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CHALLENGES FROM "60 YEARS OF TRANSLATIONAL CHRONOBIOLOGY"

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SO WHAT? Health care could change from the current, mostly spotcheck-based approach ("flying blind" [1] between visits to a care provider's office) to a relatively inexpensive since largely self-implemented continuous surveillance. This paradox of "more for less" [2, 3] (Figure 1) could be aided by a website (Figure 2 and Appendix) that automatically analyzes and interprets data with the double purpose of the long-term health surveillance of the individual participant who plans to use it for a lifetime and of medical research serving for ever-improving health care, preventively recognizing (and lowering) high disease risks (Figure 3). As a dividend, basic transdisciplinary research on the accumulating database would find numerous applications. Notable among these aims is the implicit biologic monitoring of solar variability with focus on physical mechanisms underlying the physiology and pathology of individuals and of populations, including events such as criminality, suicide and sudden cardiac death (Figure 4) [4].

I. High blood pressure: diagnosis and treatment

For everyone in 2007, "exclusive reliance on office measurement should be discouraged" [5], as suggested in 1904 [6, cf. 4] and in the interim [6-9]. A timely and time structure-based (chronomic) diagnosis and treatment of high blood pressure, affecting as many as 50 million Americans, gain from (preferably but not necessarily [10] automatic) computer-aided selfsurveillance.

Thereby, we minimize false diagnoses, i.e., maximize the number of those brought to treatment who were previously false-negatively diagnosed (masked hypertension, [5]) and minimize those diagnosed false-positively (white-coat effect, [5]), while optimizing treatment in kind, dosing, and timing, as warranted based on the monitoring [11].

A combination of a time-structural or chronomic diagnosis and chronomically timed treatment (under frequent or preferably continuous surveillance, at least at therapy initiation) could benefit a very large segment of populations in areas like the USA where most families have computer-savvy members; where these are missing, support groups can be set up and data can be analyzed on a website, as they are now analyzed worldwide within the context of an international project on the BIOSphere and the COSmos (BIOCOS) (corne001@umn.edu) [12-15].

II. A vascular variability syndrome, starting in the physiological range: detection for stroke and other severe disease prevention

1) Vascular variability abnormalities (VVAs) involve, at their outset, circadian alterations in the normal range, detected by computer comparison with reference standards from age- and gender-matched peers. These are an overswing of blood pressure or CHAT (brief for circadian

**COST AND QUALITY TRADE-OFFS (LEFT)
OR UTILIZATION OF CHRONOBIOLOGIC CONCEPTS
FOR PREVENTIVE AS WELL AS CURATIVE
MEDICAL DEVICES (RIGHT)**

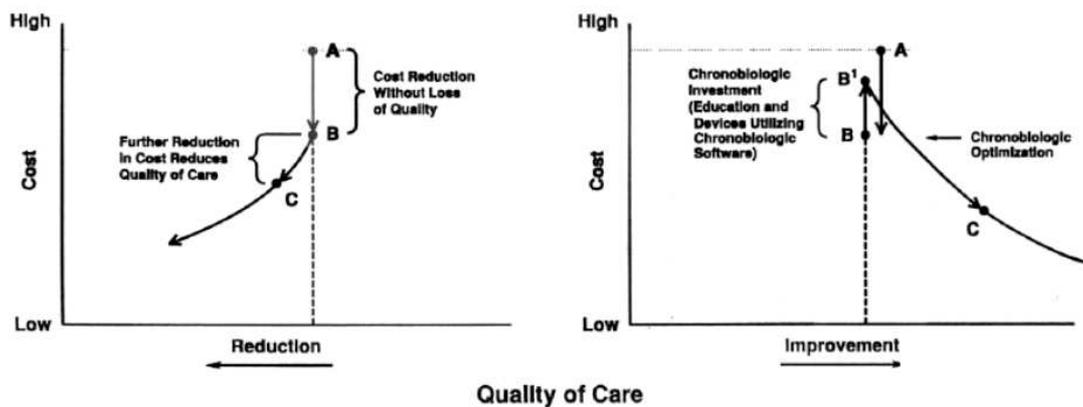


Fig. 1. Cost and quality trade-offs (left) or instrumented self-help (right) concerning blood pressure and its variability disorders, diagnosed and treated along with hypertension via a multipurpose website constituting the start of a biomedical recording system (cf. Figure 2). ©Halberg.

hyper-amplitude-tension), an above-threshold pulse pressure, an odd timing of the blood pressure but not of the heart rate rhythm and a deficient heart rate variability. These conditions, assessed by monitoring along the scale of a week, are associated with risks of ischemic stroke, myocardial infarction or nephropathy greater than the risk associated with a high blood pressure (Figure 3) [4] (Yet-to-be-recognized alterations of now-documented cycles of the length of a week, a year or decades, or of other mapped spectral components of intermediate lengths, are also documented to have signatures in human pathology, Figure 4 [4], their relatively small amplitude notwithstanding.)

