

Toward a chronomically interpreted home ABPM

The desire prevails in current everyday medical practice for the fiction of a stable, "true" blood pressure measurement, that is of "the average pressure over long periods of time"¹⁻⁶. It is mistakenly assumed that, in a long record, blood pressure is time-invariant, yet variations above and below fixed threshold (such as 140/90 or 135/85 mm Hg) are commonly seen from one day to another, from one week to another, from one month or even longer spans to the next span of similar duration, even for the 24-hour rhythm-adjusted mean value (MESOR). For instance, in the light of chronobiologic reference values, half-yearly summaries of half-hourly around-the-clock measurements, in a case studied for decades, changed from MESOR-hypertensive in one span to normotensive in the next such span. This fact and very many others⁷⁻⁹ question a diagnosis based on office measurements with one or a few 24-hour ambulatory blood pressure monitorings (ABPM), the current false platinum standard¹⁻⁶. The officially recommended goal of current WHO or national guidelines remains today to estimate a "true fixed" (yet imaginary!) pressure and to compare it with a fixed (gender-, age- and time-invariant) threshold as a reference standard. The consequence is that false negative and false positive diagnoses abound and calling them white-coat hypertension or masked hypertension does not alter the number of misdiagnoses and hence of mistreatments or of failures to treat when this is indicated.

The foregoing status quo ignores the predictable variability due to the many cycles in and around us, apparent to the unaided eye in any around-the-clock and along-the-years record. Measurements are usually lower by night than by day; they vary further, not only with the seasons, but often more so with frequencies found in the solar wind, shorter than a half-year (cis-halfyears or quinquennials) or longer than a calendar year, near- and far-transyears) and further with one cycle in one, two or more than three decades. Even the location along the 24-hour scale of high and low values can change as a function of time, not only in shift-workers or after transcontinental flights but also in severe depression.

A clearly lengthened circadian period is seen in the (acro)phase domain in row 3 of **Figure 1** during half-yearly recurring depressions lasting 2-3 months (often coexisting in this case with a 24-hour component, not seen in the figure), characterizing blood pressure and heart rate of a 61-year-old woman (JF) who experiences a circadian vascular, endocrine and behavioral ecfrequentia during her downtimes⁷. Section IV of **Figure 2**⁷ visualizes this vascular variability anomaly, VVA, or in the case of **Figure 1**, where it recurs, a vascular variability disorder, VVD. VVAs and VVDs are defined only abstractly in **Figure 2**, but they are actually diagnosed by reference to data from gender- and age-matched peers^{8;cf.7}. For the same case of JF, **Figure 3** shows that if the values during sleep are omitted, the diagnosis of ecfrequentia cannot be made⁹: the diagonal delaying course of acrophases in row 3 is no longer seen on the right where, for the analysis, values during sleep are omitted.

