chronobiology and many of the methods for chronobiologic study are inseparably tied to the name and the work of Franz Halberg."

But from a practical viewpoint, as Professor Pauly used to ask: So what?

FH: On the practical side we advocate the prevention of strokes and other severe vascular disease by cost-free chronobiologically interpreted self-monitoring of blood pressure and heart rate with automatic analyses from the Internet.[4] The detection not only of the complications of hypertension by vascular variability disorders, VVDs, but the detection of other VVDs before there is an increase in the around the clock mean (MESOR) of blood pressure (a VVD in itself) is a concern of many millions of Russians, Americans and others.[5] In the case of advanced perioral cancers, by timing radiation therapy according to the time of peak tumor temperature, the 2-year survival rate has been doubled. Cyber-implemented marker rhythmometry in the treatment of cancer is certainly a feasible, promising next step.

OS: Can the monitoring of biospheric variables serve physics?

FH: The various spectral components revealed by long time series can be used to seek answers to questions relating to pure physics (that eventually may bear on human affairs). The ~5-month cycle, a cis-halfyear found in human physiology, e.g., in a 15-year series of 17-ketosteroid excretion (19) as well as in the circulation and in sudden cardiac death, is a case in point. Is it a subharmonic of a fundamental 25-day period as suggested by Bai (45)? If so, the subharmonics suggested, if they had been present while life evolved, should be detectable in biological variables that relate to survival and that have been coded as long as that particular living matter existed. When the 25-day period and its subharmonics are not demonstrable, as is the case, an alternative hypotheses, e.g., the possibility suggested by Charles L. Wolff (46) that we are dealing with beat periods of the rotation at different solar latitudes prompts the search for Wolff's spectral components. Indeed, we do find some of these predicted components in physiological data and in pathological time series like that of suicides by women in Australia (47). We should keep on looking for further counterparts in other cases wherein evolution may allow us to backtrack further into the past than with the best tracer methods.

Humanity developed heating and air conditioning to cope with visible harsh seasons. By monitoring the invisible effects of particle radiations from the sun we may develop countermeasures for undesirable effects of spectral components in phenomena such as aggression, where the invisible spectral components replace those representing the seasons or coexist, as Prof. Mikulecky put it, yet "are stronger than" (the) year (9).

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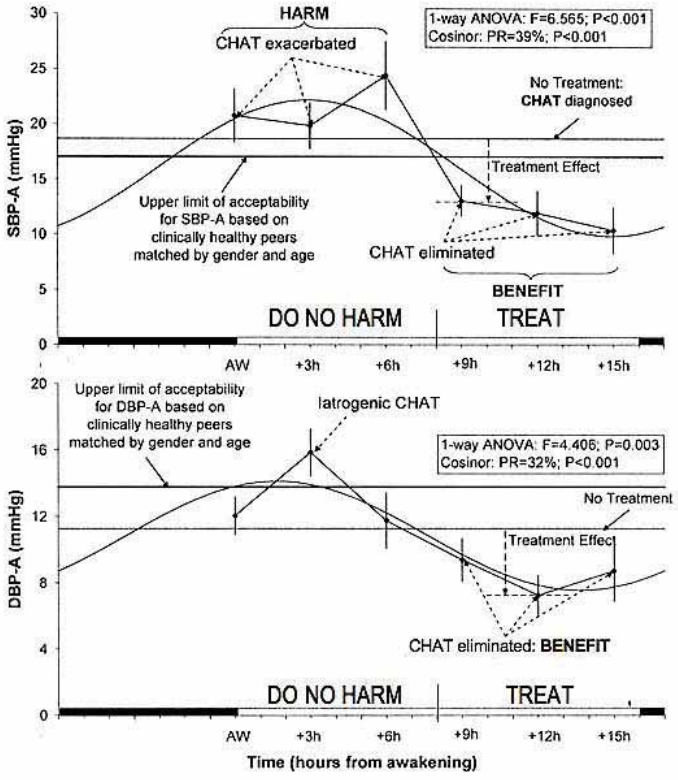
4. Thereby earliest risk elevation is detected as a vascular variability disorder, VVD and can be treated. These are great but conventionally unrecognized increases in the risk of stroke in many millions of people currently diagnosed as hypertensive. Without chronobiologically interpreted monitoring with systematic data collection and analysis, one cannot identify a change in risk from about 4 to about 100% for developing a stroke within 6 years (42, 43). If in turn the VVD-signaled risks of strokes are detected, and if such other hard events are reduced by 50% by a treatment reducing the circadian amplitude of blood pressure (44), this is an immediate return. Monitoring blood pressure and heart rate via self-help on the Internet can introduce a personalized health care for the prevention as well as treatment of stroke and other hard vascular diseases of individuals. This step can be implemented for circles of families and friends by a computer-savvy individual with inferential statistical procedures being applied automatically. The original data thus obtained and analyzed serve for health care research, and in order to monitor the biotic associations of space weather, involving climate change, economics, crime, violence and broad military-political affairs as information that constitutes an essential ingredient for the development of countermeasures for the remedy of major problems of society. What today appears to be basic may answer tomorrow a practical "So what".