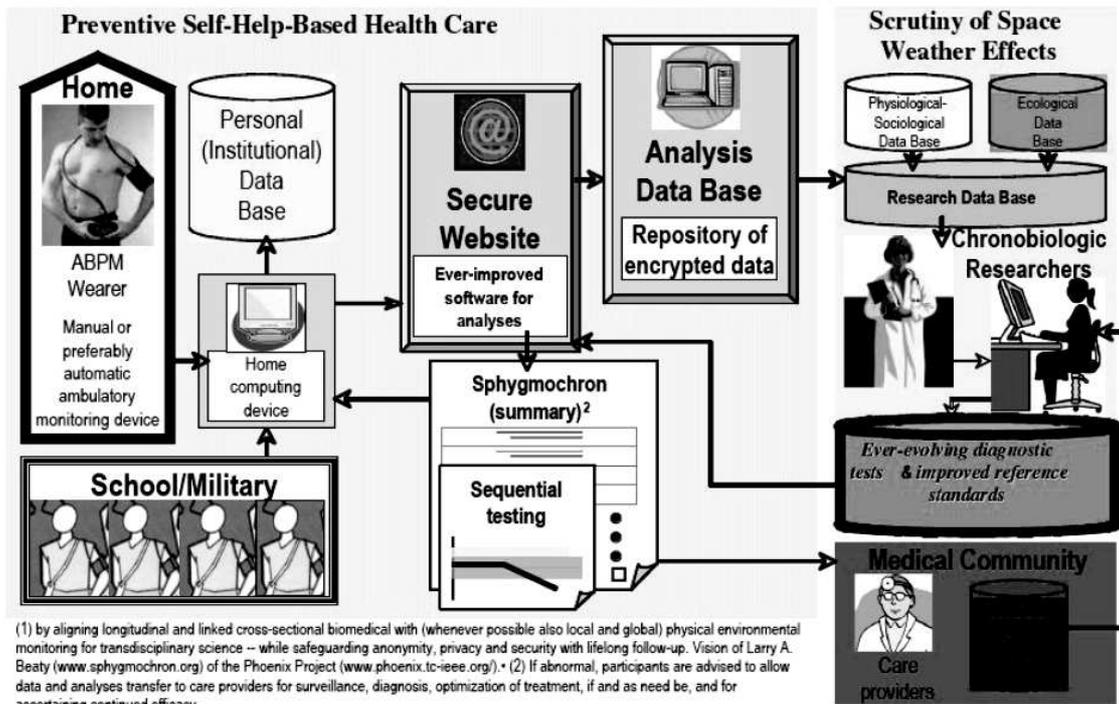
2) VVA-associated risks are also great in the absence of a high blood pressure [13; cf. 14,15].

3) Often these VVA-risks can be treated, sometimes by an intervention as simple as changing only the timing of treatment [13].

4) VVA-risks can be detected by comparing a given time series' variability structure with that of infradian-circadian reference standards obtained from presumably clinically healthy peers matched by age and gender. Day, night- and 24-hour mean values and their ratios constitute, not invariably [16], pertinent information. Sometimes the standard deviation discriminates better than the circadian amplitude, as in the case of a circadian-circaseptan deficiency in heart rate variability [13; cf. 4]; a chronomic combination of parametric and non-parametric endpoints is most useful for dealing with VVAs and also with hypertension on [9, 12, 13].

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Preventive and curative health care can yield the dividend of biomedical monitoring of space weather by time-structural analyses of ambulatory blood pressure and heart rate series ¹



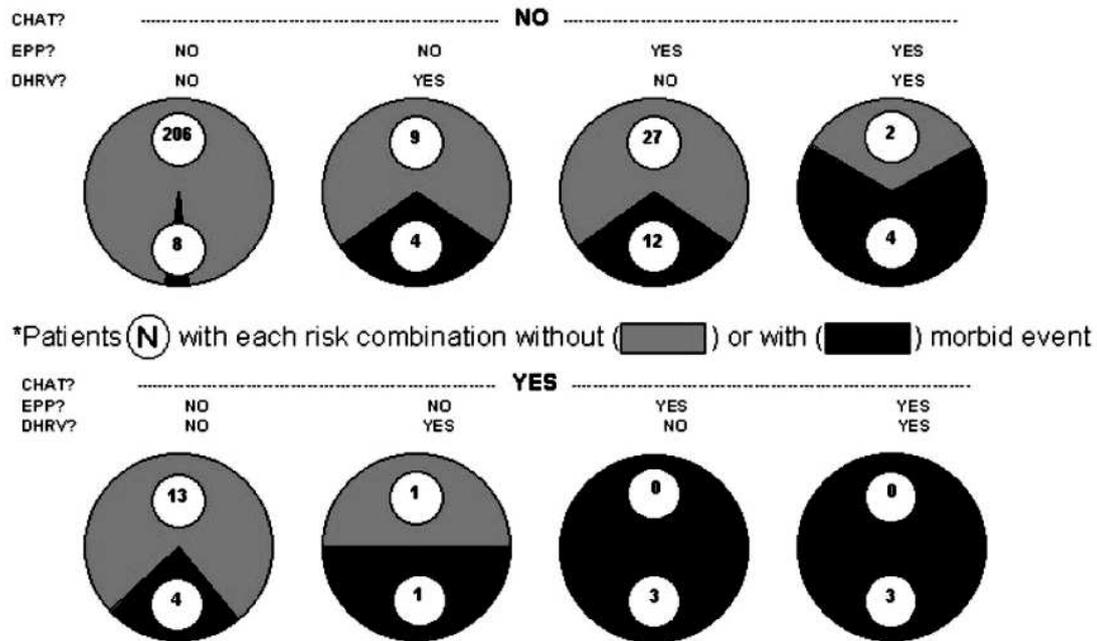
Modified from Figure 1 (Phoenix Architecture) in Adams C. Privacy requirements for low-cost chronomedical systems. Int Conf on the Frontiers of Biomedical Science: Chronobiology, Chengdu, China, September 24-26, 2006, p. 64-69.

