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Season's Appreciations 2000

Chronomics complement, among many other fields, genomics and proteomics

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In the second year of the center, its bibliography, Appendix I, shows the activities mostly of the project of the BIOsphere and the COSmos, BIOCOS, in mapping chronomes, time structures in us and around us, and their interactions in aligned physiological and physical time series. We thank the 114 authors who contributed to a total of 62 published titles (as of December 15, 2000), and thank the additional authors who contributed to a Festschrift honoring Franz, prepared by Germaine, and invited by Hans Kaiser, President of the International Society for the Study of Comparative Oncology, and John Delinassios, editor of the journals in vivo and Anticancer Research. Further thanks are due to many more individuals who participated in BIOCOS. We gratefully acknowledge the warm hospitality we enjoyed at Dr. Delinassios' International Institute of Anticancer Research in Kapandriti, near Athens, Greece, and at the Klinik Höhenried in Bernried, Germany, where we were particularly pleased to see Dr. Max Halhuber, former chief physician, in good health. His trust bore fruit three decades later thanks to Thomas Müller-Bohn and Germaine, as seen from Appendix 2 of this report. Appendix 3 deals with the unquestionable highlight of this year, a meeting in Tokyo which extended the finding of an association of certain frequencies characterizing human heart rate variability (such as the circaminutan and the about 10.5-second power) with geomagnetic disturbance to well over a dozen subjects studied by Andi Weydahl in the arctic auroral oval. Pertinent results were reported by Dr. Otsuka in a workshop on chronoastrobiology and chronotherapy organized by him on November 11 in Tokyo, to which BIOCOS participants were invited, with generously provided support for travel and unique hospitality, extended further by the travel of BIOCOS participants from Tokyo to Sapporo and from Sapporo to Urausu for a reception by Mayor Kaname Yamamoto, who seeks to extend to the residents of his city the offer of 7-day/24-hour blood pressure and heart rate monitoring, planned in Roseville, Minnesota. Another mayor interested in offering 7-day/24-hour blood pressure monitoring to his constituents is Stefano Cimicchi, of Orvieto (near Rome), Italy, in cooperation with Prof. Mario Bertini of Rome. Two of us visited the latter two cities in September 2000 for a meeting on urban planning. Under the keywords of assuring the mobility and independence of a city's residents, we advocated a stroke prevention program based on 7-day/24-hour monitoring of blood pressure and heart rate as a public service.

Earlier in the year, we visited Lund, Sweden, where we learned that the number of strokes showed an increasing trend there, as it also has in Minnesota and Arkansas. This trend was preceded by an about 50-year cycle in Minnesota, and the increase had also been found by Prof. Miroslav Mikulecký in Slovakia. Is this due, among others, to the immigration of a high-risk population, or rather is it (also) part of a natural cycle? In the latter case, a controversy may arise in assessing the effect of treatment, perhaps akin to the debate of the greenhouse effect. There may not only be global warming, but at least in several geographic locations, a (global?) increase in strokes as a feature of a planetary effect of solar non-photic activity? Thus, it was more important to have a promise from Jarmila Siegelova, Professor and Head of Functional Medicine, and clinic chief Pavel Homolka, to initiate for stroke prevention a routine 7-day/24-hour monitoring of patients in St. Anna Hospital. In Prague, we were received by Bohumil Fišer, the professor and head of physiology in Brno and active associate in research, now also Minister of Health of the Czech Republic, who added that he would try to introduce chronobiology more broadly into his country's health care. One of his promises has already materialized: he sent data revealing the about 50-year cyclicity in stroke incidence found ear-


Jarmila Siegelová


Bohumil Fišer


Pavel Homolka

lier in Minnesota, also in the Czech Republic, and again there was a recent increase. Another promise was also kept by Pavel and Jarmilka: by the time of the November 11, 2000 meeting in Tokyo, enough new data on human adults had accumulated to compare them with their earlier data on the circaseptan-over-circadian prominence in cardiovascular data of their babies, as can be gauged by the corresponding amplitudes. The ratio of a circaseptan/circadian amplitude, larger than unity in the blood pressure and heart rate of babies, was again much smaller than unity in adults, due to the circadian-over-circaseptan dominance now shown in over sixty 7-day series from adults and earlier from Japan and Minnesota. The larger-than-unity amplitude ratio early in human development has phylogenetically, or rather chronohologenetically interesting counterparts, which are two other highlights of the year 2000. For the yearly MEFA International Fair of Medical Technology and Pharmacy in Brno, Czech Republic (November 6–8, 2000)—at which we usually participate, and which one of us had the privilege to open in its scientific aspects this year, as in the past—Dewayne Hillman and George Katinas summarized the fruits of their painstaking activities focusing on data from *Acetabularia acetabulum,* kindly sent by Dr. Sigrid Berger of the Max-Planck-Institute for Cell Research (Ladenburg bei Heidelberg, Germany) and explained by her to us in very active correspondence. *Acetabularia* released into continuous light shows a large circaseptan rhythm, by far exceeding the amplitude of the circadian variation in this unicell's electrical potential, one of the most important findings made this year, aligned with the accumulating human ontogenetic data.


Thomas Müller-Bohn

For many human and other data sets, we computed ratios of amplitudes of components associated with non-photic effects of our environment such as the biological week or decade in the numerator, to the amplitudes associated primarily with photic spectral components such as the day or year, used as a reference, in the denominator. We thus found a number of cases where, as in *Acetabularia,* the non-photic effect was more pronounced than the photic one. Everything is relative, of course, and the photic effects, if they can be summarized by the amplitude of a 24-hour cosine curve actually contain non-photic contributions, e.g., by geomagnetic disturbance, as well, even if in long series the half-yearly but not any yearly component of geomagnetic disturbance is synchronized with exactly 365.25 days.

Dewayne Hillman extended circadecennians to the oxygen evolution of *Acetabularia,* insofar as the relative circadian amplitude, and also the circadian acrophase are concerned. When some of the available data obtained on this alga in light and darkness alternating at 12-hour intervals from different experiments covering more than a decade are analyzed as a pool, Dewayne Hillman and George Katinas in cooperation with Sigrid Berger and Luebbo von Lindern found further a circadecennian modulation. By analyzing the circadian amplitude referred to the mean of this variable, Dewayne corrected for differences in calibration in different experiments, that to a considerable extent can greatly bias the result. His pioneering findings on a unicellular alga that may have been around on earth 50 million years ago are a first step in a chronobiologic (chrono-) hologenesis. By the same token, the circaseptans of eukaryotic unicells such as *Acetabularia* may be viewed in the light of circaseptans found in genetic changes of bacteria in data from Piero Faraone, reported at MEFA last year. In data on the length of human babies in Denmark, Germaine's meta-analyses after detrending revealed a particularly prominent, larger than unity ratio of the amplitude of an about 21-year or circavigintunennian cycle to the about-1-year amplitude.


Jiri Dušek

The first international astrobiology conference was held at the NASA Ames Research Center (ARC) in California in April 2000. This conference omitted chronoastrobiology, despite the fact that its senior chronobiologist at ARC had planned such a meeting and ARC had funded its planning. NASA works in mysterious ways! It was hence the more important that a meeting on chronoastrobiology and chronotherapy could be held a few months later. This meeting is here discussed in detail as a follow-up on an earlier such conference in China. A NATO advanced workshop in Knossos, Crete, Greece, in June 2000 focused on the impact of magnetic storms on communications via satellite and on electrical power grids leading to blackouts. At that meeting, two of us were invited to add evidence that the "power grids" of the heart are also affected.

The senior author is also grateful for a warm ceremony in Brno, at which he received an honorary degree. He values this degree the more since it came from the home city of Gregor Mendel, who as father of genetics was most interested in terrestrial and cosmic influences. In addition, a leading hospital in Brno is now the first to introduce routine 7-day/24-hour blood pressure monitoring. We are also happy to report that Kuniaki Otsuka, Professor of Medicine at Tokyo Women's Medical University and past president of the Japanese ECG Society, to whom we owe the clinical demonstration of **c**ircadian **h**yper-**a**mplitude-**t**ension (CHAT), is now also implementing 7-day/24-hour routine blood pressure and heart rate assessment, as is Katarina Borer at the University of Michigan in Ann Arbor in the context of a study on exercise physiology. Thank you, Kuniaki, Pavel and Jarmilka, and Katarina, for this and very much more.

Appendices

1. Publications by staff members of the Halberg Chronobiology Center, 2000
2. Predictive value of the above-threshold circadian blood pressure amplitude in the perspective of decades
3. Mapping biological and physical environmental time structures, chronomes, serves biomedicine, ecology and physics

Appendix 1: Publications by staff members of the Halberg Chronobiology Center, 2000

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Appendix 2: Predictive value of the above-threshold circadian blood pressure amplitude in the perspective of decades

To evaluate the usefulness of the circadian amplitude of systolic (S) or diastolic (D) blood pressure (BP) as a prognostic tool, we tracked subjects measured manually in 1967, since in the interim, we had found that an excessive circadian SBP or DBP amplitude increases vascular disease risk generally, e.g., by 720% and 590% for cerebral ischemia and nephropathy, respectively ($P<0.05$) [1]. The circadian BP overswinging constitutes the largest risk of stroke among all factors tested, including a 24-hour mean of SBP/DBP above 130/80 mmHg, Figure 1. Ambulatory monitoring shows that the circadian blood pressure amplitude relates nonlinearly, with a threshold for variability [1], not for an imaginary putative 'true blood pressure [2, 3] to vascular events in 297 patients followed prospectively for six years, confirmed on 617 men and 562 women using the left ventricular mass index as a surrogate outcome measure [1].

METHODS. Using a mercury column sphygmomanometer, SBP, DBP_4 and DBP_5 (when the Korotkoff sound faded, then disappeared) were measured 2-3 times manually 6-7 times during waking, at 2-3h intervals, on each of two days on 63 men, 20-55 years of age, between August 26 and September 3, 1967, in Germany. Each series was analyzed by cosinor [4].

RESULTS. Only one out of 10 still alive had an excessive SBP and/or DBP amplitude, compared with seven out of 11 who died ($\chi^2=6.390$; $P<0.01$), Fig 2.

