FRANZ HALBERG: A MAVERICK AHEAD OF HIS TIME

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Франц Халберг: «бродяга в науке», опередивщий свое время

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Franz Halberg (1919—2013) was a remarkable man and an exceptional scientist. He is regarded by most as the «father» of modern chronobiology. Having realized the critical importance and far-reaching implications of biological rhythms, he undertook the tasks of (a) documenting their ubiquity at all levels of organization; (b) developing methods for their objective and quantitative characterization; (c) uncovering their rules of behavior and mapping a broad time structure of interacting multi-frequency rhythms; (d) providing the nomenclature; and (e) paving the way for important applications in medicine and biology more generally. By adding «time» to the existing body of knowledge, Halberg raised the homeostatic curtain of ignorance, thereby fundamentally changing our view of physiology. By insisting on an inferential statistical foundation, a microscopy in time was born. By adding a telescopy in time with a methodical scrutiny of non-photic and environmental influences on biota, chronomics flourished under his leadership. Herein, we review key ideas that led Halberg to build the new disciplines of chronobiology and chronomics.

Keywords: chronobiology, time, biological rhythms.

Франц Халберг (1919—2013) — замечательный человек и выдающийся ученый. Исследователи всего мира считают его «отцом» современной хронобиологии. Осознав критическое значение и далеко идущие последствия биологических ритмов, он взял на себя решение задач: (а) документирования их универсальностина на всех уровнях организации живого; (б) разработки методов их объективной и количественной характеристики; (в) раскрытия закономерностей их проявлений и отображения широкой временной структуры взаимодействующих многочастотных ритмов; (г) предоставления их номенклатуры и (д) определения перспектив их типирования для применения в медицине и биологии. Добавив характеристику «время» к существующей совокупности знаний, Халберг поднял гомеостатический занавес невежества, тем самым принципиально изменив наш взгляд на физиологию. Основываясь на общирной статистической базе, им было обосновано направление «временной микроскопии». Под его руководством было развито новое направление биоритмологии — хрономия, базирующаяся на временной «телескопии». В статье представлены ключевые идеи, которые привели Халберга к построению новых дисциплин хронобиологии и хрономии.

Ключевые слова: биоритмология, время, биологические ритмы.

Introduction

One principle guided Franz Halberg throughout his career: «Omnia metire quaecumque licet et immensa ad mensuram tempestive redige» (Measure what is measurable and render measurable in time what as yet is not), a motto fittingly also attributed to Galileo according to Giovanni dell' Acqua, the late professor of medicine at Catholic University in Rome. Halberg's deep feeling of humility and his ability to consider only the facts (data) without preconceived ideas were key attributes of his personality, as were his integrity and unwavering in front of the facts no matter the cost.

In a nutshell, chronobiology came about from the realization that rhythms are partly endogenous, and thus part of the genetic makeup and having a survival advantage. Rhythmicity from within, rather than as a consequence of responses to external stimuli, is anticipatory and preparatory. Feedback mechanisms striving toward regulation for constancy are replaced by intrinsically periodic mechanisms, which are internally coordinated by multiple collateral interactions intermodulating at multiple frequencies, the feedsideward mechanisms. Implications are far-reaching since medically there need no longer be exclusive reliance on the detection of deviations from the physiologic range to diagnose incipient or overt disease; as a step toward primary prevention, chronorisk can be assessed well within the physiologic range in terms of rhythm alterations. As a further implication, Darwinian evolution is broadened into an integrative (internal) as well as adaptive evolution [7].