Fig. 2. The Phoenix Group of volunteering electrical and electronic engineers from the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (<http://www.phoenix.tcieee.org>) is planning on developing an inexpensive, cuffless automatic monitor of blood pressure and on implementing the concept of a website (www.sphygmochron.org), described in the Appendix. © Halberg.

In exchange for a copy of the data and a promise of follow-up, as a minimum, with a yearly note on health status (and, as an optimum, by added data at intervals dependent upon results of monitoring for a lifetime):

- 5) Analyses are done free of charge at BIOCOS on data sent to corne001@umn.edu.
- 6) BIOCOS provides an opportunity to purchase automatic blood pressure and heart rate monitors for ambulatory use with an 80% reduction in cost of acquisition.
- 7) Soon a website will be freely available for all comers for such analyses, to lead to a chronomic diagnosis of risk elevation and its timely treatment, so that eventually the reference data base can be improved and new harbingers can be added to a refined diagnosis of elevated risk.
- 8) BIOCOS is already analyzing data sets with outcomes of hard events and/or proxy outcomes to compare the use of chronomic methods with that of conventional ones [16], and invites the submittal of data sets for more comparisons, notably on projects already completed that were government-supported.

Decreased Heart Rate Variability (DHRV), Circadian Hyper-Amplitude-Tension (CHAT) and Elevated Pulse Pressure (EPP) are Separate Cardiovascular Disease Risks*



*Results from 6-year prospective study on 297 (adding all Ns) patients classified by 3 risks (8 circles), supported by findings on total of 2,807 subjects for total of over 160,769 sets of blood pressure and heart rate measurements. Data from K Otsuka.

Fig. 3. Vascular variability disorders (VVAs): Circadian overswing or circadian hyperamplitude-tension (CHAT), decreased heart rate (HR) variability (HRV), an elevated pulse pressure (EPP) and an odd timing of the circadian rhythm of blood pressure (BP) (but not of HR, i.e., circadian ecpasia, not shown) are separate cardiovascular disease risks. CHAT is one of several conditions related to variability in the circulation that is associated with an increase in vascular disease risk. The circadian (or preferably circaseptan profile) with too large a pulse pressure (the difference between systolic [S] BP and diastolic [D] BP, i.e., between the heart's contraction or relaxation, or the extent of change in pressure during a cardiac cycle) and a decreased HR variability (gauged by the standard deviation of HR) in relation to a threshold, eventually derived from gender and age-matched peers, among other risk conditions (as is an abnormal circadian timing of BP but not of HR, not shown) that separates this condition from a phase shift during shift-work that may involve HR as well. Vascular disease risk is elevated in the presence of any one of these risk factors, and is elevated further when more than a single risk factor is present, suggesting that these abnormalities in variability of BP and HR are mostly independent and additive features of a premetabolic syndrome. Abnormalities in the variability of BP and HR, impossible to find in a conventional office visit (the latter aiming at the fiction of a "true" BP), can raise cardiovascular disease risk (gauged by the occurrence of a morbid event like a stroke in the next six years) from 4% to 100%. By comparison to subjects with acceptable BP and HR variability, the relative cardiovascular disease risk associated with a decreased heart rate variability (DHRV), an elevated pulse pressure (EPP) and/or circadian hyper-amplitude-tension (CHAT) is greatly and statistically significantly increased. Some of these risks, silent to the person involved and to the care provider, notably the risk of CHAT, can be reversed by chronobiologic self-help, also with a non-pharmacologic approach in the absence of an elevated BP (MESOR-hypertension). © Halberg.