5. It is practical and cost-effective to utilize Internet-based self-help via a monitoring device that can be linked to a home computer, to detect and treat what no number of office visits can reveal. When it comes to therapy, timing has now been shown to make the difference, in the use of a popular antihypertensive drug, between harm and benefit, Figure 1 (90)/ ➔

Treatment Beneficial at Certain Other Times (9,12 or 15 hours after awakening) can EXACERBATE a Pre-existing CHAT in Systolic Blood Pressure (SBP) and INDUCE CHAT in Diastolic Blood Pressure (DBP) when Given at the Wrong Time in Patient Su*



*Su, M, 66y, treated with Losartan (50 mg) and hydrochlorothiazide (12.5 mg). Each point represents 1 week of half-hourly around-the-clock monitoring after -1 month on a given treatment time.

Legend

Figure 1. Monitoring of blood pressure for treatment validation and optimization is not a luxury when, as shown on top and in the middle of this figure, the same currently popular drug Hyzaar (a combination of 12.5 mg of hydrochlorothiazide and 50 mg of Losartan) can do harm in a patient, Su in the morning, but is beneficial when taken in the same dose by the same person in the evening some months later. Medication was changed systematically, on a usual routine of living with diurnal activity and nocturnal rest. On each treatment timing in relation to awakening, Su was studied for ~1 month with the blood pressure monitored for the last week, as described in detail by Prof. Watanabe (49). In the morning the medication raised the circadian amplitude of blood pressure to an extent of exacerbating or inducing a circadian overswing (or CHAT), a risk greater than a high blood pressure, whereas at another time the same dose lowered both the circadian amplitude and MESOR, eliminating all abnormality, and thus offered benefit. The painting at the bottom by Pieter Brueghel, "The Parable of the Blind Leading the Blind", is reproduced by kind permission of the Fototeca della Soprintendenza of the BAS PSAE and of the Polo Museale of the City of Naples, in order to emphasize that CHAT is silent to both the caregiver acting on the basis of a conventionally interpreted (chronobiologically uninterpreted) 24-hour blood pressure as well as to the majority of providers treating on the basis of single measurements in their office. © Halberg.

Table: Congruent* periods of helio-geomagnetics (columns 1 & 2), the estimation of 1-minute by a healthy man over 3.5 decades (column 3) and terrorism (bottom, bold)