Solving Three Puzzles Laid the Foundation of Chronobiology

Puzzle 1. From Confusing Variability to Rhythmic Variation: From Foe to Friend

In 1948, on a fellowship from the World Health Organization Franz Halberg was assigned to work at Harvard's Peter Bent Brigham Hospital with George W. Thorn who was actively engaged in improving the diagnosis and treatment of Addison's disease and who had developed a test as a diagnostic tool for this disorder. Presumably, epinephrine failed to cause the normal drop in blood eosinophil counts in these and other patients with adrenal insufficiency due to deficient secretion of cortisone-like hormones from the adrenal cortex. Aware of the then recent Mayo Clinic demonstration of dramatic effects of cortisone in rheumatoid arthritis, Halberg's assignment was to assess the validity of the epinephrine test by injecting mice with various compounds to evaluate possible corticoid activity based on their ability to cause a drop in eosinophil counts. This was a difficult task because counts were affected by numerous external influences and differences in various mouse strains. Despite taking special precautions to upset the animals as little as possible when taking blood samples, the results were confusing because eosinophil counts varied too much. As a result, his fellowship was not renewed. At his farewell from Harvard in 1949, Thorn told him that he admired Halberg's sticking to his guns, yet it could not be that Halberg was right while «everyone else» (including senior colleagues in the same department) was wrong. A year later, at the University of Minnesota, Franz found that when he handled the animals less, there was even greater variability in the counts, but the pattern of variation became predictable, dropping from high counts in the morning to low counts in the evening. What appeared to be time of day was a major factor, and could even result in opposite conclusions at different clock hours when comparing group results. Franz realized that he could do better by using variability as an asset rather than trying to eliminate it. Instead of needing 2.8 mg of cortisone to eliminate the 24-hour rhythm for 24 hours for assaying cortisone-like activity in the mouse [26], he could increase the sensitivity to cortisone to a very few μgs (not mgs) by working in the physiologic range, carrying the tests in the ascending stage of the about-daily rhythm, once the variability in eosinophil counts became clear to him [11]. Halberg's results in the mouse were soon amply extended to humans [2] and the epinephrine test went into oblivion. By 1950, it was known that hormones from the adrenal such as cortisol lowered blood eosinophil counts. In patients without working adrenal glands, blood eosinophil counts did not change predictably in a 24-hour cycle, indicating that adrenal hormones accounted for the cyclic change in eosinophil counts. The adrenal cycle had thus been found and later confirmed [14].

Puzzle 2. Group Difference Reversals: Competing Environmental Synchronizers

In 1950, Halberg was examining the question whether an adrenocortical activation could be used to treat breast cancer and prolong life. One group of mice had only a single low-calorie meal in the morning, during the light span, and had both ovaries removed, while the other group served as control and had food freely available at all times, although they fed mostly at night during the dark span. All measurements of blood eosinophil counts were taken in the morning. The treated group had much lower counts. This was an exciting finding, but larger groups of animals were needed to verify whether steroids that depress eosinophil cell counts (and perhaps mitoses) could be a mechanism through which caloric restriction and ovariectomy act in reducing cancer incidence. Handling larger numbers of animals required starting the experiment at an earlier clock hour. This time, however, the two groups showed no difference in cell counts. Greatly alarmed, Franz repeated the experiment on even larger groups of mice, now finding that the treated mice had much higher blood eosinophil counts than the untreated controls. Halberg had the foresight to consider the possibility that when he took measurements altered the results. Using the same mice as in the last experiment, he counted eosinophils again 4 hours after the first count and then again 7 hours later. Indeed, the ratio of eosinophil counts in the two groups reversed from one time to the next. The two groups of mice had cycles that peaked at different hours, crossing each other in the morning. He further tracked the cause of the difference to the different feeding regimens. Clock hours had to be replaced by body time. The feeding schedule and the lighting regimen were competing synchronizers of circadian rhythms in blood eosinophil counts of the two groups of mice [11]. These studies further showed that caloric restriction in mice amplifies their circadian rhythm [28]. A major lesson from this work is that rhythms are the indispensable control: changes in amplitude and/or phase can overshadow any difference in mean value and lead to spurious results.

Puzzle 3. More Reversals in Group Differences: Free-running

In studies of the effect of the lighting regimen as a synchronizer, the question as to the transducer arose. Postulating that the eyes mediate the effect, blood eosinophil counts were measured in mice born anophthalmic, in blinded mice, and in control sham-operated mice. Whereas control mice had, on average, consistently high blood eosinophil counts in the middle of the daily light span and low counts during the dark span, the blinded mice showed the same result in one study and the opposite pattern three weeks later. To verify whether the difference stemmed from a circadian period slightly different from 24 hours, rectal temperature was measured every 4 hours around the clock, in some studies for the lifetime of the groups of mice investigated. These data showed the persistence of a circadian rhythm in blinded mice, albeit with a period slightly but statistically significantly different from 24 hours: mice without eyes were free-running. The cycles were not just patterns of predictable change; they were internally run rhythms of the body, kept in step by environmental cycles [14, 26].