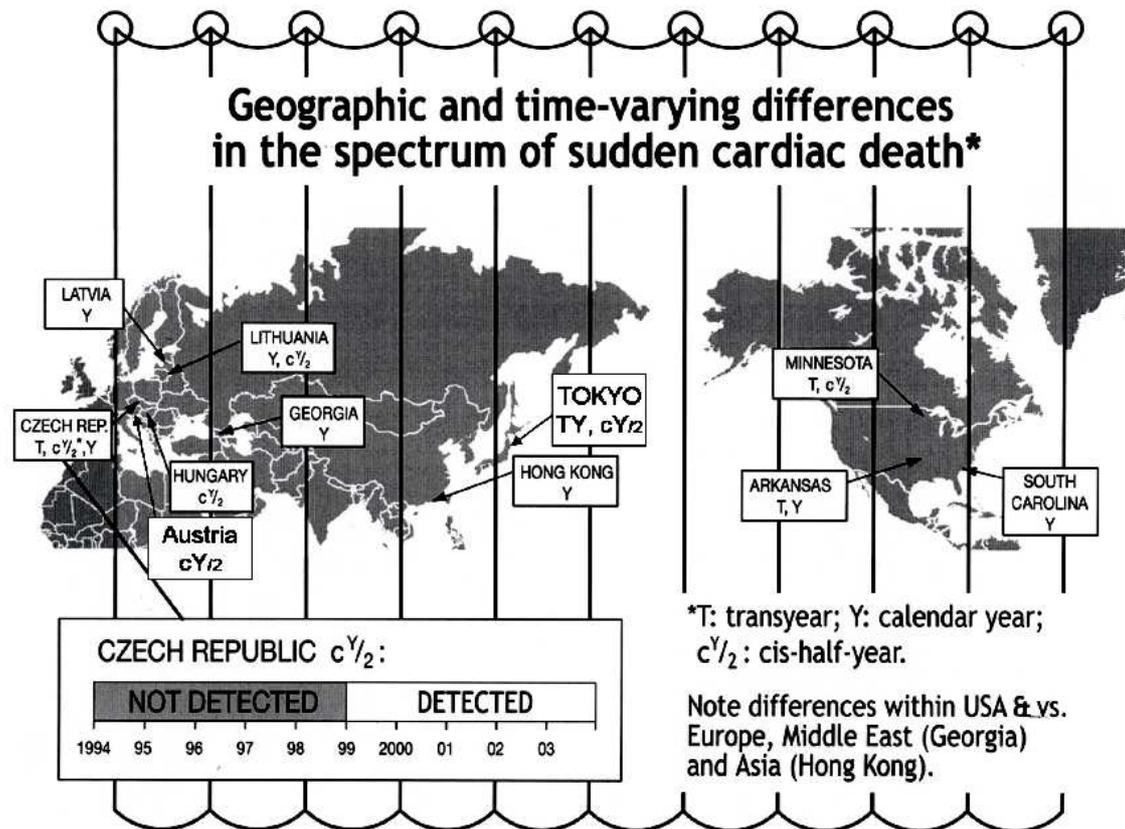


Fig. 4. In Minnesota and Tokyo, the incidence pattern of sudden cardiac death reveals about (~) 5- and ~15-month patterns. A curtain of uncertainty, because of limited available data, hides any time- and geographic (geomagnetic or dip-magnetic) site-specificity of various spectral aspects of sudden cardiac death in many other locations, with some exceptions. Thus, as compared to a transyear of about 15 months in Minnesota and in Tokyo, with a cis-half-year of about 5 months (cY/2), but no calendar year, we find both a calendar year and a transyear in Arkansas and in the Czech Republic. At the latter site a cis-half-year is detected after but not before 1999. A cishalfyear is also found in Hungary and Austria and corresponds in length to an average period of hard solar flares. Some other sites have only a calendar-year pattern. A winter peak is not surprising and has also been found in Minnesota, before cardiac arrest in association with a myocardial infarction was removed from the classification of sudden cardiac death by the 10th revision of the International Classification of Diseases (ICD10), on which this figure is based. The challenge is to detect mechanisms (magnetoperiodisms) that can override any effect of Minnesota's harsh winters, also in some mental and other body functions, and even in elderly human circulation.
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CHRONORADIOTHERAPY (Rx)

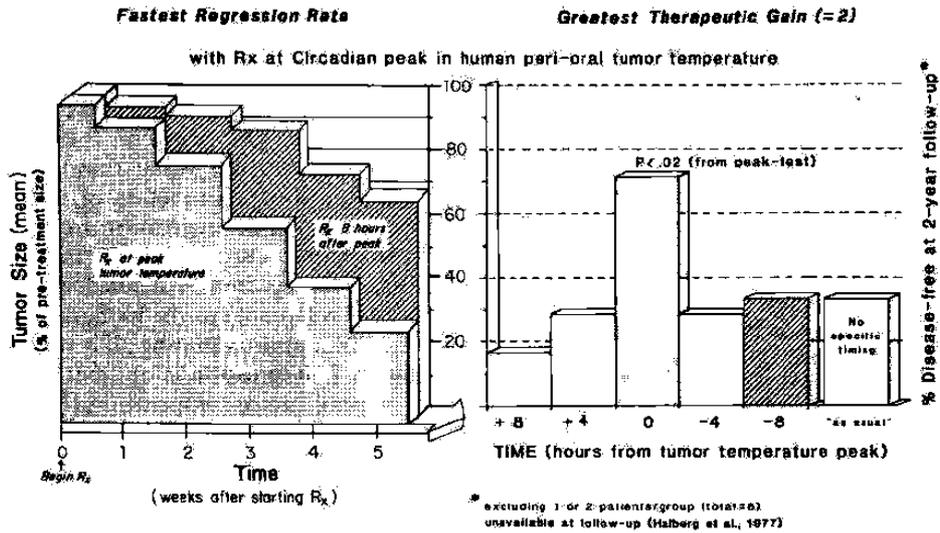


Fig. 5. Strikingly different results of radiation treatment at the peak of tumor temperature: doubling of the 2-year disease-free survival rate, as compared to treatment as usual or to treatment 4 or 8 hours before or after peak tumor temperature. © Halberg.