COMMENT. In a follow-up of nearly three decades, the finding here reported extends the results of several shorter studies carried out with ambulatory monitoring [1], and shows that systematic manual monitoring can also serve the purpose of detecting BP overswinging by research in everyday care. Since an excessive amplitude can be normalized by autogenic training or drugs [1], it

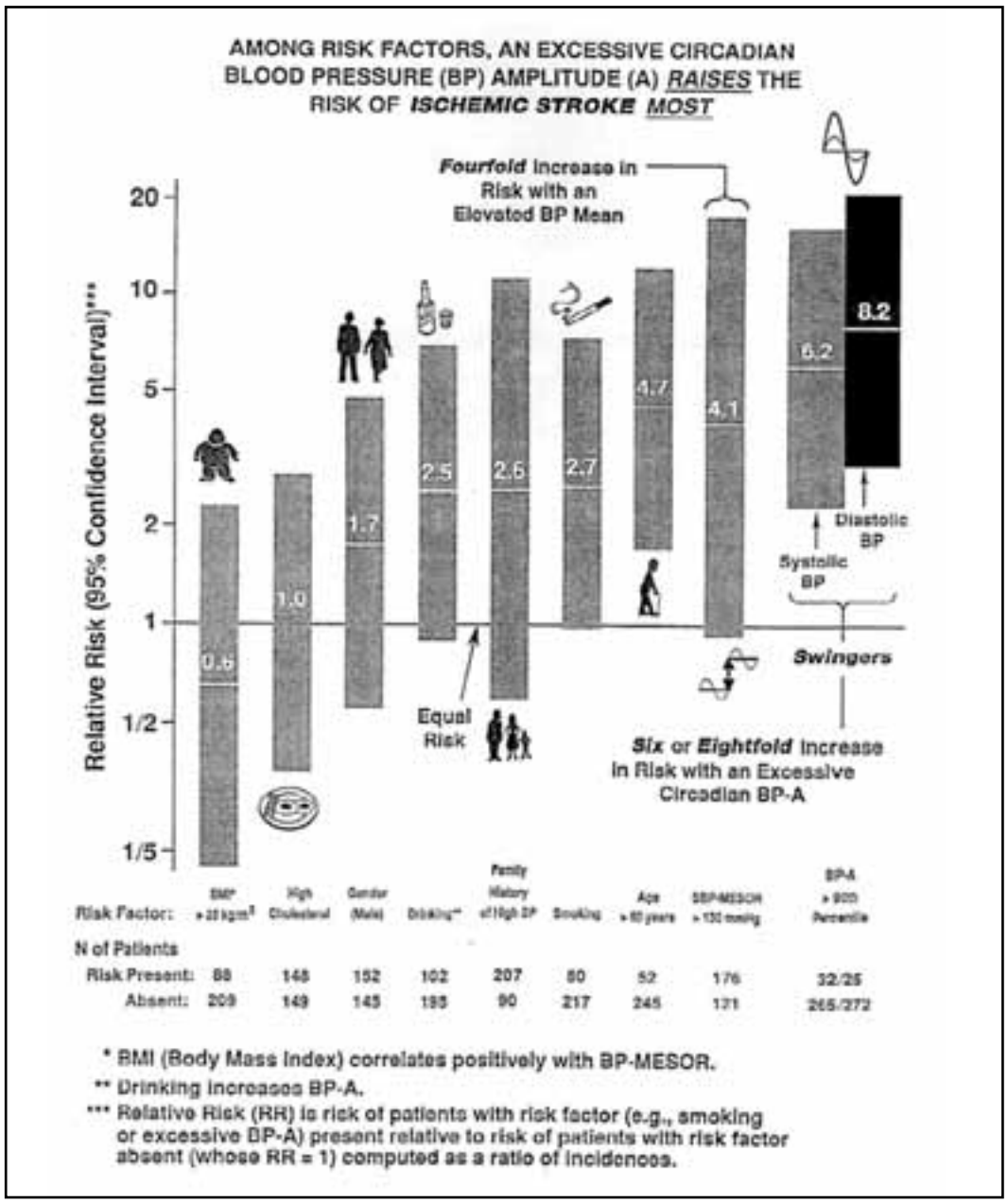

Fig. 1. An excessive circadian amplitude of diastolic blood pressure represents a 720% increase in risk of ischemic stroke (see last column on right).

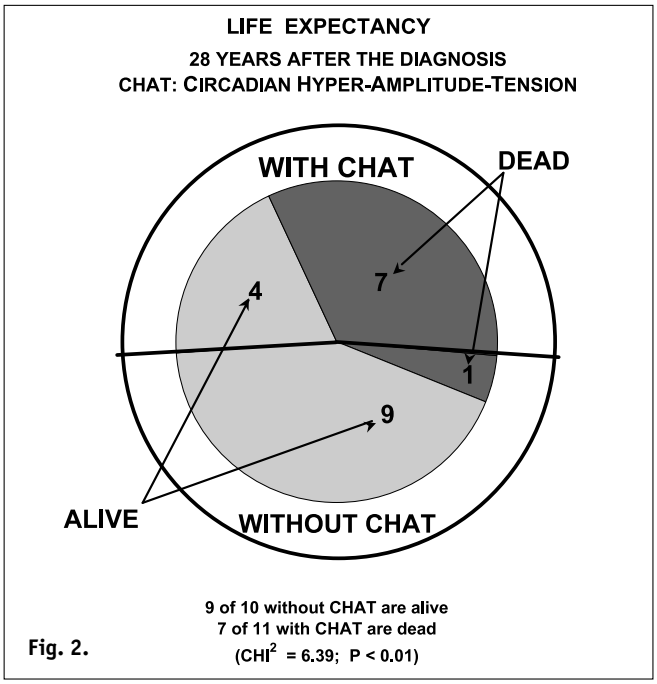

Fig. 2.

is pertinent in deciding on a treatment plan for the given patient [1]. Ambulatory monitors at a 90% reduction in cost and analyses in the light of clock-time, gender- and age-specified reference values are available for international research in practice from the University of Minnesota Chronobiology Center (corne001@tc.umn.edu).

Dedicated to the memory of Frederic C. BARTTER, at the time of this study director of the Clinical Center at the U.S. National Institutes of Health, Bethesda, Maryland, whose participation, by determining hydroxycorticosteroids on the same patients, revealed a statistically significant correlation between the overall averages of these steroids and SBP under circumstances to be discussed elsewhere.

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Appendix 3: Mapping biological and physical environmental time structures, chronomes, serves biomedicine, ecology and physics

Report of 1st International Symposium on Chronoastrobiology and Chronotherapy, a workshop held as a satellite symposium of the 7th Annual Meeting of the Japanese Society for Chronobiology, Tokyo, 11 November 2000

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Chronomics serves strange bedfellows

Long-term physiological quasi-ambulatory[1] monitoring of blood pressure and heart rate, among other variables such as those of the ECG, part of the neuroendocrinologic armamentarium, has already yielded information on the effect of geomagnetic disturbances upon human heart rate variability. Such monitoring worldwide is the link between several seemingly distant endeavors. It unites 1. those lay and medical people who wish to survey themselves in order to recognize any alterations in the otherwise neglected range of their normal variations, including changes in the neuroendocrines, for the recognition of disease risk syndromes and, if need be, wish to benefit from timely as well as timed treatment (a chronodiagnosis-based true chronotherapy), preventive, i.e., timely, as well as timed treatment with 2. those who aim at monitoring throughout ontogeny, thus hoping to learn about our origins and past environments from chronobiologic "living fossils", further 3. those who wish to assess for climatology and meteorology as well as for geo- and solar physics the role of organisms as a sensitive combination of evolving thermo-baro-magnetometers and radiation detectors to discover transdisciplinary associations, with the dividend of applied information on effects in the biosphere of weather and climate, 4. those caring for overt diseases, wishing to arrive at treatment by body time according to marker rhythms rather than without temporal and other specification beyond at best by clock-hour only, and on all of these grounds 5. those government officials who intend to reduce the cost of rehabilitation by

[1] "Quasi-" because the wearer, given an audible signal when a measurement is about to start, must remain motionless during the measurement.

preventive intervention, prehabilitation, notably of heart and brain attacks.

What's in it for biomedicine: from stroke prevention (Appendix 2) to basic geophysics

Physiological, temporal organization is much more extensive than circadian systems [1-6]. Circaseptan and circadecennian cycles are found in bacteria and other forms of life, including humans. In mammals, rhythms characterize mitoses and RNA and DNA synthesis during growth and regeneration; hormones like melatonin are secreted time-dependently along several system scales; the nervous system certainly displays rhythms, chaos and trends, that is chronomes. Environmental and organismic interactions are also cyclic along a host of frequencies [7]. These resolvable time structures, chronomes, in us have counterparts around us, also consisting of rhythms, trends and chaos, as we now recognize more and more [7]. Physiological chronomes may serve the physicist as continuously recording living endpoints. Even after death, as mortality statistics, at the population level, chronomics hint at associations and perhaps, at partly evolutionary effects of physical environmental chronomes [7], including those of a ~10.5-year Schwabe cycle. Biological clocks and calendars were an important conceptual public relations step, but there is no need to rename each cell a "clock" in particular when, like *Acetabularia acetabulum,* the cell can be characterized by a larger circaseptan than circadian amplitude once it is released into continuous light, Figure 1, and when there coexist "clocks" with different prominent periods in different variables of the same single cell, as is the case for the electrical activity of Acetabularia recorded concomitantly with apical and basal chloroplast migration, with each of the 3 variables showing a different pattern in the relative prominence of circadians and circaseptans.

There is the much broader concept of time structures, chronomes, in larger and larger systems along longer and longer periods in us, and still longer ones in populations of us and even longer ones around us. For any component in biological spectra, one looks for, and often finds, natural (as well as anthropogenic) physical environmental counterparts [7]. If coherences are found, e.g., by cross-spectra, any external and internal interactions are also looked for and are all best taken into account as far as possible on the basis of chronome maps. This was done for the case of a built-in free-running about weekly, but not exactly 7-day (circaseptan) component in spectra of human urinary 17-ketosteroid excretion (17-KS) [8]. A similar, but