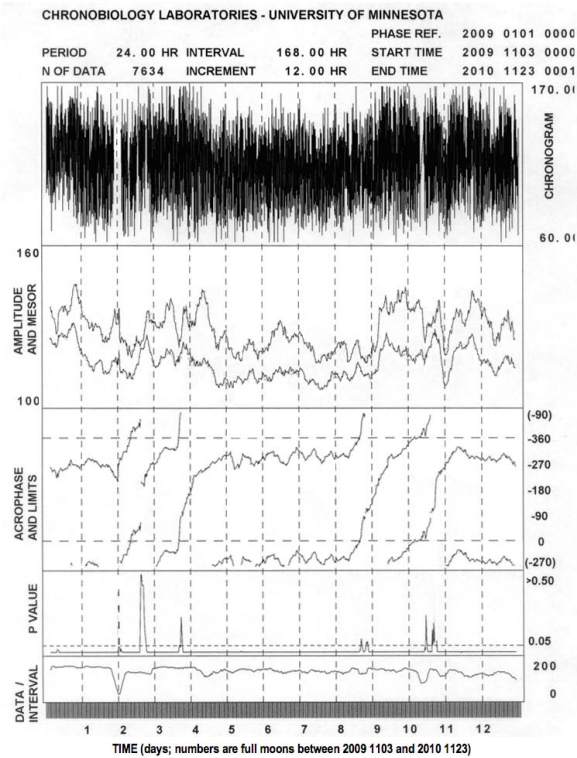


Figure 1 Chronobiologic serial section of systolic blood pressure of JF, a 61-year-old woman at start of monitoring. Dashed horizontal lines at 0° and 360° indicate midnight in row 3. Numbers on abscissa are full moons. Acrophases — peaks in the best-fitting 24-hour cosine function — in row 3 show a horizontal time course in the first 2 months indicating 24-hour synchronization; they occur at about the same time in the afternoon. They start delaying after the second full moon and run diagonally with a period longer than 24 hours, scanning this length for the next 3 months. These acrophases are resynchronized after full moon 5, only to desynchronize again after full moon 8.

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Six Vascular Variability Anomalies (VVAs) or Disorders (VVDs) (VVDs if present in several repeated weeklong profiles) *

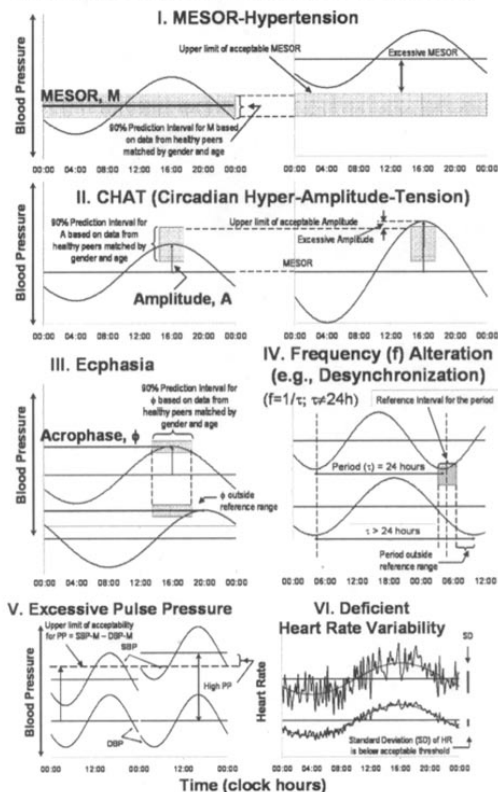


Figure 2 Abstract visualization of vascular variability anomalies, VVAs, found in 7-day around-the-clock records. If replicated several times, VVAs can be called vascular variability disorders, VVDs.

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* Validated by chronobiologic analysis of around-the-clock 7 day/24-hour records of measurements at 1-hour or shorter intervals, interpreted in the light of time-specified reference standards qualified by gender and age.

** Ecfrequentia: short for frequency (f) alteration (e.g., desynchronization) that can be Dysfrequentia when associated with symptoms and/or persisting in repeated consecutive 7-day records.

DATA OF SYSTOLIC BLOOD PRESSURE OF JF (F, 62 y) TAKEN DURING LUNAR CYCLES 11-15 OF THE SPAN FROM 2009/06/09 TO 2010/03/22, AROUND THE CLOCK (left) AND DURING WAKE-ONLY (right)
 PHASE REF: 200901010000; START TIME: 200903070000; END TIME: 201005030000