These results also documented that the lighting regimen serves as a synchronizer of circadian rhythms and that this information is transmitted through the eyes to the hypothalamus. These experiments, carried out throughout the 1950s were a key turning point when Halberg's interest shifted from the study of hormones to the puzzling cycles themselves. He next provided all the critical ingredients for a new discipline: new concepts, methods, facts, mechanisms and applications, replacing the limiting view of homeostasis by that of a partly built-in spectral structure in health. Chronobiology was born.

Milestones

The difference between blinded and control mice was very small on days 5 and 6, when the temperature probe broke. It was viewed as «Halberg's paranoia» by the director of his department who did not allow him to use departmental laboratory space to continue his experiment. This is how the rigorous demonstration of the endogenicity of the circadian adrenal cortical cycle was ultimately performed in the laboratories of a state mental hospital.

Circadian Cell Cycle

The «presumption» that rhythms may characterize nucleic acid formation was considered heretical in the 1950s. At that time, nucleic acid was regarded as the most constant feature of the body and was the (presumably time-invariant) reference standard to which any other chemical determination was to be related. In 1953, Halberg had reviewed the long-known widespread periodicity of cell division in various species, which prompted his desire to examine a periodicity in DNA formation. For this purpose, he requested a technician from Cyrus P. Barnum, then the leading Minnesotan biochemist in the field of nucleic acids. The strait-laced, by-the-book Barnum did not believe that he could assign a government grant-paid technician to the unorthodox possibility of seeking to examine the anticipated change in nucleic acid synthesis, predicted based on a regular daily periodic mitotic behavior. Franz had anticipated it based on the stunningly prominent rhythm which he had found in the cell division of growing mouse liver parenchyma.

The hypothesis was sufficiently interesting to Barnum that he offered to become the «technician» himself. Combining tracer methods, differential centrifugation and wet chemistry with physiological and histological techniques, determinations were made of the (relative) specific activity of RNA and DNA phosphorus expressed as a percentage of inorganic (or acid-soluble) phosphorus (the pool), thus approximating synthesis (not mere labelling). Rhythmicity was thus established in nucleic acid formation and in other variables, including phenomena at the membrane (phospholipid labeling), in the cytoplasm (RNA formation) and in the nucleus (DNA formation), along with the previously time-macroscopically known rhythm in liver glycogen and mitosis [1]. Moreover, in the usual sequence of events, RNA synthesis preceded DNA formation in mouse liver, contrary to the linear dogma DNA ? RNA ? protein still prevailing today at the cellular level. Knowing the stages of the circadian cell cycle thus accounted not only for obtaining an effect of pituitary growth hormone on growth with the end-point mitosis, but also for the fact that the right time has to be known for finding the effect [29, 23]. These results paved the way towards the concept of response rhythms and chronotherapy: the response to the same dose of the same stimulus applied to the same subject varies depending on the rhythm stage at which it is administered.

Susceptibility/Resistance Cycles Underlying Chronotherapy

By 1955, Franz Halberg showed that a single physical stimulus, such as the exposure to noise, could result in outcomes as different as no response or convulsion and even death as a function of the circadian stage at exposure. He showed that such response rhythms were reproducible, ubiquitous, and amenable to important clinical applications, recognizing that timing is as important as dosing. Since the discovery of clock genes that earned Jeffrey C. Hall, Michael Rosbash and Michael W. Young the 2017 Nobel Prize in Physiology or Medicine, the intricate rhythmic orchestration of gene pathways throughout the body is now being uncovered, the majority of drugs being found to directly target the products of rhythmic genes [35].

Restricted time feeding also made the difference between life and death in singly-housed mice: whereas most mice survived if fed during the early or late dark (active) span, most of them died if fed during the light (rest) span. In humans, a single daily meal was associated with weight loss if consumed as breakfast-only but not as dinner-only. Time-restricted feeding has found renewed interest today as a way to curb metabolic conditions such as overweight and diabetes [4].