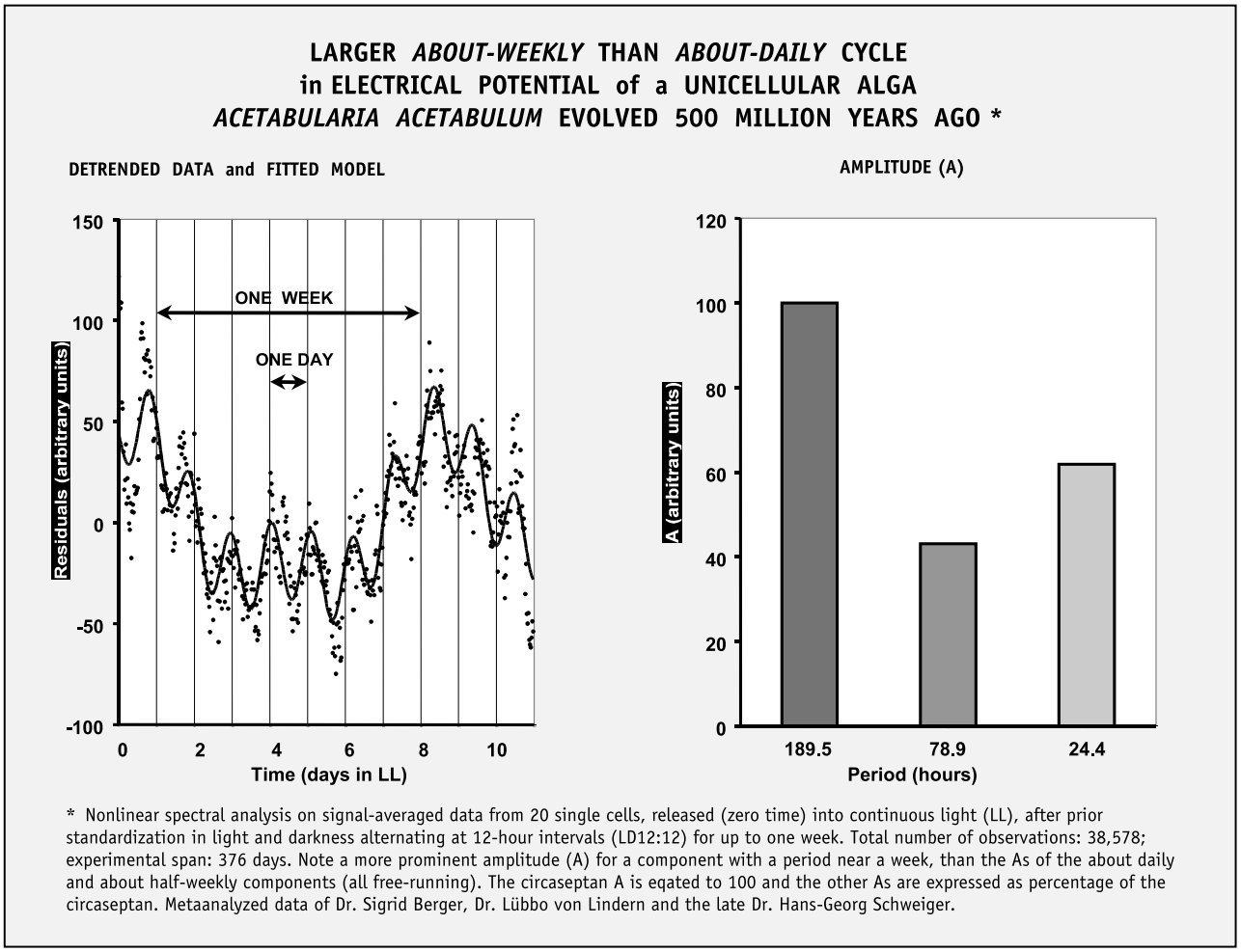


Fig. 1. The about-7-day (circaseptan) component is more prominent than the circadian rhythm in the electrical potential of *Acetabularia acetabulum* after release in continuous light.

again not exactly 7-day, natural 6.75-day counterpart stood out clearly in spectra of the geomagnetic disturbance index, K_p [9].

Schwabe cycle in breakdown products of steroid hormones?

An about 10-year (9.28-year) cycle in 17-KS was also noted [10]. During the span examined for 17-KS, Wolf's relative sunspot numbers (WN) exhibit a 10.29-year cycle and the planetary geomagnetic disturbance index, K_p, one of 7.29 years. The circadecennian 17-KS peak followed the WN peak, yet preceded rather than followed a K_p peak [10], in keeping with, but not proving, the possibility that over the long span of evolution the about 10-year period, such as that in urinary 17-KS, may have been coded in the genome, as it was in the case of the about 7-day and about-daily rhythms free-running under appropriate conditions in many variables, including 17-KS [8].

Long-term physiological monitoring in the footsteps of Santorio and Humboldt

For physicists, a putative genetic coding of certain invisible environmental cycles, reflected in accumulating biodata, points to non-photic cosmo-helio-geophysical associations, if not effects, in biota, exerted at present [11] and/or during evolution [7, 12]. For the biologist, we deal with much more than "clocks" and "calendars" [5, 6], namely with broad time structures [1], chronomes [2, 13], the topic of the international conference summarized partly herein, [14] held in generously hospitable settings in Tokyo, with follow-ups in Sapporo and Urausu. A series of contributions were made by individuals monitoring the electrocardiogram (ECG) beat to beat on themselves and others, repeatedly for at least 7 days (except for spans of daily hygiene), and in a number of cases for much longer, e.g., 70 days [15], including a series yet to be evaluated covering most of 2 years beat-to-beat [16]. These and an automatic ambulatorily monitored series of half-hourly heart rates and blood pressures, now in its 14th year, and series of self-measurements on 11 psychophysiological variables on the average 5 times a day, one of them now in its 34th year [17], complement evidence from archives covering decades on millions of individuals, and in one case covering more than a century [18].

While interest continues in the circadians whose inferential statistical mapping started half a century ago [1, 2, 19], focus has been extended to a number of other frequencies that characterize biological variability. A circaseptan system was known intuitively in antiquity and was quantified in humans in the 1960s [8]. In the new millennium, circaseptans can be shown to characterize air bacteria [20] as well as the eukaryotic unicell *Acetabularia acetabulum* [21]. A half-year cycle characterizes the human brain [22], as expressed in vasopressin-containing nuclei of the hypothalamus and in the incidence of status epilepticus [9]. In the footsteps of William Gilberd's interest in terrestrial magnetism [23], those of us impressed by the near-week in 17-KS, free-running from the social schedule, who found a 6.75-day component in geomagnetic disturbance [9] are promptly confirmed by physicists [24, 25] as soon as biological findings prompt the extension of focus from the anthropogenic exactly 7-day week, associated with magnetic disturbance by the San Francisco Bay Area Rapid Transit system [26].

Santorio Santorio [27] started 30-year monitoring of his own body weight several centuries before systematic geomagnetic recordings were instituted [28; cf. 29], but it took two more centuries after Gauss and Weber before non-photic signatures of solar and geomagnetic activity along the scale of years were demonstrated to lead, at the conference reviewed herein, to a whole system of about 10.5-year and about 21.0-year cycles, replicated in several sets of time series [14]. It must be realized that the physiology of a majority of hundreds of thousands or millions of individuals must somehow be synchronized to reveal statistically significant population rhythms and to show the degree of generality of similar cycle lengths, now actually mapped in a set of pioneering studies covering sociology at one extreme [30] and cell biology at the other [14].

Thus, the spectrum of biological population cycles in any one physiological variable was broadened to include about 10.5 and about 21-year biological equivalents corresponding, at least in period length, to the Schwabe sunspot cycle and the Hale bipolarity cycle. An about 50-year cycle in the somatometry of 25 to 100 newborns each year, covering 112 years [18], is also found in the incidence of strokes in the Czech Republic and in Minnesota, USA [7]. A broadened spectrum of rhythms with widely different frequencies in a given variable constitutes just one element of chronomes [2]. Rhythms, in their turn, organize seemingly irregular changes summarized as chaos, some of it deterministic, and gauge unidirectional trends or unique events in individuals [10], some of these one-time events like natality and mortality constituting rhythms in populations.

Cross-spectral coherences between helio-geo- and biodata from a relatively substantial archive of human somatometry from Austria, Denmark, Russia and the USA further warrant the emulation by biologists of the (thus far) more systematic governmentally sponsored geo- and cosmophysical monitoring, ongoing for centuries on earth and for decades from satellites in space. In the early 19th century, Alexander von Humboldt approached, apart from Gauss and Weber, who started their own monitoring by 1833, the Royal Society to start geomagnetic monitoring throughout the British Empire [31-35], leading in turn to the recognition by Edward Sabine of associations between the sunspot cycle, reported by Samuel Heinrich Schwabe in 1843, and certain aspects of geomagnetic disturbance [28-35].

By comparison, coordinated physiological monitoring has been a stepchild of governments thus far. Chronobiologic risk recognition in the normal range rests on the endocrine and vascular data from a Kyushu-Minnesota study sponsored by a contract with the U.S. National Cancer Institute leading to over 50,000 radioimmunoassays [36]. This study, started by Minnesotans with participation by Teruo Omae, Terukazu Kawasaki and Keiko Uezono of Japan, the latter present at the November 11, 2000, meeting, led to the development of a battery of

endocrine tests for the recognition of the risk of various diseases [36]. The collection from womb-to-tomb of blood pressure and heart rate series, with an opportunistic inclusion of the mapping of other variables, was followed by a project on the BIOsphere and the COSmos (BIOCOS), eventually including an **A**sian **C**hronome-**E**cologic study of **H**eart **R**ate **V**ariability (ACEHRV) of Kuniaki Otsuka in the ECG, that soon became **i**nternational in scope (ICEHRV).

Centuries after Santorio established insensible perspiration [27], also in the course of long-term monitoring, associations between magnetic storms and certain spectral regions of heart rate variability were demonstrated by some of us, as a follow-up on similar findings in clinically healthy astronauts [37] in earth orbit as well as in patients at a high risk of vascular disease, such as those after a myocardial infarction or those who succumb to sudden death on earth, all showing a deficit in the standard deviation of heart rate [38]. It is noteworthy that data taken by one of us (Kuniaki) on himself were found by Germaine to be abnormal and that, upon her inquiry about unusual events, first nothing unusual was reported, until it occurred to Kuniaki that there was a magnetic storm during the recording span. The separation of magnetically quiet and disturbed days then revealed a statistically significant difference that was extended thereafter to first 8 and then a larger number of subjects in the auroral oval with Andi Weydahl, in systematic long-term studies [14; cf. 39, 40]. More specifically, heart rate variability was found to be decreased in spectral regions of the ECG centered around 10.5 and 46.5 seconds, providing a physiological basis for mechanisms of a cosmo-pathology [9, 41].

Andi Weydahl

Morbidity and mortality

By the mid-1930s, Düll and Düll [42, 43] had provided solid numerical data on human health for the effect of corpuscular radiation from the sun and associated their findings on human statistics with an about 27-day cycle in sudden eruptions from the sun. Dell'Acqua then formulated a cosmopathology [44] in keeping with the visionary writing of Chizhevsky [45, 46] and much pertinent Russian literature reviewed by Dubrov [47] and later by Gamburtsev [48]. The effect mediated by geomagnetic activity was seemingly sealed with a thorough superposed epoch analysis by Stoupel [49]. A controversy arose when two large studies in the USA did not find any solar effects [50, 51]. The failure to detect any effect in extensive and well-analyzed data, may relate to their covering less than 10 years (the approximate length of a single solar cycle) [51; cf. 52], and may be due, as one of these reports explains, i.a., to differences among solar cycle stages and/or among consecutive solar cycles, shown in the interim to characterize mortality cycles from myocardial infarction in Minnesota, USA, during consecutive solar activity cycles [7, 53-55].

The association of myocardial infarction and stroke in Mexico [56] and Minnesota [7, 53] as well as in Russia [9, 49, 57-59] and Israel [49]; and its putative underlying mechanism of an effect on heart rate variability is reviewed in detail elsewhere [52]. At the November 11, 2000 Tokyo meeting, Weydahl's data not only extended the self-study of Kuniaki in Tokyo to her students, all of them showing less variability in their heart rate in the spectral region of about 1-minute cycles on magnetically disturbed as compared to magnetically quiet days; she also presented data implying the involvement of melatonin, as a mechanism in the effects of geomagnetics [61]. Even in the auroral region, the biomagnetic intensities may well be small as compared to the intensities that lead to blackouts in power grids and to failures in communications via satellites. The search for receptors, mediators and amplifiers of the effect of geophysical disturbance at specific frequencies is, however, warranted theoretically [62] and by these auroral findings [61], earlier work by Burch et al. [63] and studies in the laboratory, reviewed by Vollrath [64]. In the course of evolution, an appropriately tuned physiology may have become able to respond to probably specific frequencies, yet to be identified, among those prevailing in the natural physical environment.