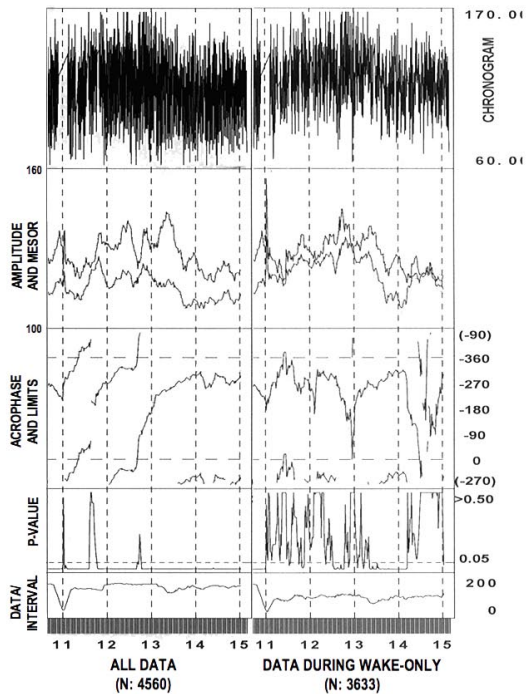


Figure 3 JF's data during sleep as well as waking are required for the diagnosis of circadian ecfrequency (left, row 3). The diagonal, systematically changing time course is missed when data during sleep are removed.

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One's view changes further when one has found trans (= beyond)-tridecadal cycles (of about 35 years) in sets of around-the-clock series covering decades. One set of about 6 daily measurements extends from 20 to beyond 60 years, an entire clinically healthy adulthood; another begins with an acceptable blood pressure, to arrive, after two decades, at a high average blood pressure (MESOR-hypertension). The MESOR, estimated by curve fitting, is usually more accurate and more precise than the arithmetic mean. In several other long series covering decades, one finds a mostly acceptable MESOR of blood pressure under treatment yet with occasional VVAs if not VVDs, all findings that must be detected to be corrected, if a high risk of severe cardiovascular disease associated with VVDs is to be avoided.

Thus, previously mysterious non-photoc, unseen features of human life become readily apparent under the virtual telescope of chronomics, the study of interactions among time structures (chronomes) in and around us, approached with glocality in time as in space. Glocality in space¹⁰⁾ means that globally valid approaches can be applied to find differences locally geographically, as Prof. Otsuka does for health surveillance in cities in Hokkaido and Kochi, as well as within the Arctic Circle and at high altitudes in the Indian subcontinent¹¹⁻¹⁵⁾.

For a methodologic temporal glocality, we can prospectively as well as retrospectively look globally at ever longer cycles with repeated passes over the same data until we dispose of an entire 4-decade-long time series for assessing any transtridecadal cycle, while the same data for blood pressure and heart rate are also analyzed in weekly and longer sections of the time series as-one-goes, locally in time for their circadian and infradian characteristics. The sections may serve the

individual for severe disease prevention, while the same blood pressures and heart rates are further pooled and aligned with time series of terrestrial and extraterrestrial weather to find, e.g., an about 35-year cycle, off and on, in rainfall and environmental temperature, important in human affairs, bearing on problems of global warming, economics and military-politics. Further nonphotic cycles include those of about (~) a week, ~ a month, 5, 6 or 16 months, as well as decadal, didecadal or transtridecadal cycles. Quinmensals, semiannuals and transannual cycles, along with circadians and circannuals, can all be monitored, e.g., by systolic blood pressure as are mental functions, to study mechanisms, e.g., of terrorism on a population basis, **Figures 4 and 5**¹⁶⁾, while initially the same data served, as noted, for the detection and personalized treatment of VVAs in 7-day around-the-clock records as a start. These 7-day profiles are to be repeated once an abnormality is found, and, if a VVD is confirmed, continuous, e.g., half-hourly monitoring is advocated, that may serve everybody anyhow, once affordable, cuff-free unobtrusive instrumentation becomes available for automatic transfer into a multilingual also automatic website that does on a large scale what is being done by a project BIOCOS for all comers free of charge.