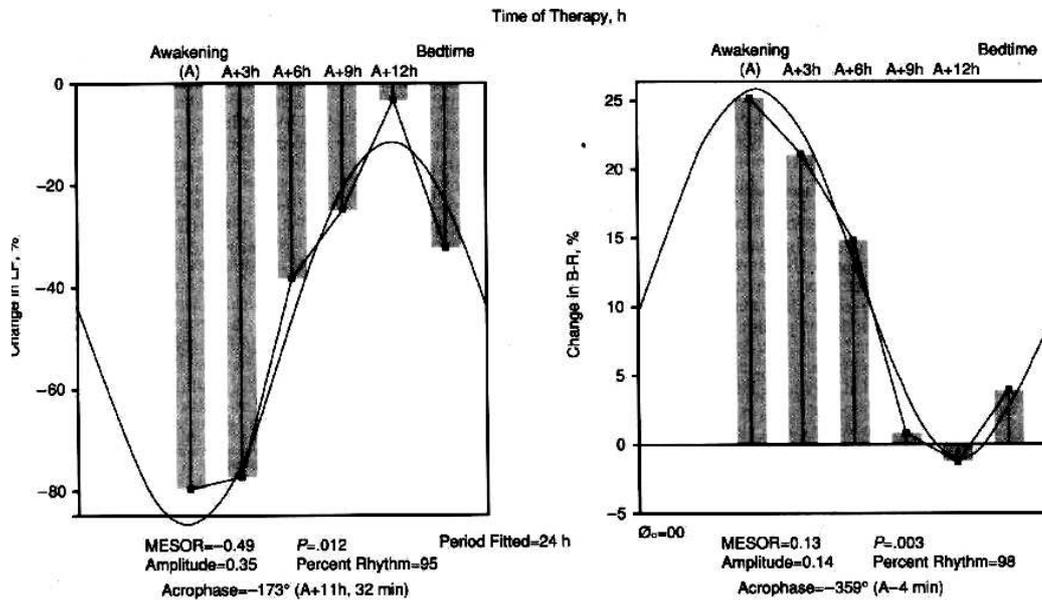


Fig. 6. Anti-clotting effect of aspirin gauged by lipoperoxides (LPs) in platelet-rich plasma and lymphocyte-adrenergic receptors (B-Rs) may be predictably present or absent as a function of timing (present after awakening, absent at bedtime). Changes are expressed as a percentage of overall pretreatment average). © Halberg.

9) At least one VVA, blood pressure overswing, is now documented to occur worldwide and to represent a risk greater than hypertension [12-15]. CHAT constitutes a gauge of both prehypertension [9, 12, 17] and prediabetes (18) and should be treated as part of a premetabolic syndrome [19].

10) Benefit from looking for a vascular variability syndrome (VVS) could be immediately available on a broad scale if the public, including preferably the health care profession and its teachers (read, among others, physiologists) can be made to review and act on the available evidence.

III. Cancer therapy

1) Timed cancer treatment by radiation (guided by the peak in perioral tumor temperature as marker) doubled 2-year disease-free survival rate -- as compared to treatment as usual, not timed, or to treatment at times 4 or 8 hours before or after peak tumor temperature [20], Figure 5.

2) Cancer chemotherapy. A patient with a 10% chance of survival in 2 years (with this prognosis, at the start of triangulated, several marker rhythms-guided timed chemotherapy) is alive and well 30 years later [21]. Again, a very poor prognosis notwithstanding, cancer-marker-guided chronochemotherapy has added years to another patient's life span, according to the founder of the specialty of oncology [22]. There are limitations: Kits for specific cancer markers are costly and any marker-rhythm-guided treatment is viewed as complex, cumbersome research while time-of-day specified therapy may fail [23].

IV. Drug and instrumentation development

Under highly standardized conditions, but not invariably, studies with one subject per timepoint, each treated at one of 5 or 6 equidistant timepoints (N-of-5 and N-of-6) covering a rhythm's period, e.g., 24 hours, have proved their use in testing a new ACTH-analogue (24) or low-dose aspirin [25], Figure 6. Such protocols could precede the current 3 stages of drug testing as a Phase-0 test (before Phases 1-3), preferably with groups of 5 or 6 subjects, again one per timepoint, added when needed.

To available devices for monitoring vascular or other variables and to devices yet to be developed, individualized sequential testing of all pertinent rhythm parameters could be added, thereby to pick-up harbingers of elevated risk [2, 3].

V. Control information, complementary to any endeavor in biomedicine and beyond

A budding atlas serves as an introduction to chronobiology on our website [26]. Chronomics is also being mapped [27-29; cf. 30-34]. This control information serves to avoid blunders that may occur without information on rhythms that may differ in phase or also in frequency among two groups being compared, Figure 7. More information is available in publications on our website (<http://www.msi.umn.edu/~halberg/>).

VI. Transdisciplinary science

New is a system of non-photic oscillations with common congruent periods in and around the biosphere. Congruence is defined by overlying or overlapping 95% confidence intervals of their periods covering a wide range of frequencies, including drifting, waxing and waning cycles of about 5 months, others shorter or longer than a year, e.g., of about 15 months length,

among others, in mental function, blood pressure and heart rate and in archival variables such as natality, morbidity and mortality. These magnetoperiodisms, coexist and compete with photoperiodism, the signature of the calendar year, in the incidence pattern of sudden cardiac death; magnetoperiodisms replace photoperiodisms in Minnesota [4; Figure 4], harsh winters notwithstanding, and can also do so in the systolic blood pressure of an elderly man, Figure 8 [4]. Some of these magnetoperiodisms are signatures of cycles found earlier by physicists at MIT in solar wind speed [35; cf. 36]. These and other non-photic signatures characterize human time estimates, mood and vigor have very low amplitudes, so that they represent more environmental information than energy, yet their importance stems from the possibility that they may reveal, in individuals, mechanisms underlying signatures of nonphotics not only in sudden cardiac death [4], but also in suicide [37], criminality and international battles [28, 38].