Marker Rhythms-Based Chronotherapy

The hours of changing resistance led to an important clinical application: the optimization of treatment by timing according to rhythms (chronotherapy). In Halberg's laboratory, the toxicity and efficacy of various anti-cancer drugs were tested. The knowledge thus gained was later translated to the clinic by his students. Halberg documented the importance of relying on marker rhythms for specifying favorable treatment times. Variables such as core temperature provide reliable information regarding body time. Whenever possible, pertinent marker variables to assess the response to treatment should be included, and triangulation used to determine the best compromise between maximal efficacy and minimal toxicity. Following this principle, the 2-year disease-free survival could be doubled in patients with cancer of the oral cavity undergoing radiotherapy at the time of peak tumor temperature [17].

In the case of cardiovascular disease, blood pressure is eminently suitable as a marker variable, both for guiding the timing of treatment and for assessing the response to treatment. Several outcome studies, conducted at the Halberg Chronobiology Center in cooperation with leading investigators worldwide within the scope of the Project on the BIOsphere and the COSmos (BIOCOS), identified alterations in the variability of blood pressure and heart rate, known as Vascular Variability Disorders (VVDs), that contributed greatly to cardiovascular disease risk beyond an elevated blood pressure. Even in the absence of an elevated blood pressure, VVDs are associated with increased cardiovascular disease risk. In the presence of high blood pressure, their presence greatly increases the risk (in one study from less than 8% to over 50%). [24, 31]. Since the presence of VVDs affects the circadian profile of blood pressure, the best timing of administering anti-hypertensive medication differs among patients, making it mandatory to individualize the chronotherapy of blood pressure [33].

Cosinor Rhythmometry

To give credibility to the new discipline of chronobiology, it was important to develop tools for the rigorous statistical detection and description of rhythms. Several limitations of the usually used periodogram had to be overcome: the time series were often short, sparse, and not necessarily equidistant. For instance, in LD50 studies testing the efficacy/toxicity of a given agent, the data consisted of 4-hourly data over 24 hours (6 samples). Treating it as a regression problem led to the cosinor, a method consisting of fitting a cosine curve by least squares to the data [25]. Halberg originally developed this method for the study of circadian rhythms. In this case, the period could be anticipated to be 24 hours, or close to 24 hours, and a linear regression equation used, both for rhythm detection by the zero-amplitude (no-rhythm) test, and for parameter estimation with a measure of their uncertainty (confidence intervals). Later, he extended the technique to assess non-sinusoidal waveforms (fit multiple-component models), to handle the analysis of non-stationary time series (chronobiologic serial section), to view a broader time structure (least squares spectra), to generalize results for the population (population-mean cosinor), to compare rhythm parameters among several time series or among several populations (parameter tests), and to estimate the periods themselves by nonlinear least squares [3]. Having introduced many new terms related to the new discipline of chronobiology and the quantitative description of rhythms, Halberg provided definitions and clarified the terminology in a comprehensive glossary ([12].

Circadians in Early Forms of Life

Armed with solid statistical tools, Halberg was first to report circadian behavior in bacteria kept in continuous darkness [17], at a time when viruses and bacteria were «cited as forms of life lacking evidence for circadian organization». Circadians have now also been reported in archea [19].

Feedsidewards

Feedsidewards describe the interaction among multiple rhythmic entities that results in predictable sequences of attenuation, no effect, and amplification of the effect of one entity (the actor) upon another entity (the reactor) as it is modified by a third entity (the modulator). A case in point is corticosterone production by bisected adrenals stimulated by ACTH 1—17 in the presence vs. absence of pineal homogenate. The endogenous components of the multi-frequency time structure are internally coordinated through feedsidewards (interactions among multiple rhythmic entities) in a network of spontaneous, reactive, and modulatory rhythms [30].