Solar Wind Speed (SWS), Geomagnetism (aa) and Terrorism (MIPT)
Show Intermittent Statistical Significance*
of a (congruent) 16.27-month (1.36-year) Component**
Lagging in MIPT behind SWS and aa

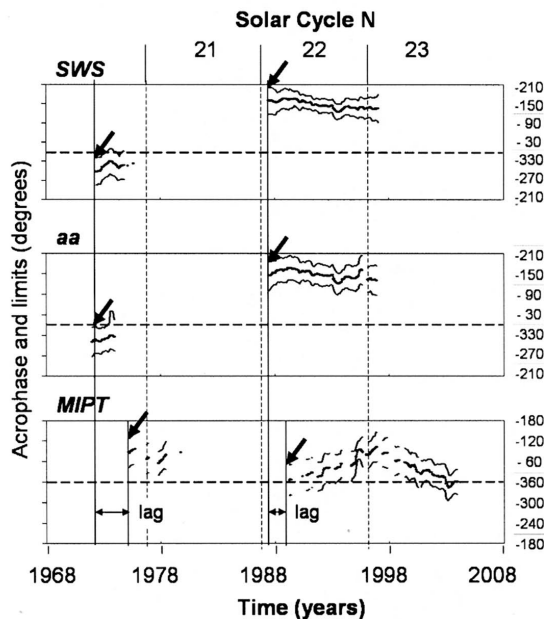


Figure 4 Weather in space, that is the speed of the solar wind, and terrestrial magnetism, may trigger terrorism at a transannual frequency, at which terrorism, as a population phenomenon, may continue to resonate after the environmental stimuli can no longer be detected. © Halberg

* Seen by bracketing dots (delineating 95% confidence intervals of the acrophase, a measure of the timing of overall high values recurring in each cycle, obtained by the fit of a 16.27-month cosine curve by chronobiologic serial section, using an 8-year interval displaced by 1 month throughout the time series.

** Solar wind speed data from the omniweb (<http://omniweb.gsfc.nasa.gov/>), aa index from NOAA (ftp://ftp.ngdc.noaa.gov/STP/GEOMAGNETIC_DATA/AASTAR) and number of terrorist acts (N/day, assessed monthly) from the Terrorism Knowledge Base (<http://www.tkb.org/>) from the Memorial Institute for the Prevention of Terrorism (MIPT).

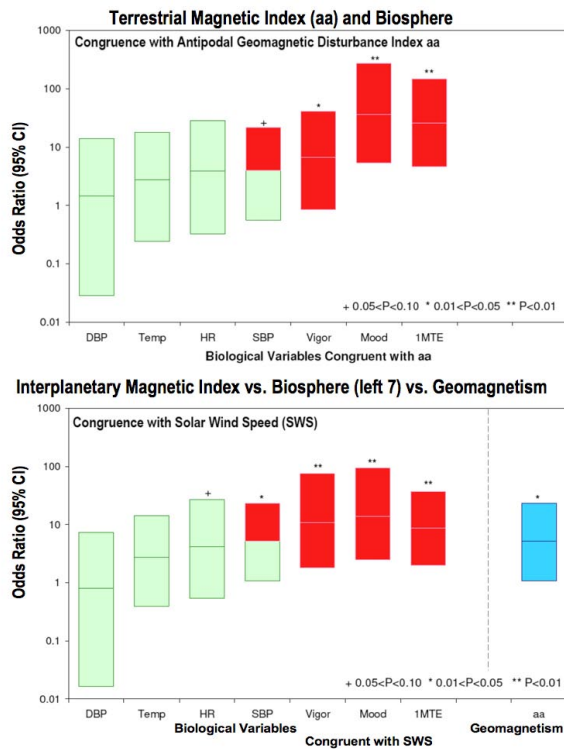


Figure 5 Some inferentially statistically validated congruences of human somatic and mental functions with the environment, gauged by the antipodal geomagnetic disturbance value (aa) (top) and solar wind speed (SWS) (bottom). While limited to a single clinically healthy case, RBS, a man aging during the study from 20 to 60 years of age, discussed in detail elsewhere, the number of congruences found for the estimation of 1-minute and for mood in the spectral range investigated (from one cycle in 2.5 years to 3 cycles per year) more than equals that of the known association of helio- and geomagnetism, commented upon in 1852 by Gen. Sir Edward Sabine (on the basis of too few data) -- "... it is certainly a most striking coincidence, that the period, and the epochs of minima and maxima, which M. SCHWABE has assigned to the variation of the solar spots, are absolutely identical with those which have here been assigned to the magnetic variations". When congruence is assessed by means of the odds ratio based on the non-central hypergeometric distribution, mental functions show higher congruence than somatic functions; among the latter, SBP is responsive, perhaps constituting a seemingly acceptable approximation for the mental functions. © Halberg