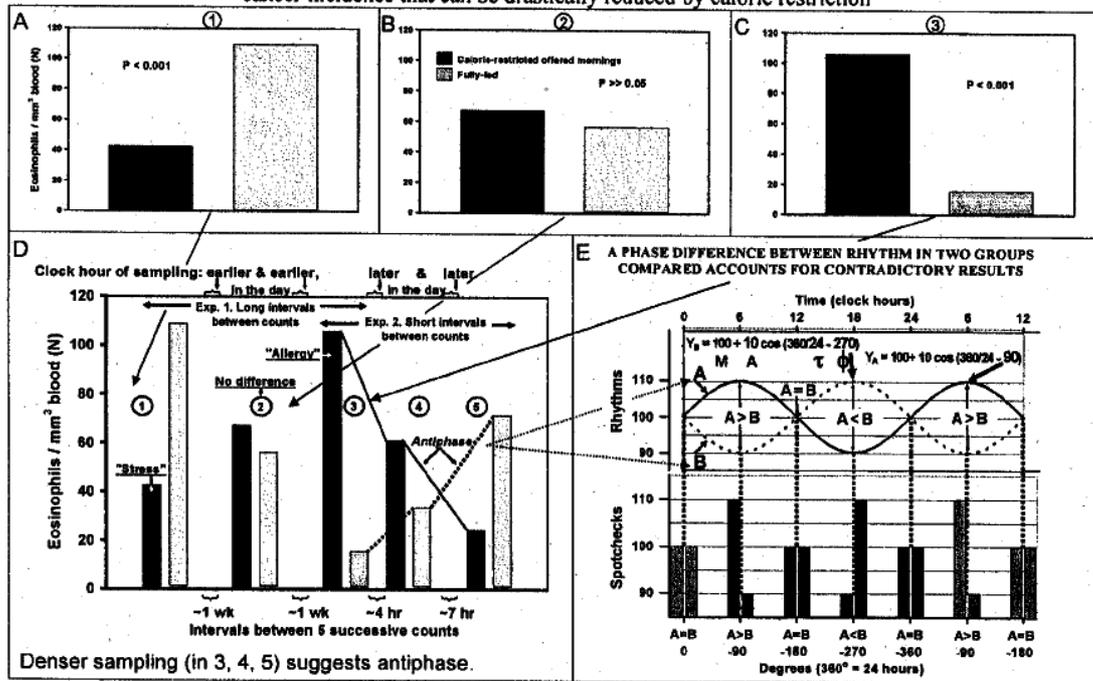
A new medical, or rather transdisciplinary specialty concerned with the ills of society could then emerge, based on longitudinal as well as transverse (cross-sectional) and hybrid (linked crosssectional) [39] physiological data aligned for analysis with those from concomitant ongoing monitoring of space weather [40] for scrutiny of any associations by superposed epochs and the effects of the subtraction and replacement of previously documented environmental spectral components on the cycles in pertinent affairs involving death in peace [4, 27, 28, 38] triggering those in war.

VII. Task for today via BIOCOS and this year via a website

Those concerned with the future of children [2, 3] could start monitoring and saving the data detecting and treating prehypertension, prediabetes and a premetabolic syndrome [9]. Those concerned about universal health care could invest into early and adult education in self-help by self-surveillance at all ages, immediately in the elderly hypertensives.

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Confusing results, that could wrongly be interpreted as "stress" or "allergy", are accounted for by the action of food (offered mornings) and light as competing synchronizers of circulating eosinophils in C₃H mice with high breast cancer incidence that can be drastically reduced by caloric restriction



www.JCircadianRhythms.com/content/pdf/1740-3391/1/2.pdf (Halberg F. et al., 2003)

Fig. 7. Importance of rhythms in assessing intervention effects, illustrated in relation to stress or allergy. **A.** Eosinophil counts seem to be lowered by fasting (and/or stress), when a 50% reduction in dietary carbohydrates and fats (with proteins, vitamins, and minerals similar to control group) was fed in the morning to C3H mice (dark column). (In this model, the naturally high incidence of breast cancer is lowered by a diet reduced in calories, not shown.) The result could have been interpreted as an adrenocortical activation and then assessed by eosinophil depression, with applications for treating breast cancer and for prolonging life. Steroids that depress eosinophil cell counts and perhaps mitoses could be a mechanism through which caloric restriction and ovariectomy act in greatly reducing cancer incidence. This tempting inference was never published.

B. In view of the importance of this finding for the etiology of cancer, results were replicated on a larger group of animals; one week later, a follow-up study with more animals started at an earlier clock-hour, yielded confusing results, showing no statistically significant difference between the two groups of mice.

C. After another week, another study starting at an even earlier clock-hour yielded results opposite to those in the first experiment when considered alone. These findings in C in themselves could have been interpreted as an allergic response, certainly contrary to the "stress" response in A.

D. Sampling at intervals of a few hours in the third study, the stages called 4 and 5, hinted at the reason for the confusion: by sampling at different clock-hours, two groups of mice were found to be characterized by a circadian rhythm with different phases. Opposite effects thus became predictable.

E. Abstract illustration of two circadian rhythms in antiphase. Differences in opposite direction or no effect are then anticipated from sampling at different clock-hours. © Halberg.