Collaterally Hierarchical Celluloneuroendocrine Mechanisms

Halberg showed that the nervous system and the adrenal cortex are both rhythmic and each can be critical for one rhythm or another, but neither is indispensable for all rhythms, as seen by the persistence of eukaryotic cellular and prokaryotic rhythms under standardized conditions in vitro. The electroencephalographically-recorded pathology in the human EEG undergoes circadian variations and the power in different frequency regions of the Berger range is circadian in human health. The adrenal cortex is essential for rhythms in blood eosinophil counts and underlies the synchronization of rhythms in phospholipid labeling and mitosis in healthy mouse ear pinna, but is dispensable for the rhythm in serum iron, which upon bilateral adrenalectomy persists with statistical significance, albeit with reduced circadian amplitude and changed phase. Likewise, removal of the suprachiasmatic nuclei (SCN) reduces the amplitude of the circadian rhythms in motor activity and water drinking to the point of their obliteration, but only reduces the amplitude of circadian rhythms of many other variables, such as alcohol drinking, plasma ACTH and corticosterone. Histologically-validated bilateral suprachiasmatic lesions are compatible with the continuance of rhythmic changes in core temperature and in a number of cellular endpoints, such as DNA labelling and cell division, invariably with an advance in phase, and usually reduced amplitude, except for the stomach and colon [24]. The presence of cell autonomous oscillators in almost every cell in the body is now well recognized. While circadian rhythms are viewed as being primarily orchestrated by the SCN, there is increasing awareness of the existence of an alternative mechanism that does not require a transcription-translation autoregulatory feedback loop for circadian rhythms to be manifested [32].

Partly Endogenous Circaseptan Rhythms

Halberg defined chronobiology as the «science objectively quantifying and investigating mechanisms of biologic time structure, including rhythmic manifestations of life». This time structure includes trends, chaos, and many periodicities beyond circadian rhythms. As a parallel to the genome, our make-up in space, Franz viewed it as the chronome, our make-up in time. Often considered as a mere response to the social schedule, about-weekly (circaseptan) components are particularly important in view of evidence for their partly endogenous nature. Like circadians, they are found at different levels of organization, notably in relation to growth, regeneration, repair and development; they free-run [22] and their period is more similar within than among twin neonates [5]; they are amplified after single stimulus induction and may resonate with circaseptans in solar activity; and treatment can be optimized by timing according to their cycle stage. They are particularly prominent very early and very late in ontogeny and phylogeny [8, 13], in keeping with the resonant frequency of ions in a weak magnetic field, involving periodicities of about a week [33].

Chronomics

Chronoastrobiology

Around 1990, Franz returned to Minnesota from a conference in Moscow, Russia, with a database of 6,304,032 calls for an ambulance (1979—1981) and data on sunspot numbers and on the vertical component of the interplanetary magnetic field, used to determine the occurrence of magnetic storms. Following in the footsteps of Chizhevsky, his Russian colleagues had found that the incidence of some pathologies recorded in this database was influenced by space weather. The challenge of analyzing this set of data and learning about heliogeophysics was a turning point for Halberg's laboratory. It was the start of a new avenue of investigation, which led to chronomics, the study of rhythms in biota as they are influenced by rhythms in the broad environment [15]. The tenet is that since biota live in an open environment, all periodic phenomena in the environment are susceptible to influence the time structure of life forms in that environment, from the about weekly variations in weather conditions on earth to the multiple oscillations characterizing the sun, the interplanetary space and the cosmos, including the about 10.5- and 21-year cycles in solar activity.

Highlights of this line of inquiry are the finding that magnetic storms are associated with a decrease in nocturnal melatonin and with a decrease in heart rate variability. Not surprisingly, these variable relate to the two organs generating strong electrical signals. The decrease in heart rate variability may be a mechanism underlying the higher incidence of mortality from myocardial infarctions (by 5% or 220 cases per year) observed in Minnesota during years of maximal solar activity by comparison with years of minimal solar activity [9].

Chronomes in us and around us

Not only do biological variables vary according to a spectrum of rhythms, spectra with near-matching periods were found for physical environmental variables. Temporal organization in and around us has led Halberg to a useful rule to seek a reciprocity of the cycles in ourselves and in physical and societal nature [13]: 1. For each non-photic periodic component in the environment, a near-matching organismic component may be sought. About 10.5-, 21-, 50-, and about 1.3- and 0.42-year cycles were thus mapped in his laboratory. 2. For each inferentially statistically validated rhythm as part of an organismic time structure, one can seek a corresponding element in the chronome of a natural physical environmental variable.