Against the background of these thoughts, it is a pleasure to introduce a book on blood pressure by Prof. Kuniaki Otsuka. We do this with deep personal affection and continue to learn from him, first from 297 cases that served to define and compare five of the major VVAs, including MESOR-hypertension and a circadian overswing or circadian hyper-amplitude-tension, CHAT. In Asians, if several of these VVDs persist and coexist, they raise cardiovascular disease risk within 6 years to nearly 100%, **Figure 6**¹⁷⁾. Second, we owe Prof. Otsuka the original introduction of a glocal approach that is global and local in space¹⁰⁻¹⁵⁾ and can be glocal in time.

For the practitioner of medicine and the educated lay person, the late Thomas G. Pickering, recipient of the prestigious Franz Volhard Award, asked in 2008 rightly^{1;cf.2-6)}: "Should doctors still measure blood pressure?"¹⁾. Pickering also advocated, as do we, an international data base of ABPM studies. His father, Sir George White Pickering, Regius Professor of Medicine at Oxford University¹⁸⁾, had delivered the first Volhard lecture in 1972. Concern about blood pressure was

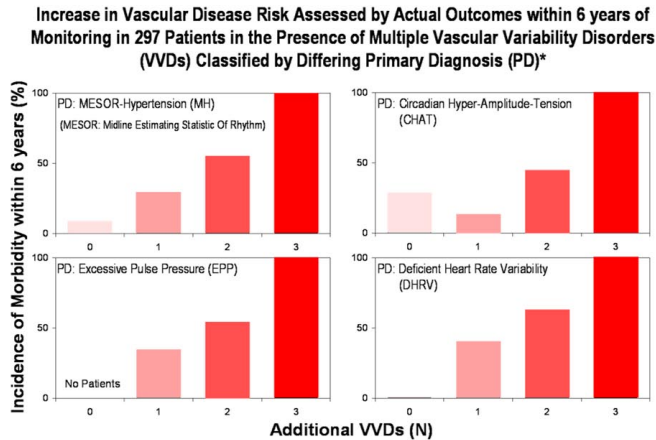


Figure 6 Prof. Kuniaki Otsuka's major original contribution: the incidence of VVDs was assessed in a clinic population of 297 patients. Blood pressure (BP) and heart rate (HR) of each subject were monitored around the clock for two days at 15-minute intervals at the start of study. Each record was analyzed chronobiologically and results interpreted in the light of time-specified reference limits qualified by gender and age. On this basis, MESOR-hypertension (MH, diagnosed in 176 patients), excessive pulse pressure (EPP), CHAT (a circadian overswing), and a deficient heart rate variability (DHRV) were identified and their incidence related to outcomes (cerebral ischemic attack, coronary artery disease, nephropathy, and/or retinopathy). Outcomes, absent at the start of study in these non-diabetic patients, were checked every six months for six years, to estimate the relative risk associated with each VVD alone (primary diagnosis, PD) or in combination with 1, 2, or 3 additional VVDs. Earlier work showed that CHAT was associated with a risk of cerebral ischemic event and of nephropathy higher than MH, and that the risks of CHAT, EPP, and DHRV were mostly independent and additive. It thus seemed important to determine the incidence of each VVD, present alone or in combination with one or more additional VVDs. The 176 patients with MH were broken down into 103 (34.7% of the population of 297 patients) with uncomplicated MH, 55 (18.5%) with MH complicated by one additional VVD, 15 (5.1%) and 3 (1.0%) with MH complicated by two or three additional VVDs. In the last group, all three patients had a