Period (years) (CI=95% confidence interval)									
Variable:	solar wind (SW)	aa	1-min time estimation (1MTE)		SW / aa	SW / 1MTE	aa / 1MTE	SW/aa/ 1MTE	none
	15.6 (15.2, 16.0)								x
		10.85 (10.78, 10.92)							x
	9.54 (9.38, 9.70)								x
			8.71 (8.52, 8.90)						x
		5.31 (5.38, 5.35)							x
			4.11 (4.06, 4.16)						x
	3.56 (3.52, 3.60)								x
			2.81 (2.76, 2.84)						x
	2.17 (2.15, 2.19)								x
		1.92 (1.89, 1.95)*	1.98 (1.94, 2.01)*	E			x		
			1.85 (1.82, 1.88)*						x
	1.69 (1.67, 1.72)*	**1.71 (1.69, 1.74)***	**1.71 (1.68, 1.74)***	**SE**				x	
	1.60 (1.58, 1.62)*								x
	1.52 (1.50, 1.54)*		**1.54 (1.52, 1.56)***	**S**		x			
	1.39 (1.37, 1.41)*¶	**1.39 (1.37, 1.41)*¶**			x				
	1.32 (1.31, 1.34)*¶								x
	1.24 (1.23, 1.26)*		1.26 (1.25, 1.27)*	S		x			
			1.16 (1.15, 1.18)*						x
	1.06 (1.05, 1.07)*	**1.06 (1.04, 1.07)**	**1.06 (1.05, 1.07)***	**SE**				x	
		0.99 (0.98, 1.01)*	**0.99 (0.98, 1.01)***	**SE**			x		
	0.91 (0.90, 0.92)*								x
	0.83 (0.82, 0.84)*		**0.82 (0.81, 0.83)***	**S**		x			
	0.72 (0.71, 0.73)*	**0.72 (0.71, 0.73)***	**0.713 (0.708,0.719)**	**SE**				x	
		0.599 (0.598,0.600)							x
	0.559 (0.557,0.561)		0.561 (0.558,0.564)	S		x			
		0.548 (0.547,0.549)							x
	0.524 (0.522,0.526)								x
	0.500 (0.499,0.501)	0.500 (0.499,0.501)			x				
		0.437 (0.436,0.438)	0.440 (0.438,0.442)	E			x		
	0.485 (0.483,0.487)								x
	0.425 (0.423,0.427)								x
	0.409 (0.407,0.411)								x
	0.355 (0.354,0.356)								x
		0.341 (0.340,0.342)	0.339 (0.338, 0.340)	**E**			x		

* Based on weekly; otherwise on daily measurements. Congruence defined by overlying or overlapping 95% confidence intervals, given in ( ). Congruence in the last column is designated as pertaining to the Sun (S) or Earth (E).

¶ The transyear of 1.34 years, with CI (1.31, 1.37), of terrorism worldwide is congruent with these environmental τs and time courses show similarities that are resolved with hypothesis testing and estimation of the uncertainty of the acrophase in Figure 3c. When more data on terrorism are analyzed, the transyear period (in the footnote to Table 2) is of 1.28 (1.26-1.29) year length overlapping with a period of 1.26 in 1-minute estimation and solar wind speed.

Solar wind/aa: 2/34 (5.882%)
Solar wind/1MTE: 5/34 (14.706%)
aa/1MTE: 4/34 (11.765%)
Solar wind, aa and 1MTE all congruent: 3/34 (8.824%)
No congruence: 19/34 (55.882%)

OS: In a tribute to Prof. Dr. Rudolf C.H. Engel on his death in 1997 (48), Prof. Dr. Dr. h.c. mult. Theodor Hellbrügge of Munich University, the founder of social pediatrics, described you as "the most important chronobiologic investigator" ("dem bedeuten **osten** chronobiologischen Forscher"). On your 70th birthday, Hellbrügge concluded that "Several generations of researchers will be needed to sum up your life's work". He has also awarded you the Arnold Lucius Gesell Prize. What broadly were your relations with Profs. Engel and Hellbrügge and with pediatrics?

