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ORIGINAL ARTICLE

Chronobiology's progress. Part II, chronomics for an immediately applicable biomedicine

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Summary
Chronomic cardiovascular surveillance serves to recognise and treat any risk elevation as well as overt disease, and to ascertain whether treatment is effective and, if so, for how long treatment effects lasts, be it for lowering an increased risk and/or in surveilling the success or failure of treatment. A treatment-associated increase in circadian amplitude of blood pressure (BP) may induce iatrogenic overswinging, also dubbed CHAT (**c**ircadian **h**yper-**a**mplitude-**t**ension), in some patients, thereby increasing cardiovascular disease risk unknowingly to care provider and receiver.

Keywords: chronobioethics – food restriction – blood pressure surveillance – CHAT – health care

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*Dedicated to Alejandro Zaffaroni, who came as a pleasant surprise with flowers and more. May a marker-guided preventive chronotherapy of elevations of the risks of diseases not only of individuals but also of societies and nations eventually evolve.

INTRODUCTION

The Halberg Chronobiology Center's 191 publications during the past 2 years (citations from which carry the suffix I in Halberg et al. 2006) constitute a report of activities in chronomics in the 5th and 6th years of a formal center (in Minneapolis) in chronobiology, the study of mechanisms of chronomes, i.e., biological time structures. Actually, it is a summary of the 56th and 57th years of endeavors in a Minnesota brand of mapping chronomes (Halberg et al. 2003a), against the recent background provided, among many other co-authors, by Kuniaki Otsuka in 2001, 2002, 2003, 2004 and 2005 and by Sergei Mikhailovich Chibisov in 2005. The following text should be read in the light of Part I, appearing in the preceding issue of this journal.

Can one "control" rhythms by "fixing", e.g., clock-hours?

The potential blunders that were learned from the study of circadians, Figs 10 and 11, and were extended to infradians, Fig. 5 in Part I, should be taken seriously in dealing with "cycles", whatever their length. Fig. 12 shows the uncertainties remaining despite the generally used but false panacea of fixing the clock-hour (or any other cycle's stage) to "eliminate" the effect of rhythms. Even when one always samples at the same clock-hour, one gets very different information, for instance, on seasonal rhythmicity depending on when one samples: by consistently using actual measurements from one vs. another time of day, one may find, in the same around-the-clock data set, "summer hypertension" or "winter hypertension". The treatment recommendation based on such spotchecks may be opposite, just as in the case of (morning) normotension vs. (evening) hypertension diagnosed in the same subject by two care providers who saw the same patient early vs. late in their office hours (Bartter 1974, Cornélissen and Halberg 1996).

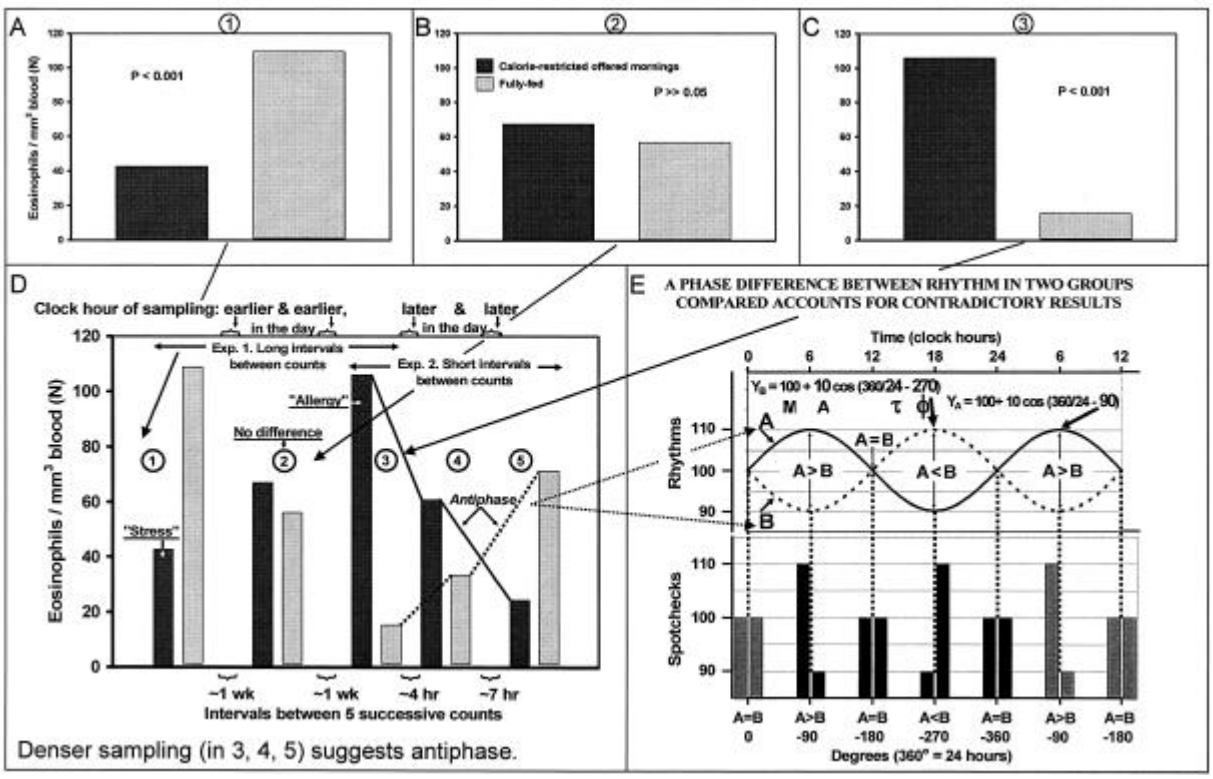

Fig. 10**. Confusing results, that could wrongly be interpreted as "stress" or "allergy",** are accounted for by the action of food (offered mornings) and light as competing synchronizers of circulating eosinophils in C_3H mice with high breast cancer incidence that can be drastically reduced by calorie restriction. Results that could be misinterpreted as being "stress" or "allergy" effects are actually due to differences in phase of 2 rhythms originally not known to be differentially synchronized, published previously only as puzzles (Halberg and Ahlgren 1980; Halberg et al. 2003a). How much research in these fields and in oncology, the theme originally investigated, is confounded by a much broader spectrum of unassessed rhythms in a yet broader time structure (Halberg et al. 2003a; cf. Halberg and Visscher 1952, Halberg et al. 1954)?

Since one cannot "eliminate" rhythms by sampling, for instance, at the same time of the day or time of the year, one runs the risk of "eliminating" reliable results, by failing to consider and assess rhythms. Likewise, focusing only upon a single "cycle", whatever its length may be, is not recommended, as seen also from Fig. 3 in Part I, but is much better than ignoring rhythms altogether. For diagnosis and treatment in health care and transdisciplinary science in general, one gains from chronomes in a figurative microscopy and telescopy of unseen as well as seen changes with time that must not be confused with the effect of clock-hours or seasons, as is too often the case.