morbid outcome within six years of the BP monitoring. Ambulatory BP monitoring over only 48 hours, used for diagnosis, is much better than a diagnosis based on casual clinic measurements, yet its results apply only to groups. With this qualification, of the 176 patients with MH, 73 (42.2%) had additional VVDs that further increase their vascular disease risk, and that are not considered in the treatment plan of these patients since current practice does not assess these VVDs. This proportion may be smaller when VVDs are diagnosed on the basis of a 7-day record (available for CHAT). Results related to EPP (bottom left), CHAT (upper right), and DHRV (bottom right) illustrate that these conditions can be present in the absence of MH in as many as 12 (4.0%) of the 297 subjects. Since they do not have MH, it is unlikely that these subjects would be treated from a conventional viewpoint, even though their vascular disease risk can be as high as or even higher than MH. Evidence suggests that treating these conditions may translate into reducing morbidity and/or mortality from vascular disease. Another lesson is that around-the-clock monitoring of BP and HR interpreted chronobiologically is needed, even in the absence of MH, to detect vascular disease risk associated with VVDs such as CHAT and DHRV, that cannot be assessed on the basis of casual clinic measurements, so that non-pharmacologic and/or pharmacologic intervention can be instituted in a timely fashion before the occurrence of adverse outcomes. Once implemented across the board rather than in selected patient populations, vascular disease could be curbed to a much larger extent at relatively low cost if the monitoring is offered directly to the public and care providers become involved only after detection of a VVD. A website has to be built to educate, interest and serve many people and to provide cost-free analyses in exchange for the deidentified data, that as a pool are used for monitoring solar effects upon the biosphere. On a small scale, these services are now provided worldwide by the world-wide BIOCOS project (corne001@umn.edu). This ongoing personalized yet also societally oriented approach is an alternative to a polypill that as yet flies blind in the sense that it neither detects nor treats VVDs and VVSS. © Halberg

* Results stem from 207 patients, among which only 34.7 % had uncomplicated MESOR-hypertension (upper left, N=0) and 40.7 % were MESOR-normotensive, including 2.4 % and 1.7 % with only CHAT or DHRV, respectively (right top and bottom, N=0). For complementary results on 1,177 untreated patients, see Hypertension 2007; 49; 237-239.

CHRONOBIOLOGY DETECTS PREDIABETES (a, TOP LEFT) AND PREHYPERTENSION (c, MIDDLE) WHEN DIPPING CLASSIFICATIONS FAIL (b, TOP RIGHT) OR MISLEAD (d, BOTTOM)