FH: From the time I arrived in Minnesota, I had a very close connection to pediatrics via Rudolf Engel, a clinical professor of pediatrics himself, who brought me as a consultant to the Cambridge State School and Hospital. During my 60 years in Minnesota, our relation with Theodor Hellbrügge was most fruitful, since he sent many of his students preparing doctoral theses to our laboratory, thus maintaining a working relation over the decades, beginning when we met at a meeting in the Semmering in 1952. My activities in pediatrics started with an exploration of the circadian rhythm in circulating blood eosinophils in newborns, a study with Robert Ulstrom (49) (which was interrupted only when I overslept and did not draw blood at the birth of my first daughter). At that time, and as far as I can today, I had a principle that whatever is being investigated on others is also a matter of self-experimentation and of studies in one's (personal and scientific) family. Irvine McQuarrie, then the head of pediatrics at the University of Minnesota, and one of his successors John Anderson, were quite positive toward chronobiology. When McQuarrie was dying and Anderson asked what he should pursue, McQuarrie indicated that pediatrics should continue to emphasize chronobiology. Decades later, this was accomplished by a cooperation with the head of neonatology, Dana Johnson, which continues today (32, 50–77). The human newborn seems to be particularly sensitive to its cosmos. This may be a reason for the infradian, notably circaseptan and circasemiseptan dominance over circadians in the immediate postnatal weeks, as signatures of geomagnetism.

OS: Do other fields relate mainly to chronomics and chronobiology?

FH: Time matters transdisciplinarily, but neuroendocrinology is a special case in point, since the cosmos influences us via nerves and hormones. Here, a new relation with Rita Jozsa (University of Pecs, Hungary) and Michal Zeman (Comenius University, Bratislava, Slovakia) replaced the loss of my laboratories at the University of Minnesota when I turned 70. I appreciated a laudatio from Peter G. Fedor-Freybergh (78), who not only wrote it before I had an opportunity to meet him, but also impeccably with his editor-wife Lilli published many of my papers in his own journal, Neuroendocrinology Letters.

OS: In a Festschrift marking your 70th birthday, Germaine Cornélissen (79) cited Donald Marquardt, a past president of the American Statistical Association: "... three facets of Franz Halberg's work are especially compelling. First is his early vision of the inherent rhythmic nature of all things biological, leading to a body of work which substantially impacts many fields beyond biology and medicine. The second feature of Franz Halberg's work that sets him apart is his incredible persistence and intellectual clarity in the face of entrenched thinking, established medical protocols, and existing disciplinary boundaries. The third feature of Franz Halberg's work is his impact in stimulating research in other disciplines. As apparent from his bibliography, he has initiated research around the world." What role did statistics play?

FH: Alan Treloar instilled respect for hypothesis testing and parameter estimation as a sine qua non. Hans Panofsky introduced me to power spectra. Eugene A. Johnson, Liang Tong, Jung-Keun Lee and in particular in the 1980s and 1990s Christopher Bingham were most helpful in developing statistical methods. Donald Marquardt not only enabled our endeavors in developing methods for the analysis of unequally spaced time series but used our data for developing statistical methods and used our procedures when he needed them personally for a timed treatment of his cancer. For that purpose, he changed his routine of sleeping and waking to have his marker rhythms adjusted to the therapist's schedule. A long-standing friendship with Douglas Wilson, president emeritus of the International Society for Clinical Biostatistics, continues to this day, with Doug (who also organized an international symposium for one of my birthdays) batting for a chronobiologic and chronomic cyber-implemented health care.

OS: What about physics?

FH: Ties have developed with cosmic physics through Tamara Breus, a solar physicist at the Russian Space Research Institute, and several historians of physics whom I have not yet met face to face. Wilfried Schroeder has invited contributions by our group to geophysical meetings and established contact with the Leibniz Society (originally the Prussian academy of science, and later that of the German Democrat-

ic Republic). My lifetime's work cannot be separated from that of Germaine Cornélissen, originally a physicist, still on my side professionally, as was my first wife Erna, until her premature demise serving science throughout her professional life by self-experimentation, as does Germaine. In her laudatios (79), Germaine emphasizes my humility: I hope she is right. As to contributions she cited, those are due much more to her than to me, and even when I am to discuss anything that occurred before she joined us in the 1970s, she almost certainly knows them in much more detail than I do (80).

OS: Any conclusions?