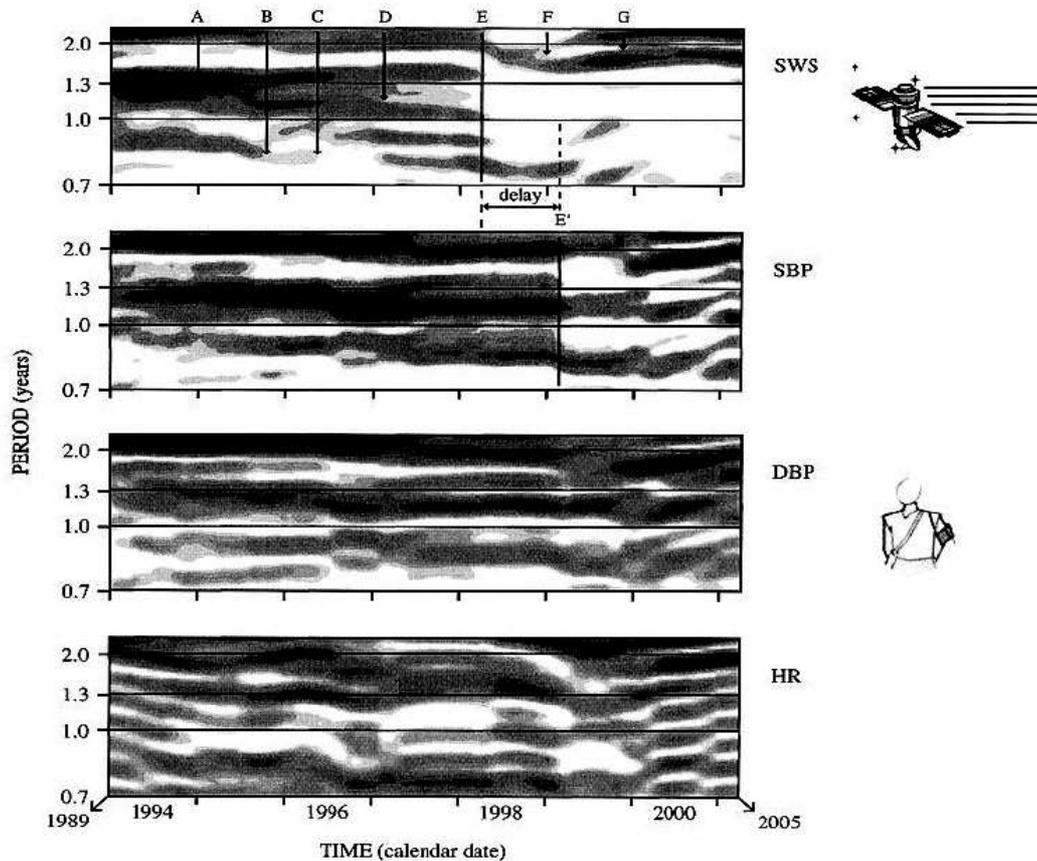


Fig. 8. Time courses of the frequency structures of the speed of the solar wind (SWS) (top) and of an elderly man's (FH) systolic and diastolic blood pressure and heart rate, SBP, DBP and HR (rows 2-4, respectively), examined by gliding spectral windows. Human systolic (S) blood pressure (BP) selectively resonates with solar wind speed (SWS) (top 2 sections). No major resonance, only minor, albeit abrupt changes in diastolic BP (DBP) or heart rate (HR) (bottom 2 sections). Rhythms in gliding spectra of SWS and SBP change in frequency (ceasing and reappearing smoothly [A] or abruptly [B, C, D]); bifurcating [D, F] and rejoining [G]); they also wax and wane in amplitude (B) (up to disappearing [C, E] and reappearing). During a nearly 16-year span there are no consistent components with a period averaging precisely 1 year in the 3 physiologic variables, possibly an effect of advancing age. While post hoc ergo propter hoc reasoning can never be ruled out, an abrupt change in the top row in SWS is followed in the second row in SBP by the disappearance of some components, suggesting that as a first demonstration, some of FH's cis- and transyear components were driven by the SW [since they disappeared with a lag of about a transyear following the disappearance (subtraction) of the same components from the SWS spectrum at E]. The persistence of other spectral features in turn suggests endogenicity, i.e., an evolutionary acquisition of solar transyear oscillations that may reflect solar dynamics for the past billions of years, just as circadians may reflect the possibly more recent alterations of light and darkness. Blood pressure and heart rate data are from a man 70 years of age at start of around-the-clock monitoring, mostly at 30-min intervals, with interruptions for nearly 16 years (N=2418 daily averages, total ~ 55000). Gliding spectra computed with interval =8 y, resolution low in time but high in frequency, increment = 1 month, trial periods from 2.5 to 0.4 y, with harmonic increment = 0.05. Darker shading corresponds to larger amplitude. © Halberg.

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CHALLENGES FROM "60 YEARS OF TRANSLATIONAL CHRONOBIOLOGY"

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APPENDIX

by Larry A. Beatty

Future direction: web-enabled software

As hardware and software technologies advance, we expect to see improvements in the convenience, cost, sensitivity of sensors, and network connectivity of blood pressure monitors that will affect how 7-day/24-hour monitoring, or preferably surveillance for much longer, is done. Making use of the analysis software available to home users interested in self-help-based, preventive health care is the subject of a recently-started website and software project, operating under the project name "sphygmochron.org" (where a summary of around-the-clock and along-the-week blood pressure and heart rate dynamics is dubbed a "sphygmochron").

We visualize, and are beginning implementation of, a website that could serve the multiple purposes of 1) persuading subjects for life-long self-help in surveilled health care by providing analyses that detect risk or disease, and guide treatment, and 2) continuing research on improving reference standards and refining the procedures that now detect treatable conditions with risks greater than hypertension. This website implements user scenarios along the lines of those documented in (1).