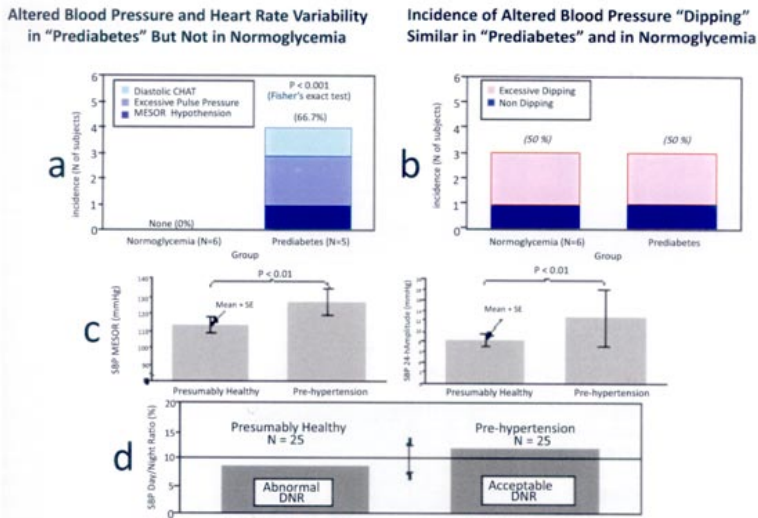


Figure 7 Top: With the relatively small sample sizes of 6 patients with a moderately elevated fasting glucose and a slightly abnormal glucose tolerance versus 6 healthy controls, all undergoing 7-day/24-hour ambulatory BP and HR monitoring, analyses indicate that a chronobiological approach works when a classification in terms of "dipping" based on the day-night ratio (DNR) fails. Indeed, no abnormality was detected in the light of time-specified reference standards qualified by gender and age among the 6 controls, but 4 of the 6 pre-diabetic patients showed one or more VVDs ($P < 0.001$). By contrast, in both groups, there were two patients with a DNR $> 20\%$ ("excessive dipping") and one patient with a DNR $< 10\%$ ("non-dipping"). It was thus impossible to discriminate the patients with pre-diabetes from the healthy controls in terms of "dipping", when a chronobiological interpretation worked²⁰.

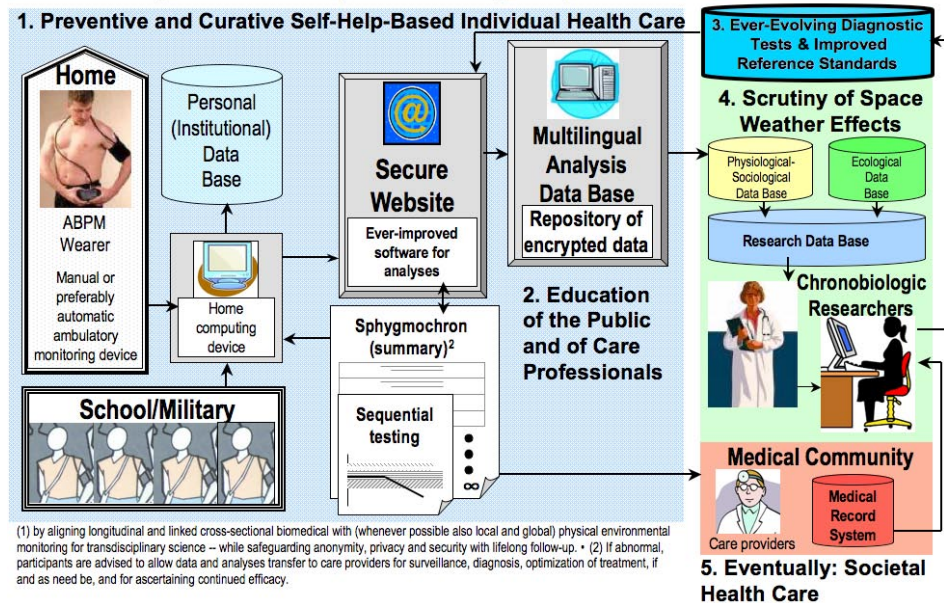
Middle and bottom: Circadian parameters and day-night ratios (DNRs) of systolic blood pressure (SBP) are compared between groups of presumably healthy MESOR-normotensive subjects and pre-hypertensive subjects with incipient signs of minimal change hypertensive retinopathy. Minimal retinal alterations, presumably reflecting an increased vascular disease risk, are associated with a higher MESOR and a larger circadian amplitude of SBP ($P < 0.01$). A classification in terms of dipping, based on the DNR of SBP, however, is misleading, as the pre-hypertensive patients as a group are "dippers" with a DNR between 10% and 20%, but the MESOR-normotensive controls as a group are non-dippers, with a DNR of SBP below 10%²². © Halberg

in the Pickering family time structure (chromosome^{1-6,18}), if not in their genome. (The Volhards — Jakob, the father [a chemist] who synthesized creatinine, and Franz, the son [a clinician], who preceded Goldblatt in focusing scholars of blood pressure on the kidney — had the kidney in their chromosomes.) As clinicians, both Sir George and Tom Pickering eventually (Tom was a fast learner^{1 vs. 2-6}) helped focus attention on the indispensability of ABPM, and Tom also on modern data bases. Hence this book is dedicated to their memories.