FH: I could not have answered my beloved pediatrician Othild's questions had she not raised them and hence put me to work in reviewing the previously summarized past (2) and the present (81) once more. My answers would not have been typed and edited on a weekend were it not for Mary Sampson, our indefatigable secretary, also I trust a chronobiologist at heart. Credit is due Gay Gaer Luce (82, 83) who early on summarized many of our studies.

I am indebted to everybody whose paths I cross, and there are many others whose names can be found in my bibliography who helped build chronobiology, chronomics and chronoastrobiology. A helpful scientist/entrepreneur, Alex Zaffaroni, built a company originally aimed at administering chronotherapy. I dedicated a colorful Introduction to Chronobiology (84) to the late Agostino Carandente, an enthusiastic physician/entrepreneur, first to put timing into the name of a drug and dear late friend. Earl E. Bakken, the developer of the implantable cardiac pacemaker, a chronobiologist/entrepreneur/benefactor and scientist at heart second to none, provided helpful comments on a regular basis as a "witness in time" (85). His unwavering support remains responsible for the continuance of our laboratory at the University of Minnesota. Our major aim in investigating the need for a universal preventive health care has been dubbed "Bakken's prehabilitation" (86–88); several papers were dedicated to him on his birthdays (89–91).

Most scientists today, apart from their research and teaching, must also be entrepreneurial, arranging meetings and spending much time in preparing grant applications. I have been very fortunate to have others often initiate meetings of the International Society for the Study of Biological Rhythms and thereafter of the International Society for Chronobiology, Gordon and other conferences. Leading entrepreneurs have joined me unexpectedly and most helpfully, so that in major projects the government or industry came to me rather than vice versa. Probably because of Hubertus Strughold, the nascent NASA asked what it could do, and built my first laboratory. Later, Colin Pittendrigh and his clock-focused colleagues suggested to NASA that I should plan a Biosatellite study on rhythms. The pharmaceutical and device industries also discovered what we were doing and Hoechst Pharmaceuticals built our laboratory in L'Aquila, Italy. Such happenings allowed me to dispense with much personal entrepreneurship.

We are currently celebrating Germaine Cornélissen's having become a US citizen. She is joining a country best characterized by the fact that a number of engineers devote every other Sunday, and some of them like Larry A. Beaty considerable time during the rest of the week, to helping others as benefactors without pay. As long as the world has Germaine and El Nolley's Phoenix Group of volunteering engineers and the project on The BIOsphere and the COSmos, it will be able to deal with its environment near and far; it may even develop countermeasures to its vicissitudes, and may optimize any benefit to be derived from invisible particle radiation from the sun as well as from visible photic irradiation.

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Rewarding Prof. Franz Halberg with O.Yu. Schmidt Medal and the Diploma *

Dear Prof. Franz Halberg,

I congratulate you on the 90th anniversary of your birth. Your multidisciplinary research approaches integrating geophysical and biological data play a very important role in development of geophysics. Taking your great achievements in this branch of the Earth sciences into account, I am glad to inform you the following:

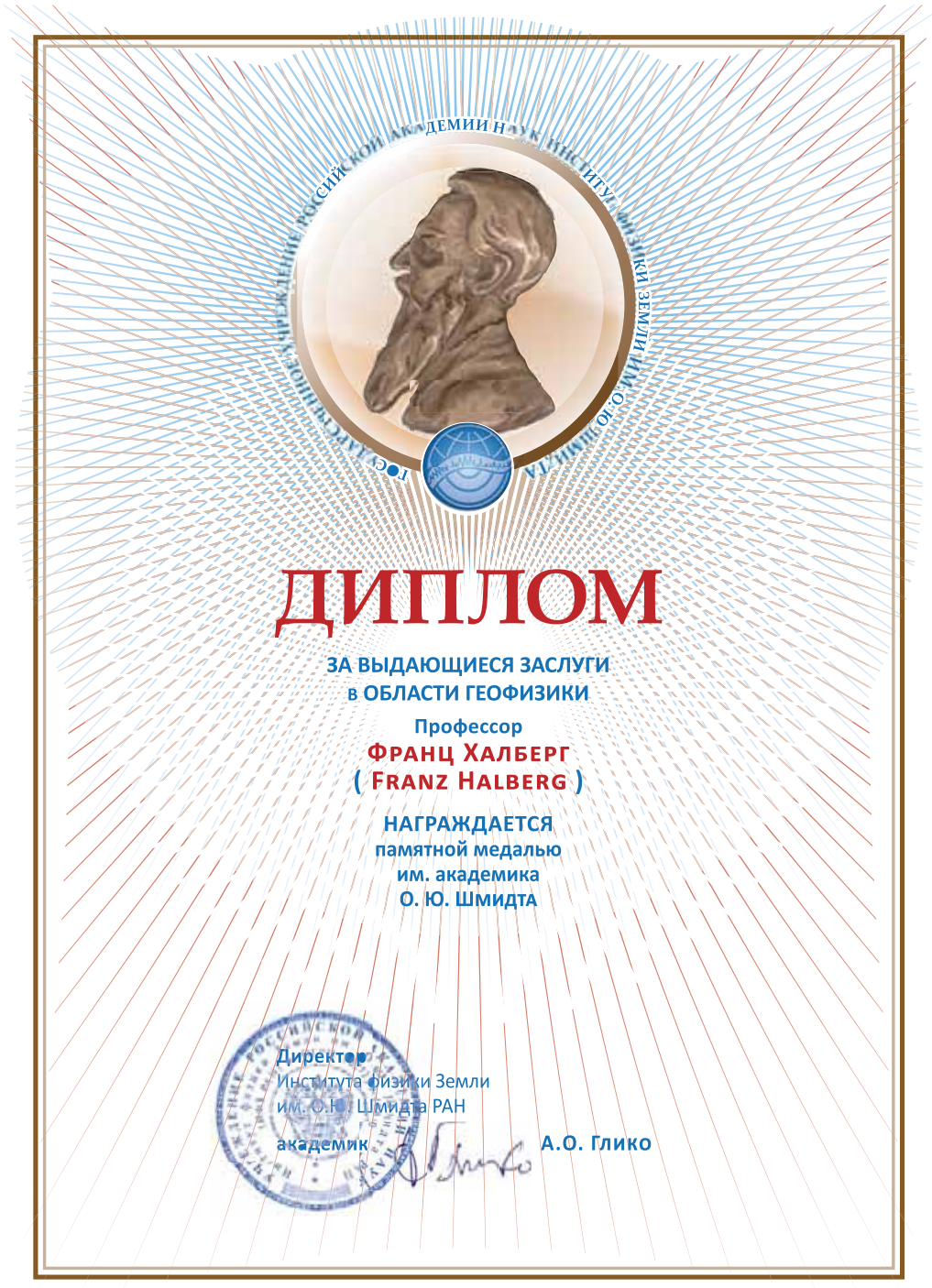
1. O.Yu. Schmidt Institute of Physics of the Earth of the Russian Academy of Sciences has awarded you with the highest awards – O.Yu. Schmidt Medal and the Diploma for outstanding merits in developmet of geophysics.
2. Two special issues of the journal «Геофизические процессы и биосфера» ("Geophysical Processes and Biosphere") are dedicated to your jubilee.
3. 3. The book "Lord of time Franz Halberg on the 90th anniversary of his birth, on 5 July 2009" is published by O.Yu. Schmidt Institute of Physics of the Earth of Russian Academy of Sciences.
4. A paper by Alexander Sidorin dealing with your contribution into the Earth sciences is submitted in the journal «История наук о Земле» ("History of the Earth Sciences").