Evolutionary speculation about circaseptans early in phylogeny and ontogeny

Along this line of thought, the findings of about 1.7-hour and 8-hour cycles and of intermittent deterministically chaotic changes in records collected by Mark Engebretson's stand-alone magnetometer in the Antarctic, also presented in Tokyo [65], are most pertinent. This magnetometer is located within the British Antarctic Survey (BAS) Automated Geophysical Observatory A80 (80.7°S, 20.4°W geographic; 66.5°S, 28.5°E geomagnetic; L shell 6.3), over 600 km from the nearest human habitat. Its data tapes are collected on once-yearly site visits for durations not exceeding 2 days. The 1-min standard deviations of these unpolluted geomagnetic variations recorded at half-second intervals, in what is commonly described as Pcs, over 58 days reveal numerical equivalents of the cycle found on the average in the action potentials recorded from the brains of eight narcoleptic humans [66-68] and at approximately that period in innumerable other sleep research.

In correspondence [69], Johann Gregor Mendel, the founder of genetics, considered those effects of "terrestrial and cosmic influences" that, once acquired by us, allow some "bastards" (Mendel's word) to survive when most others perish. Mendel was a meteorologist at heart, with many publications in that field (and only two that underlie genetics). Perhaps intuitively, he assumed that in the long course of evolution (he had his contemporary Darwin's book), some cycles outside us were coded in us. This may have happened not merely, as Darwin put it, by the Malthusian survival of the fittest in a food chain [70], but also as a result of an internal evolution [71], in the sense of the survival of those with temporally optimal integrative adjustments within their bodies (a *consensus partium in tempore),* a premise as well as a complement for Darwin-

ian evolution or more broadly for integration within the organism as a sine qua non for integration into the environment. By sole (adaptive Darwinian) focus on the latter integration, the more complete rules of feedsidewards among chronomes within an organism are neglected. An optimized temporal scheduling of the various organ systems, undergoing cycles with vastly different frequencies, constitutes a desideratum in its own right, as a basis for an internal as well as Darwinian evolution [71].

Comparative physiology reveals a temporal homology (if not recapitulation) of circaseptans in early stages of ontogeny

About 7-day or circaseptan rhythms were documented at the meeting in Tokyo for the electrical potential of a giant alga and compared with the prominence of circaseptans in early stages of crustacean and mammalian development, a temporally recapitulated feature, reminiscent of Ernst Haeckel's much-contested biogenetic law [72; cf. 73, 74]. Haeckel, who coined the term *ecology* [75], complemented Mendel and Darwin, but his law of recapitulation is now inverted and used as evidence of a paedomorphic origin, "paedomorphism" being an evolutionary theory suggesting that developmental, e.g., larval stages of existing organisms may give rise under certain conditions to totally new organisms, by the abbreviation of the life cycle of the ancestor [76]. In this context, "paedomorphism" means a retention of larval and juvenile forms by the adults, whereas otherwise the embryos of descendants would be expected to recapitulate the evolutionary stages of their ancestors occupied as adults.

The inference that the earlier the embryonic stage, the more remote the adult ancestor, implying that evolutionary novelties were added only to the end stage of development need not follow. In many spatial morphologies, the adult descendant resembles a young ancestor by retardation of development, retention of the ancestral juvenile features, while the ancestor's adult stage is discarded and a new adult stage is developed [76]. In this sense, paedomorphosis has been used to account for a successful development of humans from juvenile, not old apes [76; cf. 77]. Paedomorphosis thus means that evolutionary changes that lead to the next step take place during the early stages of development. Current focus on variability at the meeting reviewed herein is also figuratively paedomorphic, insofar as it continues in the footsteps of the relatively young Claude Bernard [78], who called the "extreme *variability*" of the internal environment one of his two major discoveries, rather than embracing the *constancy* imagined by Bernard at the end of his career [79, 80].

In view of this evidence, as P.B. Medawar [73], echoed by others [74], put it, "Haeckel is still the hero, though his portrait hangs upside down". This status quo leads McNamara in any event to posit that changes in early development are the link between Mendelian genetics and Darwinian survival of the fittest [75]. The debated status of morphologic "recapitulation" is beyond our scope herein, as is paedomorphism. Pertinently, Haeckel's heterochrony has been qualified in a chronobiologic perspective as heterochronomy [80], which adds a temporal dimension to a look at the early ontogenetic stages, in an attempt to decipher the hierarchy of evolution [77]. In a temporal morphology, i.e., in chronomes, about 7-day cycles, circaseptans, and the ~10.5-year cycles, the circadecennians, are evident early in phylogeny in bacteria and in a unicell [21, 81, see also 82] and late as well as early in human ontogeny [2, 83-86].

Hundreds of human babies undergo a larger extent of change in many circulatory or respiratory variables every week than they do every 24 hours [2, 83-86]. Insofar as data are available, a similarly large extent of about-weekly than about-daily change is found in piglets [87], in weanling rats [88], in early stages of a crayfish [89], as in the electrical potential of a giant unicell placed into continuous light [21] or in bacteria [2, 20]. A putative cosmo-helio-geophysical circaseptan signature, along with that of half-a-year [22] and about 10.5- and about 21-year cycles can have a larger amplitude than the spectrally adjacent about-daily or about-yearly component. The meeting's summary aligns the obviously rhythmic photic effects of the sun, relating to changes from day to night and from winter to summer, as the biological signatures of the day and the year, with the invisible but not less important non-photic effects in biota, from the sun and perhaps from beyond, from galactic cosmic rays, which magnetic storms displace [7].

Circadecennians (about 10.5-year cycles) accumulate rapidly

At this meeting, we also learned that human motivation may indirectly or directly be drastically influenced by the solar cycle [30], insofar as religious proselytism exhibits a circadecennian cycle, whether one analyzes the hours per day spent for the faith or success in outcome, as the number of baptisms, over several decades. As at earlier meetings [90-97], the school of Miroslav Mikulecký (Emeritus Professor and Head, 1st Medical Clinic, Faculty Hospital, Comenius University, Bratislava, Slovakia) excelled at this meeting. He and the late Boris A. Nikityuk [18, 98, 99] were missed in Tokyo, as were Terukazu Kawasaki and Teruo Omae. Earlier, Mikulecký had shown that even human productivity, represented by titles in Medline and by citations [90], undergoes an about 10-year cycle, and reaffirmed this finding, extending it to various helminthiases and other pathological conditions [97]. A circadecennian in publications citing the term "circadian" [19], proposed half a century earlier and published over 40 years ago [100], was also reported.


Miroslav Mikulecký

Ladislav Dérer

Franz Halberg

There was also a psychophysiological report on vascular mechanisms underlying mood [101]. Statistically significant cross-spectral coherence between human heart rate and blood pressure monitored mostly at 30-min intervals for well over a decade was presented [16], while circadecennians in several physiological and psychological variables, including mood, measured about 5 times a day for well over 3 decades had been published earlier

[7; cf. 17]. Pathology-related about 10.5- and 21-year biological maps presented earlier [53, 55] will have to be extended from single cases to systematic longitudinal lifetime studies in different geographic and geomagnetic locations on humans and selected other test organisms, including bacteria [20]. Genetic changes, such as mutations, could be recorded at minimal cost worldwide, on control cultures maintained for routine tests of sensitivity to antibiotics [20]. The chronome-ecologic study (ICEHRV) now involves monitoring in China, the Czech Republic, India, Italy, Japan, arctic Norway, Ukraine, and three locations in the USA. It will have to be extended to both hemispheres, i.a., to attempt to distinguish the relative roles played by planetary vs. extraplanetary variables in associations with biota by investigating whether, or to what extent there are interhemispheric similarities and differences.

Instrumentation and standards

Currently available instruments for physiological monitoring can be made less obtrusive. A "chronobra"—a brassière with built-in temperature sensors [102]—and sensors for exploring cardiac function incorporated into underwear were mentioned. Such sensors are needed both to facilitate the acquisition of physiological information for preventive health care and for basic ecology. This symposium further emphasized the opportunity for recognizing a very high risk of a stroke or other catastrophic disease by virtue of an above-threshold variability in blood pressure and/or a below-threshold variability in heart rate [53, 103] that must be diagnosed in the light of sex and age-specified reference standards [104-109]. This variability leads to a new kind of timely as well as timed intervention, aimed at lowering an asymptomatically elevated disease risk in the seemingly well person who may pass all tests as an astronaut candidate. A chronotherapy for prehabilitation may save much of the cost and may overcome the limitations to rehabilitation (e.g., after a massive stroke) that may be much more difficult to implement in extraterrestrial space. Endocrine presentations were also given at this meeting, bearing on the chronobiology of leptin [110; cf. 111] and melatonin [112, 113] extensively discussed from the viewpoint of geomagnetics elsewhere [114, 115].


Daniel G. Wall


Kuniaki Otsuka


Kaname Yamamoto

The opportunity of recognizing disease risk syndromes [116] was embraced at another mini-satellite meeting organized by Kuniaki Otsuka with Mayor Kaname Yamamoto of Urausu, Hokkaido, Japan, following one with Mayor Stefano Cimicchi, of Orvieto, Italy, about two months earlier at a conference on urban planning. Both Yamamoto and Cimicchi embraced a plan made by Daniel G. Wall during his term as mayor of Roseville, Minnesota, USA. The views of Wall and some of us, interviewed earlier in Minnesota by a Japanese video team, were published in an addendum to the proceedings [117]. Focus upon monitoring as a public service was started by Roseville's purchase of monitoring instruments [118]. Coordinated systematic physical environmental monitoring in practice is a concern for many. As noted at the outset, it serves cosmic, solar and earth physics, using endpoints from biota as sensitive tools or discriminants of effects, if, as seems possible but is not proved, one parameter of a unicellular alga should "respond" to geomagnetics, gauged by Kp, while during the same span another parameter of the same alga may "respond" to solar activity gauged by Wolf's relative sunspot number (WN) [81]. It seems particularly exciting that three variables of this alga released into continuous light have circaseptan periods around 162 hours and may exhibit differences in phase providing further evidence for the built-in nature of more than the circadian component of chronomes. Monitoring vital functions for prehabilitation serves everybody, physicist or physician, or any other individual, who needs to dispense with the equivalent of going to a scribe to write a letter, i.e., to go to a health care provider to take blood pressure readings [118, 119].