Pressure is being monitored continuously in the tires of modern cars to avoid accidents, and in small animals to develop drugs. If there is a popular demand stemming from those who read Prof. Otsuka's book, affordable, unobtrusive technology will become available to continuously monitor the individual's pressure, to allow one to know oneself, to learn from VVA analysis what one likes and dislikes, a problem as yet unsolved¹⁹, and further to treat VVAs, preferably before they become VVDs and VVSs, as well as when these latter conditions already prevail. A classification by dipping, its positive aspects on large groups notwithstanding, is no substitute; it may mislead,

Figure 7²⁰⁻²²

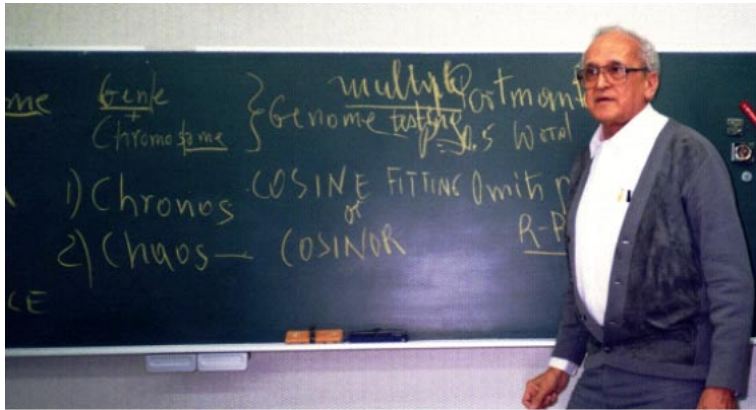
Preventive and curative health care can yield the dividend of biomedical monitoring of space weather by time-structural analyses of ambulatory blood pressure and heart rate series¹



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, originally with Larry A. Beatty (www.sphygmochron.org) of the Phoenix Project (www.phoenix.tc-ieee.org).

Figure 8 Currently, a project on The BIOSphere and the COSmos (at come001@umn.edu) provides analyses multilingually, in English, French and German (and as soon as possible in Arabic and Spanish) to all comers worldwide, in exchange for the data. These analyses serve multiple purposes transdisciplinarily: for the person monitored, the analyses diagnose any VVD and guide treatment via consultation by a care provider for lifelong self-help in continuously monitored sphygmochrons, data summaries in the light of gender, age and other temporal norms. The data in turn also serve for eventually improving reference standards (after lifetime records from disease-free subjects become available) and to look for novel harbingers in records from individuals with hard events. Furthermore, the data can be used with illustrations to educate the public and care professionals. Finally, analyses of the data flow can monitor solar activity with signatures in blood pressure and heart rate and in archived hard events. The Phoenix Project of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (<http://www.phoenix.tc-ieee.org>) is planning on developing an inexpensive, cuffless automatic monitor of BP and on implementing the concept of a website (www.sphygmochron.org) for a service providing automatic analyses in exchange for the data that in turn are to be used for refining methods and for monitoring psychophysiological effects of space weather. © Halberg

We need not fly blind²³⁾: the conventional blood pressure cuff must be removed from the physician's office; instead, home ABPM can be interpreted chronomically (C-ABPM) today by BIOCOS (come001@umn.edu) and eventually by an automatic multilingual website, **Figure 8**; it is immediately feasible for a personalized health care, e.g., for stroke prevention and further for providing data for monitoring the cosmos and eventually for the development of rational methods to prevent social diseases such as crime and terrorism. What is good for cars' tires and drug development is recommended for those who drive the cars and who may wish to avoid the need for drugs by early prevention as well as for those who wish to use these drugs with monitoring of the treatment of VVDs, as needed.



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