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Presentation

Chronomics

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Summary – Several international meetings have revealed an accumulating body of reference values for well-established about-daily and about-yearly rhythms of photic origin and evidence also for about-7-day, -27-day, -half-yearly, -10.5- and -21-yearly, and even -50-yearly rhythmicities in us as well as around us, as invisible non-photic heliogeophysical signatures possibly built into individuals and/or populations, complementing the biological year and day. In time series (biological or other) that are dense and sufficiently long, the characteristics of rhythms, chaos (deterministic and other) and trends can all be quantified as elements of structures called chronomes. Chronobiological methodology assesses uncertainties in comparisons of endpoints in all elements of chronomes, before and after: 1) changes in lifestyle, such as meal quality, quantity, timing and salting of the food; 2) preventive non-drug interventions to limit the risk of vascular disease; or 3) drug treatments for high-risk subjects as well as for those with actual vascular disease, all on a practicable, individualized and also a general population basis. A collateral hierarchy characterizes molecular to psychosocial aspects of living beings that are exposed to their socio-ecological environs and thus are synchronizable and/or otherwise manipulable by society, meals, lighting, heating, and non-photic, non-thermic environmental variations that become predictable to the extent that they appear to constitute cycles, yet adhere only to a statistical, rather than a deterministic causality. With this qualification, chronome mapping with outcomes could eventually serve an individualized optimization of lifestyle, for chronoprevention and chronotherapy as well as for inquiries into the evolution and future of life. © 2001 Éditions scientifiques et médicales Elsevier SAS

chaos / trend / rhythm / constituent / structure / time

CHAOS, TRENDS AND/OR RHYTHMS CONSTITUTING STRUCTURES IN TIME

The popular press, and also scholarly journals such as *Science* [89, 98, 102] and *Nature* [93], often regard chronobiology a subject dealing with biological clocks and calendars, eventually indicating when to eat [19, 98; cf. 33, 50, 91], to treat [33, 34, 91, 98], and when best to perform in school, at work, in hobbies or for sports. Needless to say, the question of 'when' is often raised (restricted) as to clock-hours or calendar dates. This is an important intermediate step, shown in *figure 1A*, from the concept of a putative balance or homeostasis, on the left, to the middle of this figure, to Johnson's "exceptionally substantial and durable self-winding and self-regulating physiological clock" ([67]; cf. [29]). Since there are clocks galore [89], we had best take the often-indispensable next step is from the middle to the right of *figure 1A*. The attractive simple models (middle) cannot account for more complex circumstances in an organism's time structures that contain more built-in rhythms than the circadian, and further chaos

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and trends within us, leading to possibly genetically anchored chronomes. Moreover, the rhythms of internal chronomes intermodulate with a host of cycles in the environment, while environments also contain interacting chaos and trends [13]. In this context, the complex right portion of *figure 1A* calls to mind Einstein's adage that everything must be made as simple as possible, but not simpler. Concepts such as clocks, calendars or oscillators have served as useful scaffolds, but inferential statistical methods applied to time series are needed for resolving the complex sources of variability and their underlying chronomes ([15, 84]; cf. [74])[1].

If one measures densely enough, deterministic and other chaotic endpoints can be computed in sets of environmental and biological variables such as a correlation dimension [9, 24, 84, 86] or an approximate entropy or complexity, as one element of chaos in chronomes. A second element of these chronomes consists of trends, which can be approximated by polynomials, to quantify them during development and aging, and also with, e.g., disease risk increase, starting at birth [38]. If one samples long enough, trends can turn out to be roughly periodic components *(figure 1B-D)* [39, 44]. Indeed, the third and major insofar as the predictable element of chronomes is a spectrum of periodicities or near-periodicities, in us or around us. It comprises changes with periods ranging from fractions of a second to decades, assessed before or after detrending by linear-nonlinear rhythmometry: *Figure 1E-G*, including circadians; *figure 1H*, about 10.5-year; *figure 1I-J*, about 21-year; and *figure 1K*, about 50-year cycles, the latter mainly mapped thus far in populations by neonatal anthropometry in 112 years of data, and for stroke in Minnesota, USA and in the Czech Republic only for the past half-century [43].

Data inspection (eyeballing) of time plots and analyses of variance, albeit useful, is often not sufficient for dealing separately or in combination with all the characteristics of the rhythmic component of time structure *(figure 2A, B)*; section IIA of *figure 2* (in the two swarms of measurements on the right) clearly shows why the eyeballing of original data can lead to claims that the circadian temperature rhythm is lost after ablation of the suprachiasmatic nuclei (SCN). Whether the time scale for plotting is squeezed (top of section IIA, *figure 2*) or stretched (bottom of section IIA, *figure 2*), the rhythm clearly seen in the two swarms of dots on the left seems lost on the right. After stacking, eyeballing suffices to 'see' the rhythm, e.g., in section I (top) for the SCN-ablated animals separately, or averaged in section IIB. For quantification, time-microscopic inferential statistical methodology [16, 32], also shown in *figure 2A, B*, is essential.

Macroscopy (left) and microscopy (right) in each section are aligned in sections I–V and VII–VIII of *figure 2B*. On the right, in sections I–V, VII and VIII, a time-microscopic display in polar coordinates shows the extent of change, amplitude, by the length of a vector while the vector's angle represents the acrophase, the time of high values. The ellipse around the tip of the vector represents the 95% confidence region of the amplitude-acrophase pair; when it does not overlap the center of the plot (the pole), a rhythm is demonstrated, as it is in all cases except for water drinking (section VIII), for which the ellipse covers the pole; and hence the zero-amplitude assumption tested by the ellipse is not rejected, and a rhythm is consequently not demonstrated.

Pole overlap, such as that for the case of water consumption (section VIII), is not seen for ethanol drinking. For the latter variable and all others, a rhythm is demonstrated and except for DNA labelling in the stomach, the circadian amplitude is reduced by ablation of the SCN. In all cases, the phase is advanced, as succinctly summarized in the chronome map in section VI, *figure 2B*. The usual concern about point estimates of period and phase is best complemented by uncertainty estimates, including those of amplitude and, when the density of the data permits, of waveform. Each of these parameters is to be given whenever possible with interval estimates. An indication of the uncertainties involved is particularly important when long-term treatment is the issue [16, 33, 86].

The estimation of characteristics from cosine fitting provides endpoints in several fields, from problems of eating and salting of food to treating disease, and is indispensable for otherwise silent disease risk recognition and for lowering risk by precautionary intervention. A dividend of curve-fitting is an improved assessment of a time structure-adjusted mean or MESOR, of general interest in science since,

[1] From *chronos*, time, and *nomos*, rule, rather than from alternate derivations [74].

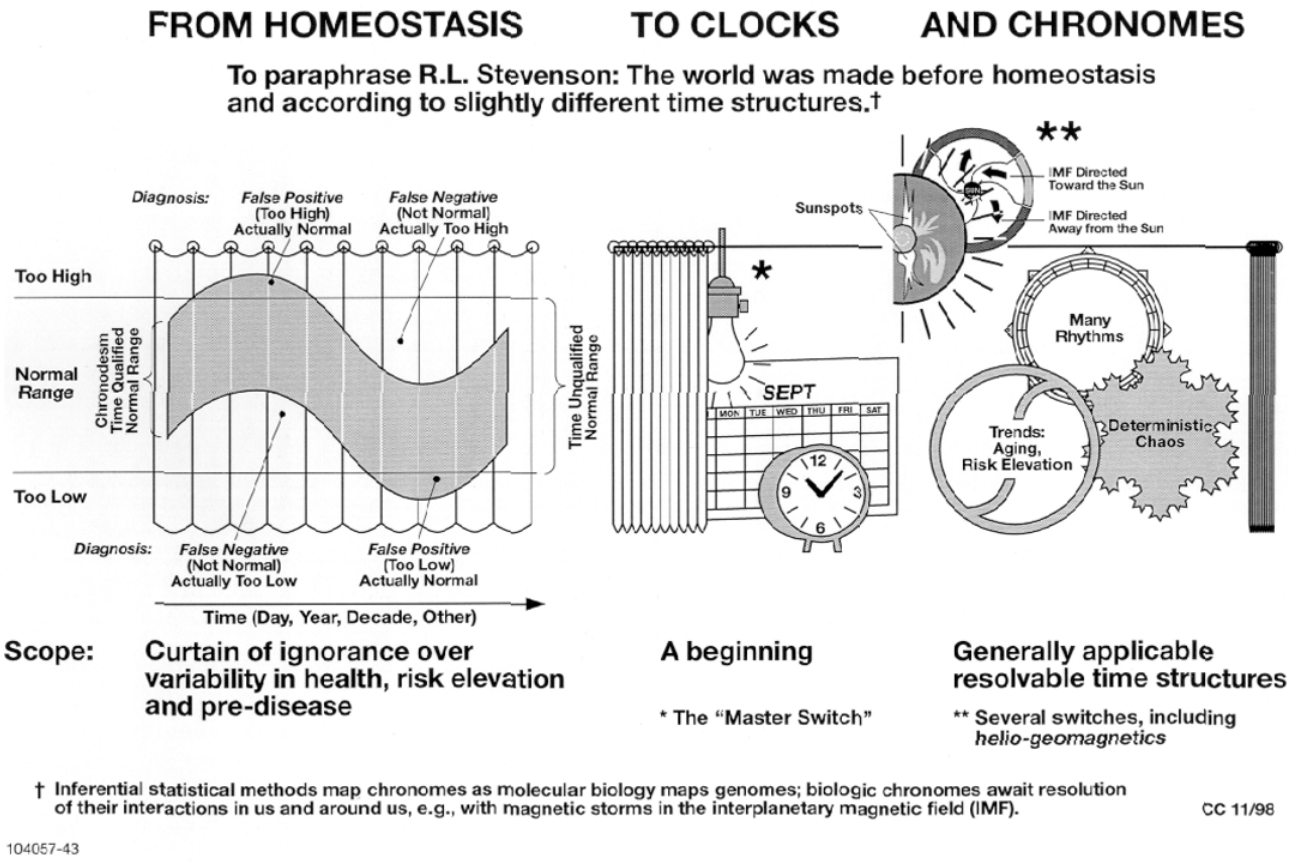


Figure 1. A. We turn from a master clock serving regulation for constancy to an integrative internal-external collateral hierarchy for physiological coordination. Homeostasis postulates that physiological processes remain largely within a certain range in health, and seeks to depart from such 'normal values' to diagnose overt disease. Thereby, variability within the normal range, however, is often dealt with as if it were narrow, random or trivial, the body striving for at least a relative 'constancy'. The alternative, rather than the complement, to this status quo, on the left of this figure is learning about the rules of rhythmic and chaotic variations that take place within the 'usual value' range that led to the postulation of a 'biological clock' that would enable the body to keep track of time. By removal and replacement experiments, it was located first in the adrenal, shown to be responsible for some but not for other circadians that persisted after brain ablation. The fact that single cells and even bacteria are genetically coded for a spectrum of rhythmic variation indicates that the concept of a 'clock' needs extension. Beyond clocks and calendars, we recognize a biological week, a biological decade and also other rules found in variability, such as deterministic chaos and long-known trends, some of which may turn out to be cycles. When the giant alga *Acetabularia*, a prominent model of a 'clock', is placed in continuous light, its spectrum of electrical activity reveals the largest amplitude for a component of about one week rather than one day. When over a decade of studies on this alga are pooled, an about 10-year cycle emerges in the data set as a whole. The alignment of spectral components and chaos and trends in and around us has also begun. Long-term longitudinal, but not yet entire lifetime monitoring of critical variables complements current linked cross-sectional (hybrid) reference values required for preventive health and environmental care. Changes occurring within the usual value range, as increasingly longer cycles are resolvable as chronomes with a (predictable multifrequency) rhythmic element, allow us to measure the dynamics of everyday life, in order to obtain, e.g., warnings before the fait accompli of disease, so that prophylactic measures can be introduced in a timely manner; and to detect heretofore largely undetected or unquantified environmental effects. The abstract sketch of the sector structure of the interplanetary magnetic field (shown on the top right by three visible arrows, the fourth being covered by another circle showing solar flares) is an idealized presentation of the sector structure in the interplanetary magnetic field. The parameters of the solar wind are much more variable than originally visualized when first described, as sketched by irregular solar flares. Associations between helio- and geomagnetic variability, myocardial infarction and stroke are accumulating and are just the tip of the iceberg, with a highly significant effect of magnetism (recognized by Gilbert in 1600), apparent in the human electrocardiogram (ECG), notably in the auroral region. In external-internal interactions, a broad spectrum of rhythms (both in the environment and in living matter) organizes deterministic and other chaos and trends. Trends pursued long enough may become low-frequency cycles, e.g., for the detection of any increased risk and so that timely action may be taken. © Halberg.

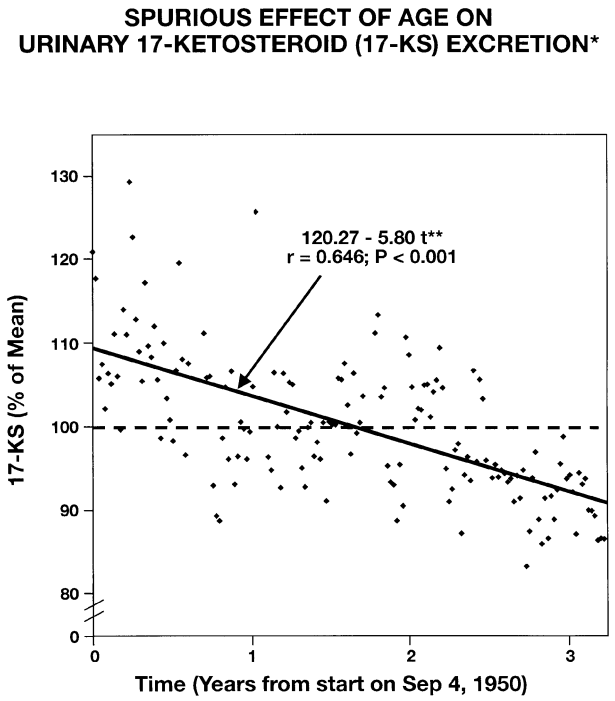


Figure 1. B. In the absence of systematic chronome mapping, with apparently ample documentation, a decrease over several years in metabolites related to the adrenal and the male gonad (in the excretion of 17-ketosteroids) may be taken as a sign of aging, notably of the declining sex gland activity, and this observation may be published as such in any professional journal (but see *figure 1C*) [39, 44]. © Halberg.

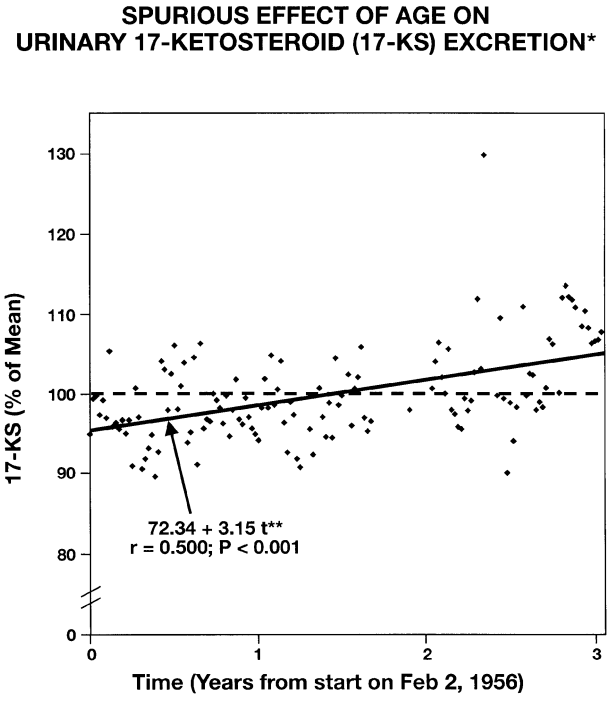


Figure 1. C. A surprising increase in steroidal metabolites (gonadal activity?) in a man in his fifties constitutes a statistically but not biologically significant effect which may encourage speculation, perhaps by post hoc ergo propter hoc reasoning about how the increase in 17-ketosteroid excretion (rejuvenation?) came about. The authors were tempted to publish *figures 1B* and *C* separately in different professional journals to show that referees are unlikely to question trends, and to validate the need for longitudinal and concomitant mapping all three elements (chaos, rhythms and trends) of chronomes instead of spotchecks for aging, irrespective of rhythms [39, 44]. © Halberg.

as compared to the arithmetic mean, in series characterized by rhythms the MESOR is usually more accurate in the case of unequidistant data, and more precise in the case of equidistant data *(figure 3)*. Recent meetings on chronomics ([80-82, 85]; cf. [42]), considering data covering somewhat more than a century, have documented time structures characterized by rhythms that replace confounding secularity *(figure 1B-D)* [39, 44]. A wealth of detailed information obtained in chronobiology on a collateral hierarchy [48] in the circadian system, ready not only as a basis for further research but some of it also for immediate utilization in everyday life, is here illustrated in a historic context.