The meetings in Tokyo and Urausu and earlier in Orvieto and Minnesota united physicians concerned with chronotherapy; scholars focusing on centenarians; pharmacologists experimenting in microgravity; and still others in a budding chronoastrobiology, while a geophysicist, Yohsuke Kamide of Nagoya, blessed the magnetosphere for shielding us:

> A hundred kilometers above the Earth's surface the atmosphere gradually ends. Our Earth, with its relatively thin layer of the atmosphere, is a giant magnet as well. The Earth resides in a vast cavity called the magnetosphere. This cavity is created by the interaction between the solar wind, a gas of charged particles flowing continuously from the Sun, and the Earth's magnetic field. Our primary interest lies in quantitatively understanding the energy flow from the Sun to the Earth's neutral atmosphere and its transformation along the way. [120]

Those caring for the elderly should realize that in advanced age, the very great jeopardy of an excessive blood pressure variability is doubled by a co-existent deficiency in heart rate variability [121]; the risk is further enlarged when superposed upon an already elevated age-dependent risk situation. The association with a magnetic storm in itself or indirectly may then become the proverbial straw that perhaps breaks the strongest camel's back [7]. For those concerned with extraterrestrial space exploration [53] in particular, there looms the very realistic threat of a biologic equivalent of the Challenger disaster, notably since the effect of magnetic storms can be demonstrated in healthy cosmonauts [37]. When a mission with travel to regions away from hospitals is involved, a massive stroke suffered by a member of a crew could have grave and costly consequences.

There is the further opportunity of a spin-off for everybody from developing the wherewithal to recognize and treat risks that are not associated with a deviation of measurements outside the physiological range. Within our everyday physiology lie effects associated with environmental features that raise the questions whether magnetism is essential to life, as is water [23], and whether

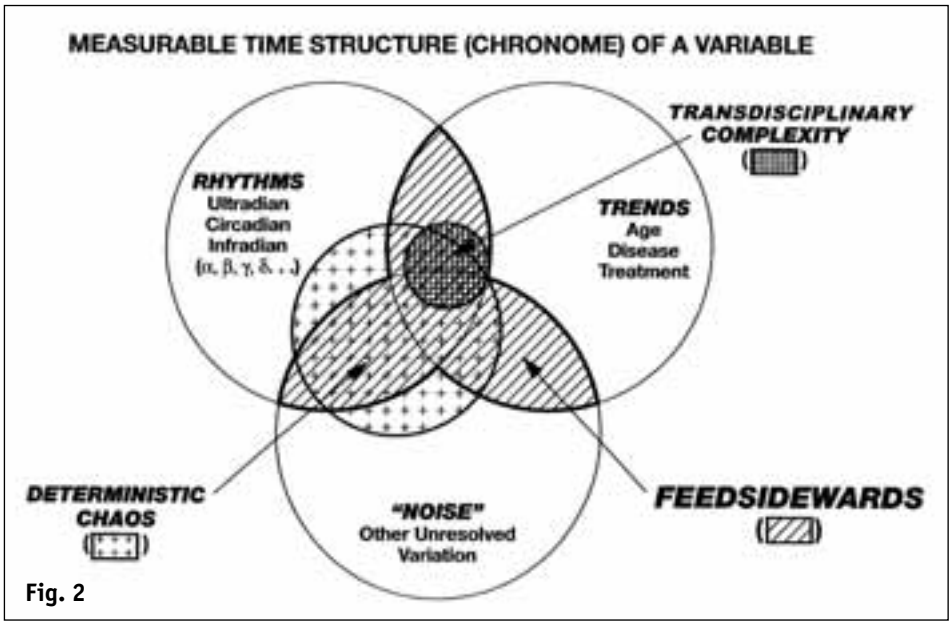


Fig. 2. Transdisciplinary complexity and feedsidewards may be found at the crossroads between several chronome components, notably multifrequency rhythms, deterministic chaos and trends. More and more components in the spectrum of physiological variation are found to have numerical physical environmental counterparts and, vice versa, for known environmental cycles, some unusual physiological counterparts (see Figure 3, top right) have been found. Cycles believed to be purely societal, such as the week, have environmental counterparts, and the geophysical half-year has its biological near-match. The components of physical or biological spectra organize irregular chaotic and complex variations and trends in endpoints of rhythms and chaos and constitute the more and more complex time structures, or chronomes.

myocardial infarctions or strokes are but pathological extemes in a dose-response curve that affects physiological growth [7, 98] and leaves its signature more in neonatal length than in neonatal weight, doing so with statistical significance in Minnesota, Denmark, Russia and Kazakhstan. A relatively minor investment into properly recorded and coded archives of human natality, morbidity, and mortality can yield ample returns. Transdisciplinary socio-psycho-physiological and medical monitoring is desirable at all levels. It can only be anticipated that governmental agencies will follow the initiative of mayors who advocate, along with clean air, clean water, and clean and safe streets, also preventive provisions for a safe circulation. Toward this aim, physiological monitoring can contribute to a timely chronotherapy with now available drugs [103, 116] and thus to the maintenance of mobility and independence for everybody, for the elderly in particular, as well as for those on extraterrestrial missions.

Pre-habilitation involves much more than circadian rhythm assessment for the recognition of vascular disease risk. Chronome mapping, like genome mapping, is more complex than the study of rhythms in RNA or DNA [122]

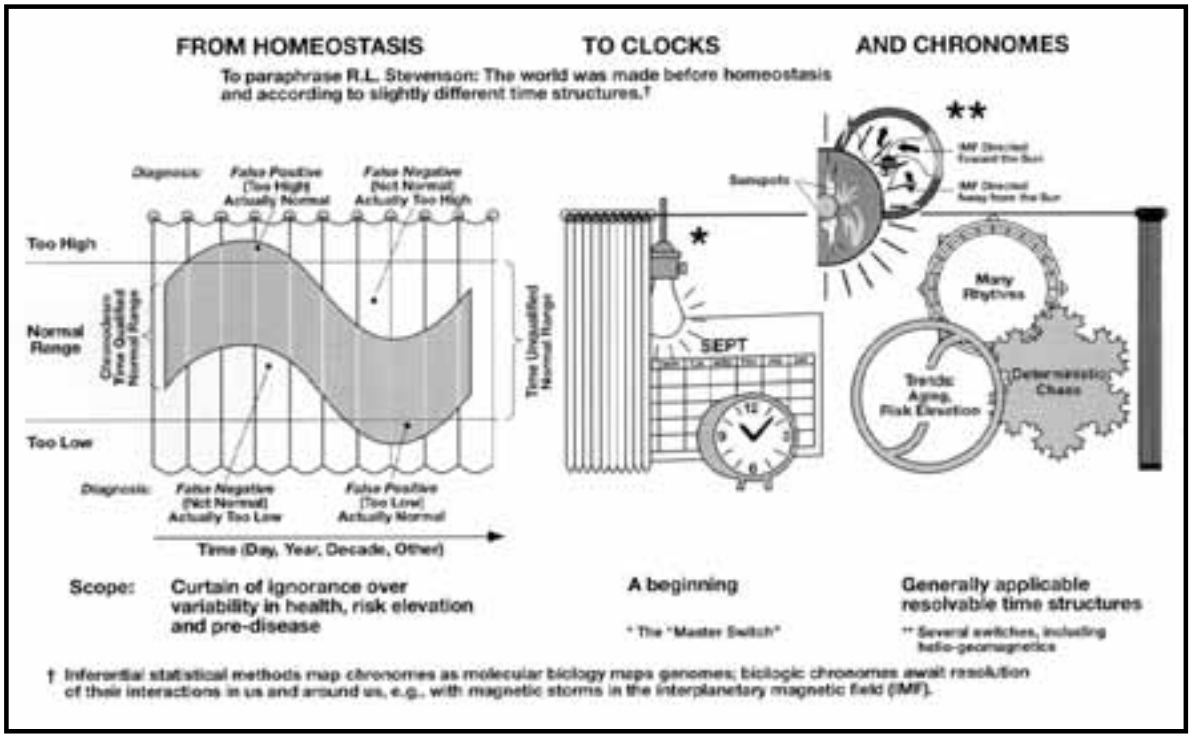


Fig. 3. Circadian systems and circannual calendars are important popularizing beginnings of chronobiology if it is realized that the cell need not be renamed a "clock" and that time structures are still broader concepts that supersede an imaginary homeostasis and constitute steps on the road toward recognizing much more complex chronomes that cannot be simplified further, without a great loss of information. Disease risk syndromes may be left unrecognized unless chronomes are resolved; and so are effects of the cosmos, that relate to amplitudes, which may be neglected in exclusive focus upon biological time measurement. Hypothesis testing and parameter estimation are essential steps to map broad time structures (chronomes) that yield more complete information than clocks and calendars in assessing partly lawful (rather than completely random) variation, that takes place within the physiological range, that in turn requires specification in time and further resolution.

but that beginning [2] can be pursued by proper mapping in an invaluable subsequent molecular biology [123-125], complemented by chronomes at all levels of organization. The integrative complement to reductionism, as the symposium showed, followed the lead of Teruo Omae and Terukazu Kawasaki in international physiological and psychological monitoring for disease risk assessment [36]. This endeavor can be coordinated with physical environmental focus and the development of appropriate instrumentation. Technology transfer from laboratory animals to ambulatory humans is a task on hand, critical for astronauts and for a budding chronoastrobiology and equally desirable for a chronomedicine of risk recognition and timely as well as timed treatment.

It was a pleasure to award (Halberg) prizes to two of the speakers, one of whom started long-term automatic around-the-clock surveillance of blood pressure and heart rate, of targetted collections of samples for the determination of hormones such as melatonin and cortisol, e.g., in saliva, and the recording and comparison of tests of positive and negative affect and cheerfulness, among others [101]. The other, we trust, will continue to work on timing exercise, such as walking [126, 127]. When situations such as exposure to a white coat have opposite effects, as a function of a circadian rhythm, so that white-coat hypertension is noted in the morning and white-coat hypotension is noted in the afternoon [116], timing should be indispensable in any transdisciplinary endeavor involving biomedicine.

The study of periodicities in physics was for long deemed unprofitable. As far back as 1675, Isaac Newton first demonstrated optical periodicity when he discovered the concentric colored rings named after him in the thin film of air between a lens and a flat sheet of glass, with the inter-ring distance depending on the thickness of the air film. Apparently he did not follow-up on this discovery. Serious pursuit of physical periodicity waited until 1843, when the transdisciplinary pharmacist and amateur astronomer Samuel Heinrich Schwabe reported the about 10.5-year cycle bearing his name. The November 2000 meeting in Tokyo vindicated Schwabe for reporting what Galileo and Newton, who had telescopes over 2 centuries before Schwabe, had missed.

For physicists, we now propose that organisms can complement their telescopes and other purely mechanical armamentarium. From bacteria to humans, living matter constitutes a sensitive combination of barometers and magnetometers and broadly radiation detectors, whether or not the many associations in biota with solar activity, several of them repeatedly confirmed, are clarified as to their underlying mechanisms. This transdisciplinary complexity, Figure 2, must be kept in mind in the transition from a chronome-unqualified and thus neglected normal range, first to biological daily and yearly time measurements, as clocks and calendars. These have served to popularize the field by intuition and by data inspection, but require inferential statistical methods to clarify the relative contributions and interactions among chronomes in us and around us, Figure 3 [1, 2]. We must refrain from oversimplification if our purpose is to deal with variability in its own right, as is done by clocks or calendars in a putative imaginary homeostasis. The clock concept is no substitute for the resolution of all components of variation with hypothesis testing and parameter estimation. Such procedures become even more critical when we deal, in data that are dense and long enough, with time structures that also have deterministic and other aspects of chaos and undergo trends, Figure 3.