Wishing you a long, healthy and happy life filled with new successes in science

Director of O.Yu. Schmidt Institute
of Physics of the Earth
of Russian Academy of Sciences
Academician Alexander O. Gliko

5 July 2009

* This was the first such award given to a non-physicist


ГОСУДАРСТВЕННОЕ УЧРЕЖДЕНИЕ РОССИЙСКОЙ АКАДЕМИИ НАУК ИНСТИТУТ ФИЗИКИ ЗЕМЛИ ИМ. О.Ю. ШМИДТА
ДИПЛОМ
ЗА ВЫДАЮЩИЕСЯ ЗАСЛУГИ
В ОБЛАСТИ ГЕОФИЗИКИ
Профессор
ФРАНЦ ХАЛБЕРГ
(FRANZ HALBERG)
НАГРАЖДАЕТСЯ
памятной медалью
им. академика
О. Ю. Шмидта
Директор
Института физики Земли
им. О.Ю. Шмидта РАН
академик
А.О. Глико

BIOGRAPHICAL SKETCH OF FRANZ HALBERG

NAME	POSITION TITLE
Halberg, Franz (DOB 07.05.19)	Professor and Director, Chronobiology Center

EDUCATION

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Cluj, Romania		1936-37	Math., Physics
University of Cluj, Romania	M.D.	1943	Medicine
Harvard Medical School, Boston, MA, USA	Fellow	1948-49	Medicine

RESEARCH AND PROFESSIONAL EXPERIENCE

Past: Scientific assistant (Wissenschaftlicher Assistent) and later university assistant (Universitäts-Assistent), Department of Anatomy, University of Innsbruck, Austria (1946-1948)

Research Fellow, Harvard Medical School; Assistant in Medicine, Peter Bent Brigham Hospital, Boston, MA (1948-1949)

On the staff of the University of Minnesota Medical School since 1949: Fellow (1949); Instructor (1950); Research Associate and Assistant Professor in Physiology (1951-1954); Assistant Professor, then Associate Professor in Division of Cancer Biology (1954-1958); Elsa A. Pardee Professor of Cancer Biology and Experimental Pathology (1958-1962)

Also Director of Research, Cambridge State School and Hospital, Cambridge, Minnesota (1950-1962)

Present: **Co-Director, Halberg Chronobiology Center,** University of Minnesota; former periodicity analysis laboratories officially affiliated at various times with the University of L'Aquila, L'Aquila, Italy; Réné Descartes University, Paris, France (under the presidency of Florian Delbarre); and Faculty of Computer Science, Autonomous University, Madrid, Spain

Career Award Professor of Laboratory Medicine and Pathology, University of Minnesota (from 1962)

Professor of Physiology and Biology, Graduate School, University of Minnesota (from 1962)

Professor of Oral Medicine and Bioengineering, Graduate School, University of Minnesota (from 1988)

Coordinator of an international project on The Biosphere and the Cosmos (BIOCOS), mapping spectra of variables in and around us, currently in 23 countries

HONORS: *Academician,* International Academy of Science (2006)*;* Leibniz Society (former Prussian, later GDR Academy of Science) (2000), French National Acad. of Medicine, Paris, France (1990); Spanish Acad. of Veterinary Science, Madrid, Spain (1987); *Honorary Member,* Romanian Nat. Acad. Med. Sci. (1995); *Hon. Doctorate,* People's Friendship Univ. of Russia, Moscow (2004); University of L'Aquila, Italy (2004); Masaryk Univ., Brno, Czech Republic (2000); Medical Institute, Tyumen, Russia (1996), Univ. of Ferrara, Italy (1992); Univ. of Montpellier, Montpellier, France (1980); World Health Organization Fellowship (1948-1949); *Hon. Professor,* Univs. of Paris, France, & L'Aquila, Italy; Technological Univ. of Madrid, Spain; Chengdu Coll. of Traditional Chinese Medicine & West China Coll. of Medical Sciences, Chengdu, China; Provincial Acad. of Traditional Chinese Medicine and Pharmacology, Xi'an, China; *Hon. Fellow,* International College of Nutrition; *Hon. Memberships,* Italian Soc. for Chronobiology, Indian Soc. for Chronobiology, Galician Soc. for Chronobiology, Alaska Medical Assn., Soc. Medica de la Plata (Argentina), Galician Pediatric Soc.; *Medals:* Univ. of Montpellier, France; Réné Descartes Univ., Paris, France; Univs. of Krakow, Poland; Ferrara, Italy; Szeged, Hungary; Santiago de Compostela, Spain; Masaryk Univ., Brno, Czech Republic (Medal of Medicine; All-Univ. Medal); Therapeutic Society of Moscow, Theodor Hellbrügge Foundation (Arnold Lucius Gesell Prize); Gold Medal of World Organization for Scientific Cooperation (WOSCO) with the Diploma of the first degree; O.Yu. Schmidt Medal of the Institute of Physics of the Earth, Russian Academy of Sciences