STARTING MILLENNIA AGO AND PERSISTING TODAY

In his scholarly studies, the late Jürgen Aschoff [3] traced the roots of thought on rhythms back to a fragment of verse by Archilochus of Paros (ca. 680–640 BC): γιγνοσχε δ′οιοΣ ϱυΘμοΣ ανΘϱοπον εχει (“Recognize which rhythm governs man”). In finding this fragment of verse by Archilochus, Aschoff demonstrated the existence of a link between solar physics and human rhythmicity which goes as far back as seven centuries before the Com-

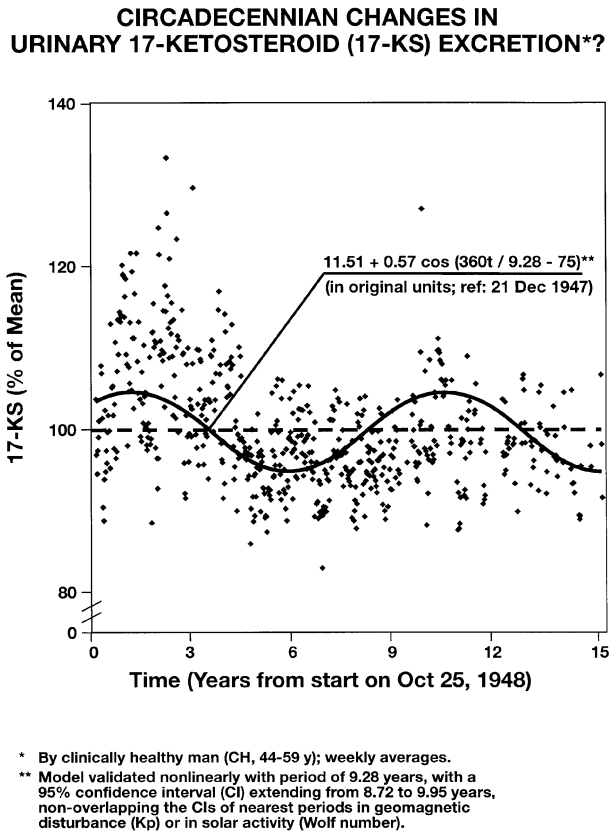


Figure 1. D. By detecting an about 9-year rhythm, this figure resolves any controversy that may have arisen from the separate viewing of *figures 1B* and *C*. To the extent that in the future such rhythmicities can be reproduced repeatedly in several different persons, and to the extent that such cycles reveal a non-overlap of the 95% confidence intervals with those of cycles in solar activity or in geomagnetic disturbance indices, one may postulate that such changes, like the circadians or the about-7-day (circaseptan) rhythms, are built into us by an evolutionary integration of life into its environmental invisible non-photic chronome in the velocity changes of the solar wind. Corpuscular effects, e.g., from the sun, complement the effect of visible light and readily recognized temperature, and can be ascertained beyond similar spectral signatures and cross-spectral coherence by remove-and-replace approaches, including superposed epochs. © Halberg.

mon Era (as validated by the date of an eclipse)[2]. Hippocrates, Aristotle and Galen were also included in Aschoff's gallery of ancestors along with other scholars up to his own day, which was crowned by his implied recognition in 1974 of, as he put it, the need for a 'cosinor beast' (read objective quantification) [3]. Rhythm 'analysis' carried out time-macroscopically and only with data inspection by the unaided eye can mislead and result in decades of erroneous inferences about an absent rhythm (e.g., see *figure 2A*, section IIA, right), whereas the stacking of the same data (sections I [top] and IIB), does reveal the rhythm, and an analysis of variance (ANOVA) establishes its statistical significance; yet none of these steps replaces the complementary and necessary computer-aided quantification of universally applicable endpoints, such as amplitudes and phases [15, 16, 32, 50]. The cosinor approach provides objective, generally applicable endpoints whereby much controversy can be avoided *(figures 1B-D* and *2A, B)*.

CENTURIES AGO AND TODAY

In a thesis published in Paris on April 23, 1814, Julien-Joseph Virey ([103]; cf. [33]) wrote that an individual who during a 24-hour period eats only once in the evening could find himself with a 'nuance of temperament' different from that of somebody who eats only in the morning. For him, "… the morning meal will be the most salutary and the most rejuvenating." Similarly, the administration of any given drug is not indicated equally at all hours (cited from [33]; original [103]). In keeping with Virey's insights, in 1937 Arthur Jores labeled the neglect of timing as "the idiocy of 'three times a day'" [68]; Werner Menzel developed the first drug pump for timed treatment [78]; and this year Stokkan et al. suggested the manipulation of both meal and drug timing [98], all at variance with what seems conventional today. At the beginning of the 21st century, three meals for nutrition, or at least a single daily dose of a long-acting drug, sometimes labelled 'chronotherapeutics' [2], do not take into account the merits of individually targeted timing by marker rhythms [45]. An affirmative answer to the importance of what we eat and with what we treat, the main topic of the sciences of nutrition and pharmacology, in no way detracts from the importance of timing, implicit in Archilochus's fragment of verse.

To Jean-Anthelme Brillat-Savarin's (1755-1826; *Physiologie du goût*), we owe the familiar aphorism (No. 4 in a list at the beginning of Volume 1), *Dis-moi ce que tu manges, je te dirai ce que tu es* ("Tell me what you eat and I will tell you who you are", or its popular paraphrase, "You are what you eat"). But

[2] Archilocus was reputedly inspired by the solar eclipse of April 6, 647 BC, which, he wrote, "made night from midday, hiding the light of the shining Sun", and this event authenticates his contribution from the 7th century BC.

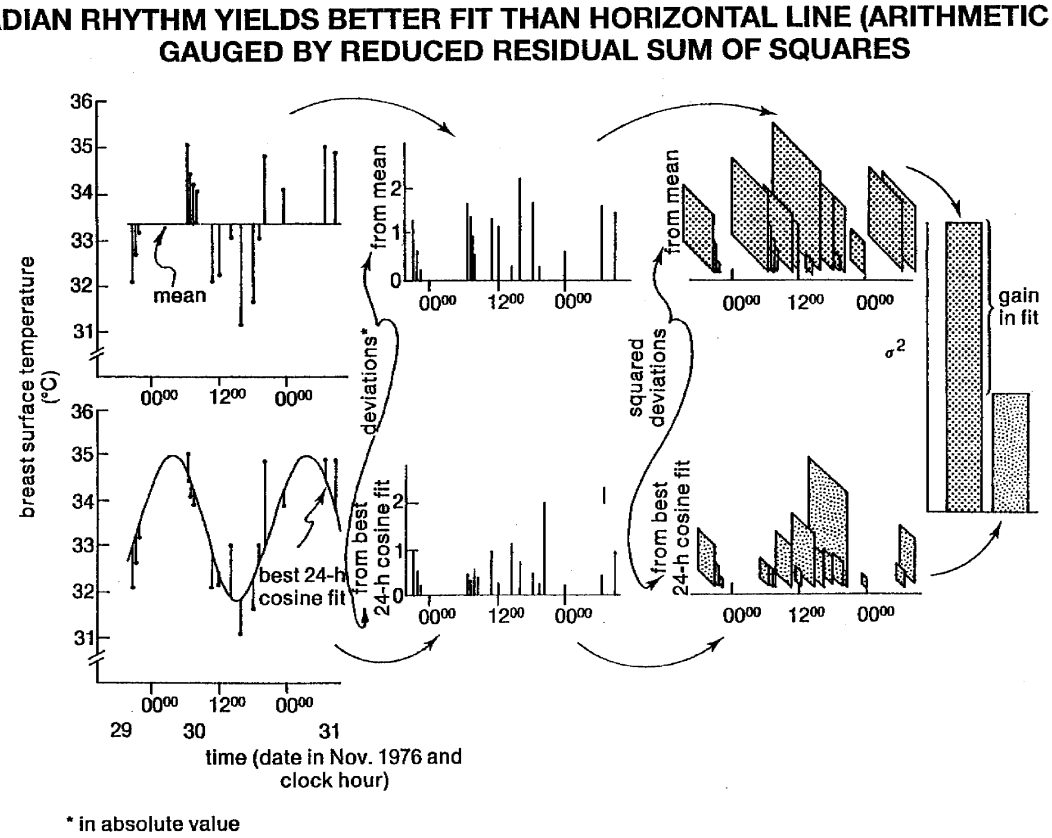


Figure 1. E. The same data set is shown – as the case may be – as a deviation (upward or downward, on the left of this figure) either from its mean shown as a horizontal line (top), or as a deviation from the best-fitting 24-hour cosine (bottom). In the next column, from left to right the deviations are shown by the length of the lines, irrespective of sign; on average, they are smaller when related to the cosine curve as compared to their mean, as best seen in the third pair toward the right, where the deviations are squared. The squares at the bottom, as deviations from the cosine curve, are obviously smaller than those at the top, as further summarized by the length of two columns on the extreme right. The thus-unqualified method of least squares underlies the computation of a mean, and is also a step for computing deviations from the mean or from other standards. A wealth of information from time series in life and other fields of science reveals the importance of a known pertinent mathematical model. In the illustrative example used herein, human breast surface temperature can be approximated by a cosine curve. The original use of least squares also depended on prior independent information on the movement of heavenly bodies in ellipses, derived from Kepler and available to Gauss. Gauss developed the least-squares method and used it to predict the location of a lost 'planet', Ceres (now classified as an asteroid), where Olbers found it on December 31, 1801. In the case of the chronome of breast surface temperature analyzed in this figure, the method awaits broad application for the detection of very early changes in the female breast prior to the appearance of cancer, rather than merely using it to look at a hot spot. © Halberg.

Brillat-Savarin's [8] third aphorism merits attention as well: *La destinée des nations dépend de la manière dont elles se nourissent* ("The destiny of nations depends on how they are nourished" [emphasis in the translations of both aphorisms ours]). In other words, 'you are *how* you eat'. Could this include the possibility, at variance with a recent explanatory note issued by the American Dietetic Association [1], that 'you are *when* you eat'?

MEAL TIMING DOES NOT SEEM TO MAKE A DIFFERENCE

Some reports on the effects of meal timing notwithstanding [19, 33, 98], the professional status quo related to the chronobiology of nutrition is probably well reflected in a display card promotion for National Nutrition Month® by the American Dietetic Association, ADA ("Your link to nutrition and

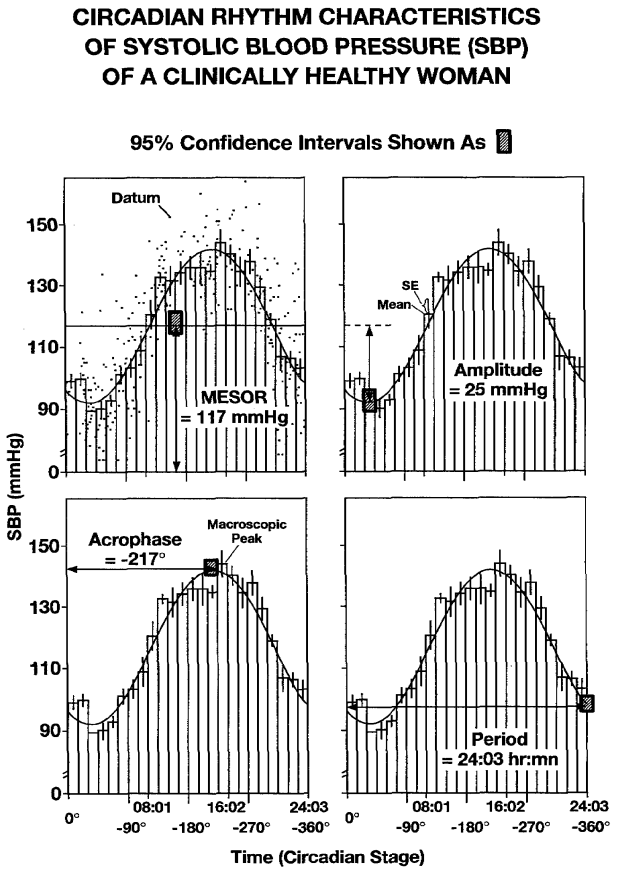


Figure 1. F. Dots only on the top left apply to all four graphs showing four of the characteristics resolved by least-squares rhythmometry by the method of Gauss visualized in *figure 1E*. The great variability of single BP notwithstanding, the relatively small hatched quadrangles or hexagons show the relatively small uncertainty of characteristics based on several days of around-the-clock measurements. © Halberg.

health") [1]. In sharp contrast with the past [50] and with the more recent suggestion of timing meals and treatments [98] is the implication of the first two questions and answers to a quiz currently distributed by the ADA [1] (italics in the original): 1. True or false: A late dinner is more likely to cause weight gain than eating the same meal earlier in the day False. The clock really doesn't make a difference. It's not *when* you eat, but *what* you eat that counts. No matter when they're eaten, calories seem to have the same effect on the body. Evidence does suggest however, that regular mealtimes, including breakfast, reduce fat intake and minimize impulsive snacking, which results in fewer total calories. Staying up late at night may lead to *extra* snacking, which can increase the total caloric intake. Weight gain would then occur, not because *when* you ate the food but rather *how much* you ate. 2. True or false: A no-salt diet protects against high blood pressure. False. If you're sodium-sensitive, then removing the salt shaker from the table does help protect against high blood pressure, or hypertension. However, sodium is the real issue, not just salt, which is 40% sodium by weight. Both salt and sodium are used widely in processed foods. Check labels so you consume just a moderate amount, about 2400 milligrams daily. To help control high blood pressure, maintain a healthy weight, be physically active, and avoid smoking.

Explicit in the answer to question 1 and implicit in the answer to question 2 is the claim, contradicted by the following evidence [50], that timing 'doesn't make a difference'.

BODY WEIGHT IN LEAN INDIVIDUALS DEPENDS ON THE TIMING OF THE MEAL

At a clinical research center, two women and four men consumed a single 2000-kilocalorie (kcal) meal in the morning each day for 1 week, after which each individual consumed the same meal in the evening for another week, on the same limited activity routine. In these studies, the effect of the sequence of meal timing was controlled by a crossover design. 'Breakfast-only' meant that the subject ate all of the kcal for the given day within 1 hour of awakening after a 23-hour fast. 'Dinner-only' meant that the subject fasted for at least 12 hours after waking on each day of the study subspan. Although activity was not measured, the subjects remained sedentary at the clinical research center throughout the study. *Figure 4A* (right) shows that when they were on the breakfast-only diet, all six subjects lost weight, whereas four out of six gained weight while eating dinner-only. The remaining two subjects lost weight on both schedules, but lost more weight on the breakfast-only than on the dinner-only diet. Using weight change (kg/week) on the dinner-only schedule as a reference, one can subtract it from the weight change in the breakfast-only diet and thus find a relative body weight loss in the breakfast-only diet of nearly 1.2 kg/week (*figure 4B*, right) [50].

In order to study the interactions between meal quality, amount and timing, 12 other lean subjects (five men and seven women) were allowed a single free-choice meal daily. For the first 3 weeks, seven

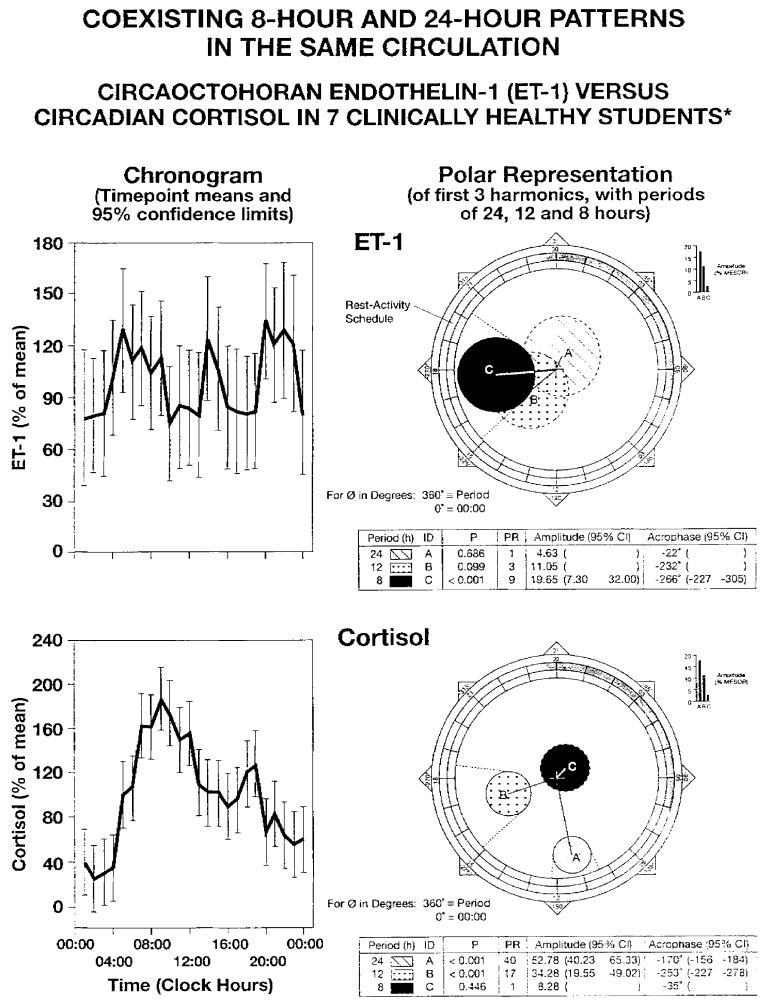


Figure 1. G. Original data: time plots of two circulating substances, endothelin-1 (top) and cortisol (bottom); are shown on the left in a polar representation, and by the cosinor method on the right. A methodological point is the non-overlap of the graph center (pole) at the top, by the darkened error ellipse of the 8-hour vector, describing by its length the extent of change or amplitude, and by its angle the time of high values, acrophase, endpoints visualized along the rectangular coordinates for BP in *figure 1F*. The non-overlap of the pole by the error ellipse corresponding to the 8-hour cosine curve fit rejects the zero 8-hour amplitude assumption, in keeping with an 8-hour rhythm for endothelin-1. This figure also shows that in the same circulation of seven healthy medical students, on the average cortisol (bottom) can reveal statistically highly significant 24-hour and 12-hour components, but no 8-hour component, since the corresponding darkened error ellipse (C) overlaps the pole, i.e., the opposite of what is seen at the top where the ellipses of the 24- and 12-hour components include the pole, results also seen from the tables accompanying the graph. Endothelin in certain individuals sometimes obeys a '24-hour clock', but at most times in most people it displays a primary 8-hour rhythm. The designation of a 'clock' has no heuristic value in this case and many others, and need not obscure the search for mechanisms. © Halberg.