Chronome maps are needed for biological and natural physical environmental data, in order to resolve a transdisciplinary chronobiocomplexity. Here, "chrono" is not one-upmanship, but an interpretation of facts relating to disciplines ranging from morphology, dealing with body length [18], to physiology, dealing with heart rate variability [7, 14, 53], to psychology, dealing with mood [7], to motivation, dealing with religious proselytism [14], and to productivity, dealing with the accumulation of scientific

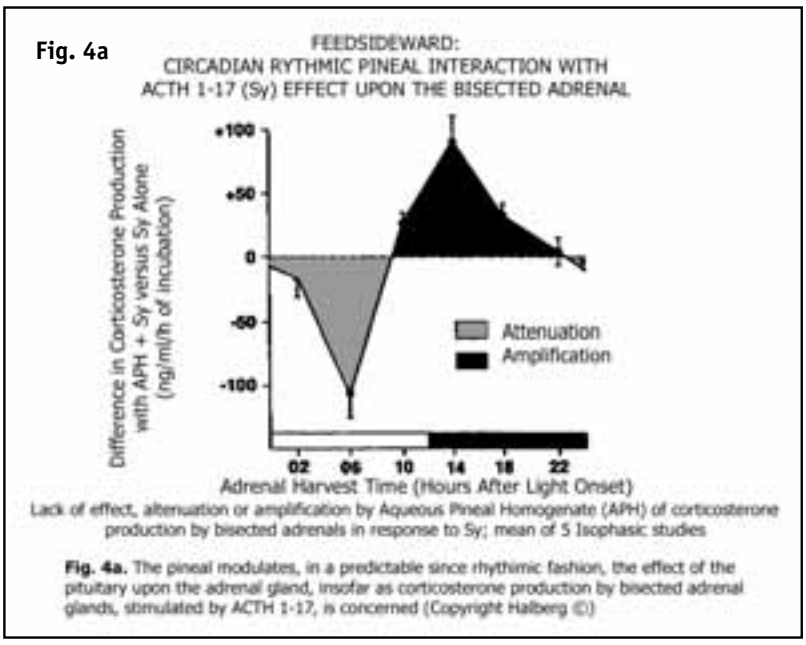
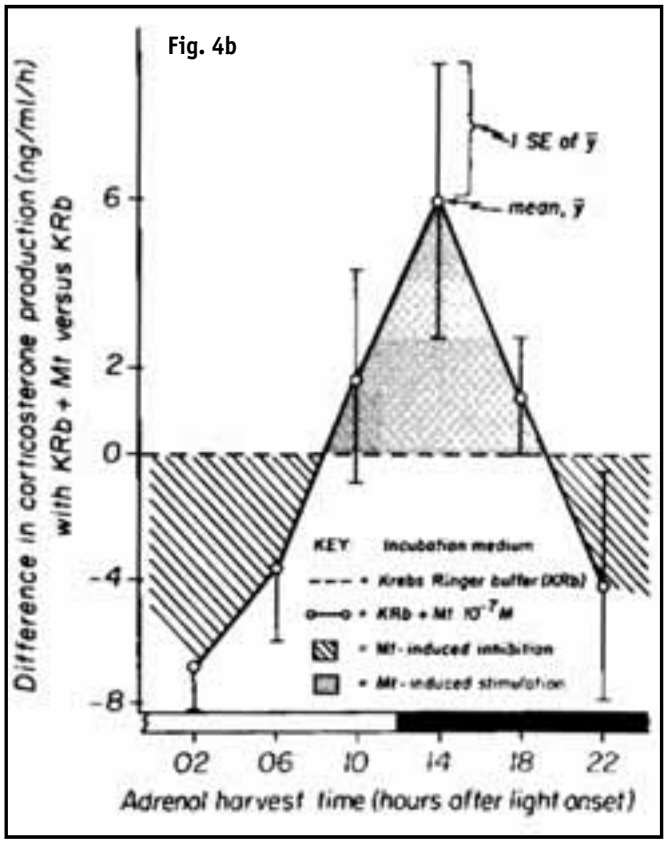
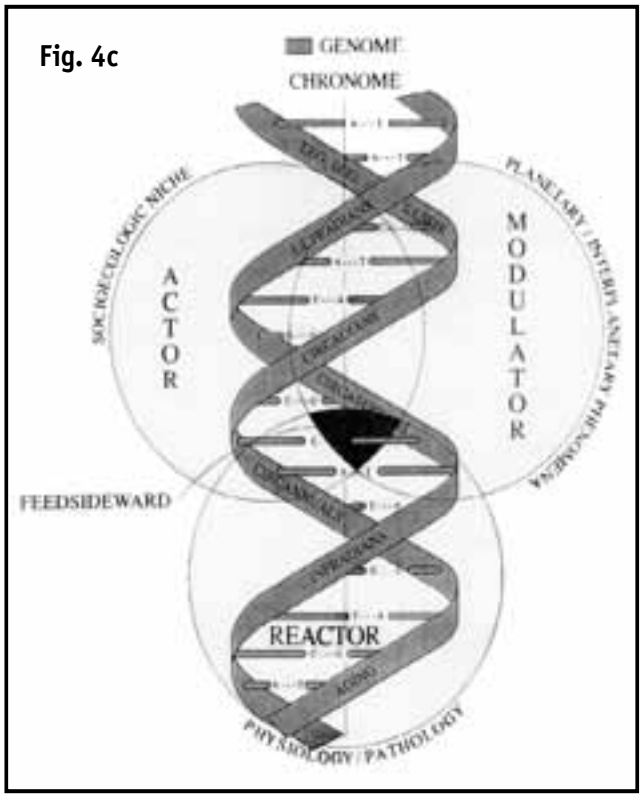
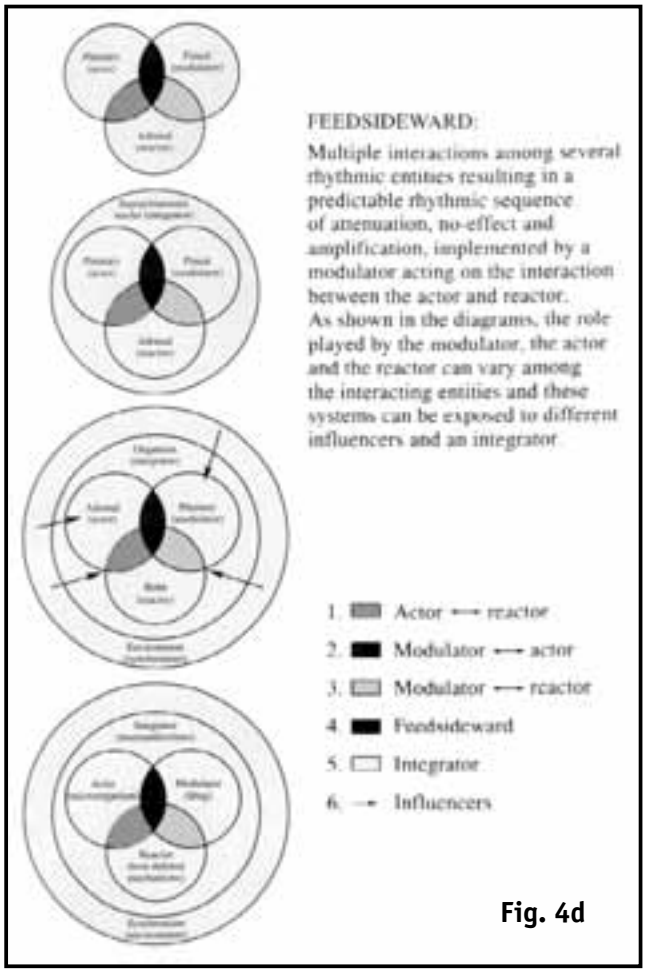


Fig. 4. The pineal, via the pituitary (**a**) or directly (**b**) upon the adrenal, can stimulate corticosterone production, can leave it unaffected or can inhibit it, the effect being circadian periodic and to that extent predictable. (**c**) Chronomodulation at different levels, interplanetary solar and galactic factors (top right) are conceived as modulating socio-ecological conditions in the habitat (top left), acting upon the healthy or sick organism as a whole. (**d**) Feedsidewards relating to the chronomodulation by the pineal of the action of the pituitary on the adrenals are summarized on top. Those in the second diagram from the top refer to the effect of the suprachiasmatic nuclei (SCN) on the circadian amplitude and acrophase. The finding of a lacking circadian rhythm (by





the failure to reject the zero-amplitude assumption) is the result of SCN removal in the case of locomotor activity and water drinking but not in a vast majority of other rhythms for variables sampled at 4-hour or shorter intervals for 24-hour or longer spans, and analyzed by inferential statistical means. The third diagram from the top refers to the chronomodulation of the effect of ACTH 1-17 upon metaphyseal DNA labelling in the rat (where stimulation is found at one time, inhibition at another time, and stimulation preceded by inhibition or inhibition preceded by stimulation at two other times, all in the same post-treatment time span investigated, depending only on the circadian administration time). Intermodulations in the case of an invading micro-organism of sufficient virulence to elicit a host response are sketched at the bottom. Feedsidewards can be found at different levels, not only at the level of the cell (e.g., DNA labelling of metaphyseal bone) or of endocrines, but also at the level of the organism as a whole (when both photic and non-photic solar effects modulate human circulating melatonin along the scale of the year) and at the level of the cosmos (when heliogeomagnetics and/or galactic cosmic rays are observed to affect heart rate variability and the incidence of myocardial infarctions, strokes, and suicides). Feedsidewards, including about 10.5-year modulations reminiscent of the solar activity cycle, concern not only physiology and pathology, but also morphology, psychology, productivity, and other aspects of sociology. Feedsidewards are defined as multiple interactions among several rhythmic entities resulting in a predictable rhythmic sequence of quantitatively and even qualitatively changing effects. These can include differences between an effect and no effect, and even rhythmic alterations of attenuation, no effect, and amplification. Such opposite changes may be implemented by a modulator in a three-entity system acting on the interaction between an actor and a reactor, or they may occur simply between an actor and a reactor, e.g., in the case of the pineal-pituitary-adrenal or of the pineal-adrenal systems, respectively. As shown in the diagrams, the role played by the modulator, the actor, and the reactor can vary among the interacting entities, and these systems can be exposed to different influences and an integrator. ■ actor ⊂ reactor; ■ modulator ⊂ actor; ■ modulator ⊂ reactor; in systems of increasing complexity from the cell to the cosmos, ■ feedsideward; □ integrator; □ influencers.