Width of mapped transdisciplinary spectrum of near-matching cycles

A spectrum of rhythms in and around us, e.g., in the nervous system from high-frequency rhythms in the up to ~1000 Hz discharges of electric fishes to circadians (Halberg et al. 1952) and circannuals in human electroencephalograms can be transdisciplinarily extended with new rhythms having periods, each given with a 95% confidence interval (CI), of 141.52 (CI: 132.14–150.40), 61.51 (CI: 59.98–63.05) and 37.81 (CI: 36.64–38.97) million years in the extinction of genera (Cornélissen et al. 2005a; cf. original findings and review by the scholarship of Rohde and Muller 2005).

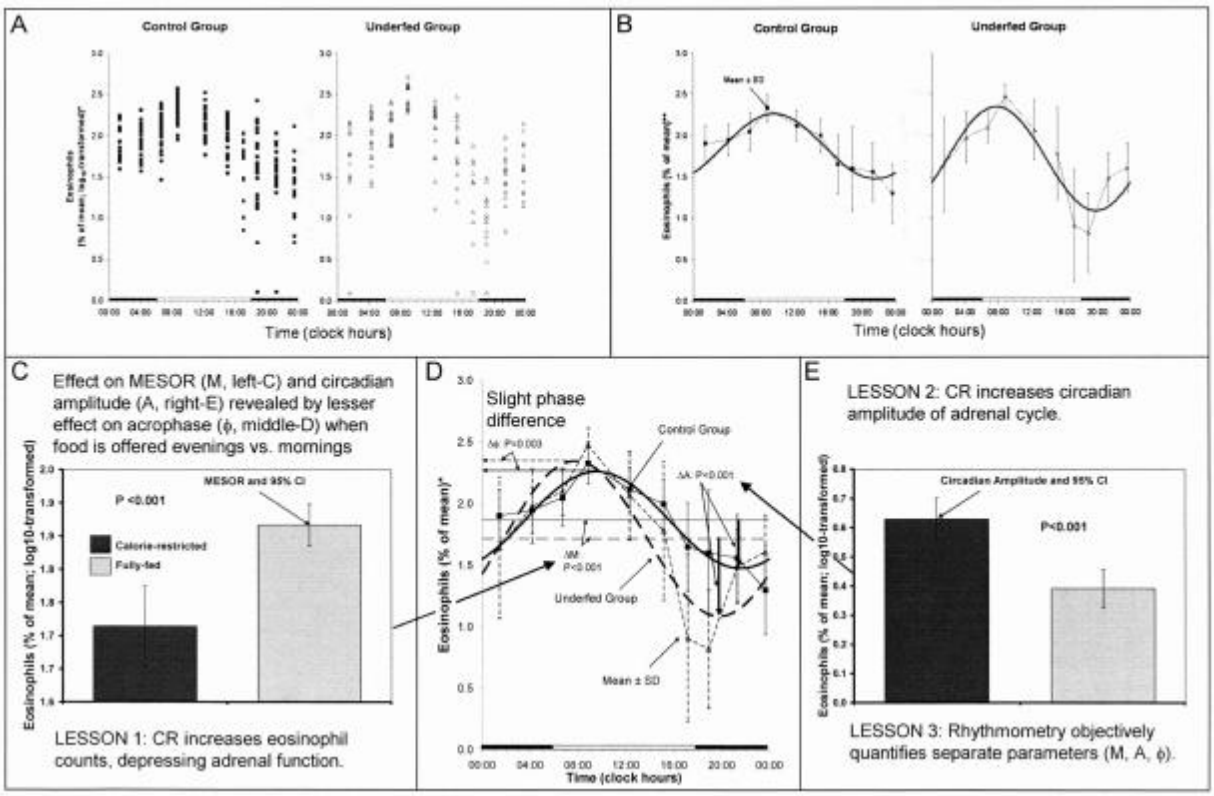

Fig. 11**. Calorie-restricted meal** offered evenings only slightly advances phase (no antiphase versus controls, as seen with morning meals), lowers MESOR and amplifies circadian eosinophil rhythm in C_3H mice with high breast cancer incidence that can be reduced by calorie restriction (CR). Contradictory "stress" or "allergy" effects were replaced by effects upon circadian rhythmic parameters (Halberg et al. 2003a). It is easier to get a parametric answer than to lose decades in uncontrolled "allergy" or "stress" research, as Fig. 10 suggests. In 2006, we have learned that the same situation – a confusing source of blunders or a new endpoint– holds for rhythms other than circadians, as seen in Figs 5 in Part I and 12, and in Maschke et al. (2003), for "stress"-related hormones.
*After $\log_{10}$-transformation of data expressed as percentage of mean. (from Halberg and Visscher 1952)

CHRONOMICS FOR AN IMMEDIATELY APPLICABLE BIOMEDICINE

It seems important to routinely complement the office measurement of BP by prior chronomics. In the case of BP, a chronomic approach could become a model for a future health care: a personalized, more or less continuous *chronomically analyzed surveillance-based evidence* is the goal. It would replace a spurious "evidence-based" medicine that only spotchecks the individual to rely on clinical results from many others also studied,

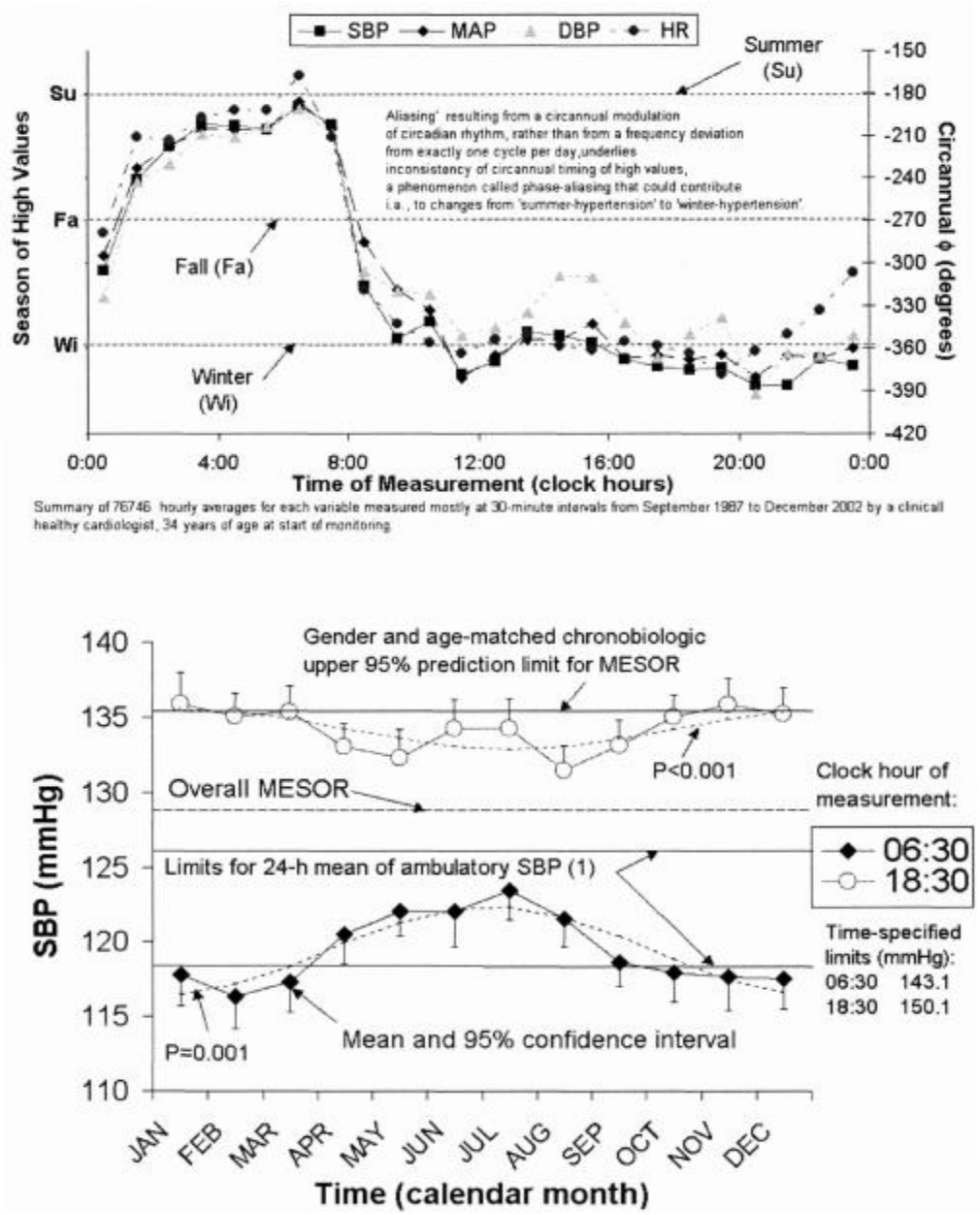

Fig. 12. **Consistent dependence upon clock hour of measurements of circannual acrophase (ϕ) of cardiovascular variables changes from fall and summer (nighttime) to winter (daytime)**. Over 76,000 half-hourly around the clock measurements of systolic, mean arterial and diastolic blood pressure and heart rate were collected with only few interruptions over 15 years by a clinically healthy cardiologist with an ambulatory monitor (Watanabe et al. 2003). Separate averages of 2 measurements for each hour of the day for most of 15 years (5479 days) constituted 24 separate series, each fitted with a 1-year cosine curve. The time of high values is in the summer for data collected between 6 and 7 a.m. and in the winter for data collected between 6 and 7 p.m. Opposite diagnoses were reported earlier (Bartter 1974; Cornélissen and Halberg 1996) as a function of time of day alone. Whether we sample consistently at one time of day or another, rhythmic changes can lead to summer vs. winter hypertension (Halberg et al. 1996, Portela et al. 1996) because the measurements were consistently taken at one clock hour rather than at another, an insufficient basis for deciding on a therapy for the long term based on a few measurements (Watanabe et al. 2003).

not necessarily pertinent to the individual considered. Since subjects in the reference population also provide no more than a spotcheck, one is likely flying blind most of the time with respect to the individual concerned (until longer, preferably lifelong reference standards become available). Today, hypothesis tests (probabilities) and parameter estimations are indispensable in research. Chronomics arrives at decisions requiring probabilities and considering 95% CIs of the estimated parameters for the individual, not only for groups or populations.

This is the more important for the individual whom research results should serve. It becomes possible to implement inferential statistics in actual practice by scrutiny of the structure of a series of systematic measurements. Variability can thus be time-structurally interpreted, what is otherwise possible neither in single nor in repeated single office measurements. Chronomics becomes practical by ambulatory monitoring in 2005 on a community basis (Otsuka 2001, 2002, 2003, 2004, 2005) but can also be implemented with self-measurements (Stinson et al. 2002). Chronomic surveillance thus serves to recognize and treat an elevation only of risk, such as an overthreshold circadian amplitude, without as well as with an elevation of MESOR, and to ascertain the success or failure of treatment, as shown in figures in sections or on pages mentioned below of an international resolution available on the Internet (Halberg et al. 1995).

Care givers and even care receivers, on their own, can, by downloading Halberg et al. (1995) and referring to cited pages:

1. Find and treat risks greater than a high BP, p. 30, sometimes by simply changing the time when they take medication, p. 41
2. Find and treat a larger risk than a high BP, even when the BP is relatively low, p. 29
3. Find and treat BP elevation outside office hours, such as a very high risk of iatrogenic stroke, from medication that acts on BP during office hours but not by night, p. 28
4. Ascertain that a diagnosis and treatment is not dependent on whether a person is seen by a provider in the morning or the afternoon, p. 16. This was the case at the NIH (Bartter 1974) and was recognized as a necessity at some average BP values by an international consensus (Halberg et al. 1995) as well as on theoretical grounds (Cornélissen and Halberg 1996).

Chronomics can thus improve conventional care by better approximating the following aims:

5. To advise people who need treatment for disorders of BP variability to get it, even when the BPs are all within conventionally acceptable limits, and
6. To advise people not to get treated, sometimes for a lifetime, when one may need neither the stigma and cost nor the side effects of treatment, mistakenly based on repeated single office measurements, or
7. To avoid trading a high risk of MESOR-hypertension for an even higher risk of CHAT by taking antihypertensive medication at an inopportune time.

Toward an implementation of these goals, the Halberg Chronobiology Center at the University of Minnesota offers free analyses of 24-hour or longer records (after appropriate arrangements, i.a., for coding are agreed upon) and the opportunity to purchase automatic ambulatorily functioning monitors at an 80% discount in price. Just as air, water and streets must be as clean and safe as possible, a blood circulation, as safe as chronomically possible, is now, as an affordable test, as near as one's e-mail, and is being used by some opinion leaders worldwide: in Japan in two cases city-wide (Hotta et al. 2005, Matsuoka et al. 2005, Murakami et al. 2005, Yamanaka et al. 2005), extending the scope of a model originally developed by the then-mayor of Roseville, Minnesota (Cornélissen et al. 2004b,c).

Fig. 13. **Chronobioethics.** The demonstration in blood pressure recording that the 20-year cycles found in religiosity, crime and war, Table 3, Part I, can be mapped in the individual, Table 2 and Fig. 9, Part I, can be a starting point for focus on diseases of nations by the study of individuals. Just as a micro-organism can multiply to produce a lethal toxin, so can a mentally ill individual, by infecting a population, produce both crime and terror. Starting with focus upon the psychophysiological mechanisms of underlying cycles of diseases of nations, complex relations will have to be resolved, perhaps the major task of applied biomedicine, if humanity is to meet the extremist challenges of our time.

Chronomics is not new.

1. Astute physicians in the pre-computer, pre-satellite era (Vallot et al. 1922) reported an association of mild and severe clinical symptoms with sunspots, Fig. 8 in Part I. Eventually, we will learn how to optimize not only felt and seen aspects of our climate, but also unseen effects identified by a remove-and-replace approach.
2. Just as microbial infections, such as cholera, were documented to flare-up with sunspots, "infections" of populations by one or a few demagogues can lead to harm and diseases of

our civilization, like crime and terror, as visualized by Chizhevsky in 1938. We will need antisepsis before an infection of the minds of the masses spreads. We need the equivalent of asepsis by learning about mechanisms yet to be uncovered that are the figurative "bacilli" infecting the masses and leading to extremes of mass murder. From this viewpoint, the demonstration that 20-year cycles can be found in an individual and that transyears, now confirmed, can be investigated by the remove-and-replace approach, holds the promise of leading to rational countermeasures.

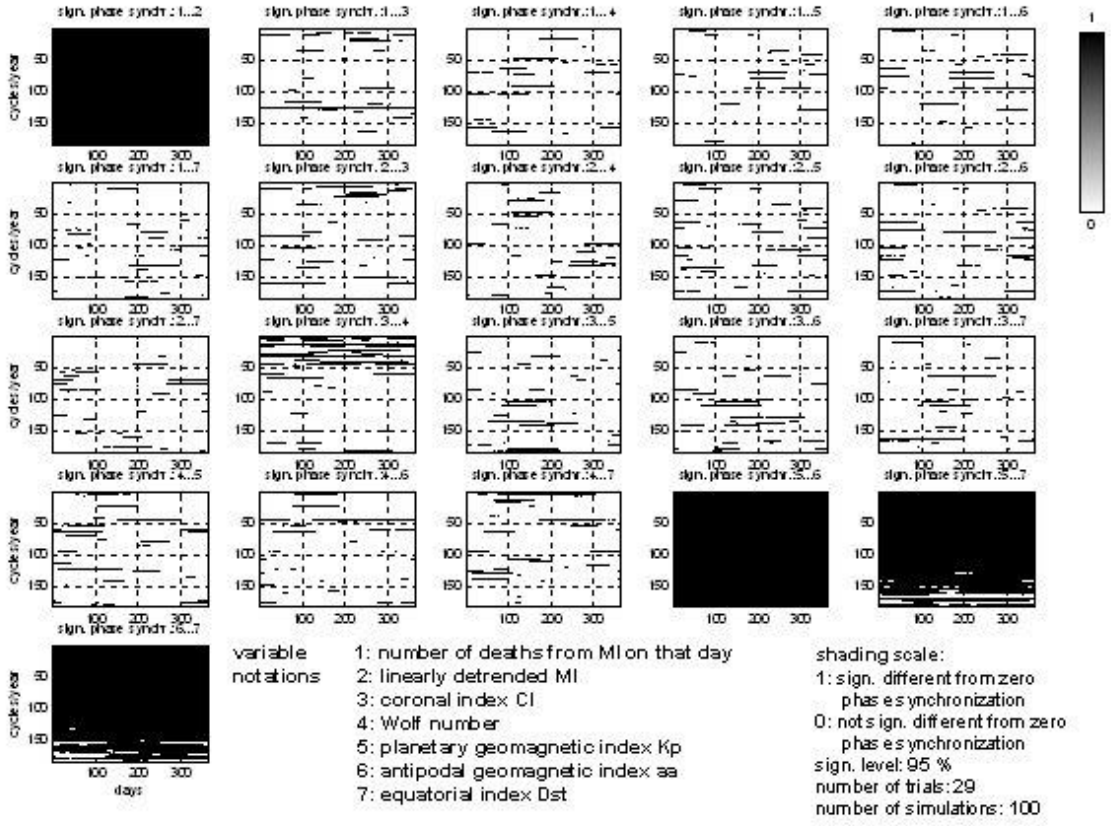

Fig. 14a**. Illustration of one of several approaches to determine non-zero phase synchronization between pairs of variables.** Data are the daily incidence of mortality from myocardial infarction in Minnesota during 1968–1996 (29 years) (variable 1), the same data series after removal of a linear decreasing trend (variable 2), and of different physical environmental variables reflecting the influence of the sun (coronal index and Wolf numbers, variables 3 and 4, respectively) or that of geomagnetism (the planetary index of geomagnetic disturbance K_p, the antipodal index of geomagnetic disturbance aa, and the equatorial index of geomagnetic activity, Dst, variables 5, 6, and 7, respectively). Thresholds for the phase synchronization index (found at each time-frequency for each pair of variables) were computed either by random permutation of trials, here represented by 29 spans of 1-year each, used as replications, by simulation of noise series, or theoretically, according to the Rayleigh distribution. The results obtained by the latter two methods are similar to those shown herein. Anticipated results are obtained, such as 1. the identical time-frequency structure of the first two variables (differing only by the presence or absence of a linear trend), 2. the very close, but not identical, time-frequency structure of K_p, aa, and Dst, K_p and aa being more similar to each other than either one with Dst, and 3. the similarity in the low-frequency region between the two solar variables. Courtesy of the late Barbara Schack (Halberg et al. 2003c).

3. First do no harm: In treating hypertension, do not produce risks greater than hypertension that will be silent both in the conventional office visit and in a conventionally interpreted 24-hour record of blood pressure, Fig. 4 in Part I. An inferential statistical approach can immediately offer P-values and 95% confidence intervals for chronomic decisions in a given individual's diagnosis and treatment. This requirement should become a must for diagnosis and treatment today in cardiology and tomorrow in fighting crime and terror.

For an individual's prevention of vascular disease by an immediate application of chronomics,

it is good to remember Theodore C. Janeway (1904): … *it is essential* that a record of the pressure be made at frequent intervals *at some time previous* (presumably to an examination), to establish the *normal level* and the *extent of the periodic variations.* When this is done, it may be possible to demonstrate changes of small extent, which, lacking this standard for comparison, would be considered within the limits of normal variation (Janeway 1904).

Decades thereafter, a magnifying-glass equivalent, the cosinor, became available and Frederic C. Bartter (of Bartter syndrome fame) wrote (1974) of a patient whose BP was diagnosed differently by two physicians who saw him at different times of day.

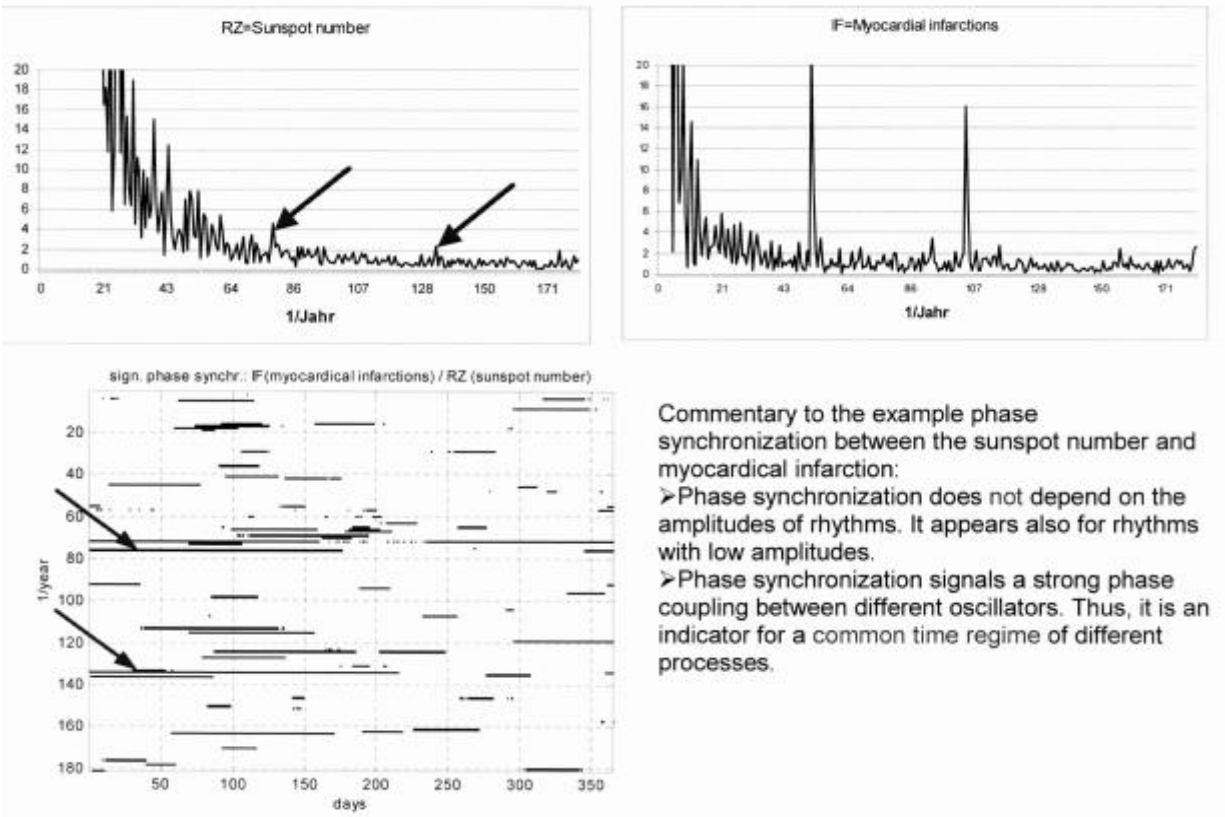

Fig. 14b**. Inferences concerning the time-varying nature of associations among physical and biological variables** drawn by the late Dr Barbara Schack, also based on results in Fig. 14a. Courtesy of the late Barbara Schack (Halberg et al. 2003c).

By conventional standards, this patient is clearly normotensive every morning. But the blood pressure determined each day at 6 in the afternoon provides especially convincing evidence that this patient is a hypertensive. My plea today is that information contained in (data curves compiled under differing circumstances, such as 24 hours a day/7 days a week) become a *routine minimal amount* of information accepted for the description of a patient's blood pressure. *The analysis of this information by cosinor should become a routine.* It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, to wit, an estimate of M (the time structure or chronome-adjusted mean, or MESOR) an estimate of (the amplitude) A itself, and finally an estimate of acrophase, ϕ (a measure of timing). In this way, a patient can be compared with himself at another time, or under another treatment, and the patient can be compared with a normal or with another patient (Bartter 1974).

Disorders of variability

The failure of current health care to treat risks greater than hypertension, that sometimes need only a change in the timing of medication, must not follow the example of Semmelweis who, in the fight for antisepsis and asepsis, accused his colleagues of being 'murderers' (Sutcliffe and Duin 1992).

We paraphrase Oliver Wendell Holmes, who had recognized the problem before Semmelweis and Lister did, and hope that chronomic facts (Holmes referred to "medical logic") will be considered and taught in modern-day schools (Halberg et al. 2000b, Kiser 2005). A single office

BP measurement cannot detect a variability disorder, nor can a day-night ratio do equally so with statistical significance in the light of outcomes (Otsuka et al. 1996, Cornélissen et al. 2000b, 2001; Bingham et al. 2005). An international project on The BIOsphere and the COSmos, BIOCOS (Halberg et al. 2000a), provides participants with an 80% reduction in the purchase price of automatic monitors of BP and HR for ambulatory use and with chronomic analyses in the light of an accumulating data base. Some readers may use this opportunity for health care of themselves or of their acquaintances (including patients) and some may decide to monitor themselves in the long term for basic science as well. Fig. 15a shows that the treatments at different times are not equivalent.

Chronomic surveillance serves to recognize and treat any risk elevation as well as overt disease, and to ascertain whether and, if so, for how long treatment effects last, be it for lowering an increased risk and/or in surveilling the success or failure of BP lowering or raising, as need be. Statistical inference can be obtained for the individual patient by means of parameter tests (Bingham et al. 1982) and by sequential tests such as the self-starting cumulative control chart (Cornélissen et al. 1997) once longitudinal records are available. A case illustrated in Fig. 15 shows that the anti-hypertensive medication is effective (Fig. 15a), the MESOR of SBP being lowered with statistical significance, as evidenced by the breakout downward outside the decision interval of the negative CUSUM line.

The initial decline coincides with the start of treatment. Relying on an N-of-1 chronobiologic

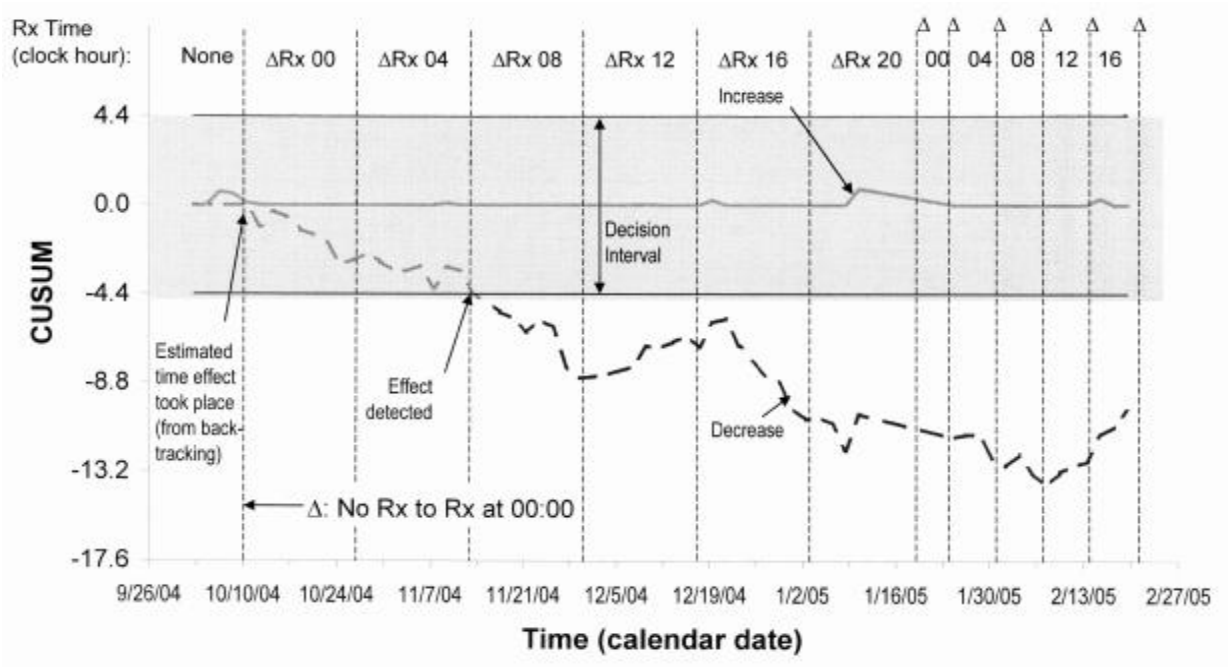

Fig. 15a**. Changing timing of medication (ΔRx) during consecutive spans shows efficacy of treatment.** An empirical approach to chronotherapy: immediately after diagnosis, one should ascertain that the treatment is effective. Optimization of treatment effects by timing can be achieved for the individual patient by systematically changing, e.g. advancing the time of treatment. Successful treatment of MESOR-hypertension assessed by a self-starting cumulative sum control chart (Cornélissen et al. 1997). To optimize his hypotensive treatment (R_x), a just-diagnosed 24-year-old individual (TT) switched his R_x first every 17 days by 4 hours and then mostly at shorter intervals. Note statistically significant decrease in MESOR, evidenced by the breakout outside the decision interval of the negative CUSUM line. With continued R_x, the blood pressure MESOR leaves the decision interval, indicating a statistically significant decrease in overall blood pressure.

pilot design, treatment time was advanced by 4 hours, initially every 17 days, and at shorter intervals thereafter. Rx 12 was associated with a reversal of the up-to-then continuous decrease. Fig. 15b indicates that for this subject, treatment in the evening is associated with an elevation in the circadian amplitude of BP. Such an increase in circadian amplitude of BP may induce iatrogenic CHAT in some patients, thereby increasing cardiovascular disease risk unknowingly. We must

not trade eliminating the lower risk of hypertension to acquire the higher risk of CHAT. The large risk of CHAT is further illustrated in Fig. 16 IIA-C.

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INSERT 1:

International consensus on the following requirements (1 and 2) and desiderata (3–11) concerning rhythms and broader chronomes (time structures) (Chibisov 2005).

Validation of the occurrence of a transient or regularly recurrent oscillation frequency:

1. A no-cycle (zero-amplitude) test (Halberg 1969, Cornélissen and Halberg 2005a, Refinetti 2006).
2. Estimation of parameters, such as period, τ, and at each τ, of the amplitude, A, phase, ϕ, and waveform, (A, ϕ) pairs of harmonics and of the uncertainties such as 95% confidence intervals of τ, A, ϕ and (A, ϕ) pairs of harmonics.
3. (Validation also by) transdisciplinary matching cycles (Halberg et al. 2000a).
4. A remove-and-replace approach, where removal within an organism is done by surgery or disease (Halberg et al. 1951) and outside organisms is done by the environment (e.g., the sun) (Cornélissen et al. 1996).

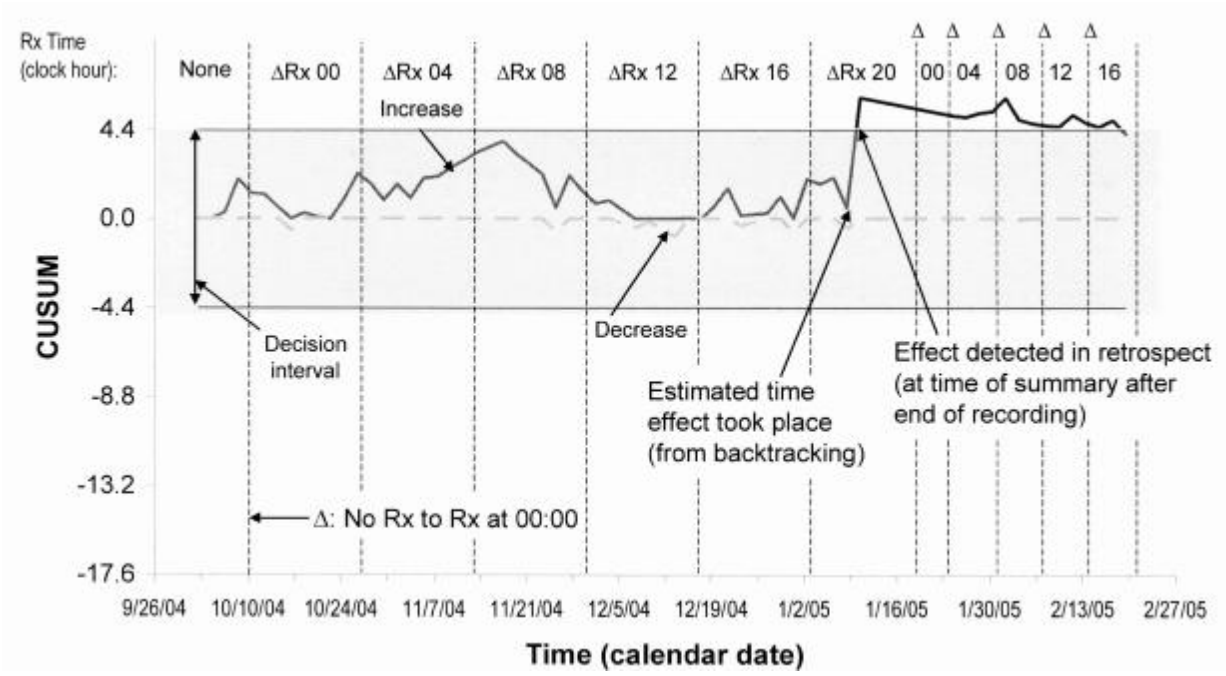


Fig. 15b. **Changing timing of medication (ΔRx) during consecutive spans shows risk of iatrogenic CHAT.** An empirical approach to chronotherapy: immediately after diagnosis, one should ascertain that one does not induce circadian hyper-amplitude-tension (CHAT) by inappropriate timing of anti-hypertensive medication. In this 24-year old man (TT) who advanced the time of treatment by 4 hours every 17 days initially and at shorter intervals thereafter, treatment in the evening was associated with iatrogenic CHAT, raising the question whether the risk of MESOR-hypertension may not have been traded for the even higher risk of stroke that CHAT represents (see p. 30 of Halberg et al. 1995). Iatrogenic circadian hyper-amplitude-tension, CHAT, induced by treatment at 20:00 daily, was silent to office visits. TT may have traded benefit (lowering of the MESOR of blood pressure, Fig. 15a) for something worse (circadian overswinging of blood pressure). This danger applies to some hypertensives (who tend to have a large circadian amplitude of blood pressure) to whom treatment time is not specified by the care provider, as was the case for TT (or is specified for bedtime). A few others who took hypertensive medication at bedtime were also found to have CHAT. The figure also shows the assessability of otherwise undetected harm by as-one-goes sequential analysis.

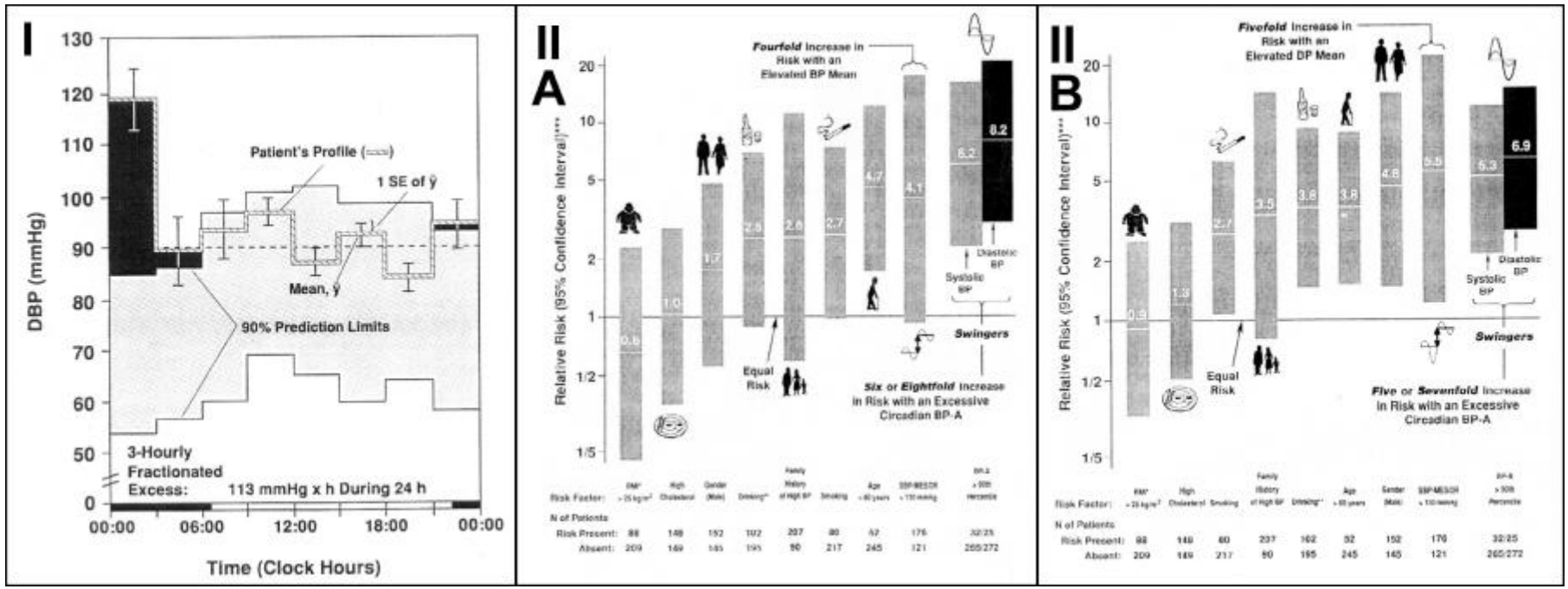
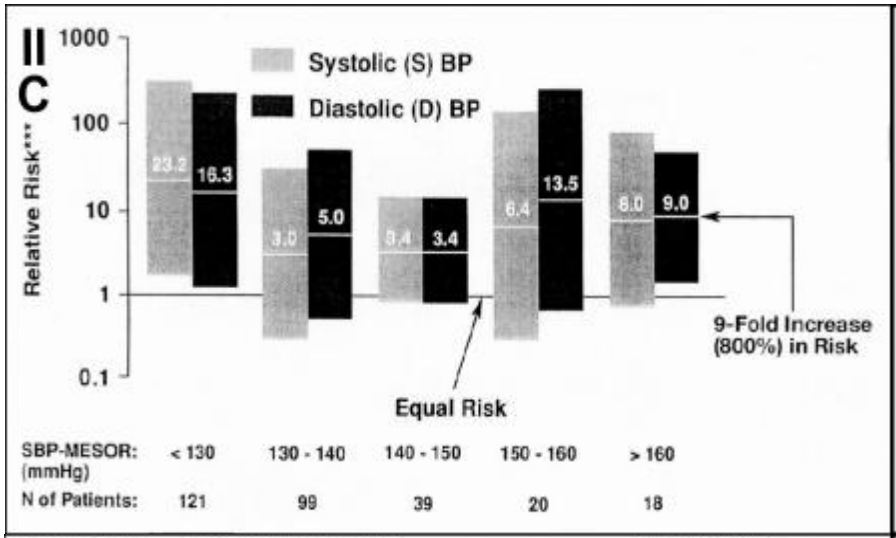
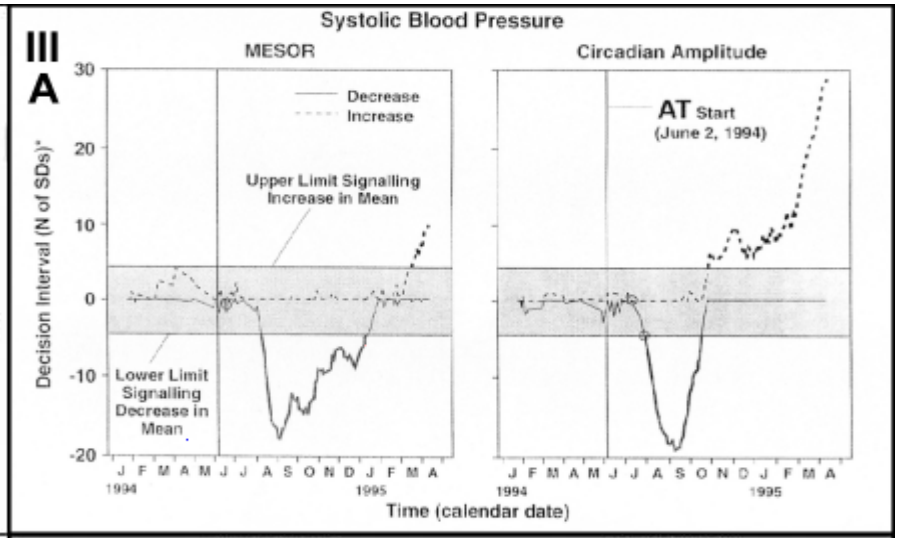


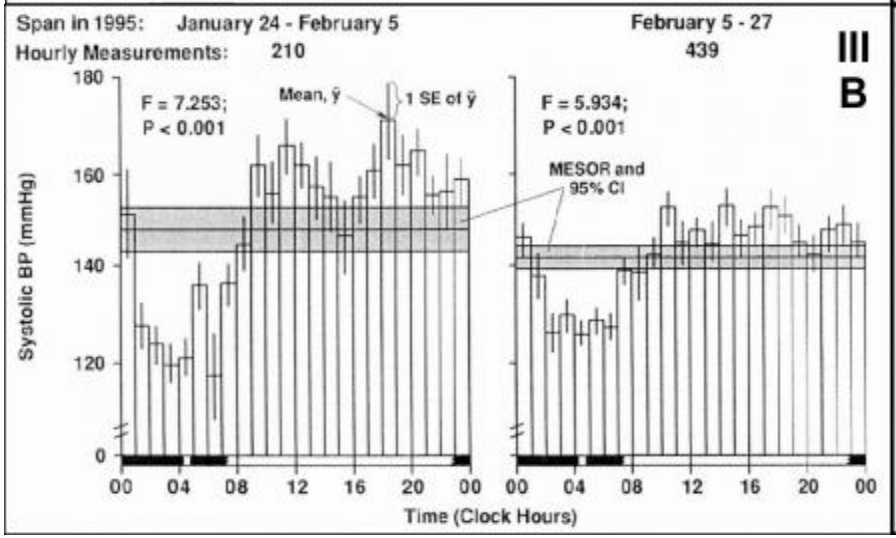
Fig. 16. **Chronomics detects nocturnal escape from treatment (I), risk of stroke and nephropathy, greater than hypertension (IIAB), even in MESOR-normotension (IIC) and monitors transient and/or lasting success of treatment (IIIA-C)*.** Illustrative results supporting the need for continued surveillance and for a chronomic analysis of the data.
Merits are:

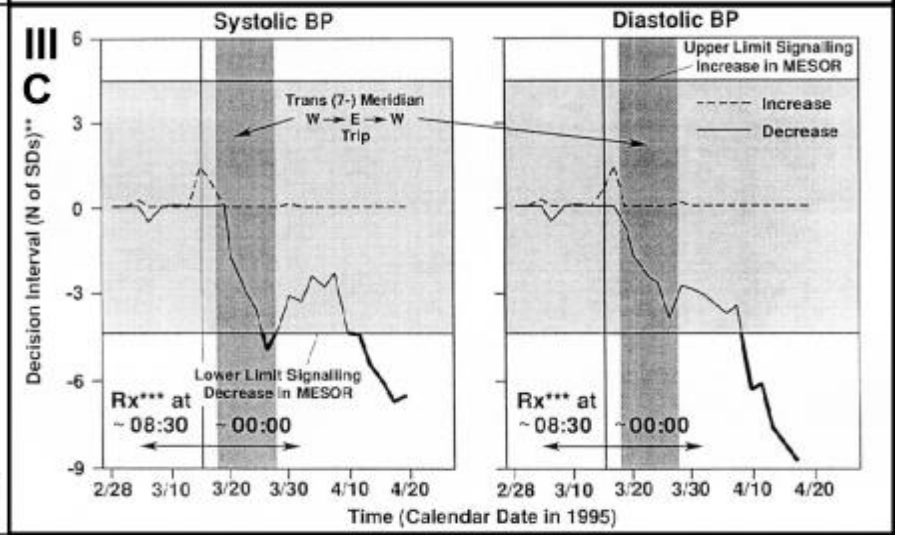
- Detection of abnormality during the night when medication is no longer effective, not seen during office visits in the afternoon (I);
- Detection of abnormal circadian pattern of blood pressure (CHAT, "overswinging") associated with a risk of cerebral ischemia and nephropathy larger than other risks (including "hypertension") assessed concomitantly (IIA and B);
- Finding that CHAT carries a very high risk even among MESOR-normotensives who do not need anti-hypertensive medication (IIC);
- Availability of statistical procedures such as a self-starting cumulative sum (CUSUM) applicable to the individual patient to determine whether an intervention such as autogenic training is effective and for how long the intervention remains effective (IIIA);
- N-of-1 designs for the optimization of treatment timing: the same dose of the same medication can further lower the same subject's blood pressure MESOR and circadian amplitude when the timing of daily administration is changed (IIIB and C), as ascertained by as-one-goes (sequential) testing and parameter tests, procedures applicable to the given individual.

Fig. I – Stacked from 11 days of around-the-clock monitoring. Office spotchecks cannot detect nocturnal pathology. Fig. II A – Among risk factors, an excessive circadian blood pressure (BP) amplitude (A) raises the risk of ischemic stroke most. Fig. II B – Among risk factors, an excessive circadian blood pressure (BP) amplitude (A) raises the risk of nephropathy most. Fig. II C – An excessive circadian blood pressure (BP) amplitude (A) is a risk factor for ischemic stroke independent from the 24-hour mean (MESOR). Fig. III A – Individualized assessment (by CUSUM) of a patient's initial response and subsequent failure to respond to autogenic training (AT) (EO, F, 59 y). Fig. III B – Individualized blood pressure chronotherapy. Lower circadian double amplitude (2A) and MESOR (M) after switching treatment time from 08:30 (left) to 04:30 (right)*. Fig. III C – Control chart assesses individualized anti-MESOR-hypertensive chronotherapy.


II C
Relative Risk***
1000
100
10
1
0.1
Systolic (S) BP
Diastolic (D) BP
23.2
16.3
3.0
5.0
3.4
3.4
6.4
13.5
6.0
9.0
9-Fold Increase (800%) in Risk
Equal Risk
SBP-MESOR: (mmHg)
< 130
130 - 140
140 - 150
150 - 160
> 160
N of Patients:
121
99
39
20
18


III A
Systolic Blood Pressure
MESOR
Circadian Amplitude
Decision Interval (N of SDs)*
30
20
10
0
-10
-20
Decrease
Increase
Upper Limit Signalling Increase in Mean
Lower Limit Signalling Decrease in Mean
AT Start
(June 2, 1994)
J F M A M J J A S O N D J F M A
1994
1995
Time (calendar date)


Span in 1995:
January 24 - February 5
February 5 - 27
Hourly Measurements:
210
439
III B
Systolic BP (mmHg)
180
160
140
120
0
F = 7.253;
P < 0.001
Mean, ȳ
1 SE of ȳ
F = 5.934;
P < 0.001
MESOR and 95% CI
00 04 08 12 16 20 00
Time (Clock Hours)


III C
Systolic BP
Diastolic BP
Decision Interval (N of SDs)**
6
3
0
-3
-6
-9
Trans (7-) Meridian W → E → W Trip
Upper Limit Signalling Increase in MESOR
Increase
Decrease
Lower Limit Signalling Decrease in MESOR
Rx*** at ~ 08:30
~ 00:00
2/28 3/10 3/20 3/30 4/10 4/20
Time (Calendar Date in 1995)

5. Check any phase-response curve, such as hours of changing resistance (Halberg 1969; Reindl et al. 1969).
6. Also do these steps at the next lower frequency if data permit.

Explanatory note

The foregoing can be reviewed in the context of:

7. Chronomes (time structures) consist of trends and chaos as well as a broad spectrum of multifrequency rhythms (Halberg et al. 2003a). Hence, if the data series is long enough, we look for trends which not only could be part of any cycle with lower frequency but can be bona fide aspects of development and aging (Halberg et al. 2001).
8. Look for nonlinearity and for endpoints of chaos in dense data.
9. Look for interactions by cross-spectral coherence and phase synchronization among series in and around us, as feedsidewards (Halberg et al. 2000c).
10. Look for relative prominence by amplitude ratios of spectrally neighboring photic and nonphotic cycles during ontogeny.
11. Look for relative prominence by amplitude ratios of spectrally neighboring photic and nonphotic cycles during phylogeny.

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