Congruence

Halberg defined selective congruence as the pairing of various biospheric cycles of certain frequencies with different environmental ones [6, 18]. It is assessed by the total or partial overlap of confidence intervals of periods of anticipated cycles between two (or more) variables. Since non-photic environmental variables (such as solar activity, solar wind speed, or geomagnetic activity) tend to be non-stationary, it is possible to determine whether changes as a function of time in the period of a given biologic variable are associated with changes observed in the period of the environmental variable. This approach complements «remove-and-replace» and superposed epoch analysis techniques for the exploration of mechanisms and triggers underlying biological periodicities with no known environmental synchronizer. The longitudinal automatic around-the-clock monitoring of variables such as blood pressure and heart rate for decades by Halberg and some of his dedicated colleagues for self-surveillance were essential to explore a selective assortment of paired periods (coperiodisms) in and around us, that are congruent by virtue of their overlapping 95% confidence intervals [19]. Their mapping is the focus of an «atlas of chronomes» currently in preparation.

Chronobioethics

With the increased realization of the ubiquity and relative prominence of biological near-matches of photic and non-photic environmental cycles, Halberg expanded his field of inquiry from biological systems to sociology and economics. Human pathology, suicides, epilepsy, heart attacks, strokes and traffic accidents had already been investigated for associations with heliogeomagnetics. Human morphology, psychology and behavior, normal as well as abnormal, had also been shown to be associated with non-photic effects of the sun and/or galactic cosmic rays [20]. It was time for Franz to turn his attention to the good and bad of society. The grids and/or the humors of the brain respond not only to magnetic storms; they also undergo motivational changes related to subtle natural environmental factors. Examples include religious proselytism undergoing about 10.5- and 21-year cycles, the incidence of homicides and wars cycling with periods of about 50 and 21 years, and an about 1.3-year (transyear) component characterizing the monthly incidence of terrorist acts, its prominence corresponding to that in geomagnetic activity and solar wind speed. Economic cycles of about 11 and 50 years were also mapped.

Concluding Remarks

Once referred to as «Halberg's paranoia», circadian rhythms have entered mainstream physiology. Many of his key ideas, from the clinical implications of the endogenicity of circadian rhythms to their presence in early forms of life, and their persistence after bilateral suprachiasmatic lesioning, have only been widely adopted by the scientific community after technology advanced to explore molecular mechanisms, when they were rediscovered. Franz was truly ahead of his time.

The evolution from chronobiology to chronomics could not have been possible without Halberg's focus on around-the-clock measurements over long spans. It started with the use of Earl Bakken's device for rest-activity-based marker rhythmometry on large groups of mice. The device, itself long-lost, is of historical interest as it preceded the unique telemetry system built with NASA support with which Halberg sowed the seeds of chronobiology. Modern telemetry systems for the experimental laboratory evolved from work done in his laboratory by one of his many students. As new technology and wireless communication become cheaper and faster, human self-surveillance is increasingly being used by ordinary citizens interested in their own health and performance, as evidenced by the «Quantified Self» movement.

Chronobiology and chronomics would not have evolved into scientific disciplines without Halberg's insistence on the rigorous analysis of data, using inferential statistics for rhythm detection and the estimation of their parameters with a measure of uncertainty.

With modern devices for the automatic and ambulatory monitoring of physiological variables such as blood pressure and heart rate, longitudinal records became available to scrutinize frequencies much lower than one cycle per day. Both the about 1.3-year transyear and the about 11-year cycle reflecting solar activity were almost invariably present in all these long records spanning 10 years or much longer (up to 50 years).

Implications are wide-ranging, notably in relation to healthcare. Chronobiology defines health positively rather than as the absence of disease. Ranges of variability in circadian characteristics are narrower for individuals than for populations. Any deviation from an individual's 'normal range' means that problems can be detected earlier, before there is deviation from the conventional population-based norms, prompting early intervention for prehabilitation (primary prevention) in preference to rehabilitation. Longitudinal monitoring can also help distinguish changes that are part of healthy aging versus the development of disease. From a basic viewpoint, rhythms are the indispensable control since differences in amplitude, phase, and/or period can overshadow any differences in mean value; if so, failure to account for rhythms is likely to yield irreproducible and spurious results.

To summarize, rhythms are the essence of life. Halberg's lifetime work helped change the world, and he was fortunate to witness the impact it made. The celebration of his achievements would not be complete without saying a few words about Franz as a person and a dear friend. He had boundless energy and an electrifying personality; «work» was not in his dictionary: only «fun». As expressed by 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. Second, one 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. Third is his impact in stimulating research in other disciplines. He has initiated research around the world, as is apparent from his bibliography posted on the website of the Halberg Chronobiology Center, where his legacy lives on, thanks to his exceptional generosity.

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