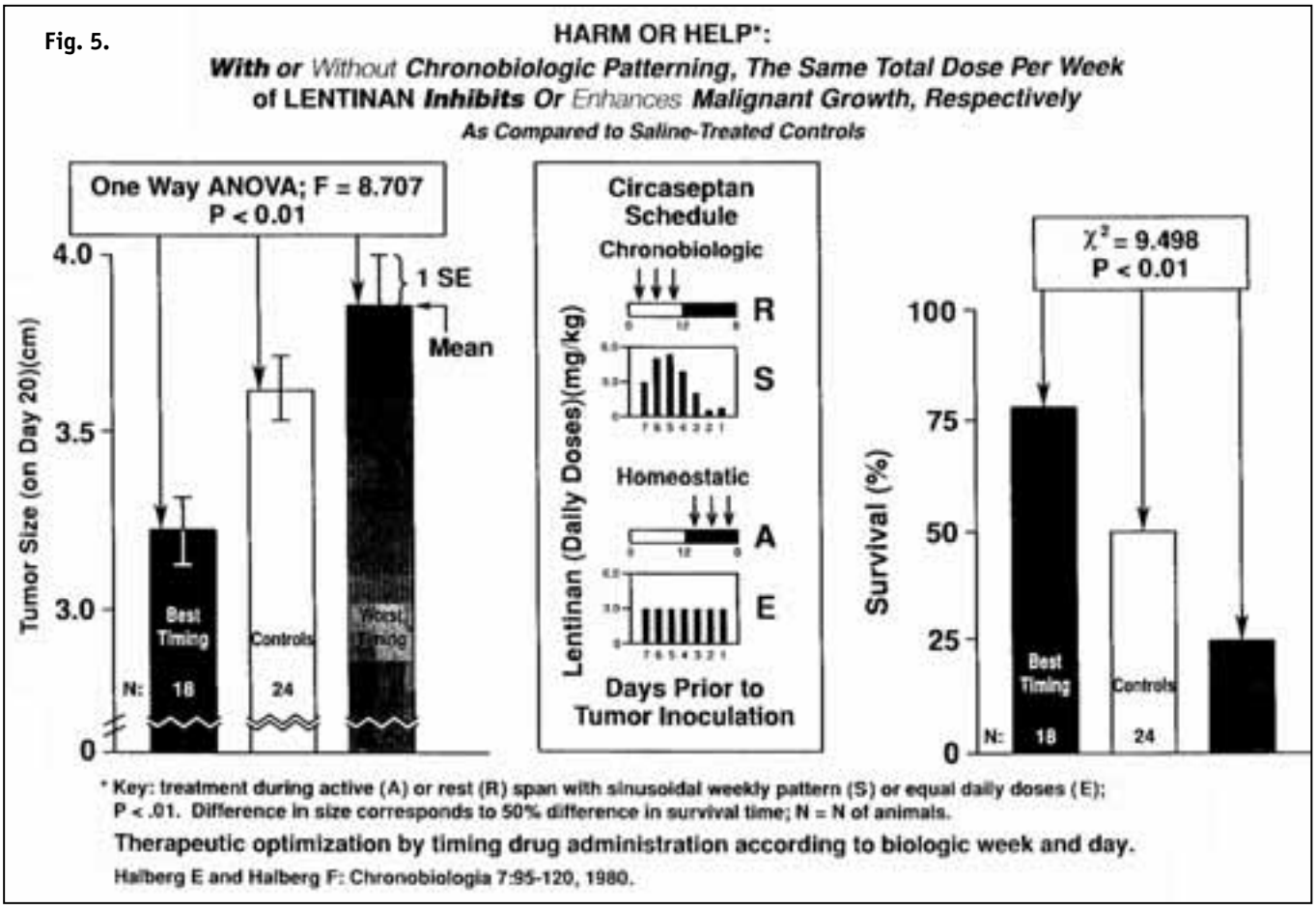


Fig. 5. Evidence documenting the need to consider circaseptan as well as circadian components for the optimization of drug administration patterns stem from studies on the immunomodulation of malignant growth. Rats bearing an immunocytoma were kept on a schedule of light (L) and darkness (D) alternating at 12-hour intervals (LD12:12); the effect of a 7-day pre-treatment with lentinan (Rx) was compared to that of pre-treatment with saline (S): the growth of the malignant tumor was inhibited and survival time was lengthened when this immunomodulator was administered daily during L, the rat's resting span, in doses varying sinusoidally from day to day as a circadian-circaseptan chronotherapy (Chr); the rest span, however, is not the usual treatment time for humans, and a systematic sinusoidal variation of doses from day to day also is not the standard practice. When treatment was given (as would be convenient for humans) during the rat's usual activity span (D) according to the habitual equal daily doses (of many conventional human treatment schedules), i.e., homeostatically (H), tumor growth was accelerated and survival shortened.

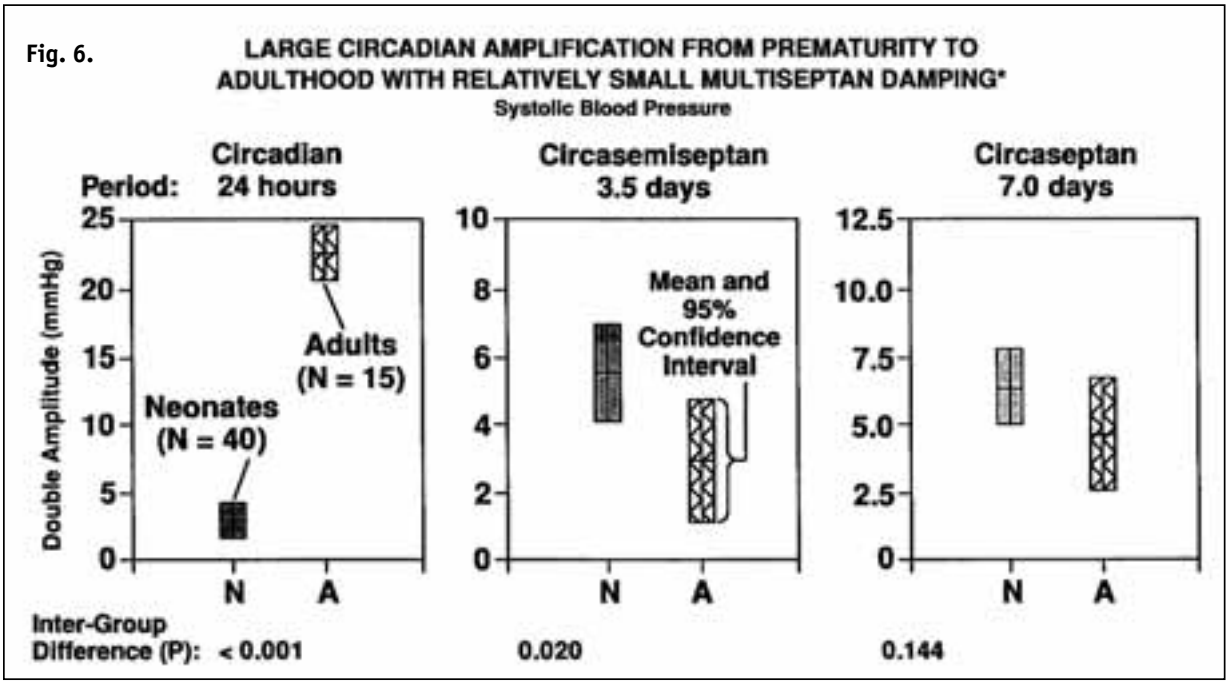
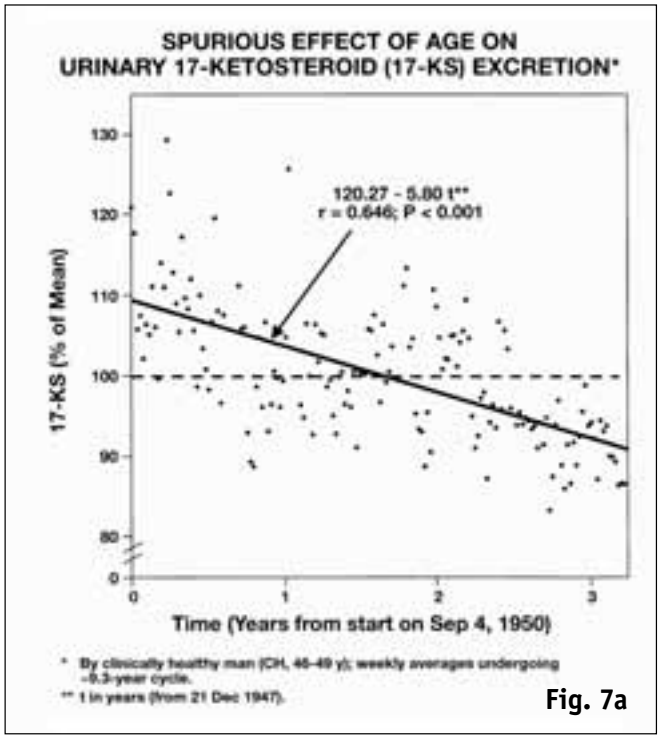
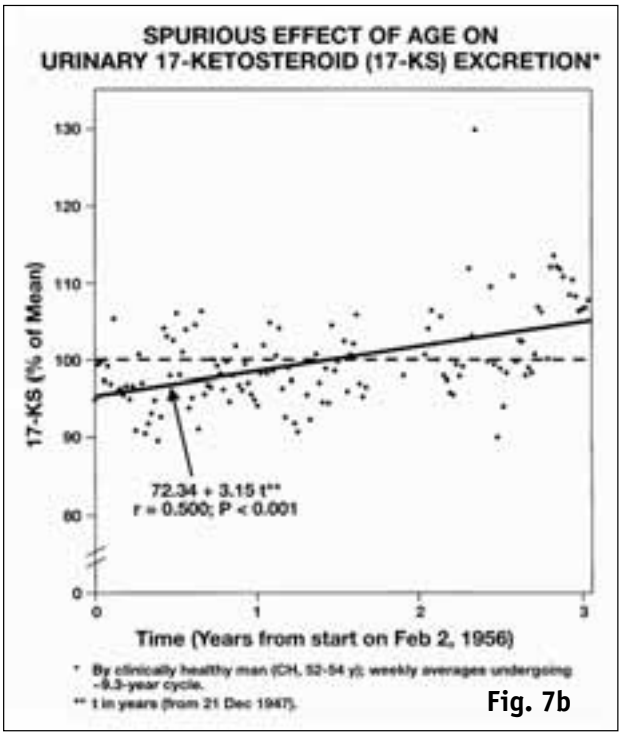


Fig. 6. In human neonatal blood pressure and heart rate, multiseptans, such as the circasemiseptan and circaseptan components, are more prominent than circadians.