SOCIETIES AND FUNCTIONS: Past: *President* emeritus, International Society for the Study of Biological Rhythms, (renamed) International Society for Chronobiology; *Vice-President (chief U.S. officer),* Intl. Soc. for Research on Civilization Diseases and the Environment; Director, Integrated Res. Program on Chronobiology, Intl. Biologic Program, U.S. Section, & Member, Program Coordinating Committee, U.S.-IBP; Member, U.S. President's Biomedical Research Panel, Neurosciences Cluster; Consultant, National Heart, Lung and Blood Inst., Bethesda, MD; Consultant, Sloan-Kettering Inst. for Cancer Res. and Memorial Hospital, New York, NY; Consultant, NASA, Life Science, Moffett Field, California; Chairman, Intl. Commission on Nomenclature in the field of physiologic periodicity; Member, Glossary Committee, Intl. Union of Physiological Sciences; Editor-in-Chief, Chronobiologia (1974-1994); Editor, International J. of Chronobiology (1973-1984); Editorial Board, Rassegna di Neurologia Vegetativa, Sleeping and Waking, Il Policlinico, Brain Dysfunction, Fortschritte der Medizin; Reader, Intl. Review of Rheumatology, Member, Program Comm., Am. Assn. for Mental Deficiency. Present: *Advisory Board,* Global Coherence Project; *Co-Editor-in-Chief,* World Heart Journal; *Honorary Editor,* Neuroendocrinology Letters; *Associate Editor,* Intl. J. of Prenatal and Perinatal Psychology and Medicine; *Editorial Board or Council,* New Trends in Experimental and Clinical Psychiatry, In vivo; *Fellow,* New York Acad. of Sciences, Am. Assn. for the Advancement of Science. *Member or Member emeritus:* American Assn. for Cancer Research; Am. Physiological Soc.; Assn. des Physiologistes de Langue Française; Cosmos Club; Endocrine Soc.; Minn. Academy of Science; Minn. Medical Foundation; Sigma Xi; Soc. for Experimental Biology and Medicine; Am. Assn. of Univ. Professors; Am. Epilepsy Soc.; Intl. Assn. for Integrative Anthropology

CONTRIBUTION: *Chronobiology:* the computer-aided science of the body's time structure (from *chronos* = time, *logos* = science and *bios* = life) (Introduced in Halberg F.: Chronobiology [Ann. Rev. Physiol. 31: 675-725, 1969], with a follow-up in Halberg F.: Quo vadis basic and clinical chronobiology: promise for health maintenance [Am. J. Anat. 168: 543-594, 1983], and documented in 2877 publications through July 2004). *Chronomics:* the mapping of chronomes (time structures), i.a., for chrono-functional genomics, accounting for quantifiable, partly predictable road maps consisting of a spectrum of rhythms with periods covering over 10 orders of magnitude, organizing chaos, and undergoing trends. *Chronobioethics:* mapping characteristics of spiritual (e.g., religious) motivation, crime and war, as well as physical and other environmental variables, pertinent to diseases of society and of those of individuals (Biomedicine and Pharmacotherapy 2001; 55 [Suppl 1]: 153-190; Neuroendocrinol Lett 2001; 22: 359-384; cf. also Introduction to Chronobiology. Medtronic Chronobiology Seminar #7, April 1994, 52 pp, http://www.msi.umn.edu/~halberg/).

PUBLICATIONS: 3282 as of 6 July 2009; complete bibliography available at http://www.msi.umn.edu/~halberg/

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