Specific components of the website design address:

- making the sphygmochron analysis available to home users, and their health care providers,
- making blood pressure data from home users available to researchers, updating the analysis software with the results of new research as time progresses,
- providing a library of educational materials for home users and health care providers,

- building a community of self-helping users consisting of those engaged in preventive health care as well as those being treated by health care providers.

The website would contribute advanced transdisciplinary basic biological as well as medical research data bases, with the biological data base aiming at a clarification of biological associations of solar and terrestrial effects in human physiology. The medical data base would serve to gradually improve the service rendered by the website to self-care recipients by a refinement of the reference standards and of the harbingers of elevated risk of severe disease. A series of updates to the existing sphygmochron software and additional analysis programs is planned for use by those who repeat monitoring sessions (annually, on some other schedule, or as warranted by analysis). To support users retrieving data directly from blood pressure monitors, the website will accept files as produced by many commercially-available devices and manufacturer-supplied analysis software.

The user of the website must be computer-literate, but can perform analyses for multiple people, including those who need help with tasks involving computers. The first major scenario to be supported includes a family member accessing the website for his spouse, children, aged parents, people with disabilities, or others who fall within the member's guardianship. The second scenario is for health care professionals or their staff members to log in and submit data for patients.

In the near term, the website supports running the sphygmochron analysis. In the long term, comparative analysis programs currently used at the Halberg Chronobiology Center at the University of Minnesota can also be run (2). The comparative analysis programs need two or more files of blood pressure data taken at different times in the person's life, or preferably a more or less continuous record, such as that taken by hypertensive opinion leaders from the time of diagnosis to their life's end. For instance, a former head of the then Hypertension/Endocrinology section of the U.S. National Institutes of Health who thereafter became director of that institution's Clinical Center believed that when hypertension is involved, one should not "fly blind" (3) (without continued surveillance by monitoring) (4).

A small, well-focused library of materials related to sphygmochron analysis, heart and blood vessel physiology, cardiac diseases, and treatments will be kept on the website. The library will contain sections for different types of users, including children, high school and college students, adult home users, and medical and health care students and professionals. The most important section might be the one for adult home users. It supports the desires of users with different backgrounds and levels of education to:

- learn advanced interpretation of sphygmochron reports, and
- research medical conditions, diseases, and treatments beyond the level of
- everyday "household" words.

To support building a community of self-helped home users interested in preventive and curative health care, a popular web mechanism currently employed by some internet users in self-help or self-directed educational situations is "forum" software, which lets users communicate with each other via leaving publicly available messages directly on the website. The envisioned website will have such forums available early in its lifetime. The concept of community-building on the internet still seems to be undergoing considerable change; we expect to watch for new trends in this area and adapt the website accordingly to accommodate desires of the users.

CHALLENGES FROM "60 YEARS OF TRANSLATIONAL CHRONOBIOLOGY"

The website will make available information about obtaining a blood pressure monitor for ambulatory use (often called an Ambulatory Blood Pressure Monitor, ABPM), since many home users, especially those interested in the self-help style of medical care, might not know how to obtain ABPMs at reasonable cost, and will have questions about ABPM quality, testing and calibration, data off-loading software, and the logistics of wearing an ABPM around the clock for a week or longer. A common question will be along the lines of "This is different from current practice. How can this information help me, and how can my doctor use it?" We plan to encourage home users to monitor themselves for longer and longer time spans to get more and more basic and applied information from the analyses available on the website.

ABPMs of varying quality and robustness are available and will be documented:

- professional models costing a few thousand dollars
- discounted professional models available to BIOCOS project participants
- home ABPM kits or projects for hobbyists

As additional models and categories of ABPMs become available over the next few years, the website will be updated with descriptions and other appropriate information, to help its users capitalize on those improvements in the convenience, cost, sensitivity of sensors, and connectivity of blood pressure monitors that will affect how 7-day/24-hour monitoring, or preferably much longer surveillance, analyzed as one goes, is done.

By 1880, Ignaz Zadek (5) had sufficient data to allow the demonstration in a metaanalysis of about-24-hour and about-7-day changes in blood pressure. By 1904, Janeway at Johns Hopkins Hospital insisted, before seeing a patient, on having enough data to evaluate periodic variations (note: variations is plural) (6). He could do so on the basis of Zadek's record. In 2007, signatures of both the about-10.5-year Schwabe cycle and 21-year Hale cycle are demonstrated in the human circulation (7), along with many other nonphotic cycles, probably magnetoperiodisms, some of which also have signatures in sudden cardiac death, an association speaking for their importance.

Assessment of these different periodicities in long populations' and individual's records will be a dividend in basic science and space weather monitoring from self-help in health care that continuously assesses variability. This longitudinal surveillance could start for many hypertensives at the time of a chronomic diagnosis (8,9) of abnormality to the time of life's end. The benefit for the individual involved would be a reduction in the number of episodes of variability disorders, by their prompt detection and treatment (while otherwise an anti-hypertensive treatment might constitute the trade of a lesser risk such as hypertension for greater risk such as a circadian blood pressure overswing). Control of a silent disease (hypertension) without bringing about a yet greater also silent risk (overswing) cannot be achieved without continuous surveillance in some cases, a critical remaining research problem awaiting studies on populations.

Every person with alterations in variability of blood pressure and heart rate should continuously monitor and analyze, and thus serve his or her own health care as well as science. The website could, in combination with existing and improved blood pressure monitors, enable the public at large to determine the need for surveillance, and then implement continuous monitoring, individual-by-individual.

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