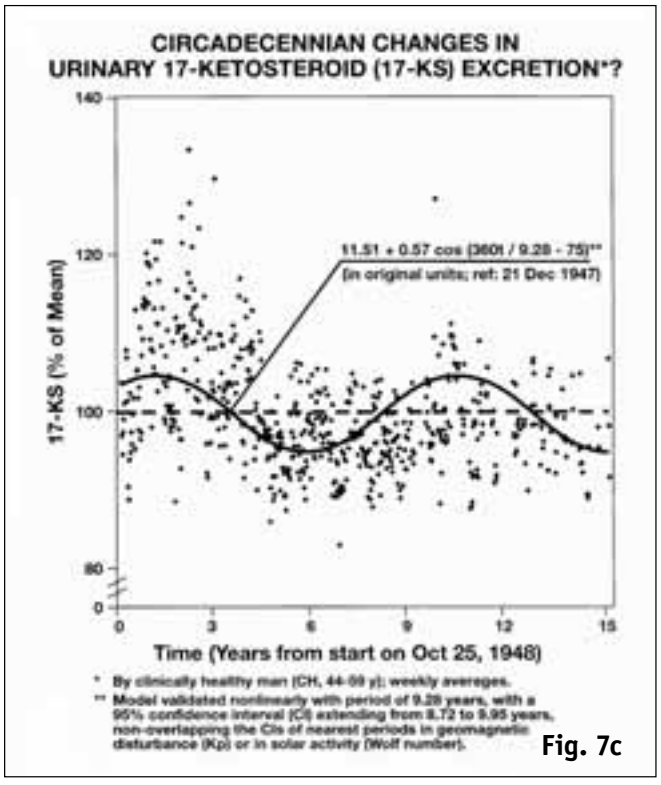


Fig. 7. (**a**) Plausible inference of biochemically and statistically highly accelerated aging supported by a decrease in steroidal breakdown products excreted by a subject in his forties, at variance, however, with his seemingly good health until his eighties and his data in 7b and 7c. Inference justified only by the unawareness of an underlying cycle. (**b**) A controversy could arise if the data of this figure were collected on another subject and were (mis)interpreted as an increase with age in 17-ketosteroid excretion, in marked contrast to the interpretation of Fig. 7a. (**c**) A biological near-match, at least numerically, of the ~10-year or circadecennian solar activity cycle resolves the problems encountered in Figs. 7a and b.

literature [14], all of which show signatures of Schwabe or Hale cycles.

Gauss is reputed to have said that "when a philosopher says something which is true, then it is trivial. When he says something that is not trivial, then it is false" [128]. (If he indeed made this statement, this may be his second mistake, in addition to that of dismissing Niels Abel's proof of the insolubility of quintic equations.) For a synthesis of all the chronobiocomplexity data, we are indebted to the philosopher Herbert Hörz. In a book on time, Hörz [129] extends Jan Christiaan Smuts' holism [130] to entities in time, writing about system times, e.g., sufficiently replicated 24-hour profiles, in dealing with circadian systems, in a broader horizon for action, in the sense of great and greater temporal wholes in time, in the still bigger whole of a multiverse with its cosmoi. At the level of DNA labelling in the cell, or in neuroendocrine interactions, or in the effect of photic vs. non-photic environmental stimuli on the pineal, we find an integrated, if not holistic, but still mechanistically, i.e., experimentally testable interdisciplinary relation. Thus, we benefit from the line of thought expressed by Smuts [130] and Hörz [129], both in philosophical terms. We only substitute ever more detailed, broader and broader chronomes to provide, in addition to the system time of Hörz chosen for a given study, spotchecks of longer time scales chosen to explore already mapped time structures.

Our dictum "Measure what is measurable and render measurable, *meaningfully in time,* what as yet is not" has stumbled first on feedsidewards, Figure 4 [2, 62, 131]. With Salvador Sanchez de la Peña, we found in a series of 11 experiments, each with 6 timepoints, that the pineal acts, circadian and circaseptan periodically, via the pituitary or directly upon the adrenal. It can stimulate corticosterone production in vitro, leave it unaffected, or inhibit it these effects recurring rhythmically and to that extent predictably [132, 133]. Next, we found the effect of the pituitary (ACTH 1-17) upon DNA labelling [134]. The

adrenal incubation studies were also extended to document the stimulation-no effect-inhibition sequence along the circaseptan scale [133]. All these observations were made in the absence of effects from dynamics of the circulation and of the central nervous system, other than those prevailing at the moment of tissue harvest. The mapping of feedsidewards, among chronomes, as a general indispensable method, reveals a transdisciplinary chronobiocomplexity that accounts for phenomena that were labeled modulation in the trivial sense (i.e., that results may be statistically significant, but may occur in either direction, occur in either direction, an unpredictable homeostatic "modulation", based on temporally unqualified feedbacks or feedforwards). The feedsideward reveals chronomodulation, to predict when one enhances and when one inhibits, e.g., a cancer, Figure 5 [135].

In another instance, at middle latitudes, the half-yearly (non-photic) geomagnetic signature in human circulating melatonin may be found in nightly data, whereas the photic year predominates in data on human circulating melatonin collected during the daily light span. The half-year may regularly predominate in the auroral oval during the daily light span as well [114]. Until continuous monitoring instruments become available, at least the inclusion of circaseptan considerations may be clinically important for some variables. With monitoring available, the half-yearly, yearly and infra-annual variations will also have to be considered.

The past half-century has documented the ubiquity, critical importance, and genetic coding of circadians. With about-yearly changes, these are visible effects from the sun, photic ones. The past decade has thoroughly documented the ubiquity and critical importance of non-photic physical environmental effects, notably those of 10.5- and 21-year Schwabe and Hale cycles. The about 7-day (circaseptan) cycles as well have a geophysical counterpart [9]. Figure 5 shows that the circaseptan pattern of a drug administration can transform a drug that stimulates malignant growth, when it is given in equal daily doses (right), into one that inhibits an immunocytoma (left), the distinction being derived from taking an about-weekly change into account [135]. In the early stages of life, the circaseptan amplitude is much greater than that of the circadian rhythm [85], phylogenetically as well as ontogenetically, as shown from Minnesota, Figure 6, and worldwide for human newborns [86] and also for pigs [87], rats [88], crabs [89] and for some variables of eukaryotic unicells released into continuous light [83], Figure 1.

When data over several solar activity cycles are analyzed, controversies are largely resolved and excess mortality from myocardial infarction stands out at the time of solar maximum [53]. The story of circadian susceptibility rhythms as just the tip of the very broad circadian system finds its counterpart in a circadecennian system, among other cycles that correspond to non-photic natural environmental effects from the sun and/or the galaxies. The accumulated evidence shows the ubiquity of circadecennians, on societal productivity, gauged by the number of scientific citations; in motivation, such as religious proselytism; in psychology, such as in mood [17]; and in physiology, such as in heart rate variability [14]. Human morphology, such as neonatal anthropometry, may reveal about 21-year cycles [18], with an amplitude sometimes larger than the clearly photic association of the same variable with the yearly cycle [14; see also 136]. The associations are further supported, beyond the hints of similar periods or correlations, by less unspecific cross-spectral coherences [7, 53] and, like in endocrinology, by remove-and-replace approaches [53], when, for instance, the sun instead of the surgeon does the removal and replacement of circaseptans in the solar wind. Controlled superposed epochs further attest to the associations [7, 53] of natural physical environmental factors, not only with human physiology or pathology, but even with probable genetic changes (sectoring) in bacteria.

Some of the population cycles, documented, for instance, by 112 years of data on neonatal body length and body weight [18], rest on large numbers of individuals, whose cycles in a majority of cases have to be in phase to yield these results. One can only speculate whether these cycles are also somehow coded in our genes. As to circadians, what may also be coded may be that very mechanism, perhaps the adrenal cortex as well as medulla, that when applied to the stimuli of daily life, brings about periodicities insofar as neuroendocrinology is concerned (Figure 4). The data on the ubiquity and broad scope of chronomes are accumulating, as the Tokyo meeting showed as its bottom line [14]. Non-photic effects from the environment interact with photic ones. Whenever they are cyclic, they become to that extent predictable. Whether we deal with heart rate variability or DNA, upon which geophysical disturbance may act directly, a hypothesis yet to be tested, the demonstrated facts of feedsidewards in these cases model more and more complex interactions that yield quantitatively and sometimes even qualitatively different results. The circadecennian charts just as the circaseptan ones need not be used for sampling in all clinical or experimental settings, whether or not the (systematic) sampling is restricted to circadian or shorter time scales. The maps of cycles and of the broader time structures are critical when one wants to distinguish the fading of virility from a mere transient stage in a circadecennian cycle in urinary 17-ketosteroid excretion [10], Figure 7.

Chronome charts are needed irrespective of the system time in which an action in biology or physics is to evolve or to be observed. In our interpretation of Herbert Hörz' "time-horizon", we need to broaden our perspective (his time-horizon) in planning and interpreting the data covering only a system time under investigation, to as many facts of the chronome as have been mapped, and many more will have to be recorded and analyzed on data extending beyond a few Hale cycles. Santorio had three decades of observations [27]. A current test pilot has 34 years of about 5 measurements on 11 variables [17]. Much denser and much longer time series are needed if we are to specify how the complexity of an organism constitutes more than the sum of its parts without resorting to vitalism or even to a purely philosophical holism. "Cogito ergo sum", attributed to Descartes, as tempting as it is, must not ignore the value of rigorous measurements, whether or not they are taken to answer specific

hypotheses. But data interpretation may well look at the spectra at hand in us and around us.

Endocrinologists of a past generation knew intuitively, but could not measure the *consensus partium,* i.e., the understanding of the parts. The study of chronomes does this task as a more complete expression for the integration of genomics and proteomics into larger and larger systems, rather than relying on the current, too-often single sample-based biology. The task of taking an entire evaluable time structure into account, including, when possible, its very broad spectrum of rhythms, seems complex and utopian at first, like the building of roads in an unknown terrain or the suggestion to take to the air, and it seems unlikely that an individual can undertake it. But in building highways, cars and airplanes to bridge distances, it must be kept in mind that once the roads and vehicles are available, they need not be built over and over again for each trip. Users may pay taxes, pay a toll or buy a ticket, and the monies so collected are used to maintain the roads or the aircraft. The mechanistic view introduced by Santorio into health care will have to account in scientific terms for rendering many transdisciplinary phenomena measurable in time and thus for resolving a transdisciplinary chronobiocomplexity, Figure 2. Those in charge of biocomplexity programs may feel like Molière's M. Jourdain: "Par ma foi! il y a plus de quarante ans que je dis de la prose *[chronobiology]* sans que j'en susse rien, et je vous suis le plus obligé du monde de m'avoir appris cela." The rhythmic occurrence of complex events tells us to what extent and when nature does or does not play dice in the very everyday physiology and psychology, everyday sociology and economics in which we spend most of our lives. Chronomes, but not biological clocks and calendars, lift the curtain of ignorance drawn over this range, so that we can recognize the need for truly preventive action, whether in our environment or in ourselves, and so that countermeasures can be instituted.

Sola chronomica perficiunt, inter alia, genetica—e.g., genomica et proteomica (Chronomics are an indispensable control, among other fields, for genetics—notably genomics and proteomics)

The general hypothesis underlying the meetings in Tokyo, Sapporo and Urausu, here considered is: chronomics are the critical complement i.a. of genetics; they resolve the dynamics of gene expression, subservient particularly to those who study genomics or proteomics. There is no other complete control for dynamic organisms than their spatio-temporal structure. Fundamental errors, like a putative homeostasis, must not lead to unavoidably great waste in genomics and proteomics, as long as the latter are based on the possible quicksand of single samples. Chronomics are an affordable approach, in keeping with available technology, which of course has to be developed further and steps toward this goal were discussed in Tokyo. It would be important for all to realize that there is no alternative for complex science, biologic or any other, than to map the dynamics, in us and around us, chronomics.

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