subjects ate the meal as breakfast, while the other five ate it as dinner. Each subject changed the order of meal timing between breakfast and dinner for a second three-week span. Subjects consuming the single free-choice meal ate fewer kcal at breakfast, on average, than at dinner time ($P < 0.01$), and as could be expected from the controlled study of a fixed 2000-kcal meal, their relative weight *loss* on the breakfast-only diet (1646 ± 116 kcal) was greater than on the dinner-only schedule (2215 ± 227 kcal;

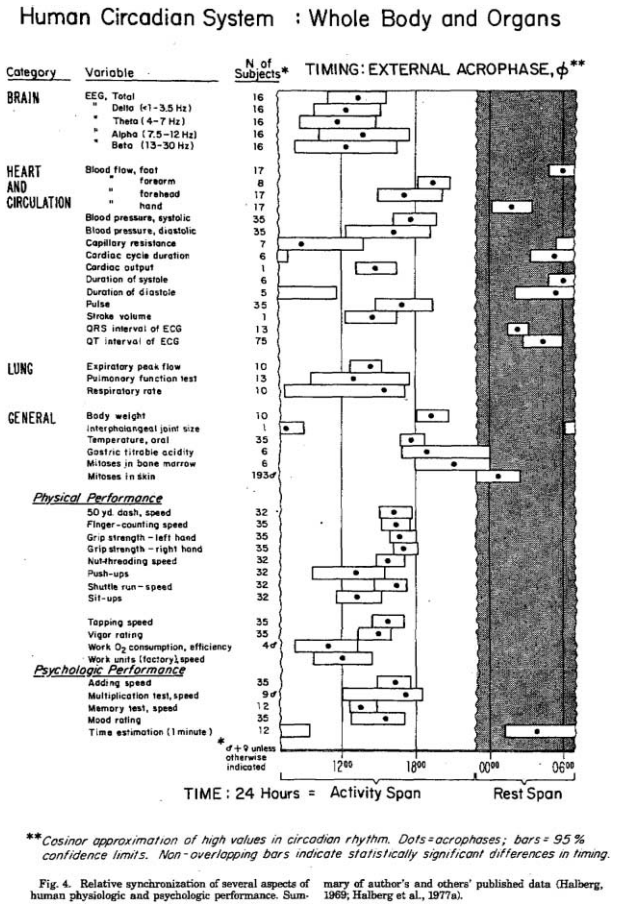


Figure 1. H. Circadian acrophase mapping is much more extensive than shown in this chart that suffices to reveal the principle of synchronization with differences in phase. Major advances beyond this chart include: 1) the preparation of such a chart for many more variables of the individual subject; 2) the extension from phases to include amplitude and waveform at all pertinent periods, in order to detect modulations with ever lower frequencies, including those shown in *figures 1I* and *J*, indeed for some individual subjects. © Halberg.

figure 4A [left]). Their weight loss, however, was smaller when compared to the breakfast-only and dinner-only results of the subjects eating a fixed 2000-kcal meal ($P < 0.05$); *figure 4A, B* (left). In addition to the effect of total caloric intake, an influence of meal quality was thus apparent: the extent of relative body weight loss on the breakfast-only diet was higher when the kind of meal to be eaten was determined (and usually disliked) rather than free choice (and less disliked); *figure 4C* [25, 33, 50].

Body weight gain or loss as a function of meal timing has also been found in catfish [57, 99], an observation that is again at variance with the cautious suggestion made by an anonymous writer for the ADA ("No matter when they're eaten, calories seem to have the same effect on the body").

MEAL TIMING ALTERS HUMAN AND MURINE CHRONOMES

The investigations comparing a single daily meal consumed as a breakfast versus that eaten as a dinner clearly show that meal timing is a way to shift the time relations among physiological rhythms in humans *(figure 5A-C*), in keeping with earlier [33, 50] and recent studies [19, 98] on laboratory animals *(figure 5D, E)* [33, 50]. Some rhythms, like that in cyclic AMP, change amplitude with a change in meal timing, but not the acrophase. The concomitant assessment of amplitude and acrophase in *figure 5A* reveals, in the cosinor plot, the quantification of an effect upon the circadian amplitude in the absence of an effect on phase, both quantified time-microscopically. It would be worthwhile determining the most favorable configuration of rhythms in order to assure peak alertness and performance during any of the critical times of day, but more sensitive performance tests than those used previously will have to be used *(figure 5C)* [25]. Note that at least in the experimental laboratory, the scrambling of the circadian rhythmic element of chronomes is associated with anticancer and life-prolonging (not shortening) effects *(figure 5F)* [11, 53, 72].

WHETHER TO ADD SALT, AND IF SO, WHEN TO SALT: BLOOD PRESSURE AND SODIUM INTAKE

With respect to question 2 of the ADA quiz [1] ("A no-salt diet protects against high blood pressure"), the answer ("sodium is the real issue, not just salt") must also be qualified. The assumption prevails that a high dietary sodium intake leads to higher blood pressure (BP) than a lower intake, increasing the risk of cardiovascular disease. A basis for this proposition is a cross-sectional study of sodium and BP in 52 different populations ([64]; cf. [73, 77]), which was criticized by Freedman and Petitti [21], who noted that of the 52 study populations, four had an association of low salt and low BP, but across the remaining 48 populations "blood pressures go down as salt levels go up – contradicting the (sodium: our addition) hypothesis. Experimental evidence sug-

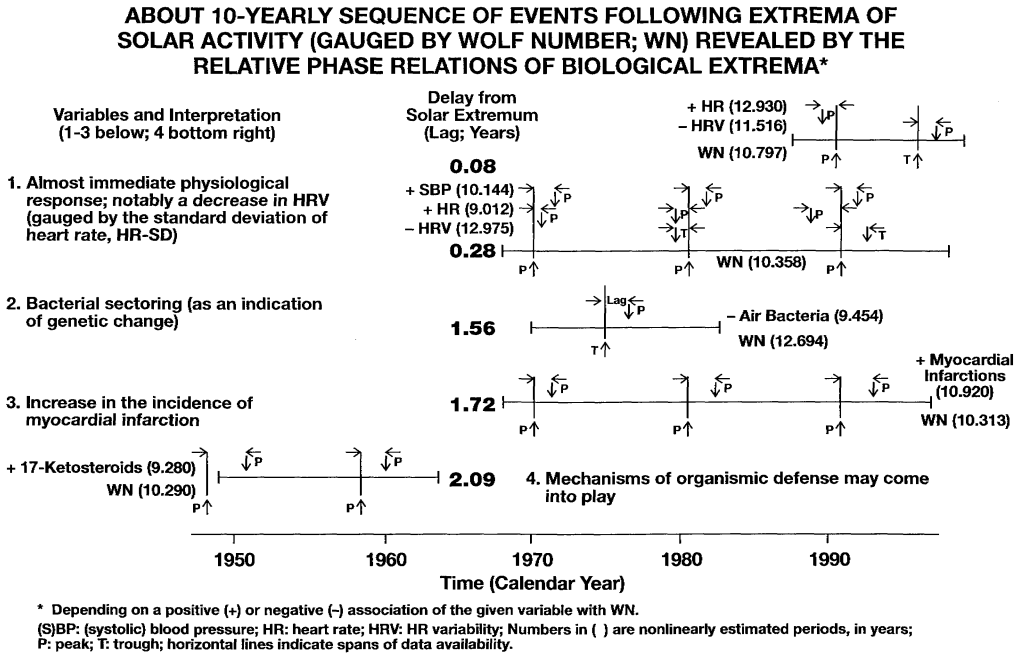


Figure 1. I. The cycles in geomagnetic disturbance (first two rows) and the Schwabe (and Hale) cycles of solar activity have counterparts in the biosphere. For phase relations, see *figure 1J*. © Halberg.

gests that the effect of a large reduction of salt intake on blood pressure is modest and health consequences remain to be determined. Funding agencies and medical journals have taken a stronger position favoring the salt hypothesis than is warranted, raising questions upon the interaction between policy, process and science" [21].

The chronobiological evidence against a sweeping sodium hypothesis is much stronger [7, 18, 40, 65, 70]. Instead of the spot checks of a long series of epidemiological studies [64, 73, 77, 79, 96, 97, 100, 101], longitudinal study under controlled conditions on small groups reveals that on the average, an extreme reduction of dietary sodium intake indeed can lower the rhythm-adjusted average BP. This is shown in *figure 6A* in a dietician-controlled study under metabolic ward conditions at the National Institutes of Health (NIH). For individuals, *figure 6B* (top) shows that on a reduced sodium intake, the MESOR of BP was statistically significantly lower in 11 out of 15 individuals, but in three it remained unchanged (NS) and in at least one other subject, it was higher (when the daily sodium intake was reduced) [18, 40], as subsequently confirmed by others [7][3].

The response must and can be more readily and objectively determined on an individualized basis by chronobiologically interpreted BP monitoring. The hypothesis of a rhythm can be tested before and after a change in sodium intake, followed by parameter estimations on each sodium-intake regimen and a parameter comparison [6]. There is thus the possibility to test one's individualized response cost-

[3] *Figure 6A, B* stems from the 1970s, when one of the present authors served asconsultant to Frederic C. Bartter, then head of the Hypertension Endocrine Branch of the NIH. In his data, we found the inverse response, when it had not yet been replicated. Later, when Bartter moved to Texas, he called to inform us that he had replicated the finding of the inverse response. Bittle and Molina published the results, crediting Barttler posthumously as a co-author [7]. Independently, L. Pöllmamm, an occupational physician in Frankfurt, Germany, also found inverse responses albeit extremely rarely, and controversy arose between him and his colleagues who dismissed the results asa regression of the mean. Pöllmann relates, though anecdotally, his experience with a factory worker who had self-measured his BP, found that it increased when he was salt-deprived (on a low.sodium diet provided by his employer), and thus always kept his own salt handy when he ate.

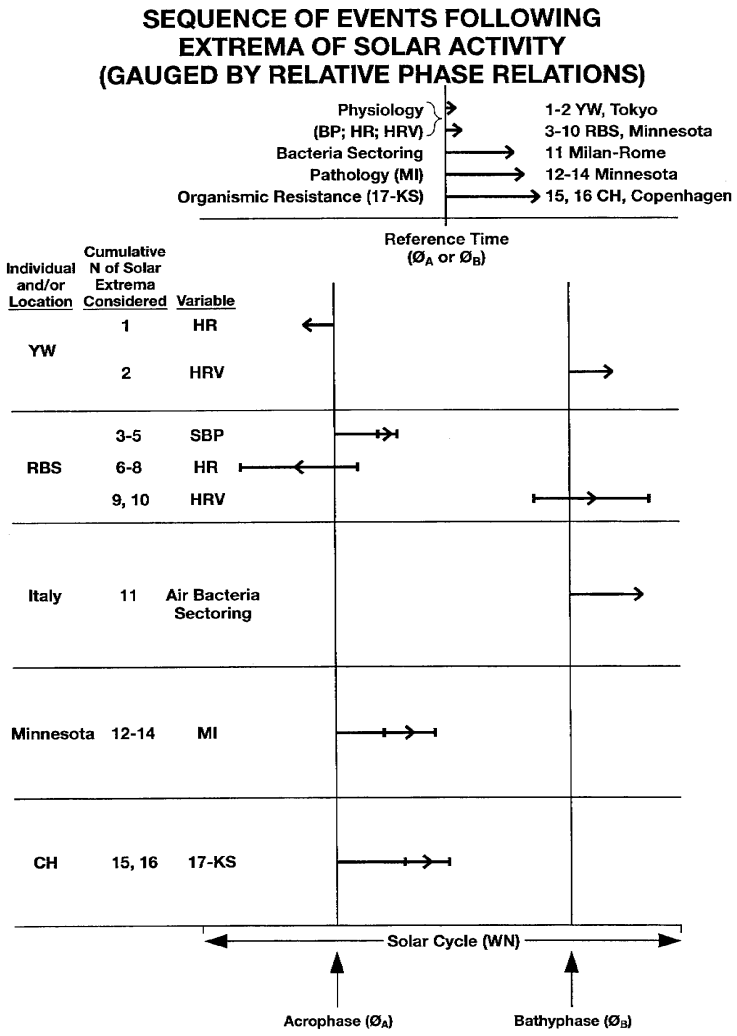


Figure 1. J. Sequence of events following extreme solar activity (gauged by relative phase relations). Delays from solar extrema in *figure 1I* are aligned, irrespective of the calendar date of study, for different subjects, locations and/or variables to reveal an apparent bunching of biological extrema with respect to those of the solar cycle. Focus on maximum or minimum depends on the documented positive or negative association of the given variable with Wolf numbers (for gauging solar activity). (S)BP: (systolic) blood pressure; HR: heart rate; HRV: heart rate variability gauged by standard deviation, SD; MI: myocardial infarction; 17-KS: urinary 17-ketosteroid excretion; WN: Wolf's relative sunspot number. Note the degree of generality of about-10-year changes shown on this chart and elsewhere for events in study populations such as in the Minnesota myocardial infarction population, or in probable genetic changes gauged by sectors in colonies of airborne bacteria (determined by Piero Faraone). This circadecennian chart can now be complemented by an about-10-year periodicity in the circadian phase and relative amplitude of oxygen evolution in *Acetabularia acetabulum*, determined by Dewayne Hillman. Miroslav Mikulecky has also mapped a set of circadecennians in human pathology, from diabetes to leptospirosis, along with changes in human productivity gauged by a cycle in numbers of published titles. From growth gauged by human neonatal and other anthropometry to religious motivation, about-21-yearly changes abound. Only illustrative examples are shown here. The limitations of single or only a few cycles are overcome in terms of numbers insofar as large numbers of individuals must be similarly timed to provide the population rhythms depicted; based in some cases upon millions of individuals; they are overcome in terms of length by a 112-year series. Furthermore, subject R.B.S. has continued to self-measure over 10 physiological variables about five times/d on the average for most days for 35 years. His example needs to be followed for lifetimes. Analyses of R.B.S.'s data serves to emphasize the need for denser automatic series so that deterministic and other chaos can also be assessed. Information on circadecennians has already suggested that many more controversies such as those that could have arisen from *figures 1B* and *C*, had the latter been obtained by different investigators on different individuals, can be avoided. The systematic government-sponsored monitoring, at least on some test pilots, seems mandatory for a solid biological and transdisciplinary science.

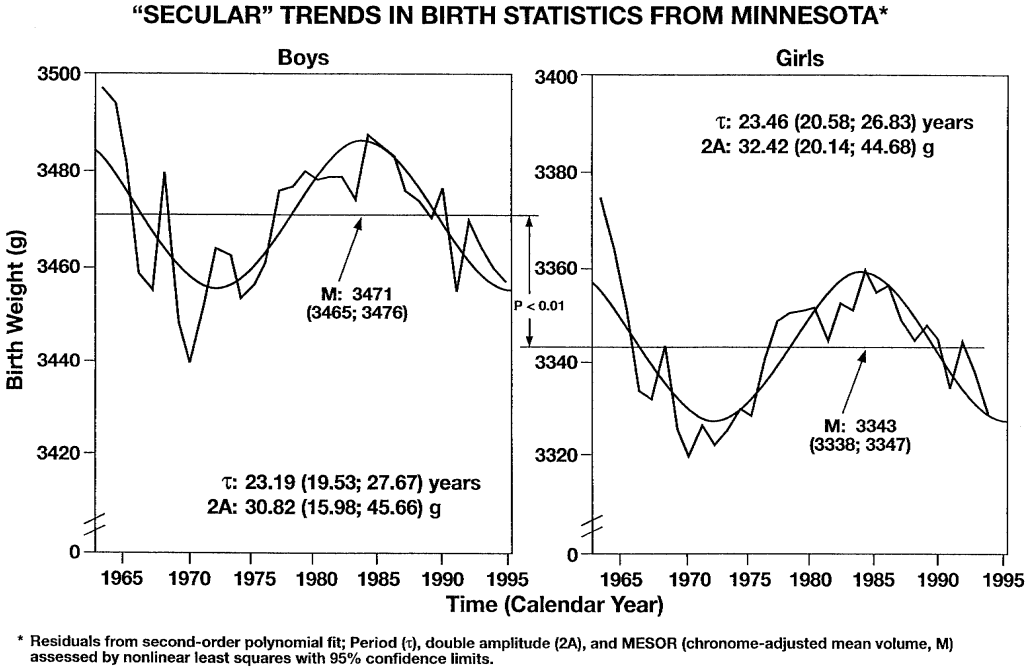


Figure 1. K. About-21-year cycles in Minnesotan neonatal birth weights, shown in this graph, also characterize detrended data (not shown) from Denmark, during the same span, but happen to be in antiphase. Moreover, in 112 years of data from the late Boris Nikityuk, results of other neonatal anthropometry show about-20-year cycles *(figure 1I)*, although birth weight is frequency-multiplied to an about-10-year cycle in Moscow but not in Alma-Ata. The near-antiphase between the time course of circavigintunennians in data from Minnesota and Denmark during the same span, documented at each site, with large numbers of individuals as well as a frequency multiplication at one of two other sites, remains a transdisciplinary challenge in a multifactorial situation. © Halberg.

effectively with ambulatory monitoring and parameter tests on the data thereby obtained. (The authors offer this test to any interested parties, who are invited to contact corne001@tc.umn.edu.) Thereby, probabilities (*P*-values) used thus far mainly for research purposes can be used for decisions concerning one's own response to a habitual manipulation of sodium intake as it may relate to BP. Such tests can be implemented cost-effectively, as indicated elsewhere. But again, timing sodium intake makes a difference *(figure 6C)* [65, 70], as seems pertinent to the vast amount of literature on the subject [64, 73, 79, 96, 97, 100, 101].

HOURS OF CHANGING SUSCEPTIBILITY AND RESISTANCE

A mammalian model of potentially fatal interactions between hunger, cold and rhythms is that of the singly housed mouse abruptly restricted to a single daily 'meal'. The short-term survival of the mouse (albeit not of the rat, with more reserves) depends on the timing of the meal in relation to a regimen of light and darkness alternating at 12-hour intervals. If feeding is permitted for 4 hours during the first part of the dark cycle each day, most of the animals survive. If feeding is permitted only for 4 hours in the early part of the light stage, most of the animals die. The stage of the circadian rhythms at the time of food presentation is thus important in determining whether or not an animal can adjust to such restriction [83].

The importance of circadian rhythms has been dramatized in a regimen with a 12-hourly alternation of light and darkness, not only by limiting access to food to certain clock-hours [83], but also by exposure of the animals to stimuli such as noise [36, 51], administering drugs [20, 31, 54, 58, 59, 88, 94] and exposure to radiation [31, 60] at different timepoints, laying the laboratory foundations of chronotherapy (*figure 7A-E*; for a discussion on LD_{50} and X-ray see [31, 60]). Even when mice are kept for several days in continuous darkness in a controlled environmental temperature, most of those treated at one circa-

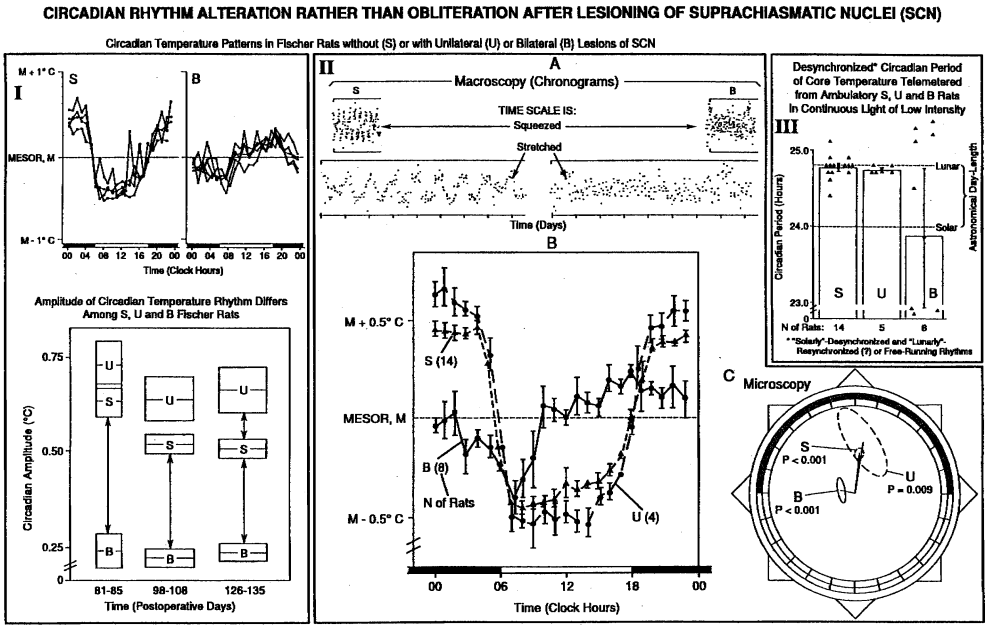


Figure 2. A. By eyeballing alone of section IIA on the right, the circadian rhythm in core temperature seems to be lost in the rat with a suprachiasmatic nucleus (SCN) lesion. Simple stacking reveals the persistence of a circadian rhythm in telemetered core temperature for individual animals (section IB, top), but with a smaller within-day change (IB) as compared to controls (IA). This finding is also seen after averaging in section IIB (bottom). Microscopy in *figure 2C*, apart from quantifying the rhythm by cosinor, reveals a great amplitude lowering by bilateral SCN ablation and a phase advancement seen as an earlier and shorter vector. Section C of figure II thus validates by the non-overlap of the center or pole of the graph by the error ellipse representing a 95% confidence region, that the removal of the SCN is compatible with the persistence of a statistically highly significant circadian rhythm in core temperature quantified with its parameters and their uncertainties. The polar cosinor displays in *figure 2B* also quantify a phase advance of rhythm after histologically validated bilateral SCN ablation in several tissues, with the exception of the stomach, which may respond to food directly rather than via the SCN, again as seen by the shorter vector for the B (SCN-ablated) group, as compared to longer and later vectors for the sham-ablated S group. When the ablation unintentionally, as discovered at post-mortem, was unilateral (U), the circadian amplitude was enhanced (section I, bottom), a finding suggesting a subtractive coupling between the two SCN. Section III of *figure 2A* is in keeping with the speculation of an effect by lunar factors upon the 'free-running' period of about 24.8 hours found in controls or unilaterally ablated animals. If this should be in part a lunar effect, it is lost in animals subjected to bilateral suprachiasmatic lesions. © Halberg.

dian time may die, whereas when the same dose of a drug is given at another circadian time, most will survive [30]. The optimization by a sinusoidally varying drug administration pattern according to about-7-day ([26, 76]; cf. [15]) as well as other rhythms can account for the difference between enhancing versus inhibiting malignant growth, and thus shortening or lengthening survival time [15, 26] *(figure 7F)*. Just as an organism's response to toxins and drugs varies according to circadian and other, e.g., about-weekly or about-yearly rhythms, so too does its response to nutrients, as indicated by circadian cycles in glucose tolerance, the rate of amino acid metabolism and the respiratory quotient, among others [10, 12, 23, 33, 47, 76, 90, 91].

In the broad context of earlier work, i.e., the liver's "ability to adapt temporally to changes in the feeding pattern" [98] and that of other organs, notably the lung [98], heart, kidney and pancreas [19], are worthy of further study regarding the manipulability of the circadian system, which is also apparent for rodents *(figure 5D)*. *Figure 5A-C* shows for humans that the timing of food intake can shift the circadian rhythm in circulating insulin and glucagon under conditions of meal timing that do not or barely change the temporal placement of the circadian rhythms in urinary cyclic AMP excretion or in circulating cortisol, respectively [23, 50]. Another recent paper reports on the resetting of circadian timing in peripheral tissues by glucocorticoids [4]. Such findings [19, 98] can all be viewed in the light of an earlier demonstration of the ability of another glucocorticoid, prednisone [92], just like meal-timing, to alter several variables in patients with asthma, and

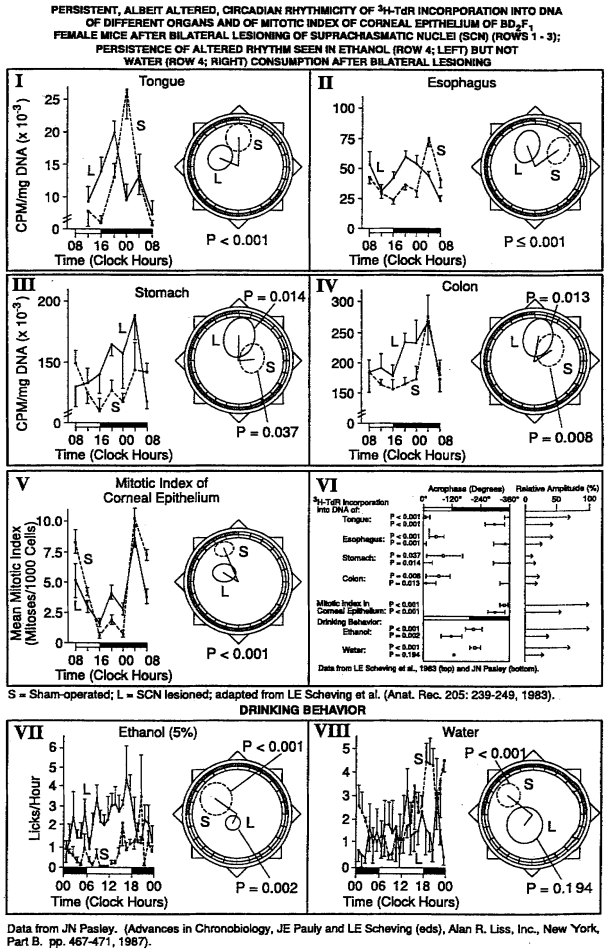


Figure 2. B. The SCN coordinates a collateral hierarchy that can be quantified in terms of amplitude and phase: the major effect of bilateral SCN ablation is thus far invariably, comparably to the behavior of core temperature in *figure 2A*, an advance in phase for the L animals in eight cases out of eight, with a reduction in amplitude except for DNA labelling in the stomach (section III). Section VI shows a microscopic phase and amplitude chart summarizing the finding in the other sections for a number of variables other than core temperature, studied as marker rhythm in *figure 2A*, confirming and extending the scope of the lesson learned in *figure 2A*: the SCN, rather than being a master clock leading to the abolition of all rhythms when ablated bilaterally, is compatible with their persistence, except for water-drinking among the functions investigated. A subjective time-macroscopic interpretation-based impression, that led to the master clock illusion (e.g., *figure 2A*; section II, right) is thus resolved by quantification. © Halberg.

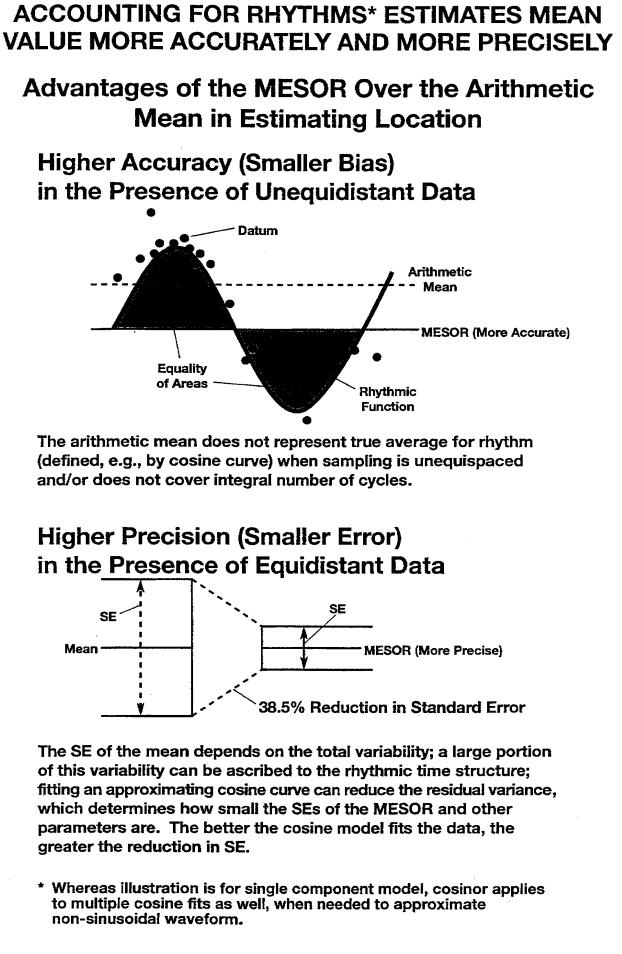


Figure 3. For any data series (whether from physics, chemistry, biology, psychology or sociology), characterized by a spectrum of rhythms, a MESOR (midline-estimating statistic of rhythm, or rather of a chronome-adjusted mean) can be computed and has merits: as compared to the arithmetic mean of the same series, the MESOR is usually more accurate and more precise. © Halberg.

the additional finding, which has not been explored recently [4, 19, 98], of a cosinor-assessed phase–response curve as a function of glucocorticoid timing [92]. These results may prompt further systematic studies around the clock involving an ever-broadening spectrum of rhythms, i.e., with a view of other chronome-documented rhythms, rather than at a single timepoint (cf. [98]).

Regarding circadians, we concur with Stokkan et al. [98], who conclude that manipulating the "entrainment of the liver (and perhaps other peripheral organs) to a specific phase might increase both the practicality and the therapeutic efficacy of timed administration of drugs or radiation," since in *figure 5E* the possibility of shifting the susceptibility rhythm to doxorubicin was demonstrated over a quarter of a century ago [33]. The use of marker rhythms has already proven itself in cancer chronoradiotherapy *(figure 7E)* [45, 46], and is also particularly attractive for the timing of drugs and also for assessing

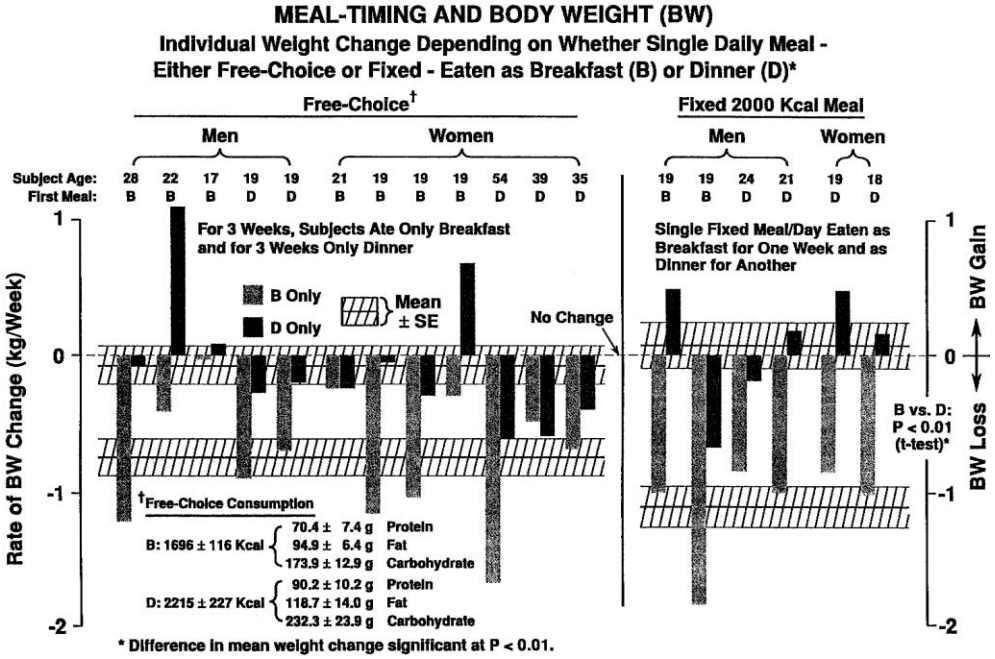


Figure 4. A. Meal timing and body weight. In two separate studies on the effect of meal timing on body weight, a total of nine men and nine women consumed as follows: some a fixed 2000 kcal meal for one week; others a single free-choice meal for three weeks, either as breakfast-only (B) or as dinner-only (D). Body weight remained more or less unchanged on the dinner-only diet; a decrease of about 1 kg/wk was noted on breakfast-only. When eating just a single meal within one hour of awakening (breakfast-only, gray bars) or not before 12 hours after awakening (dinner-only, black bars), with only one exception (subject 39), there was a relative body weight loss on the breakfast-only as compared to the dinner-only diet *(figure 4B, C)*. © Halberg.

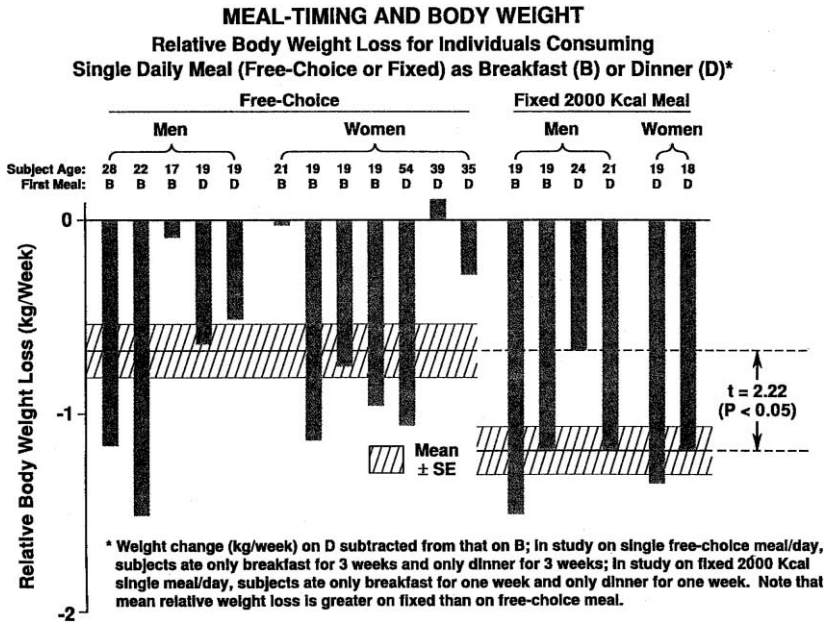


Figure 4. B. The rate of body weight change, i.e., the extent of overall relative body weight loss on breakfast-only vs dinner-only also differed significantly ($P < 0.01$) between the two schedules. © Halberg.

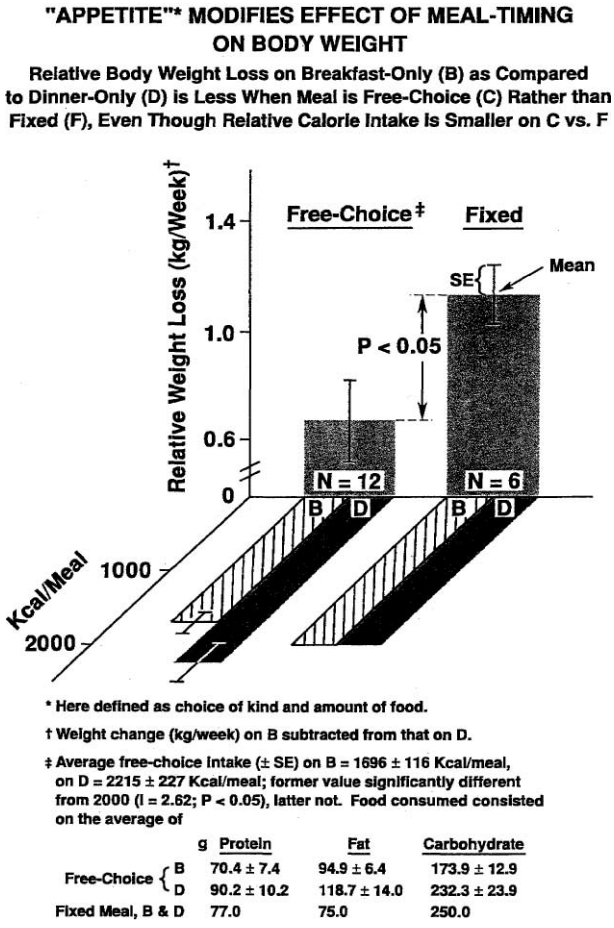


Figure 4. C. Relative body weight loss on the breakfast-only vs the dinner-only diet for each subject participating in the two studies is described in *figure 4B*. Only one volunteer gained weight on the breakfast vs dinner schedule. Overall, the difference in relative body weight loss on breakfast (B) vs dinner (D) was statistically significant ($P < 0.05$) whether a fixed 2000-calorie meal or a single free-choice meal was consumed. Weight change (kg/wk) on D was subtracted from that on B. In the study on one free-choice meal per day, subjects ate breakfast-only for three weeks and only dinner for three weeks. In the study on one fixed 2000-calorie meal per day, subjects ate only breakfast for one week and only dinner for one week. Note that mean relative weight loss is greater on fixed than on free-choice meal. © Halberg.

their effects upon malignant growth [14, 15, 28, 35, 49, 52, 61-63, 71] *(figure 8)*.

IMPLICATIONS OF CIRCADIAN RHYTHMS IN THE THERAPEUTIC INDEX

In the laboratory, a circadian rhythm in the therapeutic index was documented in 1973 [49]. It was experimentally validated by assessing doxorubicin-associated mouse breast cancer shrinkage and increase in survival time in six groups of inbred A-strain mice with spontaneous mammary cancer, fed ad libitum in the light from 06.00 to 18.00, alternating with darkness. The animals were given a fixed dose of doxorubicin i.p. at different circadian times. The numbers of survivors and caliper measurements of tumor volume were recorded to find the best timing, if any, at which doxorubicin reduced tumor size and increased survival time. On the basis of these data, the chronotherapeutic index (CTI) was defined as CTI = PST × TVC, where PST = the individual's percentage survival time relative to the overall mean (= 100%) of all treated individuals, irrespective of treatment time, and TVC = the individual's extrapolated 47-h post-treatment tumor volume change a) relative to individual extrapolated 1-h pre-treatment tumor volume; b) expressed as a ratio (a/b). Results thus analyzed showed the highest CTI (= 122%) at 22: 00 and the lowest CTI (= 8%) at 18:00. A 24-h cosine model fitted by the least squares approach showed statistical significance for the original mean survival times, for survival times expressed as a percentage of the overall mean, and for CTI *(figure 7C)* [26]. Also in the laboratory, a sinusoidal administration pattern has already led to an increase in the rate of cure *(figure 7D)* [15]. In the same studies and in human patients, we started triangulating for maximal efficacy with minimal toxicity, in that order of priority [14, 45] (cf. *figure 7E*). Tumor marker rhythms have been tested both for guiding treatment timing and as substitutes for the survival time for gauging the short-term treatment effect.

SCRAMBLING RHYTHMS

We cannot overemphasize the need for further research on chronomics, with marker rhythms both for securing the desired effect and for avoiding undesirable toxicity *(figure 7A-E)*. *Figure 5F* shows that the scrambling of rhythms can serve in cancer prevention. How it relates to treatment optimization remains to be tested. A long series of studies on ara-C *(figure 7B, D)*, then on doxorubicin *(figure 7C)* [49], and cisplatinum [14, 71] underlie a clinical study [14, 62, 63]: in the first stage, we aimed at finding the treatment time associated with least toxicity by alternating doxorubicin in the morning and cisplatinum in the evening on the one hand, and cisplatinum in the morning and doxorubicin in the evening on the

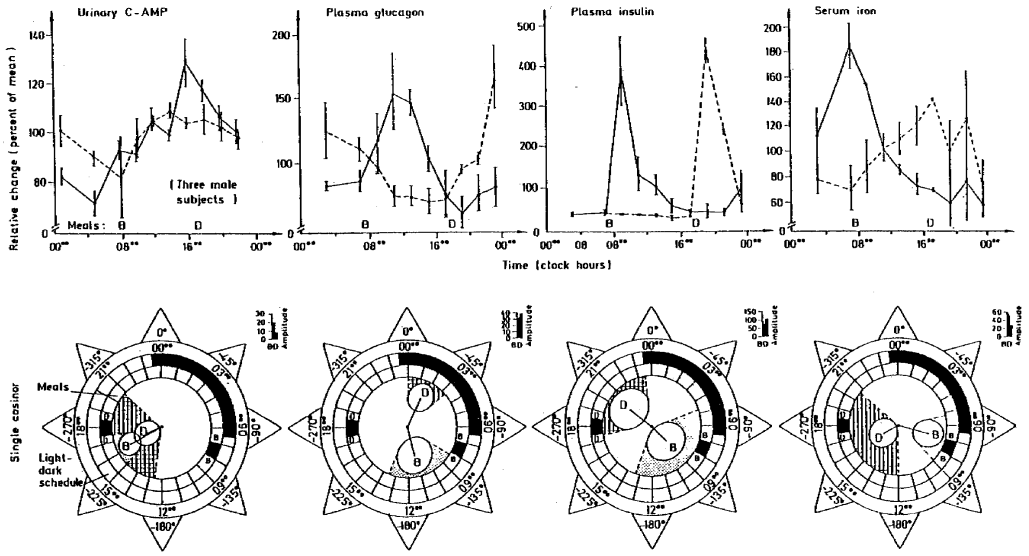


Figure 5. A. A single daily meal as breakfast-only (within one hour of getting up) vs as dinner-only (a meal at least 12 hours after getting up) has very different effects on different human circadian rhythms. A clear difference in amplitude of the circadian rhythm in urinary cyclic AMP excretion is seen with no change in the timing of this rhythm, while the timings of the circadian rhythms in circulating insulin, glucagon and iron all differ with high statistical significance, as apparent from nonoverlapping 95% confidence ellipses. © Halberg.

other. The former schedule was associated with less toxicity in this first stage of using toxicity markers [62, 63]. Thereafter, the two schedules were compared and the former schedule was found to be superior to the latter, as reported in *Science* [62]. Most interesting, and a challenge awaiting further research, was the finding that the alternating schedule was better yet [63], perhaps because it covered more, if not all circadian stages, thereby helping to kill the last cancer cell. Whether there was also an effect from scrambling rhythms in ways other than alternating the treatment remains an open question for which future study may utilize some mapped aspects of the chronomes of tumor markers [35]. Finally, the observation that some tumors may be free-running may itself render it essential to use marker rhythmometry rather than 'flying blind' ([27]; cf. [41]).

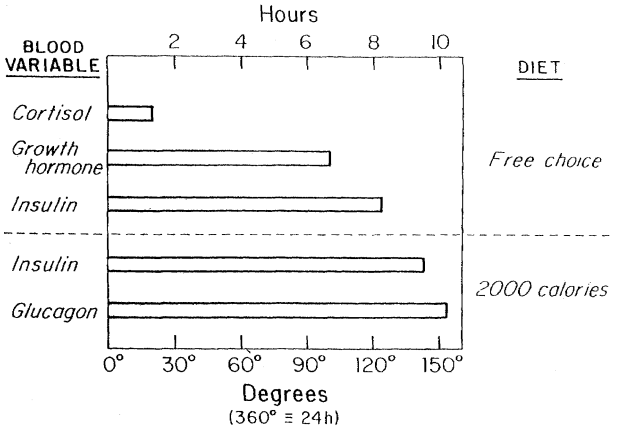


Figure 5. B. A large difference in the timing of the insulin rhythm is seen on breakfast-only vs dinner-only, whether the diet involves items of some limited choice or a fixed diet of 2000 calories/d; in the same human circulation there is just a much lesser difference in the timing of the circadian rhythm of cortisol. © Halberg.

DISEASE RISK SYNDROMES

The major purpose for the mapping of chronomes is the detection of disease-risk syndromes such as BP 'overswinging' or heart rate (HR) 'underswinging' [41]. Week-long or longer monitoring of BP and HR coupled with time-structure analyses detect an increase in disease-risk, as an indicator of the need for preventive '*prehabilitation*' [17, 37, 41]. Within the normal range of physiological variation, computer methods have already quantified chronomes that can serve as reference values. As compared with a (gender- and age-matched) peer group-derived threshold, too much BP variability, BPV (circadian hyper-amplitude-tension; CHAT) and too little heart rate variability (HRV) are indicators of high vascu-

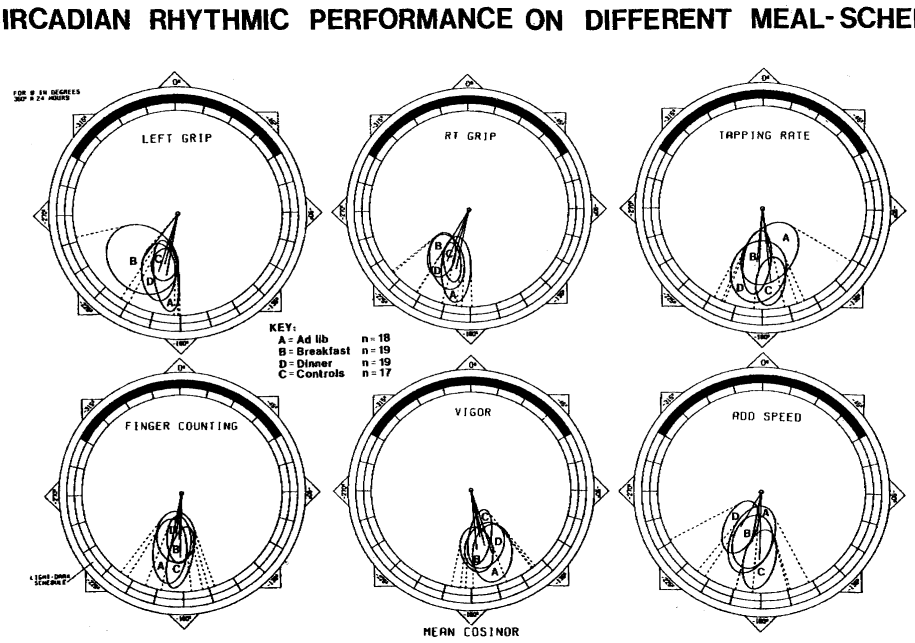


Figure 5. C. Failure of single meal timing to shift circadian changes in the performance of simple habitual tasks. © Halberg.

lar disease risk. Chronome alterations of heart rate variability (CAHRV), consist of a loss of 'jitter', e.g., a reduced circadian standard deviation (SD) of HR or of other alterations in the spectral element of the HRV chronome, such as that observeed in the circadian rhythm of the correlation dimension [84, 86], or in other endpoints of deterministic chaos, such as approximate entropy. The recognition of these alterations can again prompt prehabilitation in health rather than waiting for the fait accompli of disease, as noted elsewhere [17, 37, 41, 84].

While it has not been shown as yet that treating CHAT removes the risks of stroke and nephropathy, the possibility of eliminating CHAT by autogenic treatment or drugs has been documented [17, 41, 104, 105]. Diastolic CHAT statistically significantly increases the risk of nephropathy by 590%, even when the 24-hour average of systolic (S)/diastolic (D) BP is below 130/80 mm Hg (by comparison, decreased HRV statistically significantly increases the risk of nephropathy by 440%). CHAT may be transient; hence a seven-day period of ambulatory monitoring has been recommended by an international consensus meeting [37]. For the reliable diagnosis of an abnormality such as an overall BP elevation as well as for CHAT detection, monitoring for one week is prompted by day-to-day as well as within-day variability, long-known to be large and to characterize circadian and ultradian rhythms.

The 7-day/24-hour monitoring required for the diagnosis of CHAT is useful in any event to reliably detect an overall elevation in BP, the proven etiopathogenic factor. Indeed, high BP can be detected much more reliably with the 7-day/24-hour approach, which reveals that many measurements below 140/90 mm Hg are found during office hours in conventionally diagnosed hypertensives in the absence of antihypertensive treatment. A few patients have over 50% of their BP values below the 140/90 mm Hg limit during office hours. The merit of weeks-long automatic monitoring of subjects who may be on medication they do not need, as documented by placebo spans of a week or longer, has also been reported [75]. During office hours, normotensives can show occasional hypertensive values and vice versa. Even a 24-hour ambulatory BP average can be high for several days, then remain at an acceptable level for months or years of ambulatory monitoring thereafter. Current practice based on official guidelines needs improvement, and the 7-day automatic ambulatory monitoring is practical, and requires no further work on the part of the care pro-

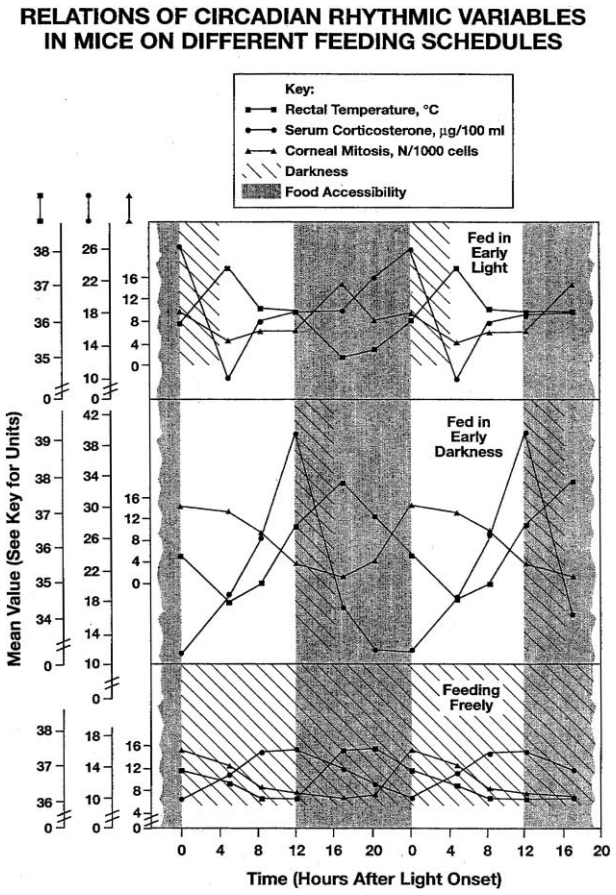
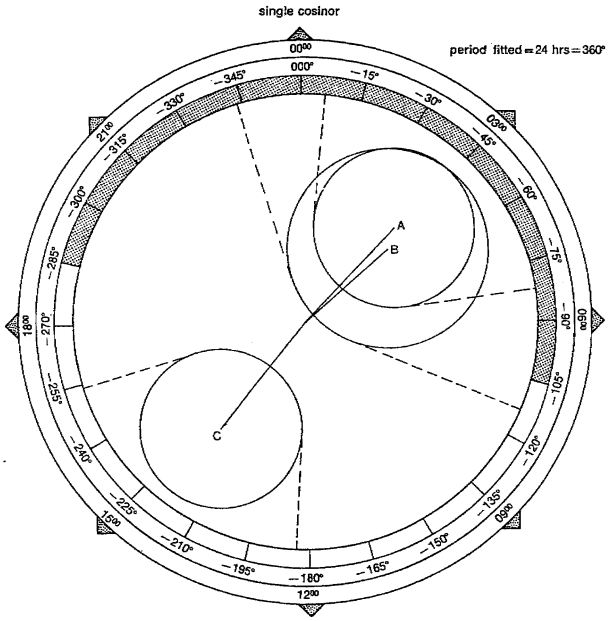


Figure 5. D. Amplification, under laboratory conditions, of circadian change by meal timing. © Halberg.

viders other than monitoring for 6 [95] or 24 hours. Instruments for research use by the practitioner are available at a substantial price reduction through the Halberg Chronobiology Center at the University of Minnesota, along with analyses and recommendations in the light of reference standards from clinically healthy peers, specified by clock-hour as well as gender and age for the Japanese as well as for Caucasians. The self-disciplined patient with diabetes, used to self-determination of blood glucose levels, can be used as a role model for many other non-diabetic patients with BP problems who can also learn self-help. Interested parties can contact the Halberg Chronobiology Center by e-mail (corne001@tc.umn.edu) or by phone (612.624-6976).



series ident	access to food (dose)	percent rhythm (%)	mesor S.E.	amplitude (conserv. 95% CI)	acrophase (conserv. 95% CI)	P F-test
A	L (I)	10	229 6	35 (15 to 56)	−43° (−7 to −78)	.001
B	L (F)	4	246 6	22 (2 to 42)	−49° (−113 to−345)	.024
C	A (I)	10	225 6	39 (17 to 62)	−218° (−183 to−254)	.001

L = limited to first 4 hrs in 12 hrs light span
A = ad lib.
I = dose by weight at injection time
F = dose fixed
CI = confidence interval

Figure 5. E. Restricting food accessibility to the first four hours of the daily 12-hour light span shifts the circadian rhythm in susceptibility of mice to the carcinostatic drug, adriamycin [33], as hypothesized subsequently [98]. Units of MESOR and amplitude = mean survival time (h) at 90% overall mortality; units of acrophase = degrees after 00^{00}, with 15°= 1 h. © Halberg.

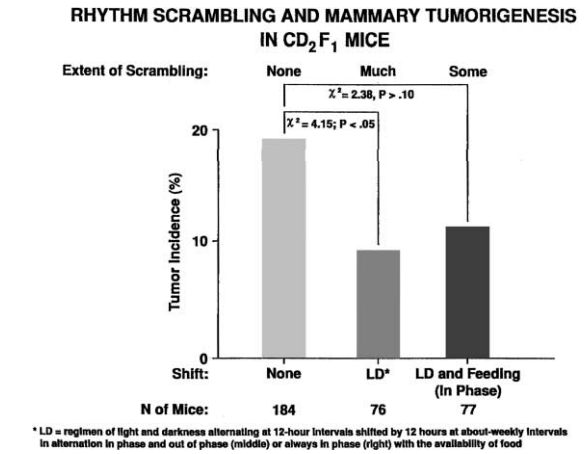
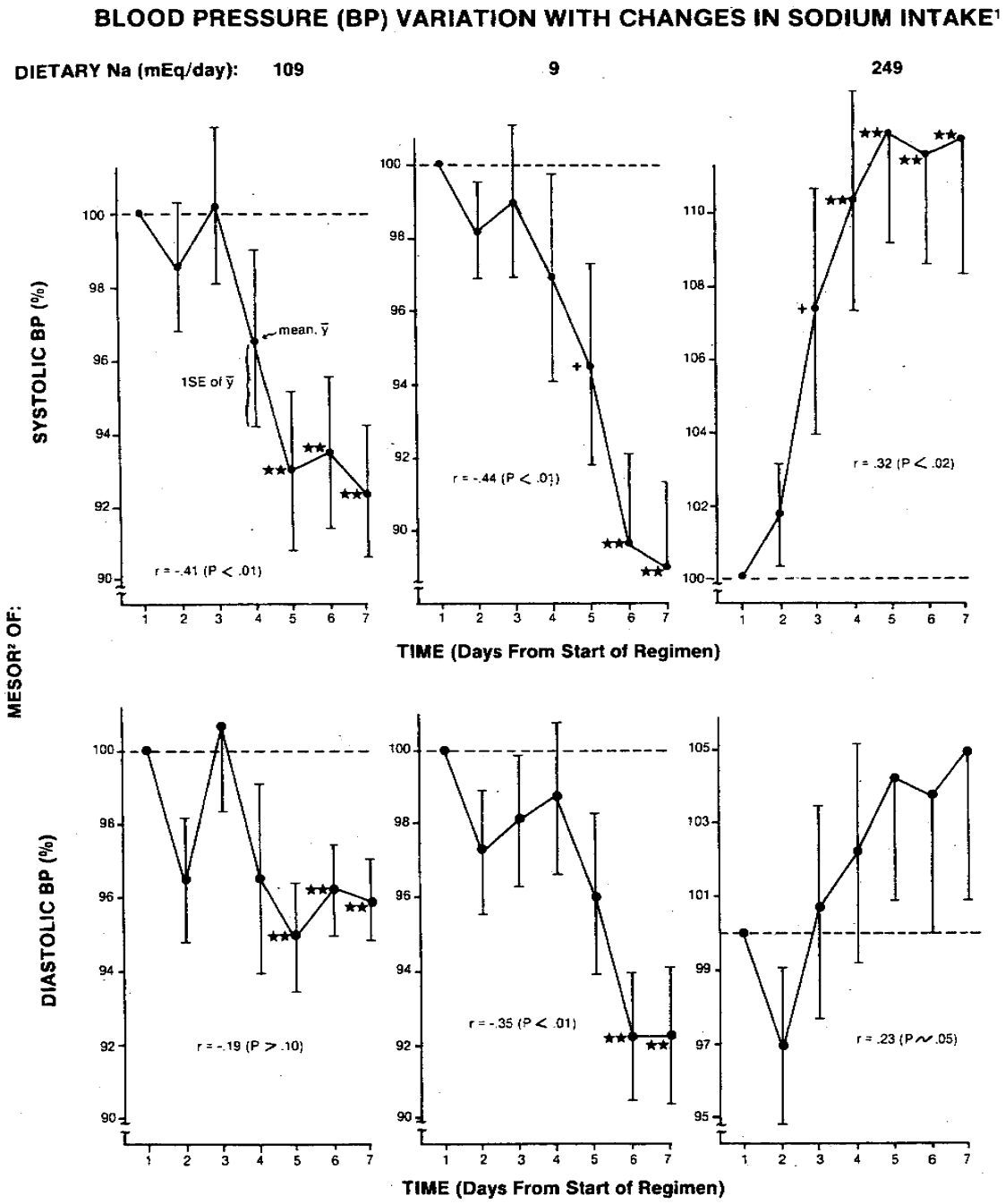


Figure 5. F. When rhythms are manipulated (if not 'exercised') by alternating the temporal placement along the 24-hour scale of a regimen of lighting into phase and again out of phase with the availability of food during a restricted span of the day, breast cancer incidence is statistically significantly lowered, rather than enhanced by a 'stress' effect. © Halberg.



1) Data from 11 subjects in study B; r and P from linear regression: ★★ P < .01; ★ P < .05; + P < .10 from Student t-test (in testing equality of mean mesor to 100%, with mesor at start of study regimen equated to 100%).

2) 24-h rhythm-adjusted mean (MESOR) expressed relative to mesor of day 1 in each stage of study.

Figure 6. A. In 11 subjects placed on a diet of 109 and then of 9 mEq of sodium/d, BP decreased on the average. Return to 249 mEq of sodium/d was associated with a rise in BP, and the effect ascertained with statistical significance by the third day of this last stage of the study for systolic (SBP) but not for diastolic blood pressure (DBP). (Original National Institutes of Health [NIH] data of F.C. Bartter, C. Delea and T. Kawasaki sent for analyses to Minnesota in the 1970s.) © Halberg.

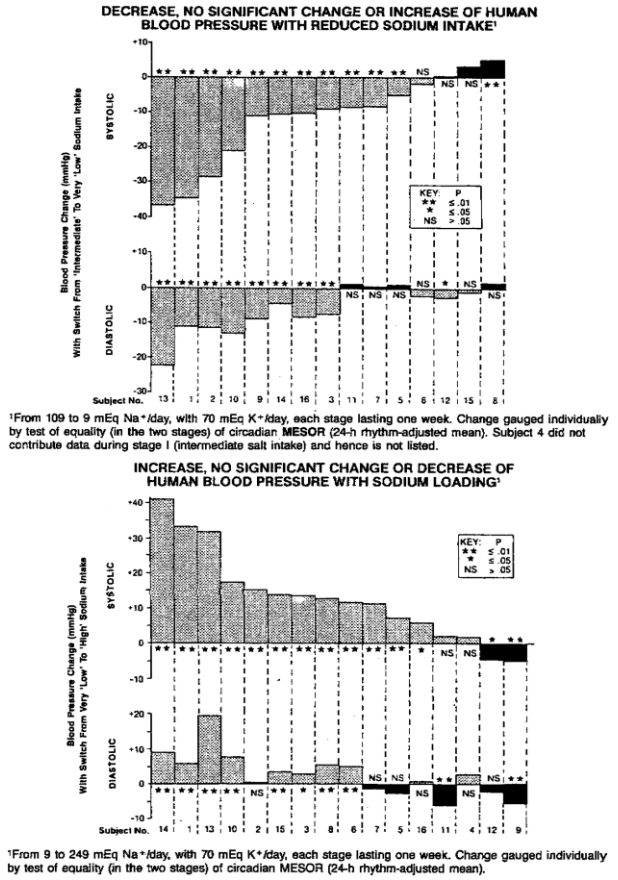


Figure 6. B. On an individualized basis, a majority of responses ascertained individually are in keeping with the 'sodium hypothesis', yet there are also non-responders and inverse responders (in black). (Original data of F.C. Bartter, C. Delea and T. Kawasaki). © Halberg.

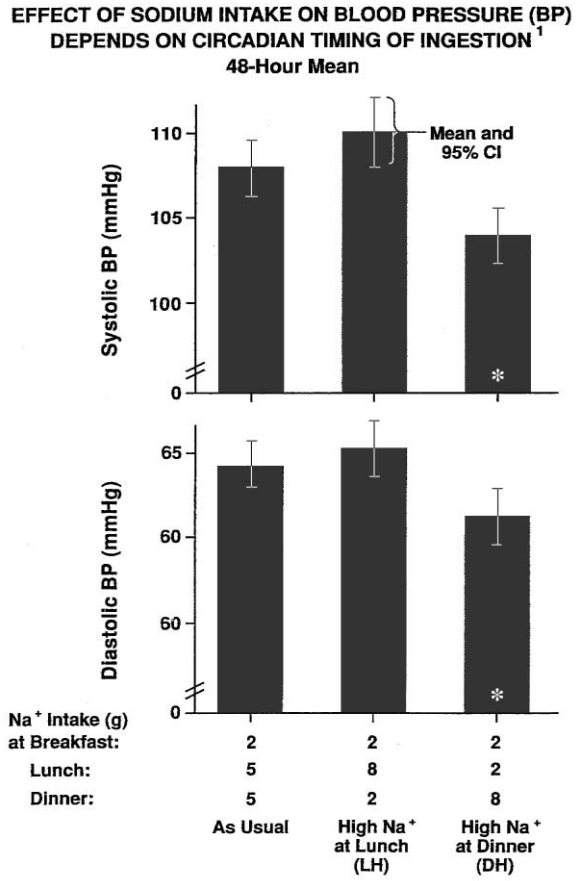


Figure 6. C. *When* to salt also plays a role [7, 18, 65, 70]. © Halberg.

CHALLENGES FOR INDUSTRY

The current disease–cure-oriented health care system does too little too late, at too great an expense for those who are able to afford it. Engineering for concomitantly resolving the internal schedules and how they are influenced by external conditions could change the status quo. Chronoengineering in the broad sense could develop a system that recognizes increased risk early enough to eventually prompt the immediate adoption of preventive measures, implemented according to an optimal schedule [17, 37]. Chronobioengineering for contemporaneous external as well as internal monitoring and decision-helping could improve the unobtrusive resolution of in-part predictable variations that occur within the physiological range, and could be of benefit to a given person in contrast to an approach based only on an average for the population. The resolution of chronomes usually yields not only a more precise and more accurate estimate of the mean value, but also new dynamic endpoints, useful for screening, diagnosis, prognosis and, when needed, for the institution of timely and timed treatment (chronotherapy). The implementation of engineering for concomitantly resolving the external and internal schedules depends on telecommunications, telehygiene, and also telemedicine.

Several factors are essential for the development of such a system. Even though much progress has already been made in each field, the different modules that have largely evolved as separate units will

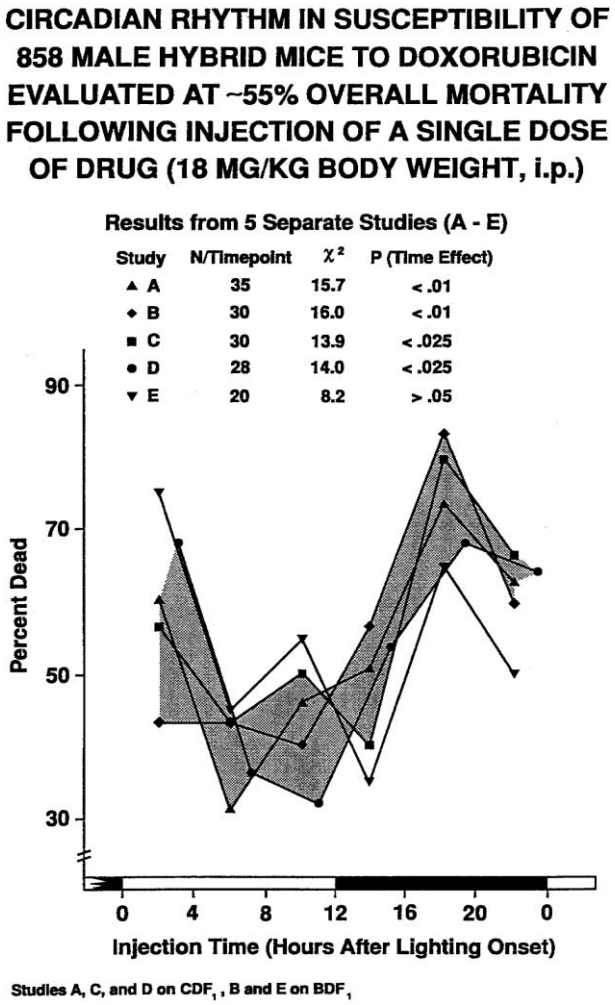


Figure 7. A. Studies in chronotoxicology with ethanol and ouabain in the 1950s ([32, 58]; cf. [31, 54, 59]) not here shown, revealed that the same dose of the same drug killed most of a group of inbred mice at one time, but was associated with a survival of the majority of animals at another rhythmically alternating and, to that extent, predictable time. Data on the tolerance of doxorubicin followed, showing the times of differential lethality. The extent of variability qualifies circadian susceptibility rhythms and leads to the suggestion of marker rhythmometry. © Halberg.

need to be integrated [17]. First, information needs to be acquired in the form of data collected at intervals over time. This is a task for the monitoring industry. Second, clinically pertinent information has to be extracted from the data series, an analytical task for which the principles of windowing, compacting and recycling by repeated passes over the accumulating data have been advocated. Last but not least is the need for reference values to serve for the inter-

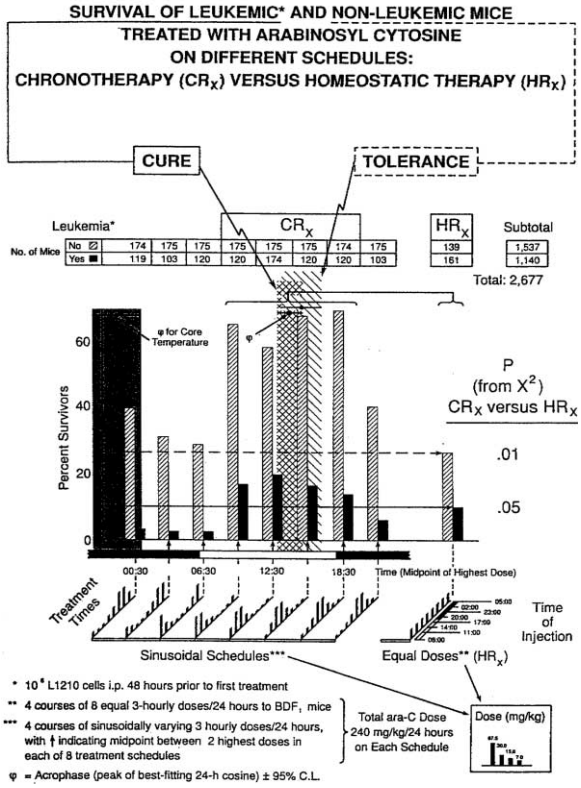


Figure 7. B. In the model chosen by contractors for the NIH, the effect of ara-C in equidistant equal doses in the treatment of L1210 leukemia was improved by redistributing the same total dose as a sinusoidal treatment pattern with gradually changing doses. Sinusoidal treatment proved to be superior from the viewpoints of tolerance (toxicity) and of effectiveness (survival time) as a step toward cure. © Halberg.

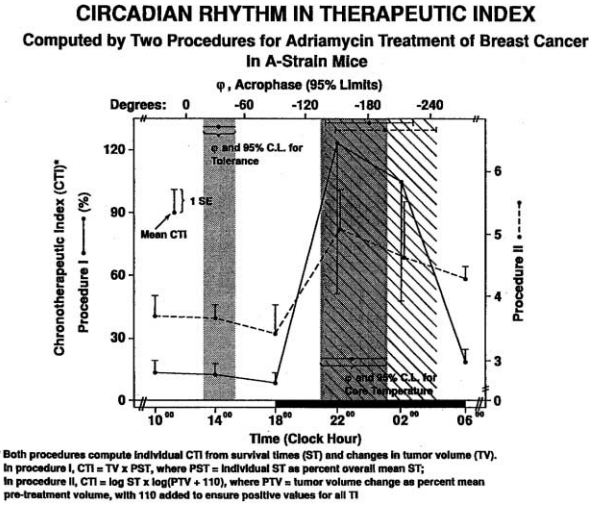


Figure 7. C. Circadian rhythm in therapeutic index demonstrated in 1973 [49], still awaiting implementation by marker rhythms for chronochemotherapy in the clinic. © Halberg.

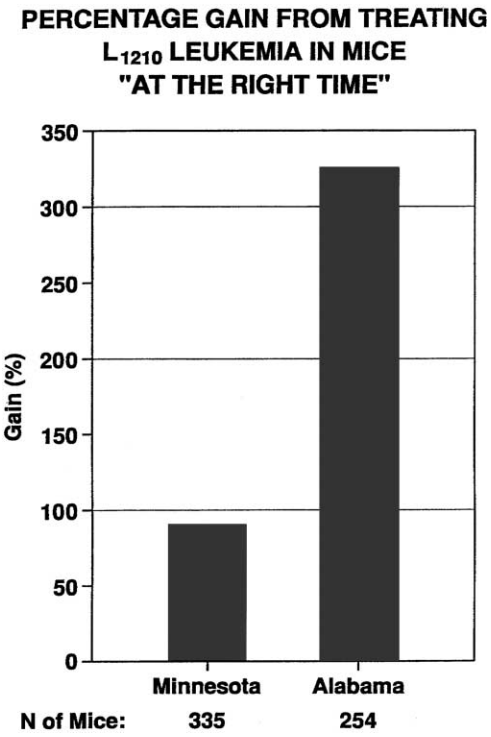


Figure 7. D. Confirmation in data published from Alabama of the merits of sinusoidal treatment, when cures are taken into account. The work in Alabama was mandated by Gordon Zubrod, the late former head of chemotherapy at the NIH, and was first published by comparing survival times without accounting for cures. It was presented in an invited lecture at the Food and Drug administration (FDA) under the title "Ignorance of chronotherapy, or rather indolence, and eventually criminal negligence". Subsequently, when a delegation of chronobiologists including the late F.C. Bartter, the late L.E. Scheving, and the senior author presented the results to the commissioner of the FDA for further testing and transfer to the clinic, the commissioner assured the delegation of full support. A member of the commissioner's staff who was a colleague in chronobiology reported, however, that after the delegation left, the commissioner called for the pursuit of "business as usual"! When the authors advocated further clinical trials, an NIH statistician present protested against action because it would have involved including "another sheet of paper" in the protocol. © Halberg.

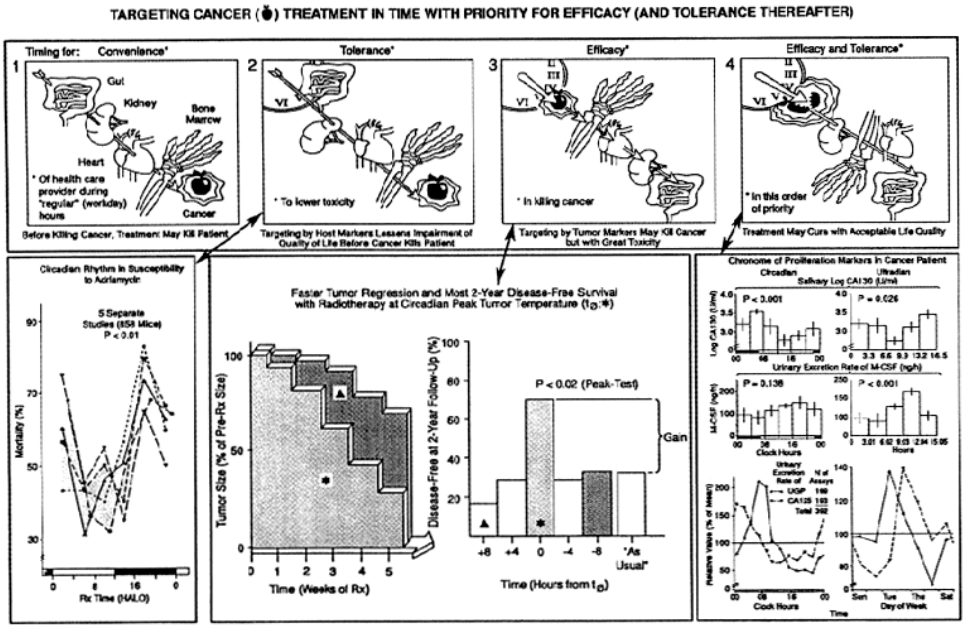


Figure 7. E. B.D. Gupta and A.K. Deka carried out the first marker rhythm-guided chronotherapy in Chandigarh, India [45]. Their data show that when perioral temperature is measured and the treatment is administered at the time of peak tumor temperature, the disease-free survival rate two years later can be doubled. The tumors are only of historical interest now, since with present-day treatment procedures, they never become large enough to interfere with eating or breathing and of sufficient size to be readily accessible for the measurement of tumor temperature as a marker, as in the case of some of the cases summarized herein. While the kind of tumor studied is only of historical interest, the results for prospective studies are nevertheless a historic demonstration of the use of marker rhythms. © Halberg.

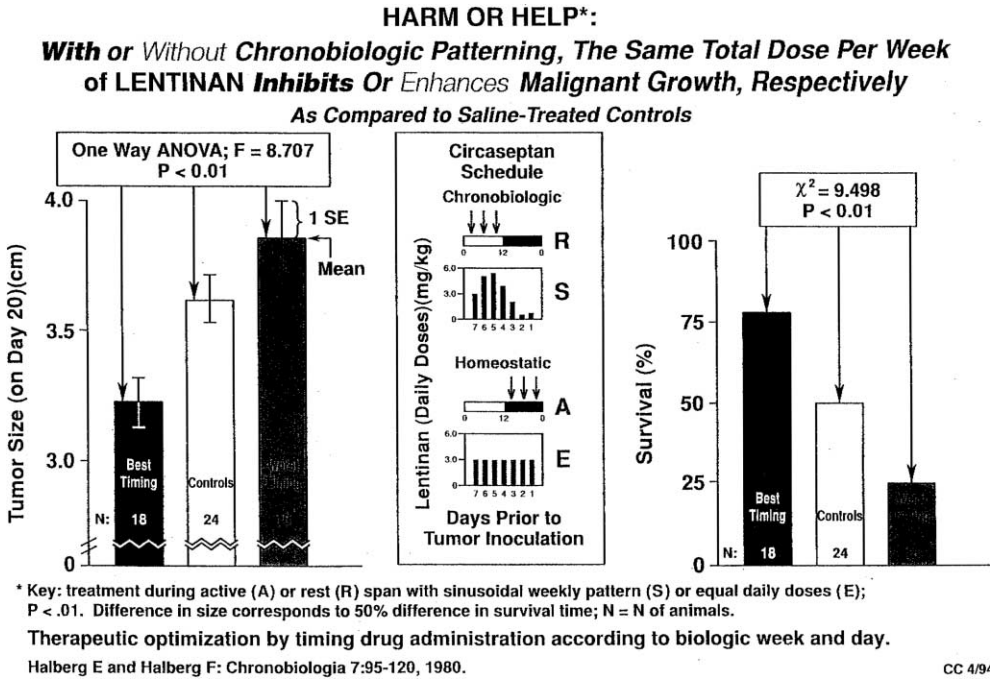


Figure 7. F. It is useful to focus on a circadian mechanism, but exclusive focus may harm the patient if critical about-weekly (circaseptan) modulations and the broader chronome are ignored. In the case summarized in this graph, the about-weekly schedule contributes to the difference between the stimulation and inhibition of a subsequently implanted immunocytoma. This finding is of critical importance for any treatment aimed at timely cancer prevention; it is possibly also pertinent for the treatment of an actual condition, cancer or other [26]. The gain from a sinusoidal vs equal-dose treatment pattern is also demonstrated for cyclosporine in the case of pancreas transplantation (not shown) [76]. © Halberg.

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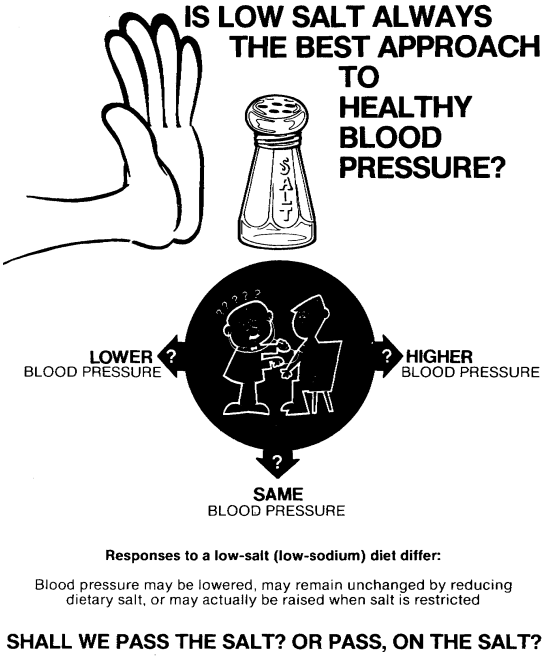

pretation of the data and the endpoints derived therefrom.

Archives constructed around the chronomes of BP and HR monitored from womb to tomb are already available and are still accumulating, yet they are lacking for several populations in the USA and abroad. Reference values for the diagnosis of CHAT or CAHRV need to be adjusted as a function not only of gender and age, but also for ethnicity, in order to determine the threshold values beyond which risk is increased [17, 37]. The integration of all three factors (monitoring, analysis of the given series, and interpretation of the results in the light of the reference values) will ultimately allow closure of the loop between instrumentation for the monitoring of vital signs and instrumentation for the delivery of timely treatment designed to maximize its efficacy and minimize its side effects. The need for analysis was visualized a quarter of a century ago [5], and that to assess the variability before an office visit nearly a full century ago [66].

The systematic monitoring of external rhythms such as those in geo- and/or anthropo-magnetics, along with physiological ones for the concurrent analysis of rhythms with longer and longer periods detects alterations anywhere around and between 40 cycles/s and the 1 cycle/10.5- or 21- or 50-year regions of the spectra of action potentials in humans [87]. Chronobiomimetic engineering for discovering both instantaneous and long-term chronorisk alterations can provide warnings of increased risk associated for example, with interplanetary magnetic storms, that may cause blackouts in the grids not only of power stations, but can also trigger myocardial infarction, stroke, and traffic accidents by acting on the grids of the heart and brain. If risk-lowering therapy is then instituted automatically, health care will be extended beyond the pacemaker-cardioverter-defibrillator, which focuses on a frequency of 1 cycle/s, yet it is also affected by chronomes as a whole. Instrumentation that automatically detects increased risk in the light of a database of reference values that can be used for chronodiagnosis is now accumulating. It should be refined to serve both chronoastrobiology and practical chronotherapy that aims at optimal treatment and assesses its effect on the basis of chronobiologically interpreted physiological and physical monitoring in time, the common link of all science.

(*Tables I and II)*

Table I. Chronobiological concepts, tools and long-term goals.

View of:	*I. Homeostatic* [107, 108, 111, 116–118] *response physiology*	*II. Chronome physiology* [26, 28, 32, 35, 37, 62, 65, 95, 106, 109, 110, 112–115, 117, 119–138]	*Utility of II*
1. Definition of normalcy, e.g., health	Negative: absence of abnormality, e.g., of disease[a]	Positive: Parametric and nonparametric assessment	Time structure: the control in whatever we do
2. Quantification of normalcy, e.g., health	Population-based: percent abnormality, e.g., morbidity and mortality	Individualized: *P*-values for statistical significance and for scientific (e.g., clinical) signification	Recognizing risk of abnormality before the fait accompli of catastrophe
3. Interpretation of reality	Putative (imaginary) set points	Chronomes: Consisting of	Chronorisk syndromes:
		a) rhythms;	1) circadian overswinging of blood pressure [37] ;or
		b) trends;	2) chronome alteration with heart rate jitter deficit; [131] or
		c) deterministic and other chaos;	3) circadian rhythm alteration [112]; or
		d) any residuals and interactions among a, b, c and d	4) altered about-yearly rhythms in circulating prolactin and TSH signaling breast and prostatic cancer risk elevation [122, 125] maintaining normal dynamics
4. Variability	Confounder	Of interest in its own right	As a tool and source of information (1)
	(foe)	(friend)	
5. Biosystems' behavior if perturbed [117]	Settling down to a steady state (constancy) or limited random 'hunting', e.g., as (mistakenly anticipated) when a single blood pressure is taken after some (≤ 30) minutes of rest [119, 121]	Dynamic chronomes [15] that characterize health within chronobiologic limits set by the intermodulation of the chronomes' a-, b-, g- and d- (spontaneous, reactive and modulating) rhythms, e.g., a large circadian change in blood pressure during ≥ 24-h bed rest [119, 121]	Positive individualized quantification of health [15, 125]
6. Analogy	Thermostats with 'hunting' noise	Pendulums in resolvable chronomes	Prediction
7. Physiologic or normal ranges of variation	Broad, random, indivisible; equated to noise; current standard for diagnosis and treatment	Structured, predictable (2); resolved into reference ranges (chronodesms) for chronomes	Circadian blood pressure amplitude (bp-a) or circadian standard deviation (SD) for detecting effect of in utero exposure to betamimetics [136]

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8. Action?	Confounder elimination [95]	Monitoring and as-one-goes analyses and, on this basis, action	Detects treatable overswinging of bp-a, which carries a 720% increase in risk of ischemic stroke (7); improves cancer treatment [28, 35]
	incompatible with detection of circadian blood pressure disorder [37]		
9. Endpoints	• Original values:	Time-specified chrones in chronomes:	Chronobiologic software:
	Casual measurements at times of convenience, not necessarily of pertinence (e.g., of 'the' blood pressure with > 40% uncertainty in diagnosis in cases of borderline hypertension) [37]:	Time-coded:	• provides information, e.g., on points 3 and 4 above
	Time-unspecified:	• original values	• guides timed treatment that has greatly prolonged the survival of cancer patients [28, 35, 62, 118]
	• mean • SE	• SD (e.g., 6 h, 24 h) • MESOR(s) • periods • amplitude(s) • waveform(s) • acrophase(s) • trends • chaotic dimensions • residuals	
10. Sources of variation	Exogenous responses to stimuli from proximity mostly from the habitat niche	Endogenous and exogenous: responses to stimuli from near and far, including cosmos [15, 110, 115, 126, 128, 129, 134]	Resolution of impact of storms in space on myocardial infarctions on earth: space weather report? (3)
11. Mechanism	Feedbacks along axes: unstructured 'modulation' like the deus ex machina in a physiological tragedy since outcomes may be unpredictable	Feedsidewards in networks with alternating outcomes: predictable (insofar as rhythmic) as a chronomodulation [15, 26, 123, 124, 135]	Predictable since rhythmic neuro-endocrino-vascular intermodulations [15] can account for outcomes that may be as different as stimulation vs inhibition of immunity
12. Hierarchy	Up/down	Collateral: Alternating primacy among intermodulating multifrequency rhythms in chronomes	Focusing on selected tasks at different times
13. Teleonomy	Righting and regulation	Anticipatory, preparatory coordination	Greater flexibility
14. Simplified analogy	Thermostat	Pendulum	—
15. Biological evolution	Darwinian, externally adaptive	More and more internal and integrative while externally adaptive to both nature and nurture	Instrumented self-help
16. Health and environmental care	Medical treatment often limited and late, given mostly after the diagnosis of overt disease (4)	Optimization according to marker chronomes (of interventions by drugs and/or devices, e.g., pacemakers, with diagnosis and treatment refined by narrowed reference range and assessment within that range of chronorisk leading to preventive treatment timed by marker rhythms (that also serve to validate effect) [8, 9, 22, 35, 42]	E.g., catastrophic and iatrogenic disease prevention [8, 40]

Table I. Chronobiological concepts, tools and long-term goals.

View of:	*I. Homeostatic* [107, 108, 111, 116–118] *response physiology*	*II. Chronome physiology* [26, 28, 32, 35, 37, 62, 65, 95, 106, 109, 110, 112–115, 117, 119–138]	*Utility of II*
17. Animal husbandry, apiculture, aquaculture and economic entomology	Convenience	Chronome-based (5)	Optimization:
			Greater efficacy; fewer undesirable effects
18. Value	Often wasteful	Cost-effective	Waste reduced
19. Seeking inanimate and animate origins	Stratigraphy for identifying, in geologically analyzed space, sequences in time; radiocarbon dating	Additional tracing of chronomo-ontogeny and chronomo-phylogeny (6) in the context of glimpses of cycles in corresponding spans of a figurative cosmo-ontogeny [5, 11, 26, 29, 37]	Adds to knowledge of the past to better optimize the future
20. Life in the scheme of physical and cultural things	Survival of the fittest with humans dominating food chains viewed in the perspective of bioenergetics in a mostly terrestrial ecology	Physically and socially chrono-modulating and thus informatively and integratively evolving biota molded by human culture;	Humans safeguard the integrity of the biosphere as it extends into the cosmos and as we speculatively, by joining the approaches by ablations [11], superimposed epochs [5, 26, 37] and resonance tests [28] concomitantly explore the temporal aspects of our origins, possibly represented by our chronomes that in turn may reflect a long-past environment
		Homo not only faber but cosmoinformans and chronomodulans in a budding broad chrono-cosmoecology [13, 32–37] (7)	
21. Investigator satisfaction	Frustrating work when (without specification of chronobiologic timing, even at the same clock-hours) one gets confusing and/or obscuring, even opposite results from the same intervention	Sheer fun: long-standing controversy is resolved by accounting for both the genetic and broadly environmental bases of the feed-sidewards among inanimate and animate cycles that constitute life; disease risk recognition promises to lead to the prevention or timed treatment of catastrophic diseases such as stroke, cancer or sudden death	Increased productivity

Just as contemporary physics, by fission and fusion, gathers more and more energy by splitting the atom, biomedicine gathers more and more information by splitting the normal value range into time structures, thereby resolving, e.g., rhythms (fission) and looking at their feedsideward interrelations (fusion) for a better understanding of an interdigitated, indivisible Janus-faced irreparable soma and psyche.

[a] Health promotion is a step in the right direction, by its recommendations of attention to diet, exercise or relaxation, as long as it is then followed by a chronobiological assessment of the effect of recommended procedures, rather than merely by the old reliance of ruling out the occurrence of values outside the normal range. [b] Location and dispersion indices include the determination from histogram of values, of means (arithmetic, geometric, harmonic), median, mode, minimum, maximum, 100% and 90% ranges, interquartile range, standard deviation (SD), standard error (SE); these endpoints are computed from time-unspecified single values in the context of the homeostatic approach, whereas in the chronobiologic framework the location and dispersion indices are used as such on time-specified samples and on time series-derived parameters, i.e., on each of the endpoints (chrones: M, A, f, [A_n, f_n], etc.) of the chronomes.

Notes

(1) An international womb-to-tomb chronome initiative with aims primarily at stroke and other catastrophic vascular disease prevention, by focus as a start upon chronocardiology in general and blood pressure and heart rate dynamics in particular. Those interested may consult the chronobiology home page on the Web at http://revilla.mac.uva.es/chrono.

(2) Information from the physiologic range for prevention, diagnosis or treatment is much refined when this range is individualized and interepreted in the light of a personalized background as well as in the context of gender-, age-, ethnicity- and chronome stage-specification.

(3) The need for forecasting storms in space should be explored further on the basis of systematic studies aligning physiological lifetime monitoring and clinical and archival statistical studies with ongoing physical data collection near and far, both for ascertaining effects and in studying countermeasures [5, 11, 26, 28, 29, 37]. Blood pressure, heart rate and other physiological and psychological monitoring would also provide basic information on any cross-spectral and other associations (feedsidewards) within and among biological and environmental chronomes while further providing reference values of medical interest.

(4) Even if some preventive measures have also been long implemented, e.g., by vaccination, and even if recently more and more hygienic measures (such as exercise and caloric, fat and sodium restriction) are also popular, all can be greatly improved by timing designed with chronobiological individualization. The alternative, current action based on group results, its unquestionable overall merits notwithstanding, fails to recognize, for instance, that the blood pressure response to salt may differ as a function of circadian stage [32], and there are indeed individuals in whom the addition of salt lowers rather than raises blood pressure [4].
(5) Even after the death of a cockroach, when bacteria take over, periodicities (e.g., in oxygen consumption) may not be 'eliminated', but continue with increased amplitude. Critical information may be lost by filtering variation deemed to be undesirable since it lies beyond one's conventional scope.
(6) Development from the egg of rhythms (some may be much older than shards) and of other constituents of chronomes to trace their homeo- or heterochronically roughly 'recapitulatory' development across species, with both ontogeny and phylogeny, perhaps tracing in their turn the concomitant development of the geocosmic environment [5, 11, 26, 28, 29, 37]. This distant basic goal can be pursued with the immediate reward of obtaining indispensable reference values for the diagnosis of two chronobiologic risk syndromes, circadian hyperamplitudetension, briefly CHAT, and chronome alterations of heart rate variability, briefly CAHRVs, just as an extreme deficit in heart rate jitter [1, 34] associated with an increase in the risk of ischemic stroke or of a myocardial infarction of 720 and 550%, respectively.

Table II. Biomedicine, solar activity and terrestrial magnetism: inferential statistical analyses, [18].

Study (reference) *Design** *Variable(s)***	*Location (latitude [geographic/ geomagnetic])*	*Population* *Sample size, age (years)*	*Sampling* *Span*	*Interval*	*Results** *Spectral components*	*Cross-spectral coherence (frequency) [period]*
I. Data longitudinally covering up to 10 Schwabe (about 10.5-year) cycles on height and other morphology						
1. Weber et al. [158]	Austria	Male recruits	10 years	Monthly	After detrending (linearly): about 10-yearly component modulating circannual variation	With *K*p:
T	(49.02•N/48.57 [northernmost]-46.27•N/46.08 [southernmost])	507,125				0.813 (2.20 year^{-1}) 5.45 months]
BH		18				With sunshine: 0.545 (1.90 year^{-1}) 6.32 months] 0.963 (0.90 year^{-1}) [13.33 months] (using 22 degrees of freedom)
2. Weber et al. [159]	Austria	Male recruits	14 years	Yearly	After detrending (linearly): common about 9.25-year component consistent among recruits from 8 separate socio-economic strata	
T	(49.02•N/48.57 [northernmost]-46.27•N/46.08 [southernmost])	713,162				
BH		18				
3. Nikityuk ([17, 145] u.p. †)	Moscow, Russia	Russian babies	i. 112 years	Yearly	About 10.5- and/or 21-year cycles	BH with *K*p:
T	(55.45•N/50.76)	25–150/year	ii. 41 years			0.819 (0.143 year^{-1}) [6.99 years]
i. BH; BW; HC		Birth				BW with *K*p:
ii. CC; AC						0.867 (0.143 year^{-1}) [6.99 years] (using 10 degrees of freedom)

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Study (reference) *Design** *Variable(s)***	*Location (latitude [geographic/ geomagnetic])*	*Population* *Sample size, age (years)*	*Sampling* *Span*	*Interval*	*Results** *Spectral components*	*Cross-spectral coherence (frequency) [period]*
4. Nikityuk ([17, 145]; u.p.↑) T BH; BW; HC; CC; AC	Alma-Ata, Kazakhstan (43.19•N/33.67)	Russian and Kazakh babies 25–150/year Birth	40 years	Yearly	About 10.5- and 21-year cycles with common characteristics for different endpoints	
5. Cornélissen ([17, 145], u.p.↑) T BW	Minnesota (45.00•N/55.00)	Newborns 2,150 122 Birth	33 years	Yearly	About 21-year cycle	
6. Otto et al. [150] T BH; BW	Germany: Berlin (52.31•N/52.06) & Leipzig (51.20•N/51.19)	Newborns 574,600 Birth	1959; 1961; 1963; 1964	Monthly	About-yearly and half-yearly changes	
7. Henneberg and Louw [148] T BH; BW (*z*-score)	South Africa (33.56•S/32.70)	Impoverished rural schoolchildren 1,522 6–18	1 year	Monthly	About-yearly change in BW and half-yearly variation in BH	
8. Garcia et al. [143, 144] H BH; BW	La Coruña, Spain (43.22•N/47.40)	Newborns 674 Birth	0–16 months	About-monthly	About-yearly and half-yearly components, more prominent by reference to the time of birth, i.e., as a partly endogenous function of age, than by reference to a fixed calendar date, i.e., as a function of exogenous factors such as sunlight, temperature and nutrition	
II. Supportive evidence on human pathology						
9. Cornélissen et al. [139] T Incidence	Worldwide	Morbidity 6,304,025 (largest only) Various ages	Meta-analysis of 47 studies		About-weekly and half-weekly patterns of incidence of cardiovascular morbid events	
10. Halberg et al. [37]	Moscow, Russia	Morbidity	3 years	Daily	About-yearly incidence of cardiovascular morbid events and half-yearly pattern of incidence of epileptic attacks	MI with *K*p:

Table II. Biomedicine, solar activity and terrestrial magnetism: inferential statistical analyses, [18].

Study (reference) *Design** *Variable(s)***	*Location (latitude [geographic/ geomagnetic])*	*Population* *Sample size, age (years)*	*Sampling* *Span*	*Interval*	*Results** *Spectral components*	*Cross-spectral coherence (frequency) [period]*
T	(55.45•N/50.76)	6,304,025				0.51 (0.315 day^{-1}) [3.17 days]
Incidence		Various ages (85,819 MIs)				MI with Bz: 0.58 (0.315 day^{-1}) [3.17 days] (using 25 degrees of freedom)
11. Düll and Düll [141]	Copenhagen, Denmark (55.43•N/55.19)	Adults	5 years	Daily	Maximal cross-correlation between magnetic storms and mortality at 1-day lag on data summarized by superimposed epochs in relation to peaks in geomagnetic disturbance (‘electron invasion’)	
T		36,000				
Morbid events		Various ages				
12. Faraone et al. [142]	Milan and Rome, Italy (45.28•N/46.31 AND 41.53•N/41.89)	Colonies of airborne bacteria and *Staphylococcus aureus* 200-250/day	12.5 (air) and 7 (staph.) years	Daily	Prominent components resembling time structure of *K*p and WN, notably with periods of about 5 and 0.5 years	Airborne bacteria with Dst:
T						0.647 (0.054 day^{-1} [18.6 days])
Sectoring in colonies of microorganisms						Staph with *K*p: 0.700 (2.262 year^{-1} [0.442 year]) and 0.660 (0.303 day^{-1} [3.3 days], using 20 degrees of freedom)
III. Supportive evidence on human physiology						
13. Portela et al. [151]	USA (45.00•N/55.00; 45.33•N/51.42; 42.19•N/53.20)	Adult males	14; 15; 26 years	5–6/day; 2/day; about-weekly	About 11-year cycles paralleling solar activity	
L		3				
BP		20; 65; 71				

Table II. Biomedicine, solar activity and terrestrial magnetism: inferential statistical analyses, [18].

Study (reference) *Design** *Variable(s)***	*Location (latitude [geographic/ geomagnetic])*	*Population* *Sample size, age (years)*	*Sampling* *Span*	*Interval*	*Results** *Spectral components*	*Cross-spectral coherence (frequency) [period]*
14. Cornélissen et al. [115]	USA (45.00•N/55.00 [25]; 41.18•N/52.19; 34.00•N/41.01; 47.17•N; 47.53)	Adults	5 selected spans between Aug 1967 and Apr 1975	1-6/day (N: 382-2840)	About 11.6-year cycle; remove-and-replace approach showing resonance of about 7-day component with corresponding variation in solar activity. When the sun 'removes' an about 7-day component from the spectrum of its velocity changes, the circaseptan HR amplitude is smaller.	
H		5				
HR		28–81				
15. Baevsky et al. [106]	Space (Soyuz space-craft)	Russian cosmonauts	2–15 min	Beat-to-beat	About 30% reduction in HR variability (gauged by standard deviation of R-R intervals) during magnetic storms vs. quiet days in extraterrestrial space	
H		49				
HR		25–50				
16. Syutkina et al. [153]	Moscow, Russia	Newborns	Up to 20 days	15 min	Correlation between nonlinearly-determined period of about 7-day component of BP and HR vs. local magnetic disturbance (*K*)	With *K*:
H	(55.45•N/50.76)	32				0.70 (around 0.3 day^{-1} and around 0.14 $hour^{-1}$) [3.33 days and 8.77 hours]
BP; HR		First month of life				(using 10 degrees of freedom)
17. Halberg et al. [37]	Minneapolis, Minnesota, USA (44.59•N/54.60)	Premature baby	Up to 26 months	Up to 1–5/day; denser at outset	Near-match of some spectral peaks of BP and HR vs *K*p	DBP with Bz:
L		1				0.74 (2.0 $week^{-1}$) [3.5 days] (using 14 degrees of freedom)
BP; HR; blood pH		Birth				
18. Halberg et al. ([146] u.p.↑)	Ancona, Italy (43.37•N/43.48)	Adult woman	1 year (267 days in isolation from society)	15-30 min	Closeness of nonlinearly-determined period of about-half-weekly component of HR vs *K*p during isolation	HR:
L		1				-with *K*p:

Table II. Biomedicine, solar activity and terrestrial magnetism: inferential statistical analyses, [18].

Study (reference) *Design** *Variable(s)***	*Location (latitude [geographic/ geomagnetic])*	*Population* *Sample size, age (years)*	*Sampling* *Span*	*Interval*	*Results** *Spectral components*	*Cross-spectral coherence (frequency) [period]*
BP; HR		28				0.558 (0.045 hour^{-1}) [22.22 hours] -with CR: 0.524 (0.138 hour^{-1}) [7.25 hours] -with 3h CR-SD: 0.546 (0.153 hour^{-1}) [6.54 hours] (using 22 degrees of freedom)
19. Watanabe et al. [156]	Tokyo, Japan	Adult man	3 years	15–30 min		With *K*p:
L	(35.42•N/25.75)	1				0.5 (0.036 day^{-1}) [27.8 days] (using 26 degrees of freedom)
BP; HR		35 (at start)				
20. Watanabe ([17, 156] u.p. ↑)	Tokyo, Japan(35.42•N/25.75)	Adult man	11 years	15–30 min monthly summary	About 10.5-year component in mean and SD of HR and in SD of SBP	HR with WN:
L		1				0.664 (1.636 year^{-1}) [7.33 months] (using 14 degrees of freedom)
BP; HR		35 (at start)				
21. Halberg et al. [37]	Minneapolis, Minnesota, USA (44.59•N/54.60)	Adult man	4 years (with interruptions)	15–30 min	About 5% increase in HR during magnetic storm and in BP on day preceding a magnetic storm on earth	
L		1				
BP; HR		68 (at start)				
22. Sothern (RBS) [17, 140, 152] u.p. ↑)	St. Paul, Minnesota, USA (45.00•N/55.00)	Minnesotan clinically healthy man	30.8 years	1–6/day (*N* 5 000/ variable; total *N* » 0.5 million values)	About 10.5- and 21-year as well as yearly ($P < 0.001$) cycles	With *K*p:
L		1				0.740 (2.03 year^{-1}) [5.91 months] (using 22 degrees of freedom)
BW; SBP; DBP; HR; RR; PEF; TE; EH; mood; vigor		20.5 (at start)				(Cross-correlation with *K*p of BP and HR maximal near lag 0)

Table II. Biomedicine, solar activity and terrestrial magnetism: inferential statistical analyses, [18].

Study (reference) *Design** *Variable(s)***	*Location (latitude [geographic/ geomagnetic])*	*Population* *Sample size, age (years)*	*Sampling* *Span*	*Interval*	*Results** *Spectral components*	*Cross-spectral coherence (frequency) [period]*
23. Halberg et al. ([147] unpublished observations)	Copenhagen, Denmark (55.43•N/55.19)	Clinically healthy man	15 years	Daily	About 9.28 yr (17-KS) or 4.18 yr (UV), 1.0 yr, 7 d and 3.5 d components, the latter two free-running from social schedule for 17-KS during last 3 yr when subject self-administered testosterone	17-KS with *K*p:
L		1				0.588 (11.98 year^{-1} [4.36 weeks] using 20 degrees of freedom)
Urine volume; urinary 17-ketosteroid excretion		44-59 years				
IV. Modulating role of melatonin?						
24. Tarquini et al.[154]	Florence, Italy (43.78•N/44.26)	Adults	3 years	4-hourly for 24 hours	About-yearly variation in MEL during daytime but half-yearly changes during nighttime at latitude of 43.47°N; half-yearly variation at 65.00°N around noon	
H		172				
Melatonin (MEL)		20–90				
25. Maggioni et al. [149]	Milan, Italy (45.28•N/46.31)	Women in 3rd trimester of pregnancy	1 year	4-hourly for 24 hours	About half-yearly variation found only in IUGR group, with 1.0 yr A and 0.5 yr (A,ϕ) difference between the two groups	
H		(14 healthy and 11 IUGR)				
Melatonin						
V. Theoretical computations						
26. Ulmer et al. [155]	For a field of about 1 nT typical of a magnetic field associated with the human circulatory system and with the interplanetary magnetic field, the oscillating period of some ions found in cells (Na^+, K^+, Ca^{++}, Mg^{++}) is about one week and that of some proteins (albumin, hemoglobin) is about 1 month, both periods corresponding to prominent components in the time structure of human physiology (computations based on the earth's magnetic field of 0.5 x 10^{-4} T typically found at mid latitudes for ions or molecules in a vacuum)					

Some analyses or meta-analyses in the Chronobiology Laboratories of the University of Minnesota in Minneapolis, Minnesota; a review of the vast literature is beyond the scope of this table.

In dealing with biomedical equivalents of the about 21-year Hale cycle (and there are components with even lower frequencies and even larger amplitudes in our anthropometric data), one cannot collect too many cycles over a single lifetime and turns for replications to populations; in the case of each of the population rhythms, one deals with findings on many individuals' cycles, as in the case of findings covering 112 years of population anthropometry; in each of the two studies by Weber et al. [24, 25]., over half a million individuals must be sufficiently concordant to allow a demonstration of the 10-year population rhythm. The 30.8 years of self-measurements of over 10 variables around the clock for a total of over half a million values provide a longitudinal validation check, supporting other evidence collected transversely, by virtue of (bio)ergodicity properties (that is the consistency of findings made transversely on populations and longitudinally on individuals, notably in relation to temporal characteristics of a process, assumed to be [bio]stationary in the sense of reproducibility of some of its characteristics).

* Strengthening and broadening the scope as to mechanisms of the propositions of Weber et al. [24] by cross-spectral coherence, superimposed epochs, and remove-and-replace approach, among other analyses on even larger and more diverse data sets. Results thus obtained reveal not only about-yearly rhythms but also other components with periods ranging from half a week to about 21 years that are not shared with sunshine. Overall, the evidence points to mechanisms complementing sunshine effects, including geomagnetic disturbance effects that may be mediated via intermodulations involving melatonin produced by the pineal gland.
Cross-spectral coherence coefficients have in common with correlation coefficients that they describe the relation between two variables. Cross-spectral coherence coefficients are less unspecific in that they describe the relationship at a specific frequency. In order to avoid listing spurious associations, only cross-spectral coherence coefficients away from spectral peaks are listed herein.
L: longitudinal; T: transverse; H: hybrid (linked cross-sectional); BH: body height; BW: body weight; HC: head circumference; CC: chest circumference; AC: abdomen circumference; BP: blood pressure (S. systolic; :D: diastolic); HR: heart rate; RR: respiratory rate; PEF. peak expiratory flow; TE: 1-minute time estimation; EH: eye-hand coordination; MI: myocardial infarctions; MEL: circulating melatonin; *K*p: geomagnetic disturbance index; WN: Wolf number of solar activity; Bz: vertical component of interplanetary magnetic field; CR: cosmic ray intensity; 3-h CR-SD: 3-hour standard deviation of CR; SD: standard deviation; †u.p.: unpublished observations.

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[4] "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. …[a] My plea today is that inform"… 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.ation 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 as given for the three statuses in this patient, an estimate of A itself, and finally an estimate of acrophase, ϕ